Gemeinsamer Bundesausschuss

Justification

to 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
Belzutifan (renal cell carcinoma, advanced, after ≥ 2 prior therapies)

of 18 September 2025

Contents

1. Legal basis

According to Section 35a paragraph 1 German Social Code, Book Five (SGB V), the Federal Joint Committee (G-BA) assess the benefit of all reimbursable medicinal products with new active ingredients. This includes in particular the assessment of the additional benefit and its therapeutic significance. The benefit assessment is carried out on the basis of evidence provided by the pharmaceutical company, which must be submitted to the G-BA electronically, including all clinical studies the pharmaceutical company have 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.
7. Number of study participants who participated in the clinical studies at study sites within the scope of SGB V, and total number of study participants.

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 decide on the benefit assessment within three months of its publication. The resolution is to be published on the internet 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 belzutifan on 1 April 2025 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 26 March 2025.

The G-BA commissioned the IQWiG to carry out the assessment of the dossier. The benefit assessment was published on 1 July 2025 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 belzutifan compared with the appropriate comparator therapy could be determined on the basis of the dossier of the pharmaceutical company, the dossier assessment prepared by the IQWiG, and the statements submitted in the written statement and oral hearing procedure. In order to determine the extent of the additional benefit, the G-BA have 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 belzutifan.

In the light of the above, and taking into account the statements received and the oral hearing, the G-BA have 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 Belzutifan (Welireg) in accordance with the product information

WELIREG is indicated as monotherapy for the treatment of adult patients with advanced clear cell renal cell carcinoma that progressed following two or more lines of therapy that included a PD-(L)1 inhibitor and at least two VEGF-targeted therapies.

Therapeutic indication of the resolution (resolution of 18.09.2025):

See the approved therapeutic indication

2.1.2 Appropriate comparator therapy

The appropriate comparator therapy was determined as follows:

Adults with advanced clear cell renal cell carcinoma after two or more prior therapies that included a PD-(L)1 inhibitor and at least two VEGF-targeted therapies

Appropriate comparator therapy for belzutifan as monotherapy:

Individualised therapy with selection of

- axitinib,
- cabozantinib,
- everolimus,
- lenvatinib in combination with everolimus and
- sunitinib

[1] General Methods, version 7.0 from 19.09.2023. Institute for Quality and Efficiency in Health Care (IQWiG), Cologne.

Criteria according to Chapter 5 Section 6 of the Rules of Procedure of the G-BA and Section 6 paragraph 2 Ordinance on the Benefit Assessment of Pharmaceuticals (AM-NutzenV):

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.

According to Section 6, paragraph 2, sentence 2 Ordinance on the Benefit Assessment of Pharmaceuticals (AM-NutzenV), the determination of the appropriate comparator therapy must be based on the actual medical treatment situation as it would be without the medicinal product to be assessed. According to Section 6, paragraph 2, sentence 3 Ordinance on the Benefit Assessment of Pharmaceuticals (AM-NutzenV), the G-BA may exceptionally determine the off-label use of medicinal products as an appropriate comparator therapy or as part of the appropriate comparator therapy if it determines by resolution on the benefit assessment according to Section 7, paragraph 4 that, according to the generally recognised state of medical knowledge, this is considered a therapy standard in the therapeutic indication to be assessed or as part of the therapy standard in the medical treatment situation to be taken into account according to sentence 2, and

1. for the first time, a medicinal product approved in the therapeutic indication is available with the medicinal product to be assessed,
2. according to the generally recognised state of medical knowledge, the off-label use is generally preferable to the medicinal products previously approved in the therapeutic indication, or
3. according to the generally recognised state of medical knowledge, the off-label use for relevant patient groups or indication areas is generally preferable to the medicinal products previously approved in the therapeutic indication.

An appropriate comparator therapy may also be non-medicinal therapy, the best possible add-on therapy including symptomatic or palliative treatment, or monitoring wait-and-see approach.

Justification based on the criteria set out in Chapter 5 Section 6, paragraph 3 VerfO and Section 6, paragraph 2 AM-NutzenV:

On 1. In addition to belzutifan, medicinal products with the active ingredients axitinib, cabozantinib, lenvatinib, sunitinib, nivolumab, everolimus and aldesleukin are approved in the present therapeutic indication.

On 2. Non-medicinal treatment is not considered. For the planned therapeutic indication, it is assumed that surgery or radiotherapy with curative objectives are not (or no longer) an option at the time of the treatment decision and that the treatment is palliative. The use of resection or radiotherapy as a palliative patient-individual therapy option for symptom control depending on the localisation and symptomatology of the metastases remains unaffected.

