Gemeinsamer Bundesausschuss

Justification

of the Resolution of the Federal Joint Committee (G-BA) on an Amendment of the Pharmaceuticals Directive: Annex XII – Benefit Assessment of Medicinal Products with New Active Ingredients according to Section 35a SGB V Secukinumab (new therapeutic indication: enthesitis-related arthritis, ≥ 6 years)

of 5 January 2023

Contents

1. Legal basis

According to Section 35a paragraph 1 German Social Code, Book Five (SGB V), the Federal Joint Committee (G-BA) assesses the benefit of reimbursable medicinal products with new active ingredients. This includes in particular the assessment of the additional benefit and its therapeutic significance. The benefit assessment is carried out on the basis of evidence provided by the pharmaceutical company, which must be submitted to the G-BA electronically, including all clinical trials the pharmaceutical company has conducted or commissioned, at the latest at the time of the first placing on the market as well as the marketing authorisation of new therapeutic indications of the medicinal product, and which must contain the following information in particular:

1. approved therapeutic indications,
2. medical benefit,
3. additional medical benefit in relation to the appropriate comparator therapy,
4. number of patients and patient groups for whom there is a therapeutically significant additional benefit,
5. treatment costs for the statutory health insurance funds,
6. requirements for a quality-assured application.

The G-BA may commission the Institute for Quality and Efficiency in Health Care (IQWiG) to carry out the benefit assessment. According to Section 35a, paragraph 2 SGB V, the assessment must be completed within three months of the relevant date for submission of the evidence and published on the internet.

According to Section 35a, paragraph 3 SGB V, the G-BA decides on the benefit assessment within three months of its publication. The resolution is to be published on the internet and forms part of the Pharmaceuticals Directive.

2. Key points of the resolution

The active ingredient secukinumab (Cosentyx) was listed for the first time on 1 June 2015 in the "LAUER-TAXE®", the extensive German registry of available drugs and their prices.

On 20 June 2022, Cosentyx received marketing authorisation for a new therapeutic indication to be classified as a major type 2 variation as defined according to Annex 2, number 2, letter a to Regulation (EC) No. 1234/2008 of the European Commission of 24 November 2008 concerning the examination of variations to the terms of marketing authorisations for medicinal products for human use and veterinary medicinal products (OJ L 334, 12.12.2008, p. 7).

On 11 July 2022, the pharmaceutical company has submitted a dossier in accordance with Section 4, paragraph 3, No.2 Ordinance on the Benefit Assessment of Pharmaceuticals (AM-

NutzenV) in conjunction with Chapter 5, Section 8, paragraph 1, number 2 of the Rules of Procedure (VerfO) of the G-BA on the active ingredient secukinumab with the new therapeutic indication for the treatment of active enthesitis-related arthritis in patients 6 years and older in due time (i.e. at the latest within four weeks after informing the pharmaceutical company about the approval for a new therapeutic indication).

The G-BA commissioned the IQWiG to carry out the assessment of the dossier. The benefit assessment was published on the website of the G-BA (www.g-ba.de) on 17 October 2022, thus initiating the written statement procedure. In addition, an oral hearing was held.

The G-BA came to a decision on whether an additional benefit of secukinumab compared with the appropriate comparator therapy could be determined on the basis of the dossier of the pharmaceutical company, the dossier assessment prepared by the IQWiG, and the statements submitted in the written statement and oral hearing procedure. In order to determine the extent of the additional benefit, the G-BA has evaluated the data justifying the finding of an additional benefit on the basis of their therapeutic relevance (qualitative), in accordance with the criteria laid down in Chapter 5, Section 5, paragraph 7 VerfO. The methodology proposed by the IQWiG in accordance with the General Methods [1] was not used in the benefit assessment of secukinumab.

In the light of the above, and taking into account the statements received and the oral hearing, the G-BA has come to the following assessment:

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

2.1.1 Approved therapeutic indication of Secukinumab (Cosentyx) in accordance with the product information

Cosentyx, alone or in combination with methotrexate (MTX), is indicated for the treatment of active enthesitis-related arthritis in patients 6 years and older whose disease has responded inadequately to, or who cannot tolerate, conventional therapy.

