Resolution

Gemeinsamer Bundesausschuss

of the Federal Joint Committee (G-BA) on an Amendment of the Pharmaceuticals Directive (AM-RL): Annex XII – Benefit Assessment of Medicinal Products with New Active Ingredients According to Section 35a SGB V Risankizumab

of 22 November 2019

At its session on 22 November 2019, the Federal Joint Committee (G-BA) resolved to amend the Directive on the Prescription of Medicinal Products in SHI-accredited Medical Care (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 on DD 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 risankizumab (plaque psoriasis) as follows:

Risankizumab

Resolution of: 22 November 2019
Entry into force on: 22 November 2019
Federal Gazette, BAnz AT DD MM YYYY Bx

Therapeutic indication (according to the marketing authorisation of 26 April 2019):

Skyrizi™ is indicated for the treatment of moderate to severe plaque psoriasis in adults who are candidates for systemic therapy.

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

a) Adult patients with moderate to severe plaque psoriasis who are not candidates for conventional therapy as part of an initial systemic therapy.

Appropriate comparator therapy:

- Adalimumab or guselkumab or ixekizumab or secukinumab

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

An additional benefit is not proven.

b) Adult patients with moderate to severe plaque psoriasis who have responded inadequately to or did not tolerate systemic therapy.

Appropriate comparator therapy:

- Adalimumab or brodalumab or guselkumab or infliximab or ixekizumab or secukinumab or ustekinumab

Extent and probability of the additional benefit of Risankizumab compared with ustekinumab:

Proof for a considerable additional benefit.

Study results according to endpoints:[1]

a) Adult patients with moderate to severe plaque psoriasis who are not candidates for conventional therapy as part of an initial systemic therapy.

No appropriate data compared with the appropriate comparator therapy were provided.

b) Adult patients with moderate to severe plaque psoriasis who have responded inadequately to or did not tolerate systemic therapy.

2 RCT UltIMMa-1 and UltIMMa-2: Risankizumab vs ustekinumab

Mortality

Endpoint	Risankizumab		Ustekinumab		Risankizumab vs ustekinumab
	N	Patients with event n (%)	N	Patients with event n (%)	RR [95% CI][a]; p value
Overall survival					
UltIMMa-1	100	0 (0)	34	0 (0)	n.c.
UltIMMa-2	90	0 (0)	36	0 (0)	n.c.
Total					n.c.

Morbidity

Endpoint	Risankizumab		Ustekinumab		Risankizumab vs ustekinumab
	N	Patients with event n (%)	N	Patients with event n (%)	RR [95% CI][a]; p value
Skin symptomatology					
Remission (PASI 100)[b]					
UltIMMa-1	100	64 (64.0)	34	5 (14.7)	4.47 [1.97; 10.14]; < 0.001
UltIMMa-2	90	56 (62.2)	36	11 (30.6)	2.07 [1.24; 3.47]; 0.006
Total[c]					2.80 [1.80; 4.36]; < 0.001
PASI 90[b]					
UltIMMa-1	100	86 (86.0)	34	13 (38.2)	2.27 [1.47; 3.50]; < 0.001
UltIMMa-2	90	74 (82.2)	36	17 (47.2)	1.74 [1.21; 2.48]; 0.003

[1] Data from the dossier evaluation of the IQWiG (A19-41) unless otherwise indicated.

Endpoint	Risankizumab		Ustekinumab		Risankizumab vs ustekinumab
	N	Patients with event n (%)	N	Patients with event n (%)	RR [95% CI][a]; p value
Total[c]					1.97 [1.49; 2.60]; < 0.001
PASI 75[b]					
UltIMMa-1	100	92 (92.0)	34	25 (73.5)	1.25 [1.01; 1.54] 0.036[d]
UltIMMa-2	90	85 (94.4)	36	28 (77.8)	1.21 [0.96; 1.53]; 0.110
Total[c]					1.24 [1.08; 1.43]; 0.002
Freedom from symptoms reported by the patient					
PSS itching 0[b]					
UltIMMa-1	100	69 (69.0)	34	13 (38.2)	1.76 [1.13; 2.75]; 0.013
UltIMMa-2	90	67 (74.4)	36	14 (38.9)	1.90 [1.25; 2.90]; 0.003
Total					1.85 [1.36; 2.51]; < 0.001
PSS pain 0[b]					
UltIMMa-1	100	82 (82.0)	34	17 (50.0)	1.59 [1.13; 2.25]; 0.008
UltIMMa-2	90	75 (83.3)	36	21 (58.3)	1.41 [1.06; 1.88]; 0.018
Total					1.49 [1.20; 1.86]; < 0.001
PSS redness 0[b]					
UltIMMa-1	100	68 (68.0)	34	12 (35.3)	1.97 [1.23; 3.16]; 0.005
UltIMMa-2	90	68 (75.6)	36	15 (41.7)	1.82 [1.22; 2.71] 0.003
Total					1.85 [1.37; 2.52]; < 0.001
PSS burning 0[b]					
UltIMMa-1	100	85 (85.0)	34	23 (67.6)	1.26 [0.98; 1.61]; 0.070[d]
UltIMMa-2	90	77 (85.6)	36	21 (58.3)	1.47 [1.10; 1.96]; 0.009
Total					1.34 [1.11; 1.63]; 0.002

