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) Dupilumab (new therapeutic indication: atopic dermatitis, 6 months to 5 years)

of 21 September 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 dupilumab (Dupixent) was listed for the first time on 1 December 2017 in the "LAUER-TAXE®", the extensive German registry of available drugs and their prices.

On 15 March 2023, dupilumab 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, sentence 7).

On 29 March 2023, the pharmaceutical company has submitted a dossier 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 dupilumab with the new therapeutic

indication "Treatment of severe atopic dermatitis in children 6 months to 5 years of age who are candidates for systemic therapy" 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 dossier assessment. The benefit assessment was published on the G-BA website (www.g-ba.de) on 3 July 2023, 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 dupilumab 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 dupilumab.

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 Dupilumab (Dupixent) in accordance with the product information

Dupixent is indicated for the treatment of severe atopic dermatitis in children 6 months to 5 years old who are candidates for systemic therapy.

Therapeutic indication of the resolution (resolution of 21.09.2023):

See new therapeutic indication according to marketing authorisation.

2.1.2 Appropriate comparator therapy

The appropriate comparator therapy was determined as follows:

Children 6 months to 5 years of age with severe atopic dermatitis who are candidates for systemic therapy

Appropriate comparator therapy for dupilumab:

A patient-individual optimized therapy regime depending on the manifestation of the disease and taking into account the previous therapy, selecting the following therapies:

- topical glucocorticoids of classes 1 to 3
- Tacrolimus (topical)

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 and Section 6 para. 2 Ordinance on the Benefit Assessment of Pharmaceuticals (AM-NutzenV):

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.

According to Section 6, paragraph 2, sentence 2 Ordinance on the Benefit Assessment of Pharmaceuticals (AM-NutzenV), the determination of the appropriate comparator therapy must be based on the actual medical treatment situation as it would be without the medicinal product to be assessed. According to Section 6, paragraph 2, sentence 3 AM-NutzenV, the G-BA may exceptionally determine the off-label use of medicinal products as an appropriate comparator therapy or as part of the appropriate comparator therapy if it determines by resolution on the benefit assessment according to Section 7, paragraph 4 that, according to the generally recognised state of medical knowledge, this is considered a therapy standard in the therapeutic indication to be assessed or as part of the therapy standard in the medical treatment situation to be taken into account according to sentence 2, and

1. for the first time, a medicinal product approved in the therapeutic indication is available with the medicinal product to be assessed,
2. according to the generally recognised state of medical knowledge, the off-label use is generally preferable to the medicinal products previously approved in the therapeutic indication, or
3. according to the generally recognised state of medical knowledge, the off-label use for relevant patient groups or indication areas is generally preferable to the medicinal products previously approved in the therapeutic indication.

An appropriate comparator therapy may also be non-medicinal therapy, the best possible add-on therapy including symptomatic or palliative treatment, or monitoring wait-and-see approach.

Justification based on the criteria set out in Chapter 5, Section 6, paragraph 3 VerfO and Section 6, paragraph 2 AM-NutzenV:

on 1. Medicinal products with the following active ingredients are approved for the present therapeutic indication:

- topical glucocorticoids of classes 1 to 4
- Tacrolimus (moderate-to-severe atopic eczema 2 years and older)
- systemic glucocorticoids (severe eczema)
- antihistamines

on 2. UV treatments (UVA/NB-UVB/balneophototherapy) are eligible as non-medicinal treatments for atopic dermatitis, 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); repeal resolution of 17 August 2023 