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Secukinumab (psoriatic arthritis) –

Addendum to Commission A20-80[1]

Addendum

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Table of contents

List of tables

Page

List of abbreviations

Abbreviation	Meaning
AE	adverse event
DLQI	Dermatology Life Quality Index
EQ-5D	European Quality of Life-5 Dimensions
FACIT	Functional Assessment of Chronic Illness Therapy-Fatigue
G-BA	Gemeinsamer Bundesausschuss (Federal Joint Committee)
HAQ-DI	Health Assessment Questionnaire-Disability Index
IQWiG	Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen (Institute for Quality and Efficiency in Health Care)
MCS	Mental Component Summary
PASDAS	Psoriatic Arthritis Disease Activity Score
PatGA	Patient Global Assessment of Disease Activity
PCS	Physical Component Summary
SF-36	Short Form (36) Health Survey
VAS	visual analogue scale

1 Background

On 12 January 2021, the Federal Joint Committee (G-BA) commissioned the Institute for Quality and Efficiency in Health Care (IQWiG) to conduct supplementary assessments for Commission A20-80 (Secukinumab – Benefit assessment according to §35a Social Code Book V) [1].

The dossier assessment used the EXCEED study [2-4], which included adult patients with active psoriatic arthritis and concomitant diagnosis of active plaque psoriasis. Of this study, the subpopulation of patients with concomitant moderate to severe plaque psoriasis was relevant for the benefit assessment to Commission A20-80, as the secukinumab dosage of 300 mg by subcutaneous injection used in the study complies with the approval [5] only for this subpopulation.

Analyses of various patient-reported outcomes on symptoms and health-related quality of life were used in the dossier assessment. In its dossier as well as in the follow-up to the oral hearing [6,7], the pharmaceutical company (hereinafter referred to as "the company") presented responder analyses for these outcomes, in particular those in which a response threshold of 15% of the scale range of the respective instrument is used. In addition, the company corrected erroneous information on study and treatment discontinuation due to adverse events (AEs) in its comments [8].

The G-BA therefore commissioned IQWiG with the assessment of the following analyses presented by the company in the commenting procedure under consideration of the information provided in the dossier:

- responder analyses on the Short Form (36) Health Survey (SF-36) with an improvement of ≥ 5 points
- responder analyses on the Functional Assessment of Chronic Illness Therapy-Fatigue (FACIT-Fatigue) with an improvement of ≥ 4 points
- responder analyses with a response threshold of 15% (of the scale range)
- data corrected by the company in the comments regarding the AEs that led to study discontinuation

The responsibility for the present assessment and the assessment result lies exclusively with IQWiG. The assessment is forwarded to the G-BA. The G-BA decides on the added benefit.

2 Assessment

2.1 Responder analyses

With reference to IQWiG's General Methods 6.0 [9], the responder analyses on physical functioning (Health Assessment Questionnaire-Disability Index [HAQ-DI], improvement of ≥ 0.35 points), fatigue (FACIT-Fatigue, improvement of ≥ 4 points) and health-related quality of life (SF-36, improvement of ≥ 5 points) presented by the company in Module 4 B of the dossier were not used for benefit assessment A20-80. According to these methods, for a response criterion to reflect with sufficient certainty a patient-noticeable change, it has to correspond to at least 15% of the scale range of an instrument if prespecified (exactly 15% of the scale range in post-hoc analyses).

Responder analyses with a response threshold of 15% of the scale range

Subsequent to the hearing, the company submitted responder analyses with a response threshold of 15% of the scale range for the above outcomes. The company additionally presented such analyses for further patient-reported outcomes of the EXCEED study.

In the following, the responder analyses submitted by the company are listed for the outcomes used in benefit assessment A20-80 [1], indicating the response threshold of 15% of the scale range in each case.

Patient-relevant outcomes with analyses for a response threshold of 15% of the scale range

Morbidity

- physical functioning (HAQ-DI):
  - proportion of patients with an improvement of ≥ 0.45 points
- health status (European Quality of Life-5 Dimensions [EQ-5D] visual analogue scale [VAS])
  - proportion of patients with improvement of ≥ 15 mm or points
- psoriatic arthritis-related pain (pain VAS)
  - proportion of patients with improvement of ≥ 15 mm or points
- patient-reported global disease activity (Patient Global Assessment of Disease Activity [PatGA] Psoriatic Arthritis Disease Activity Score [PASDAS] VAS)
  - proportion of patients with improvement of ≥ 15 mm or points
- fatigue (FACIT-Fatigue):
  - proportion of patients with an improvement of ≥ 7.8 points

Health-related quality of life

- generic health-related quality of life (SF-36):
  - Mental Component Summary (MCS): proportion of patients with an improvement of ≥ 9.6 points
  - Physical Component Summary (PCS): proportion of patients with an improvement of ≥ 9.4 points
- health-related quality of life (Dermatology Life Quality Index [DLQI])
  - patients with improvement of ≥ 4.5 points

The results of the analyses with a response threshold of 15% are used for the outcomes considered in benefit assessment A20-80 [1].

