Gemeinsamer Bundesausschuss

Resolution

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 Upadacitinib (New Therapeutic Indication: Psoriatic Arthritis)

of 15 July 2021

At its session on 15 July 2021, 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 on DD. 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 16 July 2020 last modified on 11 August 2020:

Upadacitinib

Resolution of: 15 July 2021
Entry into force on: 15 July 2021
BAnz AT TT. MM YYYY Bx

New therapeutic indication (according to the marketing authorisation of 22 January 2021):

RINVOQ is indicated for the treatment of active psoriatic arthritis in adult patients who have responded inadequately to, or who are intolerant to one or more DMARDs. RINVOQ may be used as monotherapy or in combination with methotrexate.

Therapeutic indication of the resolution (resolution of 15 July 2021):

see therapeutic indication according to marketing authorisation.

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

a) Adult patients with active psoriatic arthritis who have responded inadequately to, or who are intolerant to one or more disease-modifying anti-rheumatic drugs (DMARDs)

Appropriate comparator therapy:

- a TNF-alpha antagonist (adalimumab or certolizumab pegol or etanercept or golimumab or infliximab) or an interleukin inhibitor (ixekizumab or secukinumab or ustekinumab), if necessary in combination with methotrexate

Extent and probability of the additional benefit of upadacitinib compared to adalimumab:

Hint of a considerable additional benefit

b) Adult patients with active psoriatic arthritis who have responded inadequately to, or who are intolerant to one or more biologic disease-modifying anti-rheumatic drugs (bDMARDs).

Appropriate comparator therapy:

- switching to another biological disease-modifying antirheumatic drug (adalimumab or certolizumab pegol or etanercept or golimumab or infliximab or ixekizumab or secukinumab or ustekinumab), if necessary in combination with methotrexate

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

Additional benefit not proven

Study results according to endpoints:[1]

a) Adult patients with active psoriatic arthritis who have responded inadequately to, or who are intolerant to one or more disease-modifying anti-rheumatic drugs (DMARDs)

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	↑	Benefits in minimal disease activity (MDA), remission (DAPSA), physical functional status (HAQ-DI), and health status (EQ-5D VAS).
Health-related quality of life	↑	Advantage in SF-36 (PCS + MCS).
Side effects	↔	No relevant difference for the benefit assessment.
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		

SELECT-PsA 1 study: RCT, comparison of upadacitinib versus adalimumab (each monotherapy or combination therapy with methotrexate); minimum 56 weeks treatment duration.

Mortality

Endpoint	Upadacitinib		Adalimumab		Upadacitinib vs Adalimumab
	N	Patients with event n (%)	N	Patients with event n (%)	RR [95% CI]; p value[a]
Overall mortality					
	355	0 (0)	352	0 (0)	-

[1] Data from the dossier assessment of the IQWiG (A21-15) and from the addendum (A21-81), unless otherwise indicated.

Morbidity

Endpoint	Upadacitinib		Adalimumab		Upadacitinib vs Adalimumab
	N	Patients with event n (%)	N	Patients with event n (%)	RR [95% CI]; p value[a]
Minimal disease activity					
MDA[b,c]	355	173 (48.7)	352	141 (40.1)	1.22 [1.03; 1.44]; 0.021
Sensitivity analysis:					
ACA[d]	299	173 (57.9)	283	141 (49.8)	1.16 [1.00; 1.35]; 0.053[e]
NRI[c] with variance correction	355	173 (48.7)	352	141 (40.1)	1.22 [1.01; 1.46]; 0.037[e,f]
ICA-pc[g] with variance correction	355	201 (56.6)	352	175 (49.8)	1.14 [0.97; 1.32]; 0.104[e,f]
DAPSA ≤ 15[c,h]	355	204 (57.5)	352	184 (52.3)	1.10 [0.96; 1.25]; 0.177
Remission (DAPSA ≤ 3.3) [c,h]	355	66 (18.6)	352	39 (11.1)	1.68 [1.16; 2.42]; 0.006
Joints sensitive to pressure pain (TJC68 ≤ 1)[c]	355	164 (46.2)	352	143 (40.6)	1.14 [0.96; 1.34]; 0.139
Swollen joints (SJC66 ≤ 1)[c]	355	236 (66.5)	352	208 (59.1)	1.12 [1.00; 1.25]; 0.052
Enthesitis					
LEI = 0[c]	355	255 (71.8)	352	227 (64.5)	1.11 [1.01; 1.23]; 0.037
SPARCC Enthesitis Index = 0[c]	268	158 (59.0)	261	143 (54.8)	1.07 [0.93; 1.24]; 0.350
Dactylitis (LDI = 0)[c]	355	295 (83.1)	352	274 (77.8)	1.06 [0.99; 1.14]; 0.104
Fatigue[2]					
FACIT fatigue, improvement of ≥ 7.8 points [15%][c]	355	160 (45.1)	352	137 (38.9)	1.16 [0.97; 1.38]; 0.095
FACIT-Fatigue, improvement of ≥ 4 points[c]	355	202 (56.9)	352	180 (51.1)	1.11 [0.97; 1.28]; 0.125

