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
Risankizumab (new therapeutic indication: Crohn's Disease, pretreated)

of 15 June 2023

At its session on 15 June 2023, 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. In Annex XII, the following information shall be added after No. 4 to the information on the benefit assessment of Risankizumab in accordance with the resolution of 19 May 2022:

Risankizumab

Resolution of: 15 June 2023
Entry into force on: 15 June 2023
Federal Gazette, BAnz AT DD. MM YYYY Bx

New therapeutic indication (according to the marketing authorisation of 21 November 2022):

Skyrizi is indicated for the treatment of adult patients with moderately to severely active Crohn's disease who have had an inadequate response to, lost response to, or were intolerant to conventional therapy or a biologic therapy.

Therapeutic indication of the resolution (resolution of 15 June 2023):

See new therapeutic indication according to marketing authorisation.

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

a) Adults with moderately to severely active Crohn's disease who have had an inadequate response to, lost response to, or were intolerant to conventional therapy

Appropriate comparator therapy:

A TNF-α antagonist (adalimumab or infliximab) or integrin inhibitor (vedolizumab) or interleukin inhibitor (ustekinumab)

Extent and probability of the additional benefit of risankizumab compared to the appropriate comparator therapy:

An additional benefit is not proven.

b) Adults with moderately to severely active Crohn's disease who have had an inadequate response to, lost response to, or were intolerant to a biologic therapy TNF-α antagonist or integrin inhibitor or interleukin inhibitor).

Appropriate comparator therapy:

A change of therapy to a TNF-α antagonist (adalimumab or infliximab) or integrin inhibitor (vedolizumab) or interleukin inhibitor (ustekinumab)

Extent and probability of the additional benefit of risankizumab compared to ustekinumab:

Hint for a minor additional benefit

Study results according to endpoints:[1]

a) Adults with moderately to severely active Crohn's disease who have had an inadequate response to, lost response to, or were intolerant to conventional therapy

No suitable data versus the appropriate comparator therapy were presented.

Summary of results for relevant clinical endpoints

Endpoint category	Direction of effect/ risk of bias	Summary
Mortality	n.a.	There are no assessable data.
Morbidity	n.a.	There are no assessable data.
Health-related quality of life	n.a.	There are no assessable data.
Side effects	n.a.	There are no assessable data.
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		

[1] Data from the dossier assessment of the IQWiG (A22-133) and from the addendum (A23-40), unless otherwise indicated.

b) Adults with moderately to severely active Crohn's disease who have had an inadequate response to, lost response to, or were intolerant to a biologic therapy TNF-α antagonist or integrin inhibitor or interleukin inhibitor).

Summary of results for relevant clinical endpoints

Endpoint category	Direction of effect/ risk of bias	Summary
Mortality	↔	No deaths occurred.
Morbidity	↑	Advantages in clinical remission (including steroid-free remission), bowel symptoms
Health-related quality of life	↑	Advantages in IBDQ total score and SF-36 physical component summary score
Side effects	n.a.	There are no assessable data.

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

SEQUENCE study: Risankizumab vs Ustekinumab

Study design: randomised, open-label, two-armed

Mortality (until 09.12.2022)

Endpoint	Risankizumab		Ustekinumab		Risankizumab vs Ustekinumab
	N	Patients with event n (%)	N	Patients with event n (%)	RR [95% CI] p value[a]
Overall mortality[b]	222	0 (0.0)	224	0 (0.0)	

Morbidity (at week 24)[c]

Endpoint	Risankizumab		Ustekinumab		Risankizumab vs Ustekinumab
	N	Patients with event n (%)	N	Patients with event n (%)	RR [95% CI] p value[a]
Clinical remission (PRO-2)[d]	222	138 (62.3)	224	107 (47.7)	1.30 [1.09; 1.55]; 0.004

