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 Upadacitinib (Rheumatoid Arthritis)

of 16 July 2020

In its session on 16 July 2020, 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 upadacitinib as follows:

Upadacitinib

Resolution of: 16 July 2020
Entry into force on: 16 July 2020
Federal Gazette, BAnz AT DD MM YYYY Bx

Therapeutic indication (according to the marketing authorisation of 16 December 2019):

RINVOQ is indicated for the treatment of moderate to severe active rheumatoid arthritis in adult patients who have responded inadequately to, or who are intolerant to one or more disease-modifying anti-rheumatic drugs (DMARDs). RINVOQ may be used as monotherapy or in combination with methotrexate.

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

a1) Adult patients with moderate to severe active rheumatoid arthritis for whom there are no unfavourable prognostic factors[1] and who did not respond adequately to previous treatment with a disease-modifying anti-rheumatic agent (conventional DMARDs, including methotrexate (MTX)) or did not tolerate it; upadacitinib as monotherapy

Appropriate comparator therapy:

Alternative conventional DMARDs (e.g. MTX, leflunomide) provided that they are suitable as mono- or combination therapy

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

An additional benefit is not proven

a2) Adult patients with moderate to severe active rheumatoid arthritis for whom there are no unfavourable prognostic factors and who did not respond adequately to previous treatment with a disease-modifying anti-rheumatic agent (conventional DMARDs, including methotrexate (MTX)) or did not tolerate it; upadacitinib in combination with MTX

Appropriate comparator therapy:

Alternative conventional DMARDs (e.g. MTX, leflunomide) provided that they are suitable as mono- or combination therapy

Extent and probability of the additional benefit of upadacitinib + MTX compared with the appropriate comparator therapy:

An additional benefit is not proven

b1) Adult patients with moderate to severe active rheumatoid arthritis for whom first-line therapy with biological DMARDs (bDMARDs) or targeted synthetic DMARDs (tsDMARDs) is indicated; upadacitinib as monotherapy

[1] Unfavourable prognostic factors:
- Detection of auto-antibodies (e.g. rheumatoid factors, high levels of antibodies against citrullinated peptide antigens)
- High disease activity (demonstrated by DAS or DAS28 assessment system, swollen joints, and parameters of the acute phase reaction such as C-reactive protein and erythrocyte sedimentation rate)
- Early occurrence of joint erosion

Appropriate comparator therapy:

bDMARDs or tsDMARDs (abatacept or adalimumab or baricitinib or certolizumab-pegol or etanercept or golimumab or infliximab or sarilumab or tocilizumab or tofacitinib, in combination with MTX; if necessary as monotherapy, taking into account the respective authorisation status in the case of MTX intolerance or unsuitability)

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

An additional benefit is not proven

b2) Adult patients with moderate to severe active rheumatoid arthritis for whom first-line therapy with biological DMARDs (bDMARDs) or targeted synthetic DMARDs (tsDMARDs) is indicated; upadacitinib in combination with MTX

Appropriate comparator therapy:

bDMARDs or tsDMARDs (abatacept or adalimumab or baricitinib or certolizumab-pegol or etanercept or golimumab or infliximab or sarilumab or tocilizumab or tofacitinib, in combination with MTX; if necessary as monotherapy, taking into account the respective authorisation status in the case of MTX intolerance or unsuitability)

Extent and probability of the additional benefit of upadacitinib + MTX compared with adalimumab + MTX:

Hint for a considerable additional benefit

c1) Adult patients with moderate to severe active rheumatoid arthritis who did not respond adequately to previous treatment with one or more bDMARDs and/or tsDMARDs or did not tolerate these; upadacitinib as monotherapy

Appropriate comparator therapy:

Change of bDMARD or tsDMARD therapy (abatacept or adalimumab or baricitinib or certolizumab-pegol or etanercept or golimumab or infliximab or sarilumab or tocilizumab or tofacitinib, in combination with MTX; if necessary as monotherapy, taking into account the respective authorisation status in the case of MTX intolerance or unsuitability; or in patients with severe rheumatoid arthritis rituximab, taking into account the marketing authorisation) depending on the previous therapy.

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

An additional benefit is not proven

c2A) Adult patients with moderate to severe active rheumatoid arthritis who did not respond adequately to previous treatment with one or more bDMARDs and/or tsDMARDs or did not tolerate these; upadacitinib in combination with MTX; patients with high disease activity [DAS28 CRP > 5.1]

Appropriate comparator therapy:

Change of bDMARD or tsDMARD therapy (abatacept or adalimumab or baricitinib or certolizumab-pegol or etanercept or golimumab or infliximab or sarilumab or tocilizumab or

tofacitinib, in combination with MTX; if necessary as monotherapy, taking into account the respective authorisation status in the case of MTX intolerance or unsuitability; or in patients with severe rheumatoid arthritis rituximab, taking into account the marketing authorisation) depending on the previous therapy.

Extent and probability of the additional benefit of upadacitinib + MTX compared with abatacept + MTX:

Hint for a minor additional benefit

c2B) Adult patients with moderate to severe active rheumatoid arthritis who did not respond adequately to previous treatment with one or more bDMARDs and/or tsDMARDs or did not tolerate these; upadacitinib in combination with MTX; patients without high disease activity [DAS 28 CRP ≤ 5.1]

Appropriate comparator therapy:

Change of bDMARD or tsDMARD therapy (abatacept or adalimumab or baricitinib or certolizumab-pegol or etanercept or golimumab or infliximab or sarilumab or tocilizumab or tofacitinib, in combination with MTX; if necessary as monotherapy, taking into account the respective authorisation status in the case of MTX intolerance or unsuitability; or in patients with severe rheumatoid arthritis rituximab, taking into account the marketing authorisation) depending on the previous therapy.