[2] Against the background of the current methodological discussion, the results of two operationalisations are presented here.

Skin symptoms (PASI 100)[c]	355	151 (42.5)	352	134 (38.1)	1.10 [0.92; 1.32]; 0.286
PASI 90[c]	355	181 (51.0)	352	167 (47.4)	1.06 [0.92; 1.23]; 0.421
PASI 90[c]	355	226 (63.7)	352	201 (57.1)	1.10 [0.98; 1.24]; 0.107
Physical functional status[2]					
HAQ-DI, improvement of ≥ 0.45 points [15%][c]	297	166 (55.9)	301	131 (43.5)	1.28 [1.09; 1.51]; 0.003
HAQ-DI, improvement by ≥ 0.35 points[c]	312	193 (61.9)	319	165 (51.7)	1.19 [1.04; 1.37]; 0.013
Health status (EQ-5D VAS, improvement of ≥ 15%)[c]	355	186 (52.4)	352	146 (41.5)	1.26 [1.08; 1.48]; 0.004

Endpoint	**Upadacitinib**			**Adalimumab**			**Upadacitinib vs adalimumab**
	N[i]	Values at the start of the study MV (SD)	Mean change in the course of study MV[j] (SE)	N[i]	Values at the start of the study MV (SD)	Mean change in the course of study MV[j] (SE)	MD [95% CI]; p value[j]
Morning stiffness[k]							
Severe[l]	341	6.19 (2.66)	-3.33 (0.12)	348	5.81 (2.78)	-2.79 (0.12)	-0.54 [-0.84; -0.23]; < 0.001 Hedges' g: -0.24 [-0.39; -0.09]
Duration[m]	341	5.03 (3.05)	-2.59 (0.11)	348	4.62 (3.00)	-2.21 (0.11)	-0.38 [-0.66; -0.11]; 0.006 Hedges' g: -0.19 [-0.34; -0.04]
Axial involvement (BASDAI)[k]	341	5.68 (2.19)	-2.78 (0.11)	348	5.39 (2.19)	-2.33 (0.10)	−0.45 [−0.72; -0.19]; < 0.001 Hedges' g: -0.24 [-0.39; -0.09]
Pain (Pain NRS)[k]	347	6.20 (2.05)	-2.76 (0.10)	350	6.00 (2.11)	-2.52 (0.10)	-0.23 [-0.49; 0.03]; 0.079
Global disease activity (PtGADA)[k]	347	6.61 (2.03)	-3.10 (0.10)	350	6.39 (2.01)	-2.85 (0.10)	-0.26 [-0.51; -0.004]; 0.047 Hedges' g: -0.14 [-0.29; 0.01]