On 3. In the present therapeutic indication, the following resolutions on the benefit assessment of medicinal products with new active ingredients according to Section 35a SGB V are available:

- Lenvatinib: resolution of 1 July 2021
- Cabozantinib: resolution of 5 April 2018
- Axitinib: resolution of 21 September 2017
- Nivolumab: resolution of 20 October 2016

Guidelines of the G-BA for medicinal applications or non-medicinal treatments:

- Annex VI Part B of the Pharmaceuticals Directive – Active ingredients that cannot be prescribed in applications beyond the scope of the marketing authorisation (off-label use); last revised: 31 December 2024): II. Inhaled interleukin-2 (Proleukin®) for the treatment of renal cell carcinoma – resolution of 8 June 2016

On 4. The generally recognised state of medical knowledge was illustrated by a systematic search for guidelines as well as systematic 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”). A written statement from the German Society for Haematology and Medical Oncology (DGHO) is available for the present procedure.

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

It is assumed that the patients are generally eligible for active antineoplastic therapy, which is why best supportive care is not considered as an appropriate comparator therapy in the present case.

The therapeutic indication includes patients from the third line of treatment in the locally advanced or metastatic stage of renal cell carcinoma. The body of evidence in this therapeutic indication is limited.

The S3 guideline and the written statements of the DGHO indicate that there is no established standard for the third line of therapy. With regard to a treatment algorithm, the S3 guideline however recommends by consensus that a tyrosine kinase inhibitor (TKI)-based therapy should be administered after failure of a combination therapy of nivolumab + ipilimumab, avelumab + axitinib, nivolumab + cabozantinib, pembrolizumab + axitinib or pembrolizumab + lenvatinib, and that the respective marketing authorisations should be observed. With regard to the third line of therapy, the S3 guideline recommends - in accordance with the EAU and ASCO guidelines and

the written statements of the DGHO - that previous therapies should be taken into account when selecting the systemic therapy and that substances that were not included in the previous therapy should be given. Patients who have already received an immune checkpoint inhibitor in a previous line of therapy should not be treated again with an immune checkpoint inhibitor.

According to the DGHO's written statement, the current therapy recommendations are primarily based on the type of pretreatment, the patient's general condition and the side effects of previous therapies. In accordance with the written statement, other TKIs and the mTOR inhibitor everolimus may also be used in patients with advanced clear cell renal cell carcinoma in progression after two or more lines of therapy that included a PD-(L)1 inhibitor and at least two VEGF-targeted therapies.

Overall, the active ingredients axitinib, cabozantinib, everolimus, lenvatinib in combination with everolimus and sunitinib can therefore be considered as therapy options.

Therapy after two or more previous therapies that included a PD-(L)1 inhibitor and at least two VEGF-targeted therapies is therefore largely based on patient-individual criteria usually for the previous therapies. Therefore, the G-BA determined an individualised therapy as the appropriate comparator therapy, which includes the TKIs axitinib, cabozantinib and sunitinib, the mTOR inhibitor everolimus and lenvatinib in combination with everolimus.

Individualised therapy is based on the assumption that several treatment options, which allow an individualised medical treatment decision, are available. When making the treatment decision, previous therapies in particular must be considered, taking into account the available evidence.

The marketing authorisation and dosage specifications in the product information of the active ingredients must be considered; deviations must be justified separately.

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

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 belzutifan is assessed as follows:

Adults with advanced clear cell renal cell carcinoma after two or more prior therapies that included a PD-(L)1 inhibitor and at least two VEGF-targeted therapies

a) Adults with advanced clear cell renal cell carcinoma after two or more prior therapies that included a PD-(L)1 inhibitor and at least two VEGF-targeted therapies, for whom everolimus is the appropriate patient-individual therapy

   Hint for a minor additional benefit

b) Adults with advanced clear cell renal cell carcinoma after two or more prior therapies that included a PD-(L)1 inhibitor and at least two VEGF-targeted therapies, for whom axitinib, cabozantinib, lenvatinib in combination with everolimus or sunitinib is the appropriate patient-individual therapy

   An additional benefit is not proven.

Justification:

For the benefit assessment, the pharmaceutical company submitted the results of the LITESPARK 005 study. This is an ongoing, open-label, randomised, multicentre phase III study comparing belzutifan with everolimus. The study has been conducted in 172 study sites in Europe, North and South America, and Asia since February 2020. Patients with unresectable locally advanced or metastatic clear cell renal cell carcinoma whose disease had reached the extensive stage after or during treatment with a PD-(L)1 inhibitor and a VEGF tyrosine kinase inhibitor were enrolled in the study.

For the benefit assessment, results were presented for an on-label sub-population of 370 patients whose disease had progressed after two or more therapies that included a PD-(L)1 inhibitor and at least two VEGF-targeted therapies. Of these patients, 188 were randomised to treatment with belzutifan and 182 to treatment with everolimus, and treated in accordance with the requirements in the respective product information.

Co-primary endpoints of the study were overall survival and progression-free survival. Patient-relevant secondary endpoints were assessed in the endpoint categories of morbidity, health-related quality of life and side effects.

For the benefit assessment, the evaluations of the final data cut-off from 15.04.2024 are used.

