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 Secukinumab (Reassessment on the Basis of New Scientific Findings (Psoriatic Arthritis))

of 18 February 2021

At its session on 18 February 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 amended on DD Month YYYY (Federal Gazette, BAnz AT DD MM YYYY BX), as follows:

I. Annex XII will be amended as follows:

Annex XII shall be amended for the active ingredient secukinumab to include in alphabetical order the therapeutic indications **ankylosing spondylitis (AS, Bekhterev's disease) and psoriatic arthritis (PsA)**.

In Annex XII, the information on the active ingredient secukinumab in the therapeutic indication ankylosing spondylitis (AS; Bekhterev's disease) shall be amended as follows in accordance with the resolution of 27 November 2015 in the amended version of the resolution of 2 June 2016 (Federal Gazette, BAnz AT 7 July 2016 B4):

1. The entry "b)" in numbers 5, 6 and 8 shall be deleted in each case.

In Annex XII, the information on the active ingredient secukinumab in the therapeutic indication psoriatic arthritis (PsA) shall be amended as follows in accordance with the resolution of 27 November 2015 in the amended version of the resolution of 2 June 2016 (Federal Gazette, BAnz AT 7 July 2016 B4):

2. Number 5 letter a, number 6 letter a and number 8 letter a are hereby repealed.

3. After number 4

- the words "active psoriatic arthritis" shall be deleted;

- the words "approved therapeutic indications" shall be replaced by the words "new therapeutic indication"; and

- the sentence "Psoriatic arthritis (PSA) secukinumab (Cosentyx®), alone or in combination with methotrexate (MTX), is indicated for the treatment of adult patients with

active psoriatic arthritis when the response to previous disease-modifying anti-rheumatic drug (DMARD) therapy has been inadequate" shall be deleted.

4. Footnote 24 to the previous version shall be deleted. Footnotes 23 to 28 of the previous version will become footnotes 15 to 18.
5. The following shall be added after number 8:

Secukinumab

Resolution of: 18 February 2021
Entry into force on: 18 February 2021
Federal Gazette, BAnz AT DD MM YYYY Bx

New therapeutic indication (according to the marketing authorisation of 19 November 2015):

Cosentyx, alone or in combination with methotrexate (MTX), is indicated for the treatment of active psoriatic arthritis in adult patients when the response to previous disease-modifying anti-rheumatic drug (DMARD) therapy has been inadequate.

Therapeutic indication of the resolution (resolution of 18 February 2021):

See therapeutic indication according to marketing authorisation

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

a1) Adult patients with psoriatic arthritis whose response to previous disease-modifying anti-rheumatic drug (DMARD) therapy has been inadequate or who have not tolerated it, with concomitant moderate to severe plaque psoriasis.

Appropriate comparator therapy:

- A TNF-alpha antagonist (adalimumab or certolizumab pegol or etanercept or golimumab or infliximab) or an interleukin inhibitor (ixekizumab or ustekinumab), possibly in combination with methotrexate

Extent and probability of the additional benefit of secukinumab compared with adalimumab:

Indication of a minor additional benefit.

a2) Adult patients with psoriatic arthritis whose response to previous disease-modifying anti-rheumatic drug (DMARD) therapy has been inadequate or who have not tolerated it, without concomitant moderate to severe plaque psoriasis.

Appropriate comparator therapy:

- A TNF-alpha antagonist (adalimumab or certolizumab pegol or etanercept or golimumab or infliximab) or an interleukin inhibitor (ixekizumab or ustekinumab), possibly in combination with methotrexate

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

An additional benefit is not proven.

b) Adult patients with active psoriatic arthritis whose response to previous therapy with disease-modifying biological anti-rheumatic drugs (bDMARDs) has been inadequate or who have not tolerated it.

Appropriate comparator therapy:

- Switching to another biological disease-modifying anti-rheumatic drug (adalimumab or certolizumab pegol or etanercept or golimumab or infliximab or ixekizumab or ustekinumab), possibly in combination with methotrexate

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

An additional benefit is not proven.