Therapeutic indication of the resolution (resolution of 05.01.2023):

see new therapeutic indication according to marketing authorisation

[1] General Methods, version 6.1 from 24.01.2022. Institute for Quality and Efficiency in Health Care (IQWiG), Cologne.

2.1.2 Appropriate comparator therapy

The appropriate comparator therapy was determined as follows:

Patients 6 years and older with active enthesitis-related arthritis whose disease has responded inadequately to, or who cannot tolerate, conventional therapy

Appropriate comparator therapy for secukinumab, alone or in combination with methotrexate:

- Therapy according to doctor's instructions

Criteria according to Chapter 5, Section 6 of the Rules of Procedure of the G-BA:

The appropriate comparator therapy must be an appropriate therapy in the therapeutic indication in accordance with the generally recognised state of medical knowledge (Section 12 SGB V), preferably a therapy for which endpoint studies are available and which has proven its worth in practical application unless contradicted by the guidelines under Section 92, paragraph 1 SGB V or the principle of economic efficiency.

In determining the appropriate comparator therapy, the following criteria, in particular, must be taken into account as specified in Chapter 5, Section 6, paragraph 3 VerfO:

1. To be considered as a comparator therapy, the medicinal product must, principally, have a marketing authorisation for the therapeutic indication.
2. If a non-medicinal treatment is considered as a comparator therapy, this must be available within the framework of the SHI system.
3. As comparator therapy, medicinal products or non-medicinal treatments for which the patient-relevant benefit has already been determined by the G-BA shall be preferred.
4. According to the generally recognised state of medical knowledge, the comparator therapy should be part of the appropriate therapy in the therapeutic indication.

Justification based on the criteria set out in Chapter 5, Section 6, paragraph 3 VerfO:

On 1. In the therapeutic indication, glucocorticoids as well as non-steroidal anti-inflammatory drugs (NSAIDs) and classical disease-modifying antirheumatic drugs (cDMARDs; in this case sulfasalazine and, in polyarthritic JIA, also MTX) are approved for the treatment of juvenile idiopathic arthritis (JIA).

In the present therapeutic indication for the treatment of patients with active enthesitis-related arthritis whose disease has responded inadequately to, or who cannot tolerate, conventional therapy , the TNF-alpha inhibitors adalimumab (6 years and older) and etanercept (12 years and older) are approved.

On 2. Non-medicinal measures at the expense of the SHI are not considered as sole appropriate comparator therapy in the present therapeutic indication.

On 3. In the therapeutic indication of the enthesitis-related arthritis under consideration here, no resolutions of the G-BA are available.

On 4. The generally recognised state of medical knowledge was illustrated by a systematic search for guidelines as well as reviews of clinical studies in the present therapeutic indication.

The scientific-medical societies and the Drugs Commission of the German Medical Association (AkdÄ) were also involved in writing on questions relating to the comparator therapy in the present therapeutic indication according to Section 35a, paragraph 7 SGB V.

For the treatment of patients 6 years and older with enthesitis-related arthritis, it can first be stated that different diseases are distinguished within the JIA indication; enthesitis-related arthritis represents one of these subtypes, usually without a polyarticular course.

In view of the fact that JIA (also including enthesis-related arthritis) is usually diagnosed at an age ≤ 16 years and that JIA (e.g., in demarcation from rheumatoid arthritis diagnosed in advanced adulthood) is an independent clinical picture, the therapeutic indication to be assessed here includes patients 6 years of age and older - including children, adolescents and also adults with a corresponding diagnosis of JIA in childhood or adolescence.

The German guideline on juvenile idiopathic arthritis (S2k guideline of the DGKJ and GKJR from 2019) also takes enthesis-related arthritis into account in parts, but references are mainly made to evidence from pJIA. In the overall assessment, the guideline recommends the use of cDMARDs especially for the treatment of enthesis-related arthritis after failure of (symptomatic) NSAIDs and, if necessary, short-term use of glucocorticoids. If there is an inadequate response or intolerance to cDMARDs, the guideline advocates the use of TNFα inhibitors. The TNF-alpha inhibitors adalimumab and etanercept are approved for the treatment of active enthesis-related arthritis in patients who have had an inadequate response or intolerance to conventional therapy. The specific value of MTX in combination with a TNFα inhibitor in cases of inadequate response or intolerance to cDMARDs within enthesis-related arthritis cannot be assessed at present.

