Gemeinsamer Bundesausschuss

Resolution

of the Federal Joint Committee 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

At their session on 18 September 2025, the Federal Joint Committee (G-BA) resolved to amend the Pharmaceuticals Directive (AM-RL) in the version dated 18 December 2008 / 22 January 2009 (Federal Gazette, BAnz. No. 49a of 31 March 2009), as last amended by the publication of the resolution of D Month YYYY (Federal Gazette, BAnz AT DD.MM.YYYY BX), as follows:

I. Annex XII shall be amended in alphabetical order to include the active ingredient Belzutifan as follows:

Belzutifan

Resolution of: 18 September 2025
Entry into force on: 18 September 2025
Federal Gazette, BAnz AT DD. MM YYYY Bx

Therapeutic indication (according to the marketing authorisation of 12 February 2025):

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 September 2025):

See therapeutic indication according to marketing authorisation.

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

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:

Individualised therapy with selection of

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

Extent and probability of the additional benefit of belzutifan compared to the appropriate comparator 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

   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.

Study results according to endpoints:[1]

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

Summary of results for relevant clinical endpoints

Endpoint category	Direction of effect/ risk of bias	Summary
Mortality	↔	No relevant difference for the benefit assessment.
Morbidity	↑	Advantages in the endpoints of pain, insomnia, appetite loss and diarrhoea (EORTC QLQ-C30); advantage in the endpoint of symptomatology (FKSI-DRS)
Health-related quality of life	↔	No relevant difference for the benefit assessment.
Side effects	↑	Advantage in the endpoint of therapy discontinuation due to adverse events. In detail, advantages and disadvantages in specific AEs.
Explanations: ↑: statistically significant and relevant positive effect with low/unclear reliability of data ↓: statistically significant and relevant negative effect with low/unclear reliability of data ↑↑: statistically significant and relevant positive effect with high reliability of data ↓↓: statistically significant and relevant negative effect with high reliability of data ↔: no statistically significant or relevant difference ∅: No data available. n.a.: not assessable		

LITESPARK 005 study:

- Multicentre, randomised, controlled, unblinded phase III study
- Belzutifan versus everolimus
- Relevant sub-population: Patients with ≥ 2 prior therapies that included a PD-(L)1 inhibitor and at least two VEGF-targeted therapies (49.6% of the total population)

[1] Data from the dossier assessment of the Institute for Quality and Efficiency in Health Care (IQWiG) (A25-45) unless otherwise indicated.

Mortality

Endpoint	Belzutifan		Everolimus		Intervention vs control
	N	Median survival time in months [95% CI] *Patients with event n (%)*	N	Median survival time in months [95% CI] *Patients with event n (%)*	Hazard ratio [95% CI]; p value; Absolute difference (AD)[a]
Overall survival					
	188	21.8 [17.4; 25.8] 128 (68.1)	182	18.1 [14.2; 23.9] 125 (68.7)	0.94 [0.74; 1.21]; 0.650

Morbidity

Endpoint	Belzutifan		Everolimus		Intervention vs control
	N	Median time to event in months [95% CI] *Patients with event n (%)*	N	Median time to event in months [95% CI] *Patients with event n (%)*	Hazard ratio [95% CI]; p value; Absolute difference (AD)[a]
Progression-free survival[b]					
	188	4.6 [3.5; 7.3] 156 (83.0)	182	5.4 [3.8; 6.5] 137 (75.3)	0.72 [0.57; 0.92]; 0.008
Symptomatology (EORTC QLQ-C30 – time to 1st deterioration)[c]					
Fatigue	178	1.9 [1.1; 2.1] 126 (70.8)	164	1.9 [1.0; 2.0] 124 (75.6)	0.80 [0.62; 1.03]; 0.086
Nausea and vomiting	178	11.9 [6.4; 26.0] 80 (44.9)	164	10.0 [3.7; 15.4] 66 (40.2)	0.89 [0.64; 1.25]; 0.510
Pain	178	3.8 [2.1; 5.3] 105 (59.0)	164	2.8 [1.9; 3.0] 106 (64.6)	0.73 [0.55; 0.96]; 0.023; 1.0
Effect modification by the "age" characteristic					
< 65 years	113	3.8 [1.9; 5.3] 69 (61.1)	89	3.7 [2.8; 7.3] 51 (57.3)	1.04 [0.72; 1.49]; 0.849
≥ 65 years	65	2.8 [1.9; 20.3] 36 (55.4)	75	1.9 [1.0; 1.9] 55 (73.3)	0.41 [0.26; 0.63]; < 0.001; 0.9
					Interaction: 0.001[d]
Dyspnoea	178	8.2 [3.7; 17.5] 87 (48.9)	164	3.7 [2.8; 7.9] 84 (51.2)	0.77 [0.57; 1.05]; 0.101