Study results according to endpoints:[1]

a1) Adult patients with psoriatic arthritis whose response to previous disease-modifying anti-rheumatic drug (DMARD) therapy has been inadequate or who have not tolerated it, with concomitant moderate to severe plaque psoriasis

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 skin symptomatology
Health-related quality of life	↑	Advantage in mental component sum score of SF-36
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

EXCEED study: RCT, comparison of secukinumab vs adalimumab in each case in monotherapy, results at week 52

[1] Data from the dossier assessment of the IQWiG (A20-80) and the addendum (A21-01) unless otherwise indicated.

Mortality

Endpoint	Secukinumab		Adalimumab		Secukinumab vs adalimumab
	N	Patients with event n (%)	N	Patients with event n (%)	RR [95 % CI]; p value
Overall survival					
	110	0 (0)	101	0 (0)	-

Morbidity

Endpoint	Secukinumab		Adalimumab		Secukinumab vs adalimumab
	N	Patients with event n (%)[a]	N	Patients with event n (%)[a]	RR [95 % CI]; p value[b]
Minimal disease activity (MDA)[c]	110	51.0 (46.6)	101	39.9 (39.5)	1.17 [0.85; 1.62]; 0.325
Very low disease activity (VLDA, *presented as a supplement*)[c]	110	16.3 (14.8)	101	15.9 (15.7)	0.94 [0.49; 1.80]; 0.855
Skin symptomatology					
PASI 100	110	43.8 (39.8)	101	24.5 (24.3)	1.64 [1.08; 2.50]; 0.021
PASI 90	110	78.0 (70.9)	101	45.9 (45.4)	1.56 [1.21; 2.01]; < 0.001
PASI 75	110	98.4 (89.5)	101	67.4 (66.7)	1.34 [1.14; 1.57]; < 0.001
Physical functional status (HAQ-DI, improvement of ≥ 0.45 points, ≙ 15 % of the range of the scale)[2]	110	57.8 (52.6)	101	50.8 (50.3)	1.05 [0.80; 1.37]; < 0.749
Physical functional status (HAQ-DI, improvement of ≥ 0.35 points)[2]	110	67.60 (61.45)	101	62.99 (62.37)	0.99 [0.79; 1.23]; < 0.896
Health status (EQ-5D VAS, improvement of ≥ 15 mm, ≙ 15 % of the range of the scale)	110	58.8 (53.5)	101	60.2 (59.6)	0.90 [0.70; 1.15]; 0.388
Psoriatic arthritis-related pain (pain VAS, improvement of ≥ 15 mm, ≙ 15 % of the range of the scale)	110	74.5 (67.8)	101	71.4 (70.6)	0.96 [0.79; 1.16]; 0.671
Patient's global assessment of disease activity (PatGA PASDAS	110	87.9 (79.9)	101	78.2 (77.4)	1.03 [0.89; 1.20]; 0.671

[2] In light of the ongoing methodological discussion, both evaluations are presented here.

VAS, improvement of ≥ 15 mm, ≙ 15 % of the range of the scale)					
Fatigue (FACIT fatigue, improvement of ≥ 7.8 points, ≙ 15 % of the range of the scale)[2]	110	55.9 (50.8)	101	44.5 (44.1)	1.15 [0.86; 1.55]; 0.351
Fatigue (FACIT fatigue, improvement of ≥ 4 points)[2]	110	72.5 (65.9)	101	61.5 (60.9)	1.08 [0.87; 1.34]; 0.469

Endpoint	**Secukinumab**			**Adalimumab**			**Secukinumab vs adalimumab**
	N[d]	Values at tart of stud MV (SD)	Change at the end of study MV[e] (SE)	N[d]	Values at tart of stud MV (SD)	Change at the end of study MV[e] (SE)	MD [95% CI]; p value[e]
Enthesitis (LEI)[f]	110	1.31 (1.49)	-1.14 (0.09)	100	2.00 (1.93)	-1.21 (0.10)	0.07 [-0.21; 0.35]; 0.620
Daktylitis (LDI)[f]	110	17.64 (49.52)	-19.72 (0.51)	100	19.62 (58.36)	-18.88 (0.56)	-0.85 [-2.34; 0.65]; 0.267
Number of pressure-painful joints[f,g]	110	17.40 (9.96)	-14.92 (0.51)	100	19.70 (12.54)	-14.48 (0.56)	-0.44 [-1.94; 1.06]; 0.564
Number of swollen joints[f,g]	110	9.27 (6.53)	-8.77 (0.24)	100	10.69 (8.16)	-8.60 (0.26)	-0.17 [-0.87; 0.52]; 0.621

