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) Tralokinumab (new therapeutic indication: atopic dermatitis, 12 to 17 years)

of 12 May 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 is part of the Pharmaceuticals Directive.

2. Key points of the resolution

The active ingredient tralokinumab (Adtralza) was listed for the first time on 15 July 2021 in the "LAUER-TAXE®", the extensive German registry of available drugs and their prices.

On 14 October 2022, Adtralza 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 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 10 November 2022, i.e. at the latest within four weeks after the notification of the pharmaceutical company of the approval of a new therapeutic indication, the pharmaceutical company has submitted a dossier in due time in accordance with Section 4, paragraph 3, number 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 tralokinumab with the new therapeutic indication (atopic dermatitis, 12 to < 18 years).

The G-BA commissioned the IQWiG to carry out the assessment of the dossier. The benefit assessment was published on 15 February 2023 on the G-BA website (www.g-ba.de), thus initiating the written statement procedure. In addition, an oral hearing was held.

The G-BA came to a resolution on whether an additional benefit of tralokinumab compared to 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 1was not used in the benefit assessment of tralokinumab.

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 Tralokinumab (Adtralza) in accordance with the product information

Adtralza is indicated for the treatment of moderate-to-severe atopic dermatitis in adult and adolescent patients 12 years and older who are candidates for systemic therapy.

Therapeutic indication of the resolution (resolution of 12 May 2023):

Treatment of moderate-to-severe atopic dermatitis in adolescents 12 to 17 years of age who are eligible for systemic therapy.

2.1.2 Appropriate comparator therapy

The appropriate comparator therapy was determined as follows:

Adolescents 12 to 17 years of age with moderate-to-severe atopic dermatitis who are candidates for continuous systemic therapy

Appropriate comparator therapy for tralokinumab:

Dupilumab (if necessary, in combination with topical glucocorticoids (TCS) and/or topical calcineurin inhibitors (TCI))

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

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. Besides tralokinumab, medicinal products with the following active ingredients are approved for the present therapeutic indication:

- topical glucocorticoids of classes 2 to 4
- pimecrolimus (moderate atopic eczema) and tacrolimus (moderate to severe atopic eczema)
- systemic glucocorticoids (severe eczema)
- ciclosporin (severe atopic dermatitis)
- antihistamines
- Dupilumab
- Upadacitinib

on 2. UV treatments (UVA/NB-UVB/balneophototherapy) are eligible as non-medicinal treatment, but UVA1 is ineligible as it is not a reimbursable treatment.

on 3. In the therapeutic indication under consideration here, the following resolutions of the G-BA are available:

- Therapeutic information on tacrolimus (resolution of 4 September 2003) and pimecrolimus (resolution of 4 September 2003)
- Resolution on the benefit assessment according to Section 35a SGB V for the active ingredient dupilumab dated 20 February 2020
- Resolution on the amendment of the Directive of Prescription of Medicinal Products in SHI-accredited Medical Care (MVV-RL): "Balneophototherapy for atopic eczema," dated 20 March 2020
- Resolution on the benefit assessment according to Section 35a SGB V for the active ingredient upadacitinib dated 17 February 2022

on 4. The generally recognised state of medical knowledge on which the resolution of the G-BA is based, was illustrated by a systematic search for guidelines as well as reviews of clinical studies in the present therapeutic indication.

According to the marketing authorisation, those patients are included in the therapeutic indication who are eligible for a systemic therapy.

For the present benefit assessment, adolescent patients with moderate-to-severe atopic dermatitis for whom continuous systemic therapy is indicated are considered, as the active ingredient tralokinumab is administered as a continuous therapy and is therefore only considered in adolescents for whom continuous systemic therapy is indicated.