Steroid-free remission (PRO-2)[c, d]	222	128 (57.5)	224	93 (41.7)	1.36 [1.11; 1.65]; 0.003
Bowel symptoms (IBDQ)[e]	222	180 (80.9)	224	142 (63.5)	1.27 [1.13; 1.44]; < 0.001
Systemic symptoms (IBDQ)[e]	222	155 (70.0)	224	142 (63.4)	1.11 [0.97; 1.28]; 0.126

Health-related quality of life (at week 24)[c]

Endpoint	Risankizumab		Ustekinumab		Risankizumab vs Ustekinumab
	N	Patients with event n (%)	N	Patients with event n (%)	RR [95% CI] p value[a]
IBDQ total score[e]	222	167 (75.0)	224	134 (59.7)	1.25 [1.09; 1.44]; 0.002
Bowel symptoms (IBDQ)[e]	222	180 (80.9)	224	142 (63.5)	1.27 [1.13; 1.44]; –
Emotional functioning (IBDQ)[e]	222	137 (61.8)	224	112 (50.0)	1.24 [1.04; 1.47]; –
Social functioning (IBDQ)[e]	222	161 (72.5)	224	136 (60.5)	1.19 [1.04; 1.37]; –
Systemic symptoms (IBDQ)[e]	222	155 (70.0)	224	142 (63.4)	1.11 [0.97; 1.28]; –

Endpoint	Risankizumab			Ustekinumab			Risankizumab vs Ustekinumab
	N[f]	Values at the start of the study MV (SD)	Change at week 24 MV[h] (SE)	N[f]	Values at the start of the study MV (SD)	Change at week 24 MV[h] (SE)	MD [95% CI] p value[g]
SF-36 Physical Component Summary (PCS) score	187	38.8 (7.0)	10.1 (0.6)	183	38.4 (6.7)	6.8 (0.6)	3.35 [1.97; 4.73]; < 0.001 SMD [95% CI][h]: 0.49 [0.29; 0.70]
SF-36 Mental Component Summary (MCS) score[i]	187	37.2 (10.8)	8.1 (0.7)	183	36.6 (10.3)	6.1 (0.7)	1.91 [0.12; 3.69]; 0.036 SMD [95% CI][h]: 0.22 [0.01; 0.42]

Side effects

Endpoint	Risankizumab		Ustekinumab		Risankizumab vs Ustekinumab
	N	Patients with event n (%)	N	Patients with event n (%)	RR [95% CI] p value
AEs total	No suitable data.				
SAEs	No suitable data.				
Severe AEs	No suitable data.				
Discontinuation due to AEs	No suitable data.				

a. RR, CI and p value: generalised linear model with log link; adjusted for number of previous failed treatments with TNF-α antagonists (≤ 1, > 1) and corticosteroid administration at the start of the study (yes, no)
b. Deaths were recorded as part of the adverse events
c. Missing values were replaced by means of MI
d. Operationalised as average daily stool frequency ≤ 2.8 and average daily abdominal pain ≤ 1 (on a scale of 0-3 corresponding to 0 = no pain, 1 = mild, 2 = moderate, 3 = severe) and both respectively not worse than at the start of the study (for the endpoint of steroid-free remission: in the absence of steroids)
e. Operationalised as an improvement ≥ 15% of the scale range (IBDQ total score: 32 to 224 points; bowel symptoms: 10 to 70 points; systemic symptoms: 5 to 35 points; social functioning: 5 to 35 points; emotional functioning: 12 to 84 points)
f. Number of patients who were taken into account in the evaluation for calculating the effect estimate; the values at start of study can be based on other patient numbers
g. MV and SE (mean change at week 24 per treatment group) as well as MD, CI and p value (group comparison): MMRM; adjusted for baseline and number of previous failed treatments with TNF-α inhibitors (≤ 1, > 1) and corticosteroid administration at the start of the study (yes, no). Effect represents the difference between the treatment groups of the change from the start of the study to week 24.
h. IQWiG calculation based on MD and CI of MMRM
i. No data are available on the sub-scales of the SF-36.