Extent and probability of the additional benefit of upadacitinib + MTX compared with abatacept + MTX:

An additional benefit is not proven.

Study results according to endpoints:[2]

a1) Adult patients with moderate to severe active rheumatoid arthritis for whom there are no unfavourable prognostic factors[1] and who did not respond adequately to previous treatment with a disease-modifying anti-rheumatic agent (conventional DMARDs, including methotrexate (MTX)) or did not tolerate it; upadacitinib as monotherapy

No data submitted.

Summary of results for relevant clinical endpoints

Endpoint category	Direction of effect/ Risk of bias	Summary
Mortality	∅	No data submitted.
Morbidity	∅	No data submitted.

[2]Data from the dossier assessment of the IQWiG (A20-08) unless otherwise indicated.

Health-related quality of life	∅	No data submitted.
Side effects	∅	No data submitted.

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

a2) Adult patients with moderate to severe active rheumatoid arthritis for whom there are no unfavourable prognostic factors[1] and who did not respond adequately to previous treatment with a disease-modifying anti-rheumatic agent (conventional DMARDs, including methotrexate (MTX)) or did not tolerate it; upadacitinib in combination with MTX

No data submitted.

Summary of results for relevant clinical endpoints

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

Explanations:
↑: statistically significant and relevant positive effect with low/unclear reliability of data
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↑↑: statistically significant and relevant positive effect with high reliability of data
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b1) Adult patients with moderate to severe active rheumatoid arthritis for whom first-line therapy with biological DMARDs (bDMARDs) or targeted synthetic DMARDs (tsDMARDs) is indicated; upadacitinib as monotherapy

No data submitted.

Summary of results for relevant clinical endpoints

Endpoint category	Direction of effect/	Summary

	Risk of bias	
Mortality	∅	No data submitted.
Morbidity	∅	No data submitted.
Health-related quality of life	∅	No data submitted.
Side effects	∅	No data submitted.

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

b2) Adult patients with moderate to severe active rheumatoid arthritis for whom first-line therapy with biological DMARDs (bDMARDs) or targeted synthetic DMARDs (tsDMARDs) is indicated; upadacitinib in combination with MTX

SELECT COMPARE study: relevant sub-population of the RCT upadacitinib + methotrexate (MTX) vs adalimumab + MTX (Data cut-off at Week 26)

Mortality

Study SELECT COMPARE	**Upadacitinib + MTX**		**Adalimumab + MTX**		**Upadacitinib + MTX vs Adalimumab + MTX**
Endpoint	**N**	**Patients with event n (%)**	**N**	**Patients with event n (%)**	**RR [95% CI]; p value**
Overall Mortality	650	0 (0)	327	2 (0.6)	–[a]; 0.046[b]

Morbidity

Study SELECT COMPARE	Upadacitinib + MTX		Adalimumab + MTX		Upadacitinib + MTX vs Adalimumab + MTX
Endpoint	**N**	**Patients with event n (%)**	**N**	**Patients with event n (%)**	**RR [95% CI]; p value**
Clinical remission					
CDAI ≤ 2.8					
RNRI[c]	651	150 (23.0)	327	45 (13.8)	1.67 [1.23; 2.27]; 0.001[d]
SDAI ≤ 3.3					
RNRI[c]	651	158 (24.3)	327	45 (13.8)	1.75 [1.29; 2.38]; < 0.001[d]
Boolean definition					
RNRI[c]	651	117 (18.0)	327	32 (9.8)	1.84 [1.27; 2.65]; 0.001[d]
Low disease activity					
CDAI ≤ 10					
RNRI[c]	651	343 (52.7)	327	125 (38.2)	1.38 [1.18; 1.61]; < 0.001[d]
Sensitivity analysis: NRI[e]	651	370 (56.8)	327	151 (46.2)	1.23 [1.08; 1.41]; 0.002[d]
SDAI ≤ 11					
RNRI[c]	651	351 (53.9)	327	127 (38.8)	1.39 [1.19; 1.62]; < 0.001[d]
Sensitivity analysis: NRI[e]	651	378 (58.1)	327	156 (47.7)	1.22 [1.07; 1.39]; 0.003[d]
DAS28 CRP ≤ 3.2					
RNRI[c]	651	356 (54.7)	327	126 (38.5)	1.42 [1.22; 1.66]; < 0.001[d]
DAS28 ESR ≤ 3.2					
RNRI[c]	651	257 (39.5)	327	90 (27.5)	1.43 [1.17; 1.75]; < 0.001[d]

Study SELECT COMPARE Endpoint	Upadacitinib + MTX		Adalimumab + MTX		Upadacitinib + MTX vs Adalimumab + MTX
	N	Patients with event n (%)	N	Patients with event n (%)	RR [95% CI]; p value
Physical functional status (HAQ-DI; improvement by ≥ 0.22 points)[f]					
RNRI[c]	651	398 (61.1)	327	173 (52.9)	1.15 [1.02; 1.30]; 0.021[d]
Sensitivity analysis: NRI[e]	651	480 (73.7)	327	234 (71.6)	1.03 [0.95, 1.12]; 0.492[d]
Fatigue (FACIT fatigue; improvement ≥ 4 points)[g]					
RNRI[c]	651	367 (56.4)	327	151 (46.2)	1.22 [1.07; 1.40]; 0.004[d]