For the present patient population of adolescents with moderate-to-severe atopic dermatitis eligible for continuous systemic therapy, the active ingredient dupilumab is available as further therapeutic alternative. Based on the benefit assessment resolution of 17 May 2018, dupilumab was able to show an indication of a considerable additional benefit compared with the appropriate comparator therapy in adults. By resolution of 20 February 2020, a non-quantifiable additional benefit of dupilumab for adolescents aged 12 to 17 years was also identified. In the overall assessment of the available evidence, dupilumab represents an adequate therapeutic alternative for patients with moderate-to-severe atopic dermatitis who are candidates for a continuous systemic therapy. Therefore, there is beneficial evidence for an active ingredient that has now also proven itself in practical application.

For the active ingredient upadacitinib, the G-BA identified considerable additional benefit in adults with moderate-to-severe atopic dermatitis who are candidates for a continuous systemic therapy and for whom 30 mg upadacitinib is the appropriate dose. However, no additional benefit could be identified for adolescents (as well as for adults, for whom 15 mg upadacitinib is the appropriate dosage) as only the lower dosage of 15 mg upadacitinib is approved for adolescents aged 12 years and older, and no direct comparator data were presented for this dosage. Therefore, upadacitinib is not determined to be appropriate comparator therapy for the present patient group.

Even with permanent or continuous systemic therapy, topical glucocorticoids (TCS) in classes 2 to 4 and the calcineurin inhibitor (TCI) tacrolimus may also be indicated as topical therapy options for individual lesions or in a limited period of time.

For patients for whom continuous systemic therapy is indicated, dupilumab (in combination with TCS and/or TCI if required) is the appropriate comparator therapy.

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

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 tralokinumab is assessed as follows:

Adolescents 12 to 17 years of age with moderate-to-severe atopic dermatitis who are candidates for continuous systemic therapy

The additional benefit is not proven for the treatment of moderate-to-severe atopic dermatitis in adolescents who are candidates for a continuous systemic therapy.

Justification:

No relevant study was identified for the assessment of the additional benefit of tralokinumab compared to the appropriate comparator therapy.

For the presentation of the medical benefit, the pharmaceutical company nevertheless submits the ECZTRA 6 study conducted in the therapeutic indication. However, it does not use this study to identify the additional benefit, but the results are merely presented additionally. The ECZTRA 6 study is comparing two different doses of tralokinumab with placebo in adolescents aged 12 years and older with moderate-to-severe atopic dermatitis. An initial 16-week treatment phase was followed by a re-randomisation of patients, depending on their response.

Due to the lack of comparison with the appropriate comparator therapy, the ECZTRA 6 study is assessed as unsuitable for evaluating the additional benefit of tralokinumab in the present therapeutic indication.

No suitable data are available for the assessment of the additional benefit of tralokinumab compared to the appropriate comparator therapy in adolescents 12 years and older with moderate-to-severe atopic dermatitis for whom continuous systemic therapy is an option. This does not provide any hint for an additional benefit of tralokinumab compared to the appropriate comparator therapy. An additional benefit is 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 tralokinumab. The therapeutic indication assessed here is as follows: Treatment of moderate-to-severe atopic dermatitis in adolescents 12 to 17 years of age who are eligible for systemic therapy.

The G-BA determined dupilumab (in combination with TCS and/or TCI if required) as the appropriate comparator therapy.

No relevant study was identified for the assessment of the additional benefit of tralokinumab compared to the appropriate comparator therapy. Therefore, no suitable data are available for the assessment of the additional benefit of tralokinumab compared to the appropriate comparator therapy in adolescents 12 years and older with moderate-to-severe atopic dermatitis for whom continuous systemic therapy is an option. This does not provide any hint for an additional benefit of tralokinumab compared to the appropriate comparator therapy. An additional benefit 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 from the resolution of the G-BA on dupilumab[2] in the therapeutic indication area of moderate-to-severe atopic dermatitis in adolescents who are eligible for systemic therapy. The patient numbers stated in the dupilumab procedure were estimated to be within a plausible range.

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 Adtralza (active ingredient: tralokinumab) at the following publicly accessible link (last access: 8 May 2023):

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

Discontinuation of treatment should be considered for patients who do not show a response after 16 weeks of treatment. Some patients with an initial partial response may continue to benefit from fortnightly treatment continued beyond 16 weeks.