On the implementation of the appropriate comparator therapy

An individualised therapy with selection of axitinib, cabozantinib, everolimus, lenvatinib in combination with everolimus and sunitinib was determined as the appropriate comparator therapy. The pharmaceutical company presented the results of the LITESPARK 005 study comparing belzutifan with everolimus.

In IQWiG's dossier assessment, a separate assessment of the additional benefit was made for patients for whom a therapy with everolimus is the appropriate or inappropriate patient-individual therapy. Since the appropriate comparator therapy includes other therapy options in addition to everolimus, the LITESPARK 005 study does not allow any statements to be made on the additional benefit for patients for whom a therapy other than everolimus (axitinib, cabozantinib, lenvatinib in combination with everolimus, sunitinib) is the appropriate patient-individual therapy.

Against this background, the G-BA consider it appropriate to divide the patient population accordingly and to make the statement on additional benefit separately for patients for whom everolimus is the appropriate patient-individual therapy (patient group a) and patients for whom axitinib, cabozantinib, lenvatinib in combination with everolimus or sunitinib is the appropriate patient-individual therapy (patient group b).

Extent and probability of the additional benefit

a) Adults with advanced clear cell renal cell carcinoma after two or more prior therapies that included a PD-(L)1 inhibitor and at least two VEGF-targeted therapies, for whom everolimus is the appropriate patient-individual therapy

Mortality

Overall survival

Overall survival in the LITESPARK 005 study was operationalised as the time from randomisation to death from any cause. For the endpoint of overall survival, there was no statistically significant difference between the treatment groups.

Morbidity

Progression-free survival (PFS)

PFS is operationalised as the time from randomisation to the first documented disease progression or death from any cause, whichever came first.

The evaluation was conducted by a blinded, independent, central review committee based on RECIST criteria version 1.1.

For the PFS endpoint, there was a statistically significant difference to the advantage of belzutifan compared to everolimus.

The PFS endpoint is a composite endpoint composed of endpoints of the mortality and morbidity categories. The endpoint component "mortality" was already assessed as an independent endpoint in the present study via the endpoint "overall survival". The morbidity component assessment was not done in a symptom-related manner but exclusively by means of imaging procedures (disease progression assessed by radiology according to the RECIST criteria version 1.1).

Taking into account the aspects mentioned above, there are different opinions within the G-BA regarding the patient relevance of the endpoint PFS. The overall statement on the additional benefit remains unaffected.

Symptomatology

EORTC QLQ-C30 and FKSI-DRS

Symptomatology was assessed in the LITESPARK 005 study using the EORTC QLQ-C30 and FKSI-DRS questionnaires. For the benefit assessment, the pharmaceutical company submitted evaluations of the time to first deterioration.

Based on the EORTC QLQ-C30, there were statistically significant differences in favour of belzutifan for the symptoms of insomnia, appetite loss and diarrhoea, which are assessed as relevant advantages of belzutifan over everolimus. In addition, there was a statistically significant difference to the advantage of belzutifan for the pain endpoint.

For the pain symptom, there was an effect modification due to the "age" characteristic. For subjects ≥ 65 years of age, the subgroup analyses showed a statistically significant difference to the advantage of belzutifan. In contrast, for subjects < 65 years of age, there was no statistically significant difference between the treatment groups. These subgroup results are considered a relevant outcome of the present benefit assessment. They point out that younger patients benefit less from the therapy. However, they are considered inadequate to derive separate statements on the additional benefit in the overall assessment.

Based on the FKSI-DRS, statistically significant differences to the advantage of belzutifan over everolimus could be identified for disease symptomatology.

Health status

EQ-5D, visual analogue scale (VAS)

The health status was surveyed using the VAS of the EQ-5D questionnaire. There was no difference between the treatment groups.

In the morbidity endpoint category, the overall analysis showed relevant advantages of belzutifan in the symptoms of insomnia, appetite loss and diarrhoea as well as an advantage in pain (EORTC QLQ-C30). In addition, there was an advantage of belzutifan over everolimus in terms of disease symptomatology (FKSI-DRS).

<u>Health-related quality of life</u>

EORTC QLQ-C30

Health-related quality of life was assessed in the LITESPARK 005 study using the EORTC QLQ-C30 questionnaire and evaluations of the time to first deterioration were presented.

There was no statistically significant difference between the treatment groups.

For the social functioning scale, there was nevertheless an effect modification due to the "age" characteristic. For subjects ≥ 65 years of age, the subgroup analyses showed a statistically significant difference to the advantage of belzutifan. In contrast, for subjects < 65 years of age, there was no statistically significant difference between the treatment groups. These subgroup results are considered a relevant outcome of the present benefit assessment. They point out that younger patients benefit less from the therapy. However, they are considered inadequate to derive separate statements on the additional benefit in the overall assessment.

<u>Side effects</u>

Adverse events (AEs) in total

AEs occurred in almost all patients in both study arms. The results were only presented additionally.

Serious adverse events (SAEs), severe AEs (CTCAE grade ≥ 3)

For the endpoints of SAEs and severe AEs, there were no statistically significant differences between the treatment groups.