Study SELECT COMPARE Endpoint scale	Upadacitinib + MTX			Adalimumab + MTX			Upadacitinib + MTX vs Adalimumab + MTX
	N[h]	Values at start of study MV (SD)	Change at the end of study MV (SE)[i]	N[h]	Values at start of study MV (SD)	Change at the end of study MV (SE)[i]	MD [95% CI]; p value[i]
Number of pressure-painful joints[j]							
RLOCF[k]	604	15.1 (6.8)	−10.6 (0.4)	288	14.9 (6.9)	−9.0 (0.4)	−1.63 [−2.46; −0.81]; < 0.001
Sensitivity analysis: LOCF[l]	650	15.0 (6.9)	−11.5 (0.3)	323	15.1 (7.0)	−10.8 (0.3)	−0.65 [−1.29; −0.01]; 0.046
Number of swollen joints[j]							
RLOCF[k]	604	11.5 (5.6)	−8.4 (0.3)	288	11.5 (5.3)	−7.9 (0.4)	−0.48 [−1.13; 0.17]; 0.145
Pain (VAS)[m]							
RLOCF[k]	600	66.2 (20.8)	−36.8 (1.5)	287	66.6 (19.9)	−32.0 (1.8)	−4.88 [−8.28; −1.47]; 0.005 Hedges' g: −0.20 [−0.34; −0.06]

Study SELECT COMPARE Endpoint scale	Upadacitinib + MTX			Adalimumab + MTX			Upadacitinib + MTX vs Adalimumab + MTX
	N[h]	Values at start of study MV (SD)	Change at the end of study MV (SE)[i]	N[h]	Values at start of study MV (SD)	Change at the end of study MV (SE)[i]	MD [95% CI]; p value[i]
Patient-reported assessment of disease activity (VAS)[m]							
RLOCF[k]	600	64.7 (21.9)	−35.3 (1.6)	287	66.4 (20.8)	−29.5 (1.8)	−5.76 [−9.19; −2.33]; 0.001 Hedges' g: −0.24 [−0.38; −0.09]
Morning stiffness[m]							
Severe (NRS)							
RLOCF[k]	602	6.3 (2.3)	−3.8 (0.2)	284	6.3 (2.1)	−3.3 (0.2)	−0.48 [−0.81; −0.16]; 0.004 Hedges' g: −0.21 [−0.35; −0.07]
Duration (min)							
RLOCF[k]	603	142.6 (185.8)	−100.5 (5.7)	285	149.2 (193.7)	−90.9 (6.8)	−9.57 [−22.16; 3.03]; 0.136
Health status (EQ-5D VAS)[n]							
RLOCF[k]	596	48.6 (23.2)	19.4 (1.4)	285	49.3 (22.1)	17.2 (1.7)	2.24 [−0.92; 5.39]; 0.165

Health-related quality of life

Study SELECT COMPARE Endpoint	Upadacitinib + MTX		Adalimumab + MTX		Upadacitinib + MTX vs Adalimumab + MTX
	N	Patients with event n (%)	N	Patients with event n (%)	RR [95% CI]; p value
SF-36v2[o] (improvement by ≥ 5 points)					
Physical component score					
RNRI[c]	651	361 (55.5)	327	155 (47.4)	1.17 [1.02; 1.33]; 0.024[d]
Sensitivity analysis: NRI[e]	651	424 (65.1)	327	204 (62.4)	1.04 [0.94; 1.15]; 0.407[d]
Mental component score					
RNRI[c]	651	262 (40.2)	327	110 (33.6)	1.19 [1.00; 1.43]; 0.052[d]

Side effects

Study SELECT COMPARE Endpoint	Upadacitinib + MTX		Adalimumab + MTX		Upadacitinib + MTX vs Adalimumab + MTX
	N	Patients with event n (%)	N	Patients with event n (%)	RR [95% CI]; p value
AEs (additionally shown)	650	417 (64.2)	327	197 (60.2)	–
SAE	650	24 (3.7)	327	14 (4.3)	0.86 [0.45; 1.64]; 0.736[b]
Discontinuation because of AEs	650	23 (3.5)	327	20 (6.1)	0.58 [0.32; 1.04]; 0.066[b]
Infections (SOC, AE)	650	225 (34.6)	327	95 (29.1)	1.19 [0.98; 1.45]; 0.082[b]
Serious infections (SOC, AE)	650	12 (1.8)	327	5 (1.5)	1.21 [0.43; 3.40]; 0.791[b]

a. CI cannot be interpreted
b. Own calculation, exact unconditional test (CSZ method according to Martin Andrés et al., 1994).
c. Primary analysis; patients with missing values at week 26 and patients who changed therapy before week 26 are evaluated as non-responders; values for a change of therapy at week 26 are replaced with the last value before the change of therapy
d. Effect estimate based on a generalised linear model with treatment and stratification variable previous bDMARD treatment (yes, no) as covariates
e. Patients with missing values at week 26 are evaluated as non-responders
f. Patients with improvement by ≥ 0.22 points
g. Patients with improvement by ≥ 4 points
h. Number of patients included in the evaluation to calculate the effect estimate; values at the start of study may be based on other patient numbers.
I. Effect estimate based on a covariance analysis with treatment and stratification variable previous bDMARD treatment (yes, no) as fixed effects and value at start of study as covariate
j. Based on 28 joints
k. Primary analysis; missing values as well as values after a change of therapy are replaced with the last observed value
l. Missing values are replaced with the last value observed
m. A negative change from start of study to end of study means an improvement; a negative effect estimate means an advantage for the upadacitinib + MTX.
n. A positive change from start of study to end of study means an improvement; a positive effect estimate means an advantage for the upadacitinib + MTX.
o. Patients with improvement by ≥ 5 points; only mean value differences are available for the individual domains (physical functioning, physical role function, physical pain, general health perception, vitality, social functioning, emotional role function, psychological well-being) (see Section 2.7.4.3.2 of the IQWiG benefit assessment).

bDMARD: biologic DMARD; DMARD: disease-modifying anti-rheumatic agent; CDAI: Clinical Disease Activity Index; DAS28: DAS based on 28 joints; EQ-5D: European Quality of Life Questionnaire – 5 Dimensions; FACIT-Fatigue: Functional Assessment of Chronic Illness Therapy – Fatigue; HAQ-DI: Health Assessment Questionnaire – Disability Index; CI: confidence interval; LOCF: Last Observation carried forward; MD: mean difference; MI: multiple imputation; min: minutes; MTX: methotrexate; MW: mean value; n: number of patients with (at least 1) event; N: number of patients evaluated; NRI: non-responder imputation; NRS: numerical rating scale; RCT: randomised controlled trial; RR: relative risk; SDAI: Simplified Disease Activity Index; SD: standard deviation; SE: standard error; SF-36v2: Short Form-36 Health Survey Version 2; SOC: system organ class; SAE: serious adverse event; AE: adverse event; VAS: visual analogue scale; vs: versus.