The G-BA assumed for the patient population covered by the marketing authorisation with insufficient response to previous treatment with a conventional therapy that these patients are not (or no longer) eligible for sole (symptomatic) conventional therapy with NSAIDs and/or glucocorticoids. Irrespective of this, the use of glucocorticoids (systemic and/or intra-articular) should always be possible in the context of flare therapy.

In the overall assessment, the G-BA considers therapy according to doctor's instructions to be appropriate for patients 6 years and older with active enthesitis-related arthritis whose disease has responded inadequately to, or who cannot tolerate, conventional therapy. In the context of a therapy according to doctor's instructions, the active ingredients adalimumab and etanercept are considered suitable comparators in the present therapeutic indication for patients 6 years and older.

The findings in Annex XII do not restrict the scope of treatment required to fulfil the medical treatment mandate.

A change in the appropriate comparator therapy requires a resolution by the G-BA linked to the prior review of the criteria according to Chapter 5, Section 6, paragraph 3 Rules of Procedure.

2.1.3 Extent and probability of the additional benefit

In summary, the additional benefit of secukinumab is assessed as follows:

For patients 6 years and older with active enthesitis-related arthritis whose disease has responded inadequately to, or who cannot tolerate, conventional therapy, the additional benefit of secukinumab compared with the appropriate comparator therapy has not been proven.

Justification:

Overall, there is no suitable study available for the target population under consideration, neither for a direct nor for an indirect comparison of secukinumab versus the appropriate comparator therapy.

The pharmaceutical company refers in the dossier to the approval study CAIN457F2304. This is a study in a withdrawal design, which deviates from the target population approved for secukinumab and investigates a patient population with treatment response. Thus, all patients in the study initially received treatment with secukinumab for 12 weeks, and only patients with an American College of Rheumatology (ACR)-30 response after 12 weeks of secukinumab treatment were randomised to the secukinumab or placebo group in the second phase of the study. In the second phase of the study, continuation was compared with discontinuation of secukinumab treatment in a patient population with prior response to secukinumab. Against this background, no indirect comparison with the appropriate comparator therapy was aimed at.

In the overall assessment, no data suitable for the benefit assessment are available. An additional benefit of secukinumab compared to the appropriate comparator therapy is therefore not proven.

2.1.4 Summary of the assessment

The present assessment is the benefit assessment of a new therapeutic indication for the active ingredient secukinumab.

The therapeutic indication assessed here is: Secukinumab alone or in combination with methotrexate (MTX), is indicated for the treatment of active enthesitis-related arthritis in patients 6 years and older whose disease has responded inadequately to, or who cannot tolerate, conventional therapy.

The appropriate comparator therapy was determined by G-BA to be a therapy according to doctor's instructions.

There is no suitable study available for the target population under consideration, neither for a direct nor for an indirect comparison of secukinumab versus the appropriate comparator therapy.

For the assessment of the additional benefit, the pharmaceutical company refers to the approval study CAIN457F2304 in randomised withdrawal design. No conclusions on the additional benefit of secukinumab compared to the appropriate comparator therapy can be derived from this study.

In the overall assessment, the additional benefit of secukinumab compared to the appropriate comparator therapy is not proven.

2.2 Number of patients or demarcation of patient groups eligible for treatment

The information on the number of patients is based on the target population in statutory health insurance (SHI).

The information is based on the data provided by the pharmaceutical company in the dossier. The data are limited to the number of patients in childhood and adolescence. The calculation of the size of the target population in the overall assessment is subject to uncertainty.

2.3 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 Cosentyx (active ingredient: secukinumab) at the following publicly accessible link (last access: 10 November 2022):

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

Treatment with secukinumab should only be initiated and monitored by doctors experienced in treating adults with enthesitis-related arthritis.

2.4 Treatment costs

The treatment costs are based on the contents of the product information and the information listed in the LAUER-TAXE® (last revised: 1 December 2022).

If no maximum treatment duration is specified in the product information, the treatment duration is assumed to be one year (365 days), even if the actual treatment duration is patient-individual and/or is shorter on average. The time unit "days" is used to calculate the "number of treatments/ patient/ year", time intervals between individual treatments and for the maximum treatment duration, if specified in the product information.