Abbreviations used:
IBDQ: Inflammatory Bowel Disease Questionnaire; CI: Confidence Interval; MCS: Mental Component Summary; MD: mean difference; MI: multiple imputation; MMRM: mixed model for repeated measures; MV: mean value; n: number of patients with (at least 1) event; N: number of patients evaluated; PCS: Physical Component Summary; PRO: patient-reported endpoint; RCT: randomised controlled trial; RR: relative risk; SD: standard deviation; SE: standard error; SF-36: Short Form-36; SMD: standardised mean difference; TNF: tumour necrosis factor

2. Number of patients or demarcation of patient groups eligible for treatment

a) Adults with moderately to severely active Crohn's disease who have had an inadequate response to, lost response to, or were intolerant to conventional therapy

approx. 11,350 – 21,300 patients

b) Adults with moderately to severely active Crohn's disease who have had an inadequate response to, lost response to, or were intolerant to a biologic therapy TNF-α antagonist or integrin inhibitor or interleukin inhibitor).

approx. 7,450 – 13,950 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 Skyrizi (active ingredient: risankizumab) at the following publicly accessible link (last access: 5 April 2023):

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

Treatment with risankizumab should only be initiated and monitored by doctors experienced in treating Crohn's disease.

Discontinuation of treatment should be considered for patients who do not show signs of therapeutic benefit after 24 weeks.

4. Treatment costs

Annual treatment costs:

a) Adults with moderately to severely active Crohn's disease who have had an inadequate response to, lost response to, or were intolerant to conventional therapy

b) Adults with moderately to severely active Crohn's disease who have had an inadequate response to, lost response to, or were intolerant to a biologic therapy (TNF-α antagonist or integrin inhibitor or interleukin inhibitor).

Designation of the therapy	Annual treatment costs/ patient
Medicinal product to be assessed:	
Risankizumab[2]	Incalculable
Appropriate comparator therapy:	
Adalimumab Additionally required SHI services: Total:	€ 11,434.41 € 106.40 € 11,540.81
Infliximab Additionally required SHI services:	€ 16,683.94 € 106.40

[2] 360 mg cartridge of risankizumab is currently unavailable on the German market, therefore a cost representation is not possible.

Designation of the therapy	Annual treatment costs/ patient
Total:	€ 16,790.34
Vedolizumab	€ 14,364.18
Ustekinumab	€ 21,143.53

Costs after deduction of statutory rebates (LAUER-TAXE®) as last revised: 15 May 2023)

Other SHI services:

Designation of the therapy	Type of service	Costs/ unit	Number/ cycle	Number/ patient/ year	Costs/ patient/ year
Appropriate comparator therapy for patient populations a) and b)					
Infliximab	Surcharge for the preparation of a parenteral solution containing monoclonal antibodies	€ 100	1	6.5	€ 650

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 Risankizumab

Medicinal products with new active ingredients pursuant to Section 35a, paragraph 3, sentence 4 SGB V are medicinal products with the following new active ingredients that can be used in a combination therapy with risankizumab for the treatment of Crohn's disease on the basis of the marketing authorisation granted under Medicinal Products Act:

a) Adults with moderately to severely active Crohn's disease who have had an inadequate response to, lost response to, or were intolerant to conventional therapy

b) Adults with moderately to severely active Crohn's disease who have had an inadequate response to, lost response to, or were intolerant to a biologic therapy (TNF-α antagonist or integrin inhibitor or interleukin inhibitor).

A designation of the concomitant active ingredients shall be made in a further resolution. The adoption of the resolution will be preceded by a written and oral written statement procedure pursuant to Chapter 5, Section 19 of the Regulation, in the course of which the pharmaceutical companies concerned will be given the opportunity to comment on the planned designation.

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.

II. Entry into force

1. The resolution will enter into force on the day of its publication on the website of the G-BA on 15 June 2023.

2. The period of validity of the resolution is limited to 1 August 2028.

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

Berlin, 15 June 2023

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

Prof. Hecken