Therapy discontinuation due to AEs

For therapy discontinuation due to AEs, there was a statistically significant difference in favour of the belzutifan arm, with an effect modification for the "age" characteristic.

For subjects ≥ 65 years of age, the subgroup analyses showed a statistically significant difference to the advantage of belzutifan. In contrast, for subjects < 65 years of age, there was no statistically significant difference between the treatment groups. These subgroup results are considered a relevant outcome of the present benefit assessment. They point out that younger patients benefit less from the therapy. However, they are considered inadequate to derive separate statements on the additional benefit in the overall assessment.

Specific adverse events

In detail, there were statistically significant differences in favour of belzutifan compared to everolimus for infections and infestations (severe AE), stomatitis (AE), fever (AE), skin and subcutaneous tissue disorders (AE), fatigue (severe AE) and hyperglycaemia (severe AE).

In contrast, there were disadvantages of belzutifan compared to everolimus for the endpoints of hypoxia (severe AE), constipation (AE) and dizziness (AE).

The overall analysis of the results on side effects showed an advantage of belzutifan over everolimus in terms of therapy discontinuation due to AEs. In detail, there were advantages and disadvantages in the specific AEs.

<u>Overall assessment</u>

The LITESPARK 005 RCT which compared belzutifan with everolimus was presented for the assessment of the additional benefit of belzutifan for the treatment of patients with advanced clear cell renal cell carcinoma after two or more prior therapies. The study is suitable for the assessment of the additional benefit for patients in the therapeutic indication for whom everolimus is the appropriate patient-individual therapy. Results on mortality, morbidity, health-related quality of life and side effects are available.

The results for the overall survival endpoint showed no statistically significant difference between the treatment groups.

In the morbidity endpoint category, there were relevant advantages in the symptoms of insomnia, appetite loss and diarrhoea as well as further positive effects for the symptoms of pain (assessed using the EORTC QLQ-C30) and disease symptomatology (assessed using the FKSI-DRS). Even taking into account the clinical relevance of the symptoms mentioned in the present therapeutic indication, the advantage of belzutifan in the morbidity endpoint category is rated no more than minor overall.

In terms of health-related quality of life, there were no statistically significant differences between the treatment groups.

In the endpoint category of side effects, an advantage of belzutifan can be identified in therapy discontinuation due to AEs. In detail, there were advantages and disadvantages in the specific AEs.

For the endpoints of pain, social functioning and therapy discontinuation due to AEs, effect modifications due to the "age" characteristic are evident across endpoints. For subjects ≥ 65 years of age, the subgroup analyses showed a statistically significant difference to the advantage of belzutifan. In contrast, for subjects < 65 years of age, there was no statistically significant difference between the treatment groups. These subgroup results represent relevant results of the present benefit assessment and indicate that younger patients benefit less from the therapy. However, they are considered inadequate to derive separate statements on the additional benefit in the overall assessment.

In the overall assessment of the available results on patient-relevant endpoints, a minor additional benefit of belzutifan over everolimus was identified for the treatment of adults with advanced clear cell renal cell carcinoma after two or more prior therapies that included a PD-(L)1 inhibitor and at least two VEGF-targeted therapies and for whom everolimus is the appropriate patient-individual therapy due to the advantages in symptomatology and therapy discontinuation due to adverse events.

Reliability of data (probability of additional benefit)

The present assessment is based on the results of the open-label, randomised, multicentre phase III LITESPARK 005 study.

Overall, the risk of bias at the study level is rated as low.

For the endpoint of overall survival, there is a low risk of bias.

The open-label study design and the resulting lack of blinding in the subjective endpoint assessment are the main reasons for the increased risk of bias. The endpoint-specific risk of bias for the results of the patient-reported endpoints on morbidity and health-related quality of life is therefore rated as high. In addition, the return rate of the questionnaires fell sharply over the course of the study and differed between the study arms.

There is additional uncertainty in the reliability of data due to the effect modification by the "age" characteristic in the endpoint categories of morbidity, quality of life and side effects.

In summary, the G-BA therefore derive a hint for the identified additional benefit with regard to the reliability of data.

b) Adults with advanced clear cell renal cell carcinoma after two or more prior therapies that included a PD-(L)1 inhibitor and at least two VEGF-targeted therapies, for whom axitinib, cabozantinib, lenvatinib in combination with everolimus or sunitinib is the appropriate patient-individual therapy

No data were presented for comparison with axitinib, cabozantinib, lenvatinib in combination with everolimus or sunitinib.

An additional benefit of belzutifan over the appropriate comparator therapy is not proven for the treatment of adults with advanced clear cell renal cell carcinoma after two or more prior therapies that included a PD-(L)1 inhibitor and at least two VEGF-targeted therapies and for whom axitinib, cabozantinib, lenvatinib in combination with everolimus or sunitinib is the appropriate patient-individual therapy.

2.1.4 Summary of the assessment

The present assessment concerns the benefit assessment of the new medicinal product Welireg with the active ingredient belzutifan.