Endpoint	Risankizumab		Ustekinumab		Risankizumab vs ustekinumab
	N	Patients with event n (%)	N	Patients with event n (%)	RR [95% CI][a]; p value
Further symptomatology reported by patients (especially scaling, cracking, and bleeding)				No data collected[e]	
Absence of symptoms of hands and feet (PPASI 0)				No usable data[f]	
Absence of symptoms of fingernail (NAPSI finger 0)[b,g] *(additionally shown)*					
UltIMMa-1	68	34 (50.0)	25	10 (40.0)	1.22 [0.72; 2.06]; 0.454
UltIMMa-2	50	31 (62.0)	22	9 (40.9)	1.52 [0.89; 2.60]; 0.124
Total[c]					1.38 [0.95; 2.01]; 0.090
Absence of symptoms of the scalp (PSSI 0)[b,h]					
UltIMMa-1	91	77 (84.6)	29	15 (51.7)	1.60 [1.11; 2.31]; 0.011
UltIMMa-2	80	66 (82.5)	28	17 (60.7)	1.37 [1.00; 1.87]; 0.052
Total[c]					1.48 [1.17; 1.88]; 0.001

Endpoint	Risankizumab			Ustekinumab			Risankizumab vs ustekinumab
	N[i]	Values at start of study MV (SD)	Change at week 52 MV (SE)[j]	N[i]	Values at start of study MV (SD)	Change at week 52 MV (SE)[j]	MD [95% CI]; p value[j]
Health status (EQ-5D VAS[k])							
UltIMMa-1	99	65.95 (23.07)	12.12 (1.63)	33	70.67 (18.16)	6.14 (2.45)	5.98 [0.84; 11.13]; 0.023
UltIMMa-2	90	66.46 (21.72)	15.80 (1.58)	34	70.50 (21.81)	13.82 (2.48)	1.97 [−3.37; 7.32]; 0.466
Total[l]							4.30 [0.56; 8.04]; 0.025 *Hedges' g:* 0.32 [0.04; 0.60]

Health-related quality of life

Endpoint	Risankizumab		Ustekinumab		Risankizumab vs ustekinumab
	N	Patients with event n (%)	N	Patients with event n (%)	RR [95% CI][a]; p value
DLQI (0 or 1)[b]					
UltIMMa-1	100	75 (75.0)	34	19 (55.9)	1.30 [0.96; 1.75]; 0.089
UltIMMa-2	90	69 (76.7)	36	17 (47.2)	1.63 [1.14; 2.34]; 0.008
Total[c]					1.47 [1.16; 1.86]; 0.001

Side effects

Endpoint	Risankizumab		Ustekinumab		Risankizumab vs ustekinumab
	N	Patients with event n (%)	N	Patients with event n (%)	RR [95% CI][a]; p value
AEs *(additionally shown)*					
UltIMMa-1	100	71 (71.0)	34	28 (82.4)	-
UltIMMa-2	90	63 (70.0)	36	28 (77.8)	-
SAEs					
UltIMMa-1	100	8 (8.0)	34	3 (8.8)	0.91 [0.25; 3.22]; 0.880
UltIMMa-2	90	6 (6.7)	36	3 (8.3)	0.80 [0.21; 3.03]; 0.742
Total[c]					0.85 [0.34; 2.14]; 0.738
Discontinuation because of AEs					
UltIMMa-1	100	1 (1.0)	34	1 (2.9)	0.34 [0.02; 5.29]; 0.441
UltIMMa-2	90	0 (0.0)	36	1 (2.8)	0.14 [0.01; 3.25]; 0.218
Total[c]					0.18 [0.02; 1.95]; 0.159
Infections and infestations (SOC, AE)					
UltIMMa-1	100	47 (47.0)	34	16 (47.1)	1.00 [0.66; 1.51]; > 0.999[m]
UltIMMa-2	90	43 (47.8)	36	17 (47.2)	1.01 [0.67; 1.52]; 0.978[m]
Total					1.01 [0.75; 1.34]; 0.971[n]