Health-related quality of life

Endpoint	Secukinumab		Adalimumab		Secukinumab vs Adalimumab
	N	Patients with event n (%)	N	Patients with event n (%)	RR [95 % CI]; p value[b]
SF-36					
Improvement by 15 % of the range of the scale[2]					
Mental Component Score (MCS, improvement of 9.6 points)	110	46.1 (41.9)	101	28.8 (28.5)	1.47 [0.99; 2.19]; 0.055
Mental Component Score (PCS, improvement of ≥ 9.4 points)	110	42.8 (39.0)	101	37.9 (37.5)	1.04 [0.73; 1.49]; 0.834
Improvement of ≥ 5 points[2]					
Mental Component Score (MCS, improvement of 5 points)	110	68.5 (62.3)	101	45.3 (44.9)	1.39 [1.06; 1.83]; 0.018
Mental Component Score (PCS, improvement of ≥ 5 points)	110	66.9 (60.8)	101	62.1 (61.5)	0.99 [0.79; 1.24]; 0.929

Endpoint	Secukinumab		Adalimumab		Secukinumab vs Adalimumab
	N	Patients with event n (%)	N	Patients with event n (%)	RR [95 % CI]; p value
DLQI (0 or 1)	110	56.2[b] (51.1)	101	40.3[b] (39.9)	1.28 [0.94; 1.75]; 0.118[c]

Side effects

Endpoint	Secukinumab		Adalimumab		Secukinumab vs adalimumab
	N	Patients with event n (%)	N	Patients with event n (%)	RR [95 % CI]; p value
AEs *(presented as a supplement)*	110	74 (67.3)	101	71 (70.3)	-
SAEs	110	7 (6.4)	101	7 (6.9)	0.92 [0.33; 2.53]; 0.869
Discontinuation due to AEs[h]	110	1 (0.9)	101	3 (3.0)	0.31 [0.03; 2.90]; 0.302
Infections and infestations (SOC, AE)	110	62 (56.4)	101	48 (47.5)	1.19 [0.91; 1.54]; 0.203

a Due to the multiple imputations of missing values, the number of patients with an event is usually not a whole number.
b Combining RR, 95% CI and p-value across all imputation data sets using Rubin's rule.
c To be classified as an MDA responder, 5 of the following 7 criteria must be met, and to be classified as a VLDA responder, 7 of the 7 criteria must be met: number of pressure painful joints based on

78 joints ≤ 1, number of swollen joints based on 76 joints ≤ 1, PASI score ≤ 1 or BSA ≤ 3 %, pain (VAS) ≤ 15 mm, patient-reported global disease activity (PatGA VAS) ≤ 20 mm, HAQ-DI score (physical functional status) ≤ 0.5, LEI score (enthesitis) ≤ 1

d 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 numbers.

e MMRM evaluation of the ITT population with the variables treatment arm, visit, weight, value at baseline, interaction term treatment arm and visit, and interaction term value at baseline and visit.

f Lower (decreasing) values mean improved symptomatology; negative effects (secukinumab minus adalimumab) mean an advantage for secukinumab.

g Number of pressure painful joints based on 78 joints or number of swollen joints based on 76 joints.

h In the course of the written statement procedure, the pharmaceutical company submitted corrected data. According to this, one additional event that led to treatment discontinuation occurred in patients in the adalimumab arm. Whether this might alter the overall rate of AEs leading to treatment discontinuation is not clear from the statement.