Belzutifan is indicated as monotherapy for the treatment of adult patients with advanced clear cell renal cell carcinoma that progressed following two or more lines of therapy that included a PD-(L)1 inhibitor and at least two VEGF-targeted therapies.

An individualised therapy with selection of axitinib, cabozantinib, everolimus, lenvatinib in combination with everolimus and sunitinib was determined as the appropriate comparator therapy.

The pharmaceutical company submitted the LITESPARK 005 RCT, which compared belzutifan with everolimus. The results are relevant for the sub-population with two or more previous therapies.

The G-BA conducted a separate assessment of the additional benefit depending on the appropriate patient-individual therapy:

a) Adults with advanced clear cell renal cell carcinoma after two or more prior therapies that included a PD-(L)1 inhibitor and at least two VEGF-targeted therapies, for whom everolimus is the appropriate patient-individual therapy

and

b) Adults with advanced clear cell renal cell carcinoma after two or more prior therapies that included a PD-(L)1 inhibitor and at least two VEGF-targeted therapies, for whom axitinib, cabozantinib, lenvatinib in combination with everolimus or sunitinib is the appropriate patient-individual therapy

On a)

For overall survival, there was no difference between the treatment groups.

In the morbidity endpoint category, there were relevant advantages in the symptoms of insomnia, loss of appetite and diarrhoea as well as further positive effects for the symptoms of pain (EORTC QLQ-C30) and disease symptomatology (FKSI-DRS). Even taking into account

the clinical relevance of the symptoms mentioned in the present therapeutic indication, the advantage in morbidity is rated no more than minor overall.

For health-related quality of life, there were no differences between the treatment groups.

In terms of side effects, an advantage of belzutifan in therapy discontinuation due to AEs could be identified. In detail, there were advantages and disadvantages in the specific AEs.

For the endpoints of pain, social functioning and therapy discontinuation due to AEs, effect modifications due to the "age" characteristic are evident across endpoints. There was an advantage of belzutifan for subjects ≥ 65 years of age. For subjects < 65 years of age, there was no difference. The subgroup results represent relevant results of the present benefit assessment, but are considered inadequate to derive separate statements on the additional benefit in the overall assessment.

In the overall assessment, a minor additional benefit of belzutifan over everolimus was identified due to the advantages in symptomatology and therapy discontinuation due to adverse events. Uncertainties mainly arise due to the open-label study design and the resulting lack of blinding in the subjective endpoint assessment. An additional uncertainty results from the effect modification due to the "age" characteristic in the endpoint categories of morbidity, quality of life and side effects. The reliability of data is therefore classified in the "hint" category.

On b)

The LITESPARK 005 study is not suitable for the benefit assessment. No data were presented for comparison with axitinib, cabozantinib, lenvatinib in combination with everolimus or sunitinib.

An additional benefit compared to the appropriate comparator therapy is not proven.

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

Adults with advanced clear cell renal cell carcinoma after two or more prior therapies that included a PD-(L)1 inhibitor and at least two VEGF-targeted therapies

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

The resolution is based on the information provided by the pharmaceutical company. Uncertainties exist in particular for the following reasons:

Information from the Centre for Cancer Registry Data for 2022, which is still to be regarded as provisional, is included for the estimation of the baseline for the lower limit.

When estimating the upper limit, it is questionable whether percentage values relating to the incidence can be transferred to the two-year prevalence.

In addition, the use of percentage values that do not relate exclusively to clear cell renal cell carcinomas is fraught with uncertainty.

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 Welireg (active ingredient: belzutifan) at the following publicly accessible link (last access: 10 September 2025):

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

Treatment should only be initiated and monitored by specialists in internal medicine, haematology, and oncology, as well as specialists in internal medicine and nephrology, and other doctors from other specialist groups participating in the oncology agreement experienced in the treatment of adults with renal cell carcinoma.

This medicinal product received a conditional marketing authorisation. This means that further evidence of the benefit of the medicinal product is anticipated. The European Medicines Agency EMA will evaluate new information on this medicinal product at a minimum once per year and update the product information where necessary.

In accordance with the EMA requirements regarding additional risk minimisation measures, the pharmaceutical company must provide training material that contains information for medical professionals and patients (including patient card). The training material contains in particular information and warnings on the risk of embryo-foetal damage when taking belzutifan during pregnancy.

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 July 2025).

For the cost representation, one year is assumed for all medicinal products.

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

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.