Endpoint	Risankizumab		Ustekinumab		Risankizumab vs ustekinumab
	N	Patients with event n (%)	N	Patients with event n (%)	RR [95% CI][a]; p value

a) RR and CI from generalised linear model with treatment and stratification variables as covariates with a log link for the calculation of the RR. For the meta-analysis, the variable study was also included in the model as a fixed effect.
b) Missing values were replaced by NRI.
c) Calculated from the IPD meta-analysis with fixed effect.
d) The model did not converge and was thus calculated without stratification variables.
e) In the dossier of the pharmaceutical company, no data are available for further endpoints on patient-reported symptomatology (in particular scaling, cracking, and bleeding) (see Section 2.6.4.3.2).
f) Only those patients who had palmoplantar involvement at the beginning of the study (PPASI > 0) were evaluated. This was only about one third of the ITT population.
g) Only those patients who had an involvement of fingernails at the beginning of the study (NAPSI finger > 0) were evaluated. This was only about 64% of the ITT population.
h) Only those patients who had an involvement of the scalp at the beginning of the study (PSSI > 0) were evaluated. This was > 80% of the ITT population (UltIMMa-1: 91.0% in the risankizumab arm and 85.3% in the ustekinumab arm; UltIMMa-2: 88.9% in the risankizumab arm and 77.8% in the ustekinumab arm).
i) Number of patients who were taken into account in the evaluation for the calculation of the estimation of the effect; the values at the start of study can be based on other patient figures.
j) Effect estimation based on an ANCOVA model with treatment, stratification variables, and baseline as covariates. For the meta-analysis, the variable study is additionally included in the model as a fixed effect. Missing values were replaced by LOCF.
k) A positive change from start of study to end of study means an improvement; a positive group difference means an advantage for risankizumab.
l) Calculated from meta-analysis.
m) Calculation by the IQWiG; asymptotic 95% CI; p value from unconditional exact test (CSZ method).
n) Calculation by the IQWiG, meta-analysis with fixed effect (Mantel-Haenszel method).

ANCOVA: analysis of covariance; DLQI: Dermatology Life Quality Index; EQ-5D: European Quality of Life – 5 Dimensions; CI: confidence interval; LOCF: last observation carried forward; IPD: individual patient data; ITT: Intention to Treat; MD: mean difference; MV: Mean Value; N: Number of patients evaluated; n: number of patients with (at least one) event; NAPSI: Nail Psoriasis Severity Index; n.c.: not calculable; NRI: non-responder imputation; PASI: Psoriasis Area and Severity Index; PPASI: Palmoplantar Psoriasis Area and Severity Index; PSS: Psoriasis Symptom Scale; PSSI: Psoriasis Scalp Severity Index; RCT: randomised controlled study; RR: relative risk; SD: standard deviation; SE: standard error; SAE: serious adverse event; AE: adverse event; VAS: visual analogue scale; vs: versus

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

a) Adult patients with moderate to severe plaque psoriasis who are not candidates for conventional therapy as part of an initial systemic therapy.

approx. 3,500 – 24,400 patients

b) Adult patients with moderate to severe plaque psoriasis who have responded inadequately to or did not tolerate systemic therapy.

approx. 32,400 – 97,100 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: 20 September 2019):

>https://www.ema.europa.eu/documents/product-information/skyrizi-epar-product-information_de.pdf<

In patients who do not respond after 16 weeks of treatment, discontinuation of treatment should be considered.

4. Treatment costs

Annual treatment costs:

a) Adult patients with moderate to severe plaque psoriasis who are not candidates for conventional therapy as part of an initial systemic therapy.

Designation of the therapy	Annual treatment costs/patient
Medicinal product to be assessed:	
Risankizumab	€ 25,149.02
Additionally required SHI services	€ 74.45
Total	€ 25,223.47
Appropriate comparator therapy:	
Adalimumab	€ 11,467.34
Additionally required SHI services	€ 180.85
Total	€ 11,648.19
Guselkumab	€ 21,016.19
Ixekizumab	€ 18,086.90
Secukinumab	€ 21,104.24

Costs after deduction of statutory rebates (LAUER-TAXE®) as last revised: 1 November 2019

b) Adult patients with moderate to severe plaque psoriasis who have responded inadequately to or did not tolerate systemic therapy.

Designation of the therapy	Annual treatment costs/patient
Medicinal product to be assessed:	
Risankizumab	€ 25,149.02
Additionally required SHI services	€ 74.45
Total	€ 25,223.47
Appropriate comparator therapy:	
Adalimumab	€ 11,467.34
Additionally required SHI services	€ 180.85
Total	€ 11,648.19
Brodalumab	€ 17,991.31
Guselkumab	€ 21,016.19
Infliximab	€ 17,445.53
Additionally required SHI services	€ 180.85
Total	€ 17,626.38
Ixekizumab	€ 18,086.90
Secukinumab	€ 21,104.24
Ustekinumab	€ 21,198.06
Additionally required SHI services	€ 74.45
Total	€ 21,272.51

Costs after deduction of statutory rebates (LAUER-TAXE®) as last revised: 1 November 2019

Other services covered by SHI funds:

Designation of the therapy	Type of service	Cost per unit	Number per patient per year	Cost per patient per year
Medicinal product to be assessed				
not applicable				
Appropriate comparator therapy				
Infliximab	Surcharge for the preparation of a parenteral solution containing monoclonal antibodies	€ 71	6.5	€ 461.50

II. The resolution will enter into force on the day of its publication on the internet on the website of the G-BA on 22 November 2019.

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

Berlin, 22 November 2019

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

Prof Hecken