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 (atopic dermatitis)

of 6 January 2022

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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 of the medical product 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 relevant date for the first placing on the (German) market of the active ingredient tralokinumab in accordance with Chapter 5, Section 8, paragraph 1, number 1, sentence 2 of the Rules of Procedure of the G-BA (VerfO) is 15 July 2021. The pharmaceutical company submitted the final dossier to the G-BA in accordance with Section 4, paragraph 3, number 1 of the Ordinance on the Benefit Assessment of Pharmaceuticals (AM- NutzenV) in conjunction with Chapter 5, Section 8, paragraph 1, number 1 VerfO on 14 July 2021.

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 15 October 2021, 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 [1]was 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 patients who are candidates for systemic therapy.

Therapeutic indication of the resolution (resolution of 06.01.2022):

see therapeutic indication according to marketing authorisation.

2.1.2 Appropriate comparator therapy

The appropriate comparator therapy was determined as follows:

Adult patients with moderate-to-severe atopic dermatitis who are eligible for continuous systemic therapy

Appropriate comparator therapy:

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

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, in principle, have a marketing authorisation for the therapeutic indication.

[1] General Methods, version 6.0 from 05.11.2020. Institute for Quality and Efficiency in Health Care (IQWiG), Cologne.

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 Federal Joint Committee has already determined the patient-relevant advantage 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. 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

on 2. UV treatments (UVA/NB-UVB/balneophototherapy) are eligible as non-medicinal treatments, but UVA1 is not eligible 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)
- Resolutions on the benefit assessment according to Section 35a SGB V for the active ingredient dupilumab dated 17 May 2018 and 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," 20 March 2020

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, adult 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 adults for whom continuous systemic therapy is indicated.

For the present patient population of adults with moderate-to-severe atopic dermatitis eligible for continuous systemic therapy, the active ingredient dupilumab is available as further therapy option. 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. In the overall assessment of the available evidence, dupilumab represents an adequate therapeutic option for

patients with moderate-to-severe atopic dermatitis who are eligible for continuous systemic therapy. Therefore, there is beneficial evidence for an active ingredient that has now also proven itself in practical application.

In its resolution of 6 May 2021, the G-BA did not identify any additional benefit of baricitinib in patients with moderate-to-severe atopic dermatitis who are eligible for continuous systemic therapy, as no suitable data were available for a comparison with the appropriate comparator therapy. Upadacitinib has only recently received marketing authorisation for use in atopic dermatitis and is a new therapy option whose value cannot yet be assessed. Therefore, these two active ingredients are not found 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 (possibly in combination with TCS and/or TCI) is the appropriate comparator therapy.

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

2.1.3 Extent and probability of the additional benefit

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

Adult patients with moderate-to-severe atopic dermatitis who are eligible for continuous systemic therapy

For adult patients with moderate to severe atopic dermatitis who are eligible for continuous systemic therapy, the additional benefit for tralokinumab compared to the appropriate comparator therapy is not proven.

Justification:

For the assessment of the additional benefit of tralokinumab compared to the appropriate comparator therapy, the pharmaceutical company does not identify a direct comparative study. However, to illustrate the medical benefit, it presents the two placebo-controlled studies ECZTRA 3 and ECZTRA 7 conducted in the therapeutic indication. The pharmaceutical company does not derive any additional benefit from these. Against the background of the two studies, the pharmaceutical company states that it is conducting a systematic search for an indirect comparison between tralokinumab and the appropriate comparator therapy via the bridge comparator placebo. From this search, the pharmaceutical company says it first identifies two randomised controlled trials (study with tralokinumab: ECZTRA 7; study with dupilumab: CHRONOS), which it considers to be unsuitable after assessing the similarity of the patient population, concomitant medication and the available evaluation time points (ECZTRA 7 study: 26 weeks; CHRONOS study: 52 weeks). The pharmaceutical company states that it has refrained from presenting an indirect comparison for this reason. The pharmaceutical company, therefore, considers an additional benefit of tralokinumab compared to the appropriate comparator therapy to be not proven on the whole.