Summary of results for relevant clinical endpoints

Endpoint category	Direction of effect/ Risk of bias	Summary
Mortality	↔	No differences relevant for the benefit assessment.
Morbidity	↑	Advantage in remission, advantage in low disease activity, advantage in fatigue, advantage in physical functional status.
Health-related quality of life	↑	Advantage in quality of life.
Side effects	↔	No differences relevant 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

c1) Adult patients with moderate to severe active rheumatoid arthritis who did not respond adequately to previous treatment with one or more bDMARDs and/or tsDMARDs or did not tolerate these; upadacitinib as monotherapy

No data submitted.

Summary of results for relevant clinical endpoints

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

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

c2) Adult patients with moderate to severe active rheumatoid arthritis who did not respond adequately to previous treatment with one or more bDMARDs and/or tsDMARDs or did not tolerate these; upadacitinib in combination with MTX

SELECT CHOICE RCT: Upadacitinib + csDMARDs vs abatacept + csDMARDs, (data cut-off at Week 24), relevant sub-population upadacitinib + MTX vs abatacept + MTX

Mortality

Study SELECT CHOICE	Upadacitinib + MTX		Abatacept+ MTX		Upadacitinib + MTX vs Abatacept+ MTX
Endpoint	N	Patients with event n (%)	N	Patients with event n (%)	RR [95% CI]; p value
Overall mortality	223	1 (0.4)	215	0 (0)	2.89 [0.12; 70.63]; 0.515[a]

Morbidity

Study SELECT CHOICE Endpoint	Upadacitinib + MTX		Abatacept+ MTX		Upadacitinib + MTX vs Abatacept+ MTX
	N	Patients with event n (%)	N	Patients with event n (%)	RR [95% CI]; p value
Clinical remission					
CDAI ≤ 2.8	223	51 (22.9)	215	34 (15.8)	1.44 [0.97; 2.13]; 0.068[c, d]
SDAI ≤ 3.3	223	52 (23.3)	215	31 (14.4)	1.62 [1.08; 2.42]; 0.020[c, d]
Boolean definition	223	38 (17.0)	215	25 (11.6)	1.46 [0.92; 2.34]; 0.111[c, d]
Low disease activity					
CDAI ≤ 10[c]					
Total	223	137 (61.4)	215	115 (53.5)	1.15 [0.98; 1.36]; 0.081[b, c]
no high disease activity at the start of study [DAS28 CRP ≤ 5.1]	59	40 (67.8)	46	38 (82.6)	0.82 [0.66; 1.02][n]; 0.079
High disease activity at the start of study [DAS28 CRP > 5.1]	164	97 (59.1)	168	77 (45.8)	1.29 [1.05; 1.59][n]; 0.016
Total					Interaction: 0.004[o]
SDAI ≤ 11[c]					
Total	223	140 (62.8)	215	115 (53.5)	1.18 [1.00; 1.38]; 0.045[b, c]
no high disease activity at the start of study [DAS28 CRP ≤ 5.1]	59	42 (71.2)	46	37 (80.4)	0.89 [0.71; 1.10][n]; 0.268
High disease activity at the start of study [DAS28 CRP > 5.1]	164	98 (59.8)	168	77 (45.8)	1.30 [1.06; 1.60][n]; 0.012
Total					Interaction: 0.012[o]

Study SELECT CHOICE Endpoint	Upadacitinib + MTX		Abatacept+ MTX		Upadacitinib + MTX vs Abatacept+ MTX
	N	Patients with event n (%)	N	Patients with event n (%)	RR [95% CI]; p value
DAS28 CRP ≤ 3.2	223	148 (66.4)	215	106 (49.3)	1.35 [1.15; 1.59]; < 0.001[b, c]
DAS28 ESR ≤ 3.2	223	110 (49.3)	215	79 (36.7)	1.34 [1.08; 1.67]; 0.008[b, c]
Other					
Physical functional status (HAQ-DI; improvement by ≥ 0.22 points)[d]	223	171 (76.7)	215	149 (69.3)	1.11 [0.99; 1.24]; 0.086[b, c]
Fatigue (FACIT fatigue; improvement ≥ 4 points)[e]	223	160 (71.7)	215	141 (65.6)	1.10 [0.97; 1.25]; 0.147[b, c]