Insomnia	178	11.1 [5.5; 24.8] 81 (45.5)	164	3.7 [2.8; 5.6] 87 (53.0)	0.64 [0.47; 0.87]; 0.005; 7.4
Appetite loss	178	17.4 [9.3; 27.6] 76 (42.7)	164	3.7 [2.8; 4.7] 88 (53.7)	0.51 [0.37; 0.70]; < 0.001; 13.7
Constipation	178	15.7 [4.8; 24.9] 78 (43.8)	164	13.0 (9.0; 16.9) 59 (36.0)	1.14 [0.81; 1.61]; 0.443
Diarrhoea	178	21.6 [8.2; n.c.] 59 (33.1)	164	5.6 [3.7; 13.8] 73 (44.5)	0.53 [0.37; 0.75]; < 0.001; 16.0
Symptomatology (FKSI-DRS – time to 1st deterioration)[e]					
	179	27.2 [17.7; n.c] 62 (34.6)	165	10.1 [7.5; 16.7] 60 (36.4)	0.66 [0.46; 0.95]; 0.027; 17.1
Health status (EQ-5D VAS – time to 1st deterioration)[f]					
	179	9.3 [7.4; 20.3] 86 (48.0)	164	10.2 [5.5; 16.6] 67 (40.9)	0.90 [0.65; 1.25]; 0.528

Health-related quality of life

Endpoint	**Belzutifan**		**Everolimus**		Intervention vs control
	N	Median time to event in months [95% CI] *Patients with event n (%)*	N	Median time to event in months [95% CI] *Patients with event n (%)*	Hazard ratio [95% CI]; p value; Absolute difference (AD)[a]
Health-related quality of life (EORTC QLQ-C30 – time to 1st deterioration)[g]					
Global health status	178	4.6 [2.8; 5.6] 114 (64.0)	164	2.8 [1.9; 4.5] 99 (60.4)	0.77 [0.59; 1.02]; 0.071
Physical functioning	178	4.8 [2.8; 11.1] 100 (56.2)	164	3.1 [2.6; 4.9] 100 (61.0)	0.76 [0.57; 1.01]; 0.060
Role functioning	178	2.8 [1.9; 4.6] 114 (64.0)	164	1.9 [1.7; 2.8] 110 (67.1)	0.80 [0.61; 1.04]; 0.097
Emotional functioning	178	6.4 [3.7; 15.7] 91 (51.1)	164	4.5 [2.8; 8.3] 80 (48.8)	0.86 [0.63; 1.17]; 0.330
Cognitive functioning	178	2.8 [1.9; 4.2] 121 (68.0)	164	3.7 [2.8; 5.5] 87 (53.0)	1.13 [0.86; 1.50]; 0.371
Social functioning	178	4.8 [2.8; 12.0] 97 (54.5)	164	2.8 [1.9; 4.6] 98 (59.8)	0.76 [0.57; 1.00]; 0.054
Effect modification by the "age" characteristic					

