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: Upadacitinib (new therapeutic indication: atopic dermatitis, ≥ 12 years)

of 17 February 2022

At its session on 17 February 2022, 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 Upadacitinib in accordance with the resolution of 15 July 2021:

Upadacitinib

Resolution of: 17 February 2022
Entry into force on: 17 February 2022
Federal Gazette, BAnz AT DD. MM YYYY Bx

New therapeutic indication (according to the marketing authorisation of 20 August 2021):

Rinvoq is indicated for the treatment of moderate to severe atopic dermatitis in adults and adolescents 12 years and older who are candidates for systemic therapy.

Therapeutic indication of the resolution (resolution of 17 February 2022):

see new therapeutic indication according to marketing authorisation

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

Patients 12 years and older with moderate to severe atopic dermatitis who are candidates for continuous systemic therapy

Appropriate comparator therapy:

The appropriate comparator therapy for upadacitinib for the treatment of moderate to severe atopic dermatitis in patients 12 years and older who are candidates for continuous systemic therapy is

- Dupilumab (in combination with TCS and/or TCI if required)

Extent and probability of the additional benefit of Upadacitinib over dupilumab (in combination with TCS and/or TCI if required):

a) Adults with moderate to severe atopic dermatitis who are candidates for continuous systemic therapy and for whom 30 mg upadacitinib is the appropriate dose

   Indication of a considerable additional benefit

b) Adults with moderate to severe atopic dermatitis who are candidates for continuous systemic therapy and for whom 15 mg upadacitinib is the appropriate dose

   An additional benefit is not proven

c) Adolescents 12 to 18 years of age with moderate to severe atopic dermatitis who are candidates for continuous systemic therapy

   An additional benefit is not proven

Study results according to endpoints:[1]

a) Adults with moderate to severe atopic dermatitis who are candidates for continuous systemic therapy and for whom 30 mg upadacitinib is the appropriate dose

Summary of results for relevant clinical endpoints

Endpoint category	Direction of effect/ risk of bias	Summary
Mortality	↔	No relevant differences for the benefit assessment
Morbidity	↑↑	Advantages in remission, EASI 90, itching and patient-reported symptomatology
Health-related quality of life	∅	No data available.
Side effects	↓	Disadvantage in the overall rate of severe 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
∅: There are no usable data for the benefit assessment.
n.a.: not assessable

Heads-up study: RCT, direct comparison of upadacitinib 30 mg versus dupilumab in adults over 24 weeks

Mortality

Endpoint	Upadacitinib		Dupilumab		Upadacitinib vs Dupilumab
	N	Patients with event n (%)	N	Patients with event n (%)	RR [95% CI] p value[a]
Overall survival[b]					
	348	1 (0.3)	344	0 (0)	2.97 [0.12; 72.55] 0.505

[1] Data from the dossier assessment of the Institute for Quality and Efficiency in Health Care (IQWiG) (A21-116) unless otherwise indicated.

Morbidity

Endpoint	Upadacitinib		Dupilumab		Upadacitinib vs Dupilumab
	N	Patients with event n (%)	N	Patients with event n (%)	RR [95% CI] p value[a]
Symptomatology					
EASI 100 (remission)	348	100 (28.7)	344	48 (14.0)	2.05 [1.50; 2.79,55] < 0.001
EASI 90	348	277 (65.3)	344	197 (57.3)	1.14 [1.01; 1.28] 0.034
EASI 75	348	277 (79.6)	344	263 (76.4)	1.04 [096; 1.13] 0.303
Itching (WP-NRS 0)	348	92 (26.4)	344	29 (8.4)	3.14 [2.12; 4.63] < 0.001
Itching (WP-NRS, improvement by ≥ 4 points)	348	212 (60.8)	344	178 (51.7)	1.18 [1.03; 1.34] 0.017
Patient-reported symptomatology (HN-PGIS 0)	348	99 (28.5)	344	58 (16.9)	1.69 [1.27; 2.26] < 0.001

Health-related quality of life

Not assessed

Side effects[c]

Endpoint	Upadacitinib		Dupilumab		Upadacitinib vs Dupilumab
	N	Patients with event n (%)	N	Patients with event n (%)	RR [95% CI] p value[a]
AEs *(presented additionally)*[d]	348	269 (77.3)	344	227 (66.0)	-
SAEs[d]	348	13 (3.7)	344	7 (2.0)	1.84 [0.74; 4.55] 0.189[e]
Severe AEs (CTCAE grade ≥ 3)[d]	348	29 (8.3)	344	13 (3.8)	2.21 [1.17; 4.17] 0.015
Female	165	18 (10.9)	150	2 (1.3)	8.18 [1.93; 34.67] 0.004
Male	183	13 (7.1)	194	13 (6.7)	1.06 [0.50; 2.23] 0.877
				Interaction	0.004