Study SELECT CHOICE Endpoint scale	Upadacitinib + MTX			Abatacept+ MTX			Upadacitinib + MTX vs Abatacept+ MTX
	N[f]	Values at start of study MV (SD)	Change at end of study MV (SE)[g]	N[f]	Values at start of study MV (SD)	Change at end of study MV (SE)[g]	MD [95% CI]; p value[g]
Number of pressure-painful joints[h]	221	14.5 (6.3)	−11.7 (0.4)	212	15.7 (6.7)	−11.2 (0.4)	−0,45 [−1.29; 0.40]; 0.299[i]
Number of swollen joints[h]	221	10.4 (4.7)	−8.5 (0.3)	212	11.4 (5.1)	−8.6 (0.3)	0,09 [−0.53; 0.71]; 0.780[i]
Pain (VAS)[j]	221	68.4 (20.2)	−40.3 (1.9)	212	71.1 (18.4)	−36.0 (1.9)	−4.31 [−8.75; 0.13]; 0.057[k]
Patient-reported assessment of disease activity (VAS)[j]	223	66.7 (19.9)	−37.8 (1.9)	215	69.7 (20.0)	−35.6 (1.9)	−2.24 [−6.71; 2.22]; 0.321[k]
Health status (EQ-5D VAS)[l]	223	43.7 (22.1)	29.5 (1.5)	215	45.1 (22.8)	25.4 (1.6)	4.10 [0.43; 7.77]; 0.027[k] Hedges' g: 0.21 [0.02; 0.40]

Study SELECT CHOICE Endpoint scale	Upadacitinib + MTX			Abatacept+ MTX			Upadacitinib + MTX vs Abatacept+ MTX
	N[f]	Values at start of study MV (SD)	Change at end of study MV (SE)[g]	N[f]	Values at start of study MV (SD)	Change at end of study MV (SE)[g]	MD [95% CI]; p value[g]
Morning stiffness[j]							
Severe (NRS)	223	6.4 (2.3)	−3.9 (0.2)	215	6.4 (2.3)	−3.4 (0.2)	−0.56 [−0.98; −0.13]; 0.010[k] Hedges' g: −0.25 [−0.43; −0.06]
Duration (min)	223	170.3 (242.3)	−94.2 (19.9)	215	209.7 (318.5)	−58.2 (21.1)	−36.09 [−83.86; 11.69]; 0.136[k]

Health-related quality of life

Study SELECT CHOICE Endpoint	Upadacitinib + MTX		Abatacept+ MTX		Upadacitinib + MTX vs Abatacept+ MTX
	N	Patients with event n (%)	N	Patients with event n (%)	RR [95% CI]; p value[a]
SF-36v2[m] (improvement by ≥ 5 points)					
Physical component score	223	151 (67.7)	215	138 (64.2)	1.05 [0.92; 1.21]; 0.435[b, c]
Mental component score	223	107 (48.0)	215	104 (48.4)	0.99 [0.82; 1.21]; 0.938[b, c]

Side effects

Study SELECT CHOICE Endpoint	Upadacitinib + MTX		Abatacept+ MTX		Upadacitinib + MTX vs Abatacept+ MTX
	N	Patients with event n (%)	N	Patients with event n (%)	RR [95% CI]; p value
AEs (additionally shown)	223	148 (66.4)	215	122 (56.7)	–
SAE	223	5 (2.2)	215	1 (0.5)	4.82 [0.57; 40.93]; 0.149[a]

Study SELECT CHOICE Endpoint	Upadacitinib + MTX		Abatacept+ MTX		Upadacitinib + MTX vs Abatacept+ MTX
	N	Patients with event n (%)	N	Patients with event n (%)	RR [95% CI]; p value
Discontinuation because of AEs	223	9 (4.0)	215	5 (2.3)	1.74 [0.59; 5.10]; 0.316[a]
Infections (SOC, AE)	223	88 (39.5)	215	67 (31.2)	1.27 [0.98; 1.64]; 0.071[a]
Serious infections (SOC, AE)	223	2 (0.9)	215	0 (0)	4.82 [0.23; 99.85]; 0.309[a]

a. Effect estimation based on a generalised linear model with treatment as covariates
b. Effect estimate based on a generalised linear model with treatment and stratification variable previous bDMARD treatment (1 or 2 bDMARD therapies with the same mechanism of action versus others) as covariates
c. NRI replacement strategy: Patients with missing values are evaluated as non-responders
d. Patients with improvement by ≥ 0.22 points
e. Patients with improvement by ≥ 4 points
f. Number of patients included in the evaluation to calculate the effect estimate; values at the start of study may be based on other patient numbers.
g. Effect estimate based on a covariance analysis with treatment and stratification variable previous bDMARD treatment (1 or 2 bDMARD therapies with the same mechanism of action; other) as fixed effects and value at start of study as covariate
h. Based on 28 joints
I. Replacement of missing values with LOCF
j. A negative change from start of study to end of study means an improvement; a negative effect estimate means an advantage for the upadacitinib + MTX.
k. Replacement of missing values with MI
l. A positive change from start of study to end of study means an improvement; a positive effect estimate means an advantage for the upadacitinib + MTX.
m. Patients with improvement by ≥ 5 points; only mean value differences are available for the individual domains (physical functioning, physical role function, physical pain, general health perception, vitality, social functioning, emotional role function, psychological well-being) (see Section 2.7.4.3.2 of the IQWiG benefit assessment).
n: Effect estimate based on a generalised linear model with treatment and stratification variable previous bDMARD treatment (1 or 2 bDMARD therapies with the same mechanism of action versus others) as covariates
o: p value for the interaction term from a generalised linear model with treatment, subgroup, and treatment × subgroup as covariates

bDMARD: biologic DMARD; DMARD: disease-modifying anti-rheumatic agent; CDAI: Clinical Disease Activity Index; DAS28: DAS based on 28 joints; EQ-5D: European Quality of Life Questionnaire – 5 Dimensions; FACIT-Fatigue: Functional Assessment of Chronic Illness Therapy – Fatigue; HAQ-DI: Health Assessment Questionnaire – Disability Index; CI: confidence interval; LOCF: Last Observation carried forward; MD: mean difference; MI: multiple imputation; min: minutes; MTX: methotrexate; MW: mean value; n: number of patients with (at least 1) event; N: number of patients evaluated; NRI: non-responder imputation; NRS: numerical rating scale; RCT: randomised controlled trial; RR: relative risk; SDAI: Simplified Disease Activity Index; SD: standard deviation; SE: standard error; SF-36v2: Short Form-36 Health Survey Version 2; SOC: system organ class; SAE: serious adverse event; AE: adverse event; VAS: visual analogue scale; vs: versus.