Treatment period:

Adults with advanced clear cell renal cell carcinoma after two or more prior therapies that included a PD-(L)1 inhibitor and at least two VEGF-targeted therapies

Designation of the therapy	Treatment mode	Number of treatments/ patient/ year	Treatment duration/ treatment (days)	Treatment days/ patient/ year
Medicinal product to be assessed				
Belzutifan	Continuously, 1 x daily	365	1	365
Appropriate comparator therapy				
Monotherapies				

Designation of the therapy	Treatment mode	Number of treatments/ patient/ year	Treatment duration/ treatment (days)	Treatment days/ patient/ year
Axitinib	Continuously, 2 x daily	365	1	365
Cabozantinib	Continuously, 1 x daily	365	1	365
Everolimus	Continuously, 1 x daily	365	1	365
sunitinib	4/2 regimen: 1 x daily for 28 days, followed by a 14-day treatment-free interval	8.7	28	243.6
Lenvatinib in combination with everolimus				
Lenvatinib	Continuously, 1 x daily	365	1	365
Everolimus				

Consumption:

For dosages depending on body weight (BW) or body surface area (BSA), the average body measurements from the official representative statistics "Microcensus 2021 – body measurements of the population" were applied (average body height: 1.72 m; average body weight: 77.7 kg). This results in a body surface area of 1.91 m² (calculated according to Du Bois 1916).[2]

Adults with advanced clear cell renal cell carcinoma after two or more prior therapies that included a PD-(L)1 inhibitor and at least two VEGF-targeted therapies

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					
Belzutifan	120 mg	120 mg	3 x 40 mg	365	1,095 x 40 mg
Appropriate comparator therapy					
Monotherapies					

[2] Federal Health Reporting. Average body measurements of the population (2021, both sexes, 15 years and older), www.gbe-bund.de

Designation of the therapy	Dosage/ application	Dose/ patient/ treatment days	Consumption by potency/ treatment day	Treatment days/ patient/ year	Average annual consumption by potency
Axitinib	5 mg	5 mg	2 x 5 mg	365	730 x 5 mg
Cabozantinib	60 mg	60 mg	1 x 60 mg	365	365 x 60 mg
Everolimus	10 mg	10 mg	1 x 10 mg	365	365 x 10 mg
sunitinib	50 mg	50 mg	1 x 50 mg	243.6	243.6 x 50 mg
Lenvatinib in combination with everolimus					
Lenvatinib	18 mg	18 mg	1 x 10 mg + 2 x 4 mg	365	365 x 10 mg + 730 x 4 mg
Everolimus	5 mg	5 mg	2 x 2.5 mg	365	730 x 2.5 mg

Costs:

In order to improve comparability, the costs of the medicinal products were approximated both on the basis of the pharmacy sales price level and also deducting the statutory rebates in accordance with Section 130 and Section 130a SGB V. To calculate the annual treatment costs, the required number of packs of a particular potency was first determined on the basis of consumption. Having determined the number of packs of a particular potency, the costs of the medicinal products were then calculated on the basis of the costs per pack after deduction of the statutory rebates. Any reference prices shown in the cost representation may not represent the cheapest available alternative.

Costs of the medicinal products:

Medicinal product to be assessed					
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
Belzutifan 40 mg	90 FCT	€ 17,830.31	€ 1.77	€ 1,015.00	€ 16,813.54
Appropriate comparator therapy					
Axitinib 5 mg	56 FCT	€ 1,060.52	€ 1.77	€ 58.09	€ 1,000.66
Cabozantinib 60 mg	30 FCT	€ 4,931.43	€ 1.77	€ 278.34	€ 4,651.32
Everolimus 2.5 mg	30 TAB	€ 111.21	€ 1.77	€ 4.74	€ 104.70
Everolimus 10 mg	30 TAB	€ 419.63	€ 1.77	€ 19.38	€ 398.48
Lenvatinib 4 mg	30 HC	€ 1,329.12	€ 1.77	€ 72.96	€ 1,254.39
Lenvatinib 10 mg	30 HC	€ 1,329.12	€ 1.77	€ 72.96	€ 1,254.39
Sunitinib 50 mg[3]	30 HC	€ 395.27	€ 1.77	€ 30.37	€ 363.13
Abbreviations: FCT = film-coated tablets; HC = hard capsules; TAB = tablets					

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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.

2.5 Designation of 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 the assessed medicinal product

According to Section 35a, paragraph 3, sentence 4, the G-BA 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.

Basic principles of the assessed medicinal product

A designation in accordance with Section 35a, paragraph 3, sentence 4 SGB V requires that it is examined based on the product information for the assessed medicinal product whether it

[3] Fixed reimbursement rate

can be used in a combination therapy with other medicinal products in the assessed therapeutic indication. In the first step, the examination is carried out on the basis of all sections of the currently valid product information for the assessed medicinal product.

If the assessed medicinal product contains an active ingredient or a fixed combination of active ingredients in the therapeutic indication of the resolution (assessed therapeutic indication) and is approved exclusively for use in monotherapy, a combination therapy is not considered due to the marketing authorisation under Medicinal Products Act, which is why no designation is made.