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: .15 April 2023).

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 varies from patient to patient 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.

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.

Tralokinumab is indicated for the treatment of patients 12 years and older with moderate-to-severe atopic dermatitis and may be used in combination with topical corticosteroids and/or topical calcineurin inhibitors. Thus, if applicable, the corresponding costs for the combination medicinal products are incurred both for the medicinal product under assessment and for the appropriate comparator therapy and are not listed separately.

[2] Resolution of the G-BA on the benefit assessment of medicinal products with new active ingredients in accordance with Section 35a SGB V of 20 February 2020

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				
Tralokinumab	Continuously, every 14 days	26.1	1	26.1
	or			
	Continuously, every 28 days	13.0	1	13.0
Appropriate comparator therapy				
Dupilumab	Continuously, every 14 days	26.1	1	26.1

Consumption:

Designation of the therapy	Dosage/ application	Dose/ patient/ treatment days	Consumption by potency/ treatment day	Treatment days/ patient/ year	Average annual consumption by potency
Medicinal product to be assessed					
Tralokinumab	300 mg	300 mg	2 x 150 mg	13.0	26 x 150 mg
	or				
	300 mg	300 mg	2 x 150 mg	26.1	52.2 x 150 mg
Appropriate comparator therapy					
Dupilumab	200 mg	200 mg	1 x 200 mg	26.1	26.1 x 200 mg
	or				
	300 mg	300 mg	1 x 300 mg	26.1	26.1 x 300 mg

Costs:

In order to improve comparability, the costs of the medicinal products were approximated both on the basis of the pharmacy sales price level and also deducting the statutory rebates in accordance with Section 130 and Section 130a SGB V. To calculate the annual treatment costs, the required number of packs of a particular potency was first determined on the basis of consumption. Having determined the number of packs of a particular potency, the costs of the medicinal products were calculated on the basis of the costs per pack after deduction of the statutory rebates.

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					
Tralokinumab 150 mg	12 SFI	€ 4,208.95	€ 2.00	€ 406.43	€ 3,800.52
Appropriate comparator therapy					
Dupilumab 200 mg	6 SFI	€ 4,337.25	€ 2.00	€ 418.99	€ 3,916.26
Dupilumab 300 mg	6 SFI	€ 4,337.25	€ 2.00	€ 418.99	€ 3,916.26
Abbreviation: SFI = solution for injection					

LAUER-TAXE® last revised: 15 April 2023

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.

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 Tralokinumab

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 26 October 2021, the Subcommittee on Medicinal Products determined the appropriate comparator therapy.

On 10 November 2022, the pharmaceutical company submitted a dossier for the benefit assessment of tralokinumab to the G-BA in due time in accordance with Chapter 5, Section 8, paragraph 1, number 2 VerfO.

By letter dated 10 November 2022 in conjunction with the resolution of the G-BA of 1 August 2011 concerning the commissioning of the IQWiG to assess the benefits 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 tralokinumab.

The dossier assessment by the IQWiG was submitted to the G-BA on 27 January 2023, and the written statement procedure was initiated with publication on the G-BA website on 15 February 2023. The deadline for submitting statements was 9 March 2023.

The oral hearing was held on 27 March 2023.

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 3 May 2023, and the proposed resolution was approved.

At its session on 12 May 2023, the plenum adopted a resolution to amend the Pharmaceuticals Directive.

Chronological course of consultation

Session	Date	Subject of consultation
Subcommittee Medicinal products	26 October 2021	Determination of the appropriate comparator therapy
Working group Section 35a	22 March 2023	Information on written statements received; preparation of the oral hearing
Subcommittee Medicinal products	27 March 2023	Conduct of the oral hearing
Working group Section 35a	5 April 2023	Consultation on the dossier assessment by the IQWiG, assessment of the written statement procedure
Subcommittee Medicinal products	3 May 2023	Concluding discussion of the draft resolution
Plenum	12 May 2023	Adoption of the resolution on the amendment of Annex XII AM-RL

Berlin, 12 May 2023

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

Prof. Hecken