Summary of results for relevant clinical endpoints for c2A (patients with high disease activity [DAS28 CRP > 5.1])

Endpoint category	Direction of effect/ Risk of bias	Summary
Mortality	↔	No deaths occurred.
Morbidity	↑	Advantage in low disease activity
Health-related quality of life	↔	No differences relevant for the benefit assessment.
Side effects	↔	No differences relevant 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

Summary of results for relevant clinical endpoints for c2B (patients without high disease activity [DAS28 CRP ≤ 5.1])

Endpoint category	Direction of effect/ Risk of bias	Summary
Mortality	↔	No deaths occurred.
Morbidity	↔	No differences relevant for the benefit assessment.
Health-related quality of life	↔	No differences relevant for the benefit assessment.
Side effects	↔	No differences relevant 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

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

a) Adult patients with moderate to severe active rheumatoid arthritis for whom there are no unfavourable prognostic factors[1] and who did not respond adequately to previous treatment

with a disease-modifying anti-rheumatic agent (conventional DMARDs, including methotrexate (MTX)) or did not tolerate it (a1+ a2)

approx. 12,130–33720 patients

b) Adult patients with moderate to severe active rheumatoid arthritis for whom first-line therapy with biological DMARDs (bDMARDs) or targeted synthetic DMARDs (tsDMARDs) is indicated (b1+b2)

approx. 58,980–127630 patients

c) Adult patients with moderate to severe active rheumatoid arthritis who did not respond adequately to previous treatment with one or more bDMARDs and/or tsDMARDs or did not tolerate these (c1+c2)

approx. 16,600–26860 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: 30 June 2020):

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

In accordance with the specifications of the European Medicines Agency (EMA) regarding additional measures for risk minimisation, the pharmaceutical company must provide training material as well as a patient identification card. The training material for healthcare professionals includes instructions on how to deal with the possible side effects of upadacitinib, in particular severe and opportunistic infections, including TB and shingles.

Treatment should be started by a doctor experienced in the diagnosis and treatment of rheumatoid arthritis.

The use of the medicinal product must also be carefully considered against the background of a comparatively new principle of action and the associated remaining uncertainties in the risk profile compared with established therapies.

4. Treatment costs

Annual treatment costs:

a1) Adult patients with moderate to severe active rheumatoid arthritis for whom there are no unfavourable prognostic factors[1] and who did not respond adequately to previous treatment with a disease-modifying anti-rheumatic agent (conventional DMARDs, including methotrexate (MTX)) or did not tolerate it; upadacitinib as monotherapy

Designation of the therapy	Annual treatment costs per patient
Medicinal product to be assessed	
Upadacitinib	€ 15,640.25

Designation of the therapy	Annual treatment costs per patient
Additionally required SHI services Total	€ 180.44 € 15,820.69
Appropriate comparator therapy for patient population a1	
Methotrexate	€ 51.98 – 129.14
Leflunomide	€ 601.41 – 939.07
Sulfasalazine	€ 328.10 – 492.15
Chloroquine phosphate	€ 99.44
Hydroxychloroquine sulphate	€ 181.49

Costs after deduction of statutory rebates (LAUER-TAXE®) as last revised: 15 June 2020)

a2) Adult patients with moderate to severe active rheumatoid arthritis for whom there are no unfavourable prognostic factors[1] and who did not respond adequately to previous treatment with a disease-modifying anti-rheumatic agent (conventionalDMARDs, including methotrexate (MTX)) or did not tolerate it; upadacitinib in combination with MTX

Designation of the therapy	Annual treatment costs per patient
Medicinal product to be assessed	
Upadacitinib Methotrexate Additionally required SHI services Total	€ 15,640.25 € 51.98 – 129.14 € 180.44 € 15,872.67 – 15,949.83
Appropriate comparator therapy for patient population a2	
Methotrexate	€ 51.98 – 129.14
Leflunomide	€ 601.41 – 939.07
Sulfasalazine	€ 328.10 – 492.15
Chloroquine phosphate	€ 99.44
Hydroxychloroquine sulphate	€ 181.49

Costs after deduction of statutory rebates (LAUER-TAXE®) as last revised: 15 June 2020)

b1) Adult patients with moderate to severe active rheumatoid arthritis for whom first-line therapy with biological DMARDs (bDMARDs) or targeted synthetic DMARDs (tsDMARDs) is indicated; upadacitinib as monotherapy

Designation of the therapy	Annual treatment costs per patient
Medicinal product to be assessed	
Upadacitinib Additionally required SHI services Total	€ 15,640.25 € 106.40 € 15,746.65
Appropriate comparator therapy for patient population b1	
Abatacept Methotrexate	€ 18,672.08 € 51.98 – 129.14