< 65 years	113	2.9 [1.9; 8.4] 62 (54.9)	89	2.8 [1.9; 12.5] 50 (56.2)	0.98 [0.67; 1.43]; 0.923
≥ 65 years	65	8.3 [2.8; 16.9] 35 (53.8)	75	2.7 [1.8; 3.9] 48 (64.0)	0.46 [0.29; 0.73]; 0.001; 5.6
				Interaction:	0.050[h]

Side effects

Endpoint	**Belzutifan**		**Everolimus**		Intervention vs control
	N	Median time to event in months [95% CI] *Patients with event n (%)*	N	Median time to event in months [95% CI] *Patients with event n (%)*	Hazard ratio [95% CI]; p value
Adverse events (AEs, presented additionally)					
	186	0.4 [0.3; 0.5][i] 185 (99.5)	177	0.3 [0.3; 0.4][i] 175 (98.9)	–
Serious adverse events (SAE)					
	186	22.7 [13.5; n.c.][i] 83 (44.6)	177	15.9 [11.8; 28.2][i] 69 (39.0)	0.93 [0.67; 1.29]; 0.651
Severe adverse events (CTCAE grade ≥ 3)					
	186	6.4 [3.7; 8.9][i] 123 (66.1)	177	4.6 [3.4; 6.7][i] 105 (59.3)	0.88 [0.67; 1.15]; 0.340
Therapy discontinuation due to adverse events					
	186	n.r. 13 (7.0)	177	31.4 [24.0; n.c.][i] 25 (14.1)	0.35 [0.17; 0.70]; 0.003
Effect modification by the "age" characteristic					
< 65 years	120	n.r. 9 (7.5)	97	31.4 [n.c.] 7 (7.2)	0.66 [0.23; 1.87]; 0.435
≥ 65 years	66	n.r. 4 (6.1)	80	n.r. [24.0; n.c.] 18 (22.5)	0.21 [0.07; 0.63]; 0.005
				Interaction:	0.033[d]
Specific adverse events					
Hypoxia (PT, CTCAE grade ≥ 3)[g]	186	n.r. 26 (14.0)	177	n.r. 1 (0.6)	22.33 [3.02; 165.09]; 0.002
Anaemia (PT, CTCAE grade ≥ 3)[g]	186	27.5 [16.5; n.c.][i] 58 (31.2)	177	n.r. [15,7; n.c.][i] 30 (16.9)	1.41 [0.90; 2.21]; 0.133

Pneumonitis (PT, CTCAE grade ≥ 3)[g]	No suitable data				
Infections and infestations (SOC, CTCAE grade ≥ 3)[g]	186	n.r. 23 (12.4)	177	27.5 [14.4; n.c.][i] 37 (20.9)	0.38 [0.22; 0.66]; < 0.001
Constipation (PT, AEs)	186	n.r. 32 (17.2)	177	n.r. 10 (5.6)	2.86 [1.40; 5.85]; 0.004
Stomatitis (PT, AEs)	186	n.r. 5 (2.7)	177	n.r. [13,4; n.c.][i] 65 (36.7)	0.05 [0.02; 0.13]; < 0.001
Fever (PT, AEs)	186	n.r. 12 (6.5)	177	n.r. 22 (12.4)	0.38 [0.18; 0.78]; 0.008
Vertigo (PT, AEs)	186	n.r. [34,2; n.c.][i] 30 (16.1)	177	n.r. 2 (1.1)	11.41 [2.70; 48.16]; < 0.001
Skin and subcutaneous tissue disorders (SOC, AEs)	186	n.r. [25,3; n.c.][i] 48 (25.8)	177	4.6 [1.7; n.c.][i] 89 (50.3)	0.36 [0.25; 0.51]; < 0.001
Fatigue (PT, severe AEs)[g]	186	n.r. 1 (0.5)	177	n.r. 10 (5.6)	0.07 [0.01; 0.53]; 0.010
Hyperglycaemia (PT, severe AEs)[g]	186	n.r. 3 (1.6)	177	n.r. 11 (6.2)	0.17 [0.04; 0.64]; 0.009