A designation is also not considered if the G-BA have decided on an exemption as a reserve antibiotic for the assessed medicinal product in accordance with Section 35a, paragraph 1c, sentence 1 SGB V. The additional benefit is deemed to be proven if the G-BA have decided on an exemption for a reserve antibiotic in accordance with Section 35a, paragraph 1c, sentence 1 SGB V; the extent of the additional benefit and its therapeutic significance are not to be assessed by the G-BA. Due to the lack of an assessment mandate by the G-BA following the resolution on an exemption according to Section 35a, paragraph 1c, sentence 1 SGB V with regard to the extent of the additional benefit and the therapeutic significance of the reserve antibiotic to be assessed, there is a limitation due to the procedural privileging of the pharmaceutical companies to the effect that neither the proof of an existing nor an expected at least considerable additional benefit is possible for exempted reserve antibiotics in the procedures according to Section 35a paragraph 1 or 6 SGB V and Section 35a paragraph 1d SGB V. The procedural privileging of the reserve antibiotics exempted according to Section 35a, paragraph 1c, sentence 1 SGB V must therefore also be taken into account at the level of designation according to Section 35a, paragraph 3, sentence 4 SGB V in order to avoid valuation contradictions.

With regard to the further examination steps, a differentiation is made between a "determined" or "undetermined" combination, which may also be the basis for a designation.

A "determined combination" exists if one or more individual active ingredients which can be used in combination with the assessed medicinal product in the assessed therapeutic indication are specifically named.

An "undetermined combination" exists if there is information on a combination therapy, but no specific active ingredients are named. An undetermined combination may be present if the information on a combination therapy:

- names a product class or group from which some active ingredients not specified in detail can be used in combination therapy with the assessed medicinal product, or
- does not name any active ingredients, product classes or groups, but the assessed medicinal product is used in addition to a therapeutic indication described in more detail in the relevant product information, which, however, does not include information on active ingredients within the scope of this therapeutic indication.

Concomitant active ingredient

The concomitant active ingredient is a medicinal product with new active ingredients that can be used in combination therapy with the assessed medicinal product for the therapeutic indication to be assessed.

For a medicinal product to be considered as a concomitant active ingredient, it must be classified as a medicinal product with new active ingredients according to Section 2 paragraph 1 Ordinance on the Benefit Assessment of Pharmaceuticals (AM-NutzenV) in conjunction with

the corresponding regulations in Chapter 5 of the Rules of Procedure of the G-BA as of the date of the present resolution. In addition, the medicinal product must be approved in the assessed therapeutic indication, whereby a marketing authorisation is sufficient only for a sub-area of the assessed therapeutic indication.

Based on an "undetermined combination", the concomitant active ingredient must be attributable to the information on the product class or group or the therapeutic indication according to the product information of the assessed medicinal product in the assessed therapeutic indication, whereby the definition of a product class or group is based on the corresponding requirements in the product information of the assessed medicinal product.

In addition, there must be no reasons for exclusion of the concomitant active ingredient from a combination therapy with the assessed medicinal product, in particular no exclusive marketing authorisation as monotherapy.

In addition, all sections of the currently valid product information of the eligible concomitant active ingredient are checked to see whether there is any information that excludes its use in combination therapy with the assessed medicinal product in the assessed therapeutic indication under marketing authorisation regulations. Corresponding information can be, for example, dosage information or warnings. In the event that the medicinal product is used as part of a determined or undetermined combination which does not include the assessed medicinal product, a combination with the assessed medicinal product shall be excluded.

Furthermore, the product information of the assessed medicinal product must not contain any specific information that excludes its use in combination therapy with the eligible concomitant active ingredient in the assessed therapeutic indication under marketing authorisation regulations.

Medicinal products with new active ingredients for which the G-BA have decided on an exemption as a reserve antibiotic in accordance with Section 35a, paragraph 1c, sentence 1 SGB V are ineligible as concomitant active ingredients. The procedural privileging of the reserve antibiotics exempted according to Section 35a, paragraph 1c, sentence 1 SGB V also applies accordingly to the medicinal product eligible as a concomitant active ingredient.

Designation

The medicinal products which have been determined as concomitant active ingredients in accordance with the above points of examination are named by indicating the relevant active ingredient and the invented name. The designation may include several active ingredients, provided that several medicinal products with new active ingredients may be used in the same combination therapy with the assessed medicinal product or different combinations with different medicinal products with new active ingredients form the basis of the designation.

If the present resolution on the assessed medicinal product in the assessed therapeutic indication contains several patient groups, the designation of concomitant active ingredients shall be made separately for each of the patient groups.

Exception to the designation

The designation excludes combination therapies for which - patient group-related - a considerable or major additional benefit has been determined by resolution according to Section 35a, paragraph 3, sentence 1 SGB V or it has been determined according to Section 35a, paragraph 1d, sentence 1 SGB V that at least considerable additional benefit of the combination can be expected. In this context, the combination therapy that is excluded from

the designation must, as a rule, be identical to the combination therapy on which the preceding findings were based.

In the case of designations based on undetermined combinations, only those concomitant active ingredients - based on a resolution according to Section 35a, paragraph 3, sentence 1 SGB V on the assessed medicinal product in which a considerable or major additional benefit had been determined - which were approved at the time of this resolution are excluded from the designation.