Designation of the therapy	Annual treatment costs per patient
Additionally required SHI services Total	€ 106.40 € 18,830.46 – 18,907.62
Adalimumab Additionally required SHI services Total	€ 11,510.19 € 106.40 € 11,616.59
Adalimumab Methotrexate Additionally required SHI services Total	€ 11,510.19 € 51.98 – 129.14 € 106.40 € 11,668.57 – 11,745.73
Baricitinib Additionally required SHI services Total	€ 14,328.26 € 106.40 € 14,434.66
Baricitinib Methotrexate Additionally required SHI services Total	€ 14,328.26 € 51.98 – 129.14 € 106.40 € 14,486.64 – 14,563.80
Certolizumab pegol Additionally required SHI services Total	€ 19,538.16 € 106.40 € 19,644.56
Certolizumab pegol Methotrexate Additionally required SHI services Total	€ 19,538.16 € 51.98 – 129.14 € 106.40 € 19,696.54 – 19,773.70
Etanercept Additionally required SHI services Total	€ 8,458.79 € 106.40 € 8,565.19
Etanercept Methotrexate Additionally required SHI services Total	€ 8,458.79 € 51.98 – 129.14 € 106.40 € 8,617.17 – 8,694.33
Golimumab Methotrexate Additionally required SHI services Total	€ 20,688.36 € 51.98 – 129.14 € 106.40 € 20,846.74 – 20,923.90
Infliximab Methotrexate Additionally required SHI services Total	€ 12,512.92 – 25,025.83 € 51.98 – 129.14 € 106.40 € 12,671.30 – 25,261.37
Sarilumab	€ 17,299.30
Sarilumab Methotrexate Total	€ 17,299.30 € 51.98 – 129.14 € 17,351.28 – 17,428.44
Tocilizumab	€ 22,127.17
Tocilizumab Methotrexate Total	€ 22,127.17 € 51.98 – 129.14 € 22,179.15 – 22,256.31
Tofacitinib	€ 13,215.49

Designation of the therapy	Annual treatment costs per patient
Additionally required SHI services Total	€ 106.40 € 13,321.89
Tofacitinib Methotrexate Additionally required SHI services Total	€ 13,215.49 € 51.98 – 129.14 € 106.40 € 13,373.87 – 13,451.03

Costs after deduction of statutory rebates (LAUER-TAXE®) as last revised: 15 June 2020)

b2) Adult patients with moderate to severe active rheumatoid arthritis for whom first-line therapy with biological DMARDs (bDMARDs) or targeted synthetic DMARDs (tsDMARDs) is indicated; upadacitinib in combination with MTX

Designation of the therapy	Annual treatment costs per patient
Medicinal product to be assessed	
Upadacitinib Methotrexate Additionally required SHI services Total	€ 15,640.25 € 51.98 – 129.14 € 106.40 € 15,798.63 – 15,875.79
Appropriate comparator therapy for patient population b2	
Abatacept Methotrexate Additionally required SHI services Total	€ 18,672.08 € 51.98 – 129.14 € 106.40 € 18,830.46 – 18,907.62
Adalimumab Additionally required SHI services Total	€ 11,510.19 € 106.40 € 11,616.59
Adalimumab Methotrexate Additionally required SHI services Total	€ 11,510.19 € 51.98 – 129.14 € 106.40 € 11,668.57 – 11,745.73
Baricitinib Additionally required SHI services Total	€ 14,328.26 € 106.40 € 14,434.66
Baricitinib Methotrexate Additionally required SHI services Total	€ 14,328.26 € 51.98 – 129.14 € 106.40 € 14,486.64 – 14,563.80
Certolizumab pegol Additionally required SHI services Total	€ 19,538.16 € 106.40 € 19,644.56
Certolizumab pegol Methotrexate Additionally required SHI services Total	€ 19,538.16 € 51.98 – 129.14 € 106.40 € 19,696.54 – 19,773.70
Etanercept Additionally required SHI services	€ 8,458.79 € 106.40

Designation of the therapy	Annual treatment costs per patient
Total	€ 8,565.19
Etanercept Methotrexate Additionally required SHI services Total	€ 8,458.79 € 51.98 – 129.14 € 106.40 € 8,617.17 – 8,694.33
Golimumab Methotrexate Additionally required SHI services Total	€ 20,688.36 € 51.98 – 129.14 € 106.40 € 20,846.74 – 20,923.90
Infliximab Methotrexate Additionally required SHI services Total	€ 12,512.92 – 25,025.83 € 51.98 – 129.14 € 106.40 € 12,671.30 – 25,261.37
Sarilumab	€ 17,299.30
Sarilumab Methotrexate Total	€ 17,299.30 € 51.98 – 129.14 € 17,351.28 – 17,428.44
Tocilizumab	€ 22,127.17
Tocilizumab Methotrexate Total	€ 22,127.17 € 51.98 – 129.14 € 22,179.15 – 22,256.31
Tofacitinib Additionally required SHI services Total	€ 13,215.49 € 106.40 € 13,321.89
Tofacitinib Methotrexate Additionally required SHI services Total	€ 13,215.49 € 51.98 – 129.14 € 106.40 € 13,373.87 – 13,451.03

Costs after deduction of statutory rebates (LAUER-TAXE®) as last revised: 15 June 2020)

c1) Adult patients with moderate to severe active rheumatoid arthritis who did not respond adequately to previous treatment with one or more bDMARDs and/or tsDMARDs or did not tolerate these; upadacitinib as monotherapy

Designation of the therapy	Annual treatment costs per patient
Medicinal product to be assessed	
Upadacitinib Additionally required SHI services Total	€ 15,640.25 € 106.40 € 15,746.65
Appropriate comparator therapy for patient population c1	
Abatacept Methotrexate Additionally required SHI services Total	€ 18,672.08 € 51.98 – 129.14 € 106.40 € 18,830.46 – 18,907.62