Health-related quality of life

Endpoint	Upadacitinib		Adalimumab		Upadacitinib vs Adalimumab
	N	Patients with event n (%)	N	Patients with event n (%)	RR [95% CI]; p value[a]
SF-36[2)]					
PCS, improvement by ≥ 9.4 points [15%][c]	355	180 (50.7)	352	135 (38.4)	1.32 [1.12; 1.57]; 0.001
PCS, improvement by ≥ 5 points[c]	355	246 (69.3)	352	194 (55.1)	1.26 [1.12; 1.41]; < 0.001
MCS, improvement of ≥ 9.6 points [15 %][c]	355	96 (27.0)	352	59 (16.8)	1.63 [1.22; 2.18]; < 0.001
MCS, improvement by ≥ 5 points[c]	355	152 (42.8)	352	115 (32.7)	1.31 [1.08; 1.59]; 0.006

Side effects

Endpoint	Upadacitinib		Adalimumab		Upadacitinib vs Adalimumab
	N	Patients with event n (%)	N	Patients with event n (%)	RR [95% CI]; p value[a]
AEs *(presented additionally)*	355	272 (76.6)	352	272 (77.3)	-
SAEs	355	23 (6.5)	352	28 (8.0)	0.81 [0.48; 1.39]; 0.449
Discontinuation because of AEs[h]	355	16 (4.5)	352	23 (6.5)	0.69 [0.37; 1.28]; 0.241
Infections and infestations (SOC, AEs)	355	192 (54.1)	352	167 (47.4)	1.14 [0.99; 1.32]; 0.078

a RR, 95% CI and p-value from a generalised linear model adjusted for DMARD treatment at start of study (yes, no) or without adjustment (side effects endpoints).
b To be classified as an MDA responder, 5 of the following 7 criteria must be met: TJC68 ≤ 1; SJC66 ≤ 1; PASI score ≤ 1 or BSA ≤ 3%; patient-reported pain assessment ≤ 1.5; PtGADA ≤ 2, HAQ-DI ≤ 0.5, and LEI ≤ 1.
c Missing values replaced by NRI.
d Evaluation is based solely on fully observed adults.
e IQWiG's own calculation, asymptotic
f IQWiG calculation, variance estimation according to the Data Set Re-Sizing Approach.
g In both treatment groups, the missing values are replaced according to the observed risk in the control group.
h The sum score of the DAPSA is collected as follows: SJC66 + TJC68 + pain (measured by NRS with a range of values from 0 to 10) + PtGADA (measured by NRS with a range of values from 0 to 10) + CRP (in mg/dl). The DAPSA is an open-ended scale starting at 0, with higher scores reflecting more severe disease activity.
i Number of adults 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.

j MV and SE (change in each treatment arm) and MD, 95% CI and p-value (group comparison): MMRM evaluation with the variables treatment, visit, DMARD treatment at the start of study, value at start of study, and the interaction term treatment and visit.
k Recorded on a scale of 0 to 10; lower (decreasing) values mean lower disease activity or symptomatology; negative effects (intervention minus control) mean an advantage for the intervention.
l Recorded using the BASDAI Item 5.
m Recorded using BASDAI item 6.

Abbreviations used:
ACA: Available Case Analysis; BASDAI: Bath Ankylosing Spondylitis Disease Activity Index; BSA: Body Surface Area; CRP: C-reactive protein; DAPSA: Disease Activity in Psoriatic Arthritis; DMARD: disease-modifying antirheumatic therapy; EQ-5D: EuroQoL - 5 Dimensions; FACIT: Functional Assessment of Chronic Illness Therapy; HAQ-DI: Health Assessment Questionnaire - Disability Index; ICA-pc: Imputed Case Analysis according to Control Group Risk; CI: Confidence interval; LDI: Leeds Dactylitis Index; LEI: Leeds Enthesitis Index; MCS: Mental Component Score; MD: Mean difference; MDA: minimal disease activity; MMRM: mixed model for repeated measures; MV: mean value; n: number of patients evaluated; n: number of patients with (at least 1) event; NRI: Non-Responder Imputation; NRS: Numerical Rating Scale; PASI: Psoriasis Area and Severity index; PtGADA: patient-reported global disease activity; RCT: randomised controlled trial; RR: relative risk; SD: Standard deviation; SE: Standard error; SF-36: Short Form 36; SJC66: Swollen Joint Count - 66 joints; SOC: System organ class; SPARCC: Spondyloarthritis Research Consortium of Canada; SAE: serious adverse event; TJC68: Tender Joint Count - 68 joints; AE: adverse event; VAS: visual analogue scale

b) Adult patients with active psoriatic arthritis who have responded inadequately to, or who are intolerant to one or more biologic disease-modifying anti-rheumatic drugs (bDMARDs).