[a] Indication of absolute difference (AD) only in case of statistically significant difference; own calculation
[b] Information from Module 4 of the benefit assessment dossier from 26 March 2025.
[c] An increase in EORTC QLQ-C30 score by ≥ 10 points compared to the start of the study is considered a clinically relevant deterioration (scale range: 0 to 100).
[d] Cox proportional hazards model with treatment and subgroup as covariates and interaction between treatment and subgroup (p value using likelihood ratio test)
[e] A decrease in FKSI-DRS score by ≥ 6 points compared to the start of the study is considered a clinically relevant deterioration (scale range: 0 to 36).
[f] A decrease in EQ-5D VAS score by ≥ 15 points compared to the start of study is considered a clinically relevant deterioration (scale range: 0 to 100).
[g] A decrease in EORTC QLQ-C30 score by ≥ 10 points compared to the baseline is considered a clinically relevant deterioration (scale range: 0 to 100).
[h] Unrounded p value of the interaction < 0.05
[i] Own calculation: Conversion from weeks to months

Abbreviations used:
AD = Absolute Difference; CTCAE = Common Terminology Criteria for Adverse Events; EORTC = European Organisation for Research and Treatment of Cancer; FKSI-DRS = Functional Assessment of Cancer Therapy Kidney Symptom Index – Disease-Related Symptoms; HR = hazard ratio; CI = confidence interval; N = number of patients evaluated; n = number of patients with (at least one) event; n.c. = not calculable; n.r. = not reached; PT = preferred term; QLQ-C30 = Quality Of Life Questionnaire – Core 30; RCT = randomised controlled trial; SOC = System organ class; SAE = serious adverse event; AE = adverse event; VAS = visual analogue scale; vs = versus

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 available.

Summary of results for relevant clinical endpoints

Endpoint category	Direction of effect/ risk of bias	Summary
Mortality	∅	No data available.
Morbidity	∅	No data available.
Health-related quality of life	∅	No data available.
Side effects	∅	No data available.

Explanations:
↑: statistically significant and relevant positive effect with low/unclear reliability of data
↓: statistically significant and relevant negative effect with low/unclear reliability of data
↑↑: statistically significant and relevant positive effect with high reliability of data
↓↓: statistically significant and relevant negative effect with high reliability of data
↔: no statistically significant or relevant difference
∅: No data available.
n.a.: not assessable

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

Approx. 65 to 940 patients

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.

4. Treatment costs

Annual treatment costs:

The costs for the first year of treatment are presented.

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	Annual treatment costs/ patient
Medicinal product to be assessed:	
Belzutifan	€ 204,564.74
Appropriate comparator therapy:	
Monotherapies	
Axitinib	€ 13,044.32
Cabozantinib	€ 56,591.06
Everolimus	€ 4,848.17
sunitinib	€ 2,948.62
Lenvatinib in combination with everolimus	
Lenvatinib	€ 45,785.24

Designation of the therapy	Annual treatment costs/ patient
Everolimus	€ 2,547.70
Total	€ 48,332.94

Costs after deduction of statutory rebates (LAUER-TAXE®) as last revised: 1 September 2025)

Costs for additionally required SHI services: not applicable

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

In the context of the designation of medicinal products with new active ingredients pursuant to Section 35a, paragraph 3, sentence 4 SGB V, the following findings are made:

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.

The designation of combinations exclusively serves the implementation of the combination discount according to Section 130e SGB V between health insurance funds and pharmaceutical companies. 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.

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.

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.

II. The resolution will enter into force on the day of its publication on the website of the G-BA on 18 September 2025.

The justification to this resolution will be published on the website of the G-BA at www.g-ba.de.

Berlin, 18 September 2025

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

Prof. Hecken