Legal effects of the designation

The designation of combinations is carried out in accordance with the legal requirements according to Section 35a, paragraph 3, sentence 4 and is used exclusively to implement the combination discount according to Section 130e SGB V between health insurance funds and pharmaceutical companies. The designation is not associated with a statement as to the extent to which a therapy with the assessed medicinal products in combination with the designated medicinal products corresponds to the generally recognised state of medical knowledge. The examination was carried out exclusively on the basis of the possibility under Medicinal Products Act to use the medicinal products in combination therapy in the assessed therapeutic indication based on the product information; the generally recognised state of medical knowledge or the use of the medicinal products in the reality of care were not the subject of the examination due to the lack of an assessment mandate of the G-BA within the framework of Section 35a, paragraph 3, sentence 4 SGB V.

The findings made neither restrict the scope of treatment required to fulfil the medical treatment mandate, nor do they make statements about expediency or economic feasibility.

Justification for the findings on designation in the present resolution:

Adults with advanced clear cell renal cell carcinoma after two or more prior therapies that included a PD-(L)1 inhibitor and at least two VEGF-targeted therapies

No designation of medicinal products with new active ingredients that can be used in combination therapy pursuant to Section 35a, paragraph 3, sentence 4 SGB V, as the active ingredient to be assessed is an active ingredient authorised in monotherapy.

References:
Product information for belzutifan (Welireg); Welireg 40 mg film-coated tablets; last revised: February 2025

2.6 Percentage of study participants at study sites within the scope of SGB V in accordance with Section 35a, paragraph 3, sentence 5 SGB V

The medicinal product belzutifan is a medicinal product placed on the market from 1 January 2025. In accordance with Section 35a, paragraph 3, sentence 5 SGB V, the G-BA must determine whether a relevant percentage of the clinical studies on the medicinal product were conducted within the scope of SGB V. This is the case if the percentage of study participants who have participated in the clinical studies on the medicinal product to be assessed in the therapeutic indication to be assessed at study sites within the scope of SGB V is at least five per cent of the total number of study participants.

The calculation is based on all studies that were submitted as part of the benefit assessment dossier in the therapeutic indication to be assessed in accordance with Section 35a, paragraph 1, sentence 3 SGB V in conjunction with Section 4, paragraph 6 AM-NutzenV. Approval studies include all studies submitted to the regulatory authority in the authorisation dossier for the assessment of the clinical efficacy and safety of the medicinal product in the therapeutic indication to be assessed.

The percentage of study participants in the clinical studies of the medicinal product conducted or commissioned by the pharmaceutical company in the therapeutic indication to be assessed who participated at study sites within the scope of SGB V (German Social Security Code) is less than 5 per cent (2.6%) of the total number of study participants.

The clinical studies of the medicinal product in the therapeutic indication to be assessed were therefore not conducted to a relevant extent within the scope of SGB V.

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 their session on 28 June 2022, the Subcommittee on Medicinal Products determined the appropriate comparator therapy.

A review of the appropriate comparator therapy took place once the positive opinion was granted. The Subcommittee on Medicinal Products determined the appropriate comparator therapy at their session on 25 February 2025.

On 26 March 2025, the pharmaceutical company submitted a dossier for the benefit assessment of belzutifan to the G-BA in due time in accordance with Chapter 5 Section 8, paragraph 1, number 1, sentence 2 VerfO.

By letter dated 28 March 2025 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 belzutifan.

The dossier assessment by the IQWiG was submitted to the G-BA on 26 June 2025, and the written statement procedure was initiated with publication on the G-BA website on 1 July 2025. The deadline for submitting statements was 22 July 2025.

The oral hearing was held on 11 August 2025.

By letter dated 12 August 2025, the IQWiG was commissioned with a supplementary assessment. The addendum prepared by IQWiG was submitted to the G-BA on 29 August 2025.

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

The evaluation of the written statements received and the oral hearing was discussed at the session of the Subcommittee on 9 September 2025, and the proposed draft resolution was approved.

At their session on 18 September 2025, the plenum adopted a resolution to amend the Pharmaceuticals Directive.

Chronological course of consultation

Session	Date	Subject of consultation
Subcommittee on Medicinal Products	28 June 2022	Determination of the appropriate comparator therapy
Subcommittee on Medicinal Products	25 February 2025	New determination of the appropriate comparator therapy
Working group Section 35a	06 August 2025	Information on written statements received; preparation of the oral hearing
Subcommittee on Medicinal Products	11 August 2025	Conduct of the oral hearing, commissioning of the IQWiG with the supplementary assessment of documents
Working group Section 35a	20 August 2025 03 September 2025	Consultation on the dossier evaluation by the IQWiG and evaluation of the written statement procedure
Subcommittee on Medicinal Products	09 September 2025	Concluding discussion of the draft resolution
Plenum	18 September 2025	Adoption of the resolution on the amendment of the Pharmaceuticals Directive

Berlin, 18 September 2025

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

Prof. Hecken