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
∅: there are no usable data for the benefit assessment.
n.a.: not assessable

No suitable data submitted.

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

a) Adult patients with active psoriatic arthritis who have responded inadequately to, or who are intolerant to one or more disease-modifying anti-rheumatic drugs (DMARDs).

approx. 20,100 patients

b) Adult patients with active psoriatic arthritis who have responded inadequately to, or who are intolerant to one or more biologic disease-modifying anti-rheumatic drugs (bDMARDs).

approx. 9,000 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: 11 March 2021):
https://www.ema.europa.eu/documents/product-information/rinvoq-epar-product-information_de.pdf

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

In accordance with the European Medicines Agency (EMA) requirements regarding additional risk minimisation measures, the pharmaceutical company must provide training material and a patient identification card. The training material for medical professionals includes instructions on managing the potential side effects associated with upadacitinib, particularly severe and opportunistic infections including TB and herpes zoster.

The use of the drug must also be carefully weighed against established therapies against the background of a comparatively new mode of action and the associated still existing uncertainties in the risk profile.

4. Treatment costs

Annual treatment costs:

a) Adult patients with active psoriatic arthritis who have responded inadequately to, or who are intolerant to one or more disease-modifying anti-rheumatic drugs (DMARDs).

Designation of the therapy	Annual treatment costs/patient
Medicinal product to be assessed:	
Upadacitinib Additionally required SHI services Total	€ 15,056.17 € 180.64 € 15,236.81
Appropriate comparator therapy:	
Adalimumab Additionally required SHI services Total	€ 11,434.37 € 180.64 € 11,615.01
Certolizumab pegol Additionally required SHI services Total	€ 12,428.65 € 180.64 € 12,609.29
Etanercept Additionally required SHI services Total	€ 11,412.46 € 180.64 € 11,593.10
Golimumab Additionally required SHI services Total	€ 10,415.64 € 180.64 € 10,596.28
Infliximab Additionally required SHI services Total	€ 16,683.89 € 180.64 € 16,864.53
Ixekizumab	€18,087.16
Secukinumab	€ 10,343.44 - € 20,686.88
Ustekinumab Additionally required SHI services Total	€ 21,326.37 € 74.24 € 21,400.61

Costs after deduction of statutory rebates (LAUER-TAXE® as last revised: 15 June 2021)

Other SHI services:

Designation of therapy	Type of service	Costs/ unit	Number/ cycle	Number/ patient/ year	Costs/ patient/ year
Infliximab	Surcharge for the preparation of a parenteral solution containing monoclonal antibodies	€ 71	1	6.5	€ 461.50

b) Adult patients with active psoriatic arthritis Adult patients with active psoriatic arthritis who have responded inadequately to, or who are intolerant to one or more biologic disease-modifying anti-rheumatic drugs (bDMARDs).

Designation of the therapy	Annual treatment costs/patient
Medicinal product to be assessed:	
Upadacitinib Additionally required SHI services Total	€ 15,056.17 € 180.64 € 15,236.81
Appropriate comparator therapy:	
Adalimumab Additionally required SHI services Total	€ 11,434.37 € 180.64 € 11,615.01
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Ixekizumab	€18,087.16
Secukinumab	€10,343.44 - € 20,686.88
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Designation of therapy	Type of service	Costs/ unit	Number/ cycle	Number/ patient/ year	Costs/ patient/ year
Infliximab	Surcharge for the preparation of a parenteral solution containing monoclonal antibodies	€ 71	1	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 15 July 2021.

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

Berlin, 15 July 2021

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

Prof. Hecken