The procedure of the pharmaceutical company is comprehensible. The ECZTRA 3 and ECZTRA 7 studies are randomised, double-blind studies, investigating tralokinumab therapy in adult patients with moderate-to-severe atopic dermatitis who are eligible for systemic therapy. Placebo was used as comparator therapy in both studies. Thus, the appropriate comparator therapy dupilumab has not been implemented. In line with the assessment of the pharmaceutical company, the studies are therefore not suitable for assessing the additional benefit of tralokinumab compared to the appropriate comparator therapy.

Overall, the pharmaceutical company does not present any direct or indirect comparative evidence for the present question and does not derive any additional benefit compared to the appropriate comparator therapy.

No suitable data are available for the assessment of the additional benefit of tralokinumab compared to the appropriate comparator therapy in adult patients with moderate-to-severe atopic dermatitis for whom systemic therapy is an option. This does not provide any hint for an additional benefit of tralokinumab compared with the appropriate comparator therapy; an additional benefit is therefore not proven.

2.1.4 Summary of the assessment

The present assessment is the benefit assessment of the new medicinal product Adtralza with the active ingredient tralokinumab, which is approved for the treatment of "moderate-to-severe atopic dermatitis in adults who are eligible for systemic therapy".

Dupilumab (in combination with TCS and/or TCI if required) was determined by the G-BA as an appropriate comparator therapy.

In line with the assessment of the pharmaceutical company, no relevant study was identified by means of the completeness check for the assessment of the additional benefit of tralokinumab compared to the appropriate comparator therapy. Furthermore, the pharmaceutical company does not submit any data for the assessment of the additional benefit.

No suitable data are available for the assessment of the additional benefit of tralokinumab compared to the appropriate comparator therapy in adult patients with moderate-to-severe atopic dermatitis for whom systemic therapy is an option. This does not provide any hint for an additional benefit of tralokinumab compared with the appropriate comparator therapy; an additional benefit is therefore 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 adults who are eligible for systemic therapy.

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: 3 January 2022):

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: 1 December 2021).

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.

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 approved as such or in combination with topical corticosteroids and/or topical calcineurin inhibitors for the treatment of moderate-to-severe atopic dermatitis in adults. The active ingredient of the appropriate comparator therapy, dupilumab, can also be used both as part of a monotherapy and 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 therefore 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 17 May 2018

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	1 x every 28 days	13	1	13
	or			
	1 x every 14 days	26.1	1	26.1
Appropriate comparator therapy				
Dupilumab	1 x 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	Annual average consumption by potency
Medicinal product to be assessed					
Tralokinumab	300 mg	300 mg	2 x 150 mg	13	26 x 150 mg
	or				
	300 mg	300 mg	2 x 150 mg	26.1	52.2 x 150 mg
Appropriate comparator therapy					
Dupilumab	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 then 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	€ 4,337.01	€ 1.77	€ 244.41	€ 4,090.83
Appropriate comparator therapy					
Dupilumab 300 mg	6 SFI	€ 4,337.01	€ 1.77	€ 244.41	€ 4,090.83
Abbreviations: SFI = solution for injection					

LAUER-TAXE® last revised: 1 December 2021

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. 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 27 April 2021, the Subcommittee on Medicinal Products determined the appropriate comparator therapy.

On 14 July 2021, 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 1, sentence 2 VerfO.

By letter dated 14 July 2021 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 13 October 2021, and the written statement procedure was initiated with publication on the website of the G-BA on 15 October 2021. The deadline for submitting written statements was 5 November 2021.

The oral hearing was held on 22 November 2021.

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 21 December 2021, and the proposed resolution was approved.

At its session on 6 January 2022, the plenum adopted a resolution to amend the Pharmaceuticals Directive.

Chronological course of consultation

Session	Date	Subject of consultation
Subcommittee Medicinal product	27 April 2021	Determination of the appropriate comparator therapy
Working group Section 35a	16 November 2021	Information on written statements received; preparation of the oral hearing
Subcommittee Medicinal product	22 November 2021	Conduct of the oral hearing, if necessary: Commissioning of the IQWiG with the supplementary assessment of documents
Working group Section 35a	30 November 2021 14 December 2021	Consultation on the dossier assessment by the IQWiG, assessment of the written statement procedure
Subcommittee Medicinal product	21 December 2021	Concluding discussion of the draft resolution
Plenum	6 January 2022	Adoption of the resolution on the amendment of Annex XII AM-RL

Berlin, 6 January 2022

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

Prof. Hecken