Abbreviations used:
BSA: Body Surface Area; DLQI: Dermatology Life Quality Index; EQ-5D: European Quality of Life Questionnaire 5 Dimensions; FACIT: Functional Assessment of Chronic Illness Therapy; HAQ- DI: Health Assessment Questionnaire – Disability Index; ITT: Intention to treat; CI: confidence interval; LDI: Leeds dactylitis index; LEI: Leeds enthesitis index; MD: mean difference, MDA: minimal disease activity; MMRM: mixed model with repeated measurements; MV: mean value; n: number of patients with (at least 1) event, N: Number of patients evaluated; PASDAS: Psoriatic Arthritis Disease Activity Score; PASI: Psoriasis Area and Severity Index; PatGA: Patient's Global Impression of Severity; RCT: randomised controlled study; RR: relative risk; SD: standard deviation, SE: standard error; SF36: Short Form-36 Health Survey; SOC: system organ class; SAE: serious adverse event; AE: adverse event; VAS: visual analogue scale; VLDA: very low disease activity

a2) Adult patients with psoriatic arthritis whose response to previous disease-modifying anti-rheumatic drug (DMARD) therapy has been inadequate or who have not tolerated it, without concomitant moderate to severe plaque psoriasis.

Summary of results for relevant clinical endpoints

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

b) Adult patients with active psoriatic arthritis whose response to previous therapy with disease-modifying biological anti-rheumatic drugs (bDMARDs) has been inadequate or who have not tolerated it.

Summary of results for relevant clinical endpoints

Endpoint category	Direction of effect/ Risk of bias	Summary
Mortality	∅	No data available.
Morbidity	∅	No data available.
Health-related quality of life	∅	No data available.
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n.a.: not assessable

No suitable data were submitted.

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

a) Adult patients with psoriatic arthritis whose response to previous disease-modifying anti-rheumatic drug (DMARD) therapy has been inadequate or who have not tolerated it.

approx. 20,100 patients

b) Adult patients with active psoriatic arthritis whose response to previous therapy with disease-modifying biological anti-rheumatic drugs (bDMARDs) has been inadequate or who have not tolerated it.

approx. 9,000 patients

11. 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 Cosentyx (active ingredient: secukinumab) at the following publicly accessible link (last accessed: 9 December 2020):
https://www.ema.europa.eu/documents/product-information/cosentyx-epar-product-information_en.pdf

Treatment with secukinumab should only be initiated and monitored by specialists who are experienced in the treatment of patients with HIV infection.

In patients who have not responded to 16 weeks of treatment, consideration should be made on whether to discontinue treatment. Some patients with an initially partial response improve over time if treatment is continued beyond 16 weeks.

12. Treatment costs

Annual treatment costs:

a) Adult patients with psoriatic arthritis whose response to previous disease-modifying anti-rheumatic drug (DMARD) therapy has been inadequate or who have not tolerated it.

Designation of the therapy	Annual treatment costs/patient
Medicinal product to be assessed:	
Secukinumab	€ 10,343.44–20,686.88
Appropriate comparator therapy:	
Adalimumab Additionally required SHI services Total	€ 11,510.06 € 180.64 € 11,690.70
Certolizumab pegol Additionally required SHI services Total	€ 19,808.29 € 180.64 € 19,988.93
Etanercept Additionally required SHI services Total	€ 16,885.18 € 180.64 € 17,065.82
Golimumab Additionally required SHI services Total	€ 20,974.88 € 180.64 € 21,155.52
Infliximab Additionally required SHI services Total	€ 16,683.89 € 180.64 …€ 16,864.53
Ixekizumab	€ 18,087.16
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: 1 February 2021

Other services covered by SHI funds:

Designation of the 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 whose response to previous therapy with disease-modifying biological anti-rheumatic drugs (bDMARDs) has been inadequate or who have not tolerated it.

Designation of the therapy	Annual treatment costs/patient
Medicinal product to be assessed:	
Secukinumab	€ 10,343.44–20,686.88
Appropriate comparator therapy:	
Adalimumab Additionally required SHI services Total	€ 11,510.06 € 180.64 € 11,690.70
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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 18 February 2021.

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

Berlin, 18 February 2021

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

Prof. Hecken