Designation of the therapy	Annual treatment costs per patient
Adalimumab Additionally required SHI services Total	€ 11,510.19 € 106.40 € 11,616.59
Adalimumab Methotrexate Additionally required SHI services Total	€ 11,510.19 € 51.98 – 129.14 € 106.40 € 11,668.57 – 11,745.73
Baricitinib Additionally required SHI services Total	€ 14,328.26 € 106.40 € 14,434.66
Baricitinib Methotrexate Additionally required SHI services Total	€ 14,328.26 € 51.98 – 129.14 € 106.40 € 14,486.64 – 14,563.80
Certolizumab pegol Additionally required SHI services Total	€ 19,538.16 € 106.40 € 19,644.56
Certolizumab pegol Methotrexate Additionally required SHI services Total	€ 19,538.16 € 51.98 – 129.14 € 106.40 € 19,696.54 – 19,773.70
Etanercept Additionally required SHI services Total	€ 8,458.79 € 106.40 € 8,565.19
Etanercept Methotrexate Additionally required SHI services Total	€ 8,458.79 € 51.98 – 129.14 € 106.40 € 8,617.17 – 8,694.33
Golimumab Methotrexate Additionally required SHI services Total	€ 20,688.36 € 51.98 – 129.14 € 106.40 € 20,846.74 – 20,923.90
Infliximab Methotrexate Additionally required SHI services Total	€ 12,512.92 – 25,025.83 € 51.98 – 129.14 € 106.40 € 12,671.30 – 25,261.37
Sarilumab	€ 17,299.30
Sarilumab Methotrexate Total	€ 17,299.30 € 51.98 – 129.14 € 17,351.28 – 17,428.44
Tocilizumab	€ 22,127.17
Tocilizumab Methotrexate Total	€ 22,127.17 € 51.98 – 129.14 € 22,179.15 – 22,256.31
Tofacitinib Additionally required SHI services Total	€ 13,215.49 € 106.40 € 13,321.89

Designation of the therapy	Annual treatment costs per patient
Tofacitinib Methotrexate Additionally required SHI services Total	€ 13,215.49 € 51.98 – 129.14 € 106.40 € 13,373.87 – 13,451.03
Rituximab Methotrexate Additionally required SHI services Total	€ 6,708.32 – 13,416.64 € 51.98 – 129.14 € 106.40 € 6,866.70 – 13,652.18

Costs after deduction of statutory rebates (LAUER-TAXE®) as last revised: 15 June 2020)

c2) Adult patients with moderate to severe active rheumatoid arthritis who did not respond adequately to previous treatment with one or more bDMARDs and/or tsDMARDs or did not tolerate these; upadacitinib in combination with MTX (c2A and c2B)

Designation of the therapy	Annual treatment costs per patient
Medicinal product to be assessed	
Upadacitinib Methotrexate Additionally required SHI services Total	€ 15,640.25 € 51.98 – 129.14 € 106.40 € 15,798.63 – 15,875.79
Appropriate comparator therapy for patient population c2 (c2A and c2B)	
Abatacept Methotrexate Additionally required SHI services Total	€ 18,672.08 € 51.98 – 129.14 € 106.40 € 18,830.46 – 18,907.62
Adalimumab Additionally required SHI services Total	€ 11,510.19 € 106.40 € 11,616.59
Adalimumab Methotrexate Additionally required SHI services Total	€ 11,510.19 € 51.98 – 129.14 € 106.40 € 11,668.57 – 11,745.73
Baricitinib Additionally required SHI services Total	€ 14,328.26 € 106.40 € 14,434.66
Baricitinib Methotrexate Additionally required SHI services Total	€ 14,328.26 € 51.98 – 129.14 € 106.40 € 14,486.64 – 14,563.80
Certolizumab pegol Additionally required SHI services Total	€ 19,538.16 € 106.40 € 19,644.56
Certolizumab pegol Methotrexate Additionally required SHI services Total	€ 19,538.16 € 51.98 – 129.14 € 106.40 € 19,696.54 – 19,773.70

Designation of the therapy	Annual treatment costs per patient
Etanercept Additionally required SHI services Total	€ 8,458.79 € 106.40 € 8,565.19
Etanercept Methotrexate Additionally required SHI services Total	€ 8,458.79 € 51.98 – 129.14 € 106.40 € 8,617.17 – 8,694.33
Golimumab Methotrexate Additionally required SHI services Total	€ 20,688.36 € 51.98 – 129.14 € 106.40 € 20,846.74 – 20,923.90
Infliximab Methotrexate Additionally required SHI services Total	€ 12,512.92 – 25,025.83 € 51.98 – 129.14 € 106.40 € 12,671.30 – 25,261.37
Sarilumab	€ 17,299.30
Sarilumab Methotrexate Total	€ 17,299.30 € 51.98 – 129.14 € 17,351.28 – 17,428.44
Tocilizumab	€ 22,127.17
Tocilizumab Methotrexate Total	€ 22,127.17 € 51.98 – 129.14 € 22,179.15 – 22,256.31
Tofacitinib Additionally required SHI services Total	€ 13,215.49 € 106.40 € 13,321.89
Tofacitinib Methotrexate Additionally required SHI services Total	€ 13,215.49 € 51.98 – 129.14 € 106.40 € 13,373.87 – 13,451.03
Rituximab Methotrexate Additionally required SHI services Total	€ 6,708.32 – 13,416.64 € 51.98 – 129.14 € 106.40 € 6,866.70 – 13,652.18

Costs after deduction of statutory rebates (LAUER-TAXE®) as last revised: 15 June 2020)

Other services covered by SHI funds:

Designation of the therapy	Type of service	Costs per unit	Number per patient per year	Costs per patient per year
Medicinal product to be assessed				
not applicable				
Appropriate comparator therapy for patient population b				

Infliximab	Surcharge for the preparation of a parenteral solution containing monoclonal antibodies	€ 71	6.5	€ 461.50
Appropriate comparator therapy for patient population c				
Rituximab	Surcharge for the preparation of a parenteral solution containing monoclonal antibodies	€ 71	2–4	€ 142.00 – 284.00
Infliximab			6.5	€ 461.50

II. The resolution will enter into force with effect from the day of its publication on the internet on the website of the G-BA on 16 July 2020.

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

Berlin, 16 July 2020

Federal Joint Committee
in accordance with Section 91 SGB V
The Chair

Prof. Hecken