For the recording of health-related quality of life using the SF-36, it should be noted that the company determined the response threshold of 15% of the scale range for the normalized values of the sum scores (MCS and PCS) in 2 different ways, which it referred to as "scale in practice" and "theoretical scale". The response thresholds for the "scale in practice" method lead to response thresholds of 9.6 points for the PCS and 9.4 points for the PCS. The approach is consistent with the approach described in dossier assessment A20-90 [10] taking into account the observed values of a norm sample from 2009. From this, response thresholds of 10 points were derived for both sum scores. The analyses presented by the company were therefore relevant for the present assessment and were used. The approach according to the "theoretical scale" arrives at deviating response thresholds of 12.5 points for the MCS and 11.2 points for the PCS and, as described in A20-90, is based on minimizing and maximizing the PCS and MCS on the basis of the 2009 norm sample. A detailed explanation of this can be found in dossier assessment A20-90 [10]. The analyses according to the "theoretical scale" method are presented as supplementary information in Appendix B.

For the recording of health-related quality of life using the DLQI, a responder analysis of the proportion of patients with DLQI 0 or 1 at the end of the study, which was used to derive the added benefit of secukinumab, was available in benefit assessment A20-80. The analyses on the DLQI with a response threshold of 15% of the scale range submitted by the company with the comments [8] are presented in Table 4 in Appendix B. Both analyses consistently show no statistically significant difference between the treatment groups.

Risk of bias

For the risk of bias of the results for the patient-reported outcomes used here, the information provided by the company in the commenting procedure overall did not result in any change in comparison with benefit assessment A20-80 [1].

The results for the outcomes "physical functioning" (HAQ-DI) and "psoriatic arthritis-related pain" (pain VAS) have a high risk of bias due to the differing response rates to the questionnaires between the treatment arms in the course of the study.

There was a low risk of bias for the results of the following outcomes: patient-reported global disease activity (PatGA PASDAS VAS), health status (EQ-5D VAS), fatigue (FACIT-Fatigue), and health-related quality of life (SF-36).

Results of the analyses with a response threshold of 15% of the scale range

The results of the responder analyses with a response threshold of 15% of the scale range for the outcomes used in the benefit assessment are presented in Table 1.

Table 1: Results (morbidity and health-related quality of life, 15% response threshold) – RCT, direct comparison: secukinumab vs. adalimumab

Study Outcome category Outcome	Secukinumab		Adalimumab		Secukinumab vs. adalimumab
	N	Patients with event n (%)[a]	N	Patients with event n (%)[a]	RR [95% CI]; p-value[b]
EXCEED					
Morbidity					
Physical functioning (HAQ-DI)[c]	110	57.8 (52.6)	101	50.8 (50.3)	1.05 [0.80; 1.37]; 0.749
Health status (EQ-5D VAS)[d]	110	58.8 (53.5)	101	60.2 (59.6)	0.90 [0.70, 1.15]; 0.388
Psoriatic arthritis-related pain (pain VAS)[d]	110	74.5 (67.8)	101	71.4 (70.6)	0.96 [0.79; 1.16]; 0.671
Patient-reported global disease activity (PatGA PASDAS VAS)[d]	110	87.9 (79.9)	101	78.2 (77.4)	1.03 [0.89; 1.20]; 0.671
Fatigue (FACIT-Fatigue)[e]	110	55.9 (50.8)	101	44.5 (44.1)	1.15 [0.86; 1.55]; 0.351
Health-related quality of life					
SF-36					
Mental Component Summary (MCS)[f]	110	46.1 (41.9)	101	28.8 (28.5)	1.47 [0.99; 2.19]; 0.055
Physical Component Summary (PCS)[g]	110	42.8 (39.0)	101	37.9 (37.5)	1.04 [0.73; 1.49]; 0.834

a. Due to the multiple imputation of missing values, there is usually no whole number of patients with event.
b. Combining of RR, 95% CI and p-value across all imputation data sets using Rubin's rule.
c. Patients with improvement of ≥ 0.45 points (corresponds to 15% of the scale range).
d. Patients with improvement of ≥ 15 mm or points (corresponds to 15% of the scale range).
e. Patients with improvement of ≥ 7.8 points (corresponds to 15% of the scale range).
f. Patients with improvement of ≥ 9.6 points (corresponds to 15% of the scale range).
g. Patients with improvement of ≥ 9.4 points (corresponds to 15% of the scale range).

CI: confidence interval; EQ-5D: European Quality of Life-5 Dimensions; FACIT: Functional Assessment of Chronic Illness Therapy; HAQ-DI: Health Assessment Questionnaire-Disability Index; n.: number of patients with (at least one) event; N: number of analysed patients; PASDAS: Psoriatic Arthritis Disease Activity Score; PatGA: Patient Global Assessment of Disease Activity; RCT: randomized controlled trial; RR: relative risk; SF-36: Short Form (36) Health Survey; VAS: visual analogue scale; vs.: versus

Morbidity

Physical functioning (HAQ-DI), health status (EQ-5D VAS), psoriatic arthritis-related pain (pain VAS), patient-reported global disease activity (PatGA PASDAS VAS), fatigue (FACIT-Fatigue)

No statistically significant difference between treatment groups was shown for any of the following outcomes: physical functioning (HAQ-DI), health status (EQ-5D VAS), psoriatic arthritis-related pain (pain VAS), patient-reported global disease activity (PatGA PASDAS VAS), and fatigue (FACIT-Fatigue). In each case, this resulted in no hint of an added benefit of secukinumab in comparison with adalimumab; an added benefit is therefore not proven.

Health-related quality of life

No statistically significant difference between the treatment groups was shown for the health-related quality of life outcomes recorded with the MCS and PCS of the SF-36. In each case, this resulted in no hint of an added benefit of secukinumab in comparison with adalimumab; an added benefit is therefore not proven.

Summary

Overall, there was no statistically significant difference for any of the outcomes mentioned. The conclusion on the added benefit of secukinumab from dossier assessment A20-80 is therefore not changed.

Responder analyses on other response thresholds – FACIT-Fatigue and SF-36

As explained above, the responder analyses on fatigue (FACIT fatigue, improvement of ≥ 4 points) presented by the company in Module 4 B of the dossier are not relevant for the benefit assessment A20-80. In accordance with the commission, the results of these analyses are presented in Table 4 in Appendix A.

The same applies to the SF-36. The responder analyses on health-related quality of life (PCS and MCS of the SF-36, improvement of ≥ 5 points) presented by the company in Module 4 B of the dossier are not relevant for benefit assessment A20-80. In addition to responder analyses for the improvement of ≥ 5 points, the company also submitted analyses for the improvement of ≥ 2.5 points of the PCS and MCS in the commenting procedure. The results of both analyses are also presented in Table 4 in Appendix A.

2.2 Data corrected by the company in the comments regarding the AEs that led to study discontinuation

With its comments [8], the company submitted corrected tables on the individual AEs that led to study discontinuation and the individual AEs that led to treatment discontinuation. The corrections had resulted for the company from the check of the result tables after submission of the dossier.

In analogy to the dossier assessment, the AEs leading to treatment discontinuation are presented because, in the present case, these represent the outcome "discontinuation due to AEs" more comprehensively than the AEs leading to study discontinuation.

The results of AEs leading to treatment discontinuation are presented in Table 3 in Appendix A. With the corrected data, there was one additional event for patients in the adalimumab arm that led to treatment discontinuation. It is not clear from the company's comments whether this changed the overall rate of AEs leading to treatment discontinuation. However, this was of no consequence for benefit assessment A20-80, as even an increase in the total number of patients in the adalimumab arm by one event did not result in a statistically significant effect.

2.3 Summary

The data subsequently submitted by the company in the commenting procedure have not changed the conclusion on the added benefit of secukinumab from dossier assessment A20-80.

The following Table 2 shows the result of the benefit assessment of secukinumab under consideration of dossier assessment A20-80 and the present addendum.

Table 2: Secukinumab – probability and extent of added benefit

Research question	Subindication	ACT[a]	Probability and extent of added benefit
1	Alone or in combination with methotrexate in adult patients with active psoriatic arthritis who have responded inadequately to previous DMARD therapy[b, c]	A TNF-alpha antagonist (**adalimumab** or certolizumab pegol or etanercept or golimumab or infliximab) or an IL-17 inhibitor (ixekizumab), possibly in combination with methotrexate	Secukinumab alone in patients with concomitant moderate to severe plaque psoriasis: ▪ patients < 65 years: hint of a considerable added benefit[d] ▪ patients ≥ 65 years: added benefit not proven[e] Secukinumab in combination with methotrexate, or in patients without concomitant moderate to severe plaque psoriasis: ▪ added benefit not proven
2	Alone or in combination with methotrexate in adult patients with active psoriatic arthritis who have responded inadequately to previous bDMARD therapy[b]	Switch to another biologic disease-modifying antirheumatic (adalimumab or certolizumab pegol or etanercept or golimumab or infliximab or ixekizumab or ustekinumab), possibly in combination with methotrexate	Added benefit not proven

a. Presentation of the respective ACT specified by the G-BA. In cases where the company, because of the G-BA's specification of the ACT, could choose a comparator therapy from several options, the respective choice of the company is printed in **bold**.
b. According to the G-BA, the patient population considered for research questions 1 and 2 also includes patients who have not tolerated previous DMARD therapy.
c. The patient population considered for research question 1 consists of bDMARD-naive patients.
d. The added benefit results solely from an advantage in skin symptoms (PASI 100).
e. Depending on the data constellation, there may also be a lesser benefit of secukinumab.

ACT: appropriate comparator therapy; bDMARD: biologic DMARD; DMARD: disease-modifying antirheumatic drug; G-BA: Federal Joint Committee; IL: interleukin; PASI: Psoriasis Area and Severity Index; TNF: tumour necrosis factor

The G-BA decides on the added benefit.

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Appendix A – Results on the outcome "discontinuation due to AEs"

Table 3: Discontinuation due to AEs – RCT, direct comparison: secukinumab vs. adalimumab

Study	Patients with event n (%)	
SOC[a] PT[a]	Secukinumab N = 110	Adalimumab N = 101
EXCEED		
Musculoskeletal and connective tissue disorders	0 (0)	1 (1.0)
Intervertebral disc protrusion	0 (0)	1 (1.0)
Nervous system disorders	0 (0)	1 (1.0)
Paraesthesia	0 (0)	1 (1.0)
Skin and subcutaneous tissue disorders	1 (0.9)	2 (2.0)
Palmoplantar pustulosis	1 (0.9)	0 (0)
Psoriasis	0 (0)	2 (2.0)

a. MedDRA version: ND in Module 4 B; it is assumed that MedDRA version 22.0 was used (see [4]).

AE: adverse event; MedDRA: Medical Dictionary for Regulatory Activities; n: number of patients with at least one event; N: number of analysed patients; ND: no data; RCT: randomized controlled trial; vs.: versus

Appendix B – Results of the responder analyses on FACIT-Fatigue, SF-36 and DLQI

Table 4: Results (morbidity and health-related quality of life) – RCT, direct comparison: secukinumab vs. adalimumab

Study Outcome category Outcome	Secukinumab		Adalimumab		Secukinumab vs. adalimumab
	N	Patients with event n (%)[a]	N	Patients with event n (%)[a]	RR [95% CI]; p-value[b]
EXCEED					
Morbidity					
Fatigue (FACIT-Fatigue)[c]	110	72.5 (65.9)	101	61.5 (60.9)	1.08 [0.87; 1.34]; 0.469
Health-related quality of life					
SF-36					
2.5 points[d]					
Mental Component Summary (MCS)	110	77.7 (70.7)	101	59.1 (58.5)	1.21 [0.98; 1.49]; 0.080
Physical Component Summary (PCS)	110	80.4 (73.1)	101	73.6 (72.9)	1.00 [0.85; 1.19]; 0.972
5 points[e]					
Mental Component Summary (MCS)	110	68.5 (62.3)	101	45.3 (44.9)	1.39 [1.06; 1.83]; 0.018
Physical Component Summary (PCS)	110	66.9 (60.8)	101	62.1 (61.5)	0.99 [0.79; 1.24]; 0.929
12.5 points[f]					
Mental Component Summary (MCS)	110	36.7 (33.4)	101	22.9 (22.7)	1.47 [0.92; 2.34]; 0.104
11.2 points[g]					
Physical Component Summary (PCS)	110	31.5 (28.6)	101	32.4 (32.1)	0.89 [0.58; 1.37]; 0.604
DLQI[h]	110	77.0 (70.0)	101	72.4 (71.7)	0.98 [0.82; 1.17]; 0.801

a. Due to the multiple imputation of missing values, there is usually no whole number of patients with event.
b. Combining of RR, 95% CI and p-value across all imputation data sets using Rubin's rule.
c. Patients with improvement of ≥ 4 points.
d. Patients with improvement of ≥ 2.5 points.
e. Patients with improvement of ≥ 5 points.
f. Patients with improvement of ≥ 12.5 points (alternative calculation of the company for the response threshold of 15% of the scale range according to the "theoretical scale").
g. Patients with improvement of ≥ 11.2 points (alternative calculation of the company for the response threshold of 15% of the scale range according to the "theoretical scale").
h. Patients with improvement of ≥ 4.5 points (corresponds to 15% of the scale range).

CI: confidence interval; DLQI: Dermatology Life Quality Index; FACIT: Functional Assessment of Chronic Illness Therapy; n: number of patients with (at least one) event; N: Number of analysed patients; RCT: randomized controlled trial; RR: relative risk; SF-36: Short Form (36) Health Survey; vs.: versus