For the cost representation, only the dosages of the general case are considered. Patient-individual dose adjustments (e.g., because of side effects or comorbidities) are not taken into account when calculating the annual treatment costs.

In general, initial induction regimens are not taken into account for the cost representation, since the present indication is a chronic disease with a continuous need for therapy and, as a rule, no new titration or dose adjustment is required after initial titration.

For dosages depending on body weight, the average body measurements from the official representative statistics “Microcensus 2017 – body measurements of the population” were applied. The average body weight of a 6-year-old child is therefore 23.6 kg with an average height of 1.22 m. The average weight of a 17-year-old person is 67.0 kg with an average height of 1.74 m. This results in a body surface area of 0.9 m^2 for children aged 6 and 1.81 m^2 for 17-year-olds (calculated according to Du Bois 1916).

Treatment period:

Designation of the therapy	Treatment mode	Number of treatments/ patient/ year	Treatment duration/ treatment (days)	Treatment days/ patient/ year
Medicinal product to be assessed				
Secukinumab	Continuously, 1 x month	12.0	1	12.0
Methotrexate, if necessary	Continuously, 1 x every 7 days	52.1	1	52.1
Appropriate comparator therapy				
Therapy according to doctor's instructions	Different from patient to patient			

Consumption:

Designation of the therapy	Dosage/ application	Dose/ patient/ treatment days	Consumption by potency/ treatment day	Treatment days/ patient/ year	Annual average consumption by potency
Medicinal product to be assessed					
Secukinumab					
	Patients weighing below 50 kg				
	75 mg	75 mg	1 x 75 mg	12.0	12.0 x 75 mg
	Patients weighing above 50 kg				
	150 mg	150 mg	1 x 150 mg	12.0	12.0 x 150 mg
Methotrexate, if necessary					
	Children and adolescents				
	10 – 30 mg/m^2 BSA = 9 mg – 54.3 mg	9 mg – 55 mg	1 x 10 mg – 3 x 15 mg + 1 x 10 mg	52.1	52.1 x 10 mg – 156.3 x 15 mg + 52.1 x 10 mg
	Adults				
	7.5 mg - 20 mg[2]	7.5 mg - 20 mg	1 x 7.5 mg - 2 x 10 mg	52.1	52.1 x 7.5 mg - 104.2 x 10 mg
Appropriate comparator therapy					
Therapy according to doctor's instructions	Different from patient to patient				

[2] According to the product information, a weekly dose of 20 mg methotrexate should generally not be exceeded in adults.

Costs:

Costs of the medicinal products:

Designation of the therapy	Packaging size	Costs (pharmacy sales price)	Rebate Section 130 SGB V	Rebate Section 130a SGB V	Costs after deduction of statutory rebates
Medicinal product to be assessed					
Secukinumab 75 mg	1 SFI	€ 406.37	€ 1.77	€ 0.00	€ 404.60
Secukinumab 150 mg	6 SFI	€ 4,653.99	€ 1.77	€ 0.00	€ 4,652.22
Methotrexate 7.5 mg[3]	30 TAB	€ 33.71	€ 1.77	€ 1.77	€ 30.17
Methotrexate 10 mg[3]	30 TAB	€ 41.59	€ 1.77	€ 2.40	€ 37.42
Methotrexate 15 mg[3]	30 TAB	€ 57.75	€ 1.77	€ 3.68	€ 52.30
Appropriate comparator therapy					
Therapy according to doctor's instructions	Different from patient to patient				
Abbreviations: SFI = solution for injection, TAB = tablets, IFE = solution for injection in a pre-filled syringe					

LAUER-TAXE® last revised: 1 December 2022

Costs for additionally required SHI services:

Only costs directly related to the use of the medicinal product are taken into account. If there are regular differences in the necessary use of medical treatment or in the prescription of other services in the use of the medicinal product to be evaluated and the appropriate comparator therapy in accordance with the product information, the costs incurred for this must be taken into account as costs for additionally required SHI services.

Medical treatment costs, medical fee services, and costs incurred for routine examinations (e.g., regular laboratory services such as blood count tests) that do not exceed the standard expenditure in the course of the treatment are not shown.