Discontinuation due to AEs	348	11 (3.2)	344	4 (1.2)	2.72 [0.87; 8.45] 0.084
Infections (SOC, AE)[f]	348	161 (46.3)	344	133 (38.7)	1.20 [1.00; 1.43] 0.044
Serious infections (SOC, SAE)[f]	348	4 (1.1)	344	2 (0.6)	1.98 [0.36; 10.72] 0.533[g]
Conjunctivitis (PT, AE)	348	5 (1.4)	344	35 (10.2)	0.14 [0.06; 0.36] < 0.001
Eye disorders (SOC, AE)	348	26 (7.5)	344	49 (14.2)	0.52 [0.33; 0.82] 0.005
Acne (PT, AE)	348	64 (18.4)	344	11 (3.2)	5.75 [3.09; 10.71] < 0.001

[a] Unless otherwise stated: GLM (log link), treatment and vIGA-AD as covariates
[b] Fatalities were recorded as part of AEs
[c] GLM with treatment as covariate
[d] Without the PT atopic dermatitis
[e] Normal distribution approximation, Wald test
[f] All AEs of the MedDRA SOC "Infections and infestations" are used for the assessment of infections, all SAEs are used for the assessment of serious infections
[g] IQWiG calculation, RR [95% CI] (asymptotic) and p value (unconditional exact test, CSZ method).

Abbreviations used:
CTCAE = Common Terminology Criteria for Adverse Events; EASI = Eczema Area and Severity Index; GLM = generalised linear model; HN-PGIS = Head and Neck-Patient Global Impression of Severity; CI = confidence interval; N = number of patients evaluated; n = number of patients with (at least one) event; PT: preferred term; RCT = randomised controlled trial; RR = relative risk; SOC = system organ class; SAE = serious adverse event; AE = adverse event; vIGA-AD: Validated Investigator Global Assessment for Atopic Dermatitis; WP-NRS = Worst Pruritus Numerical Rating Scale; vs = versus

b) <u>Adults with moderate to severe atopic dermatitis who are candidates for continuous systemic therapy and for whom 15 mg upadacitinib is the appropriate dose</u>

Summary of results for relevant clinical endpoints

Endpoint category	Direction of effect/ risk of bias	Summary
Mortality	∅	There are no usable data for the benefit assessment.
Morbidity	∅	There are no usable data for the benefit assessment.
Health-related quality of life	∅	There are no usable data for the benefit assessment.
Side effects	∅	There are no usable data for the benefit assessment.

Explanations:
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No suitable data submitted.

c) Adolescents 12 to 18 years of age with moderate to severe atopic dermatitis who are candidates for continuous systemic therapy

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No suitable data submitted.

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

Patients 12 years and older with moderate to severe atopic dermatitis who are candidates for continuous systemic therapy

approx. 57,300 to 62,600 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 RINVOQ (active ingredient: upadacitinib) at the following publicly accessible link (last access: 3 February 2022):

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

Treatment with upadacitinib should be initiated and supervised by a physician experienced in diagnosing and treating of conditions for which upadacitinib is indicated.

Discontinuation of upadacitinib should be considered for patients who do not show signs of therapeutic benefit after 12 weeks of treatment.

In accordance with the European Medicines Agency (EMA) requirements regarding additional risk minimisation measures, the pharmaceutical company must provide training material that contains information for medical professionals and patients. The training material includes instructions on how to manage the potential side effects associated with upadacitinib, particularly severe and opportunistic infections including tuberculosis and herpes zoster. It also points out the need for an effective contraceptive method.

4. Treatment costs

Annual treatment costs:

Designation of the therapy	Annual treatment costs/ patient
Medicinal product to be assessed:	
Upadacitinib Additionally required SHI services Total:	€ 15,057.14 - € 29,887.82 € 180.64 € 15,237.78 - € 30,068.46
Appropriate comparator therapy:	
Dupilumab	€ 17,796.15

Costs after deduction of statutory rebates (LAUER-TAXE®) as last revised: 1 February 2022)

II. The resolution will enter into force on the day of its publication on the website of the G-BA on 17 February 2022.

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

Berlin, 17 February 2022

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

Prof. Hecken