Because there are no regular differences in the necessary use of medical treatment or in the prescription of other services in the use of the medicinal product to be evaluated and the appropriate comparator therapy in accordance with the product information, no costs for additionally required SHI services had to be taken into account.

[3] Fixed reimbursement rate

2.5 Medicinal products with new active ingredients according to Section 35a, paragraph 3, sentence 4 SGB V that can be used in a combination therapy with Secukinumab

According to Section 35a, paragraph 3, sentence 4, the Federal Joint Committee shall designate all medicinal products with new active ingredients that can be used in a combination therapy with the assessed medicinal product for the therapeutic indication to be assessed on the basis of the marketing authorisation under Medicinal Products Act.

In accordance with Section 2, paragraph 1, sentence 1 Ordinance on the Benefit Assessment of Pharmaceuticals (AM-NutzenV), only medicinal products containing active ingredients whose effects are not generally known in medical science at the time of initial marketing authorisation are to be considered within the framework of the designation of medicinal products with new active ingredients that can be used in a combination therapy. According to Section 2, paragraph 1, sentence 2 Ordinance on the Benefit Assessment of Pharmaceuticals (AM-NutzenV), a medicinal product with a new active ingredient is considered to be a medicinal product with a new active ingredient for as long as there is dossier protection for the medicinal product with the active ingredient that was authorised for the first time.

The designation of the combination therapies is based solely on the specifications according to Section 35a, paragraph 3, sentence 4. The G-BA does not conduct a substantive review based on the generally recognised state of medical knowledge. Thus, the designation is not associated with a statement as to the extent to which a therapy with the designated medicinal product with new active ingredient in combination with the medicinal product to be assessed corresponds to the generally recognised state of medical knowledge.

3. Bureaucratic costs calculation

The proposed resolution does not create any new or amended information obligations for care providers within the meaning of Annex II to Chapter 1 VerfO and, accordingly, no bureaucratic costs.

4. Process sequence

At its session on 7 May 2019, the Subcommittee on Medicinal Products determined the appropriate comparator therapy.

A review of the appropriate comparator therapy took place once the positive opinion was granted. The Subcommittee on Medicinal Products determined the appropriate comparator therapy at its session on 14 June 2022.

On 11 July 2022, the pharmaceutical company submitted a dossier for the benefit assessment of secukinumab to the G-BA in due time in accordance with Chapter 5, Section 8, paragraph 1, number 2, sentence 2 VerfO.

By letter dated 12 July 2022 in conjunction with the resolution of the G-BA of 1 August 2011 concerning the commissioning of the IQWiG to assess the benefit of medicinal products with new active ingredients in accordance with Section 35a SGB V, the G-BA commissioned the IQWiG to assess the dossier concerning the active ingredient secukinumab.

The dossier assessment by the IQWiG was submitted to the G-BA on 11 October 2022, and the written statement procedure was initiated with publication on the website of the G-BA on 17 October 2022. The deadline for submitting written statements was 7 November 2022.

The oral hearing was held on 21 November 2022.

In order to prepare a recommendation for a resolution, the Subcommittee on Medicinal Products commissioned a working group (Section 35a) consisting of the members nominated by the leading organisations of the care providers, the members nominated by the SHI umbrella organisation, and representatives of the patient organisations. Representatives of the IQWiG also participate in the sessions.

The evaluation of the written statements received and the oral hearing was discussed at the session of the subcommittee on 20 December 2022, and the proposed resolution was approved.

At its session on 5 January 2023, the plenum adopted a resolution to amend the Pharmaceuticals Directive.

Chronological course of consultation

Session	Date	Subject of consultation
Subcommittee Medicinal products	7 May 2019	Determination of the appropriate comparator therapy
Subcommittee Medicinal products	14 June 2022	Examination of the appropriate comparator therapy
Working group Section 35a	16 November 2022	Information on written statements received; preparation of the oral hearing
Subcommittee Medicinal products	21 November 2022	Conduct of the oral hearing
Working group Section 35a	30 November 2022 14 December 2022	Consultation on the dossier assessment by the IQWiG, assessment of the written statement procedure
Subcommittee Medicinal products	20 December 2022	Concluding discussion of the draft resolution
Plenum	5 January 2023	Adoption of the resolution on the amendment of Annex XII AM-RL

Berlin, 5 January 2023

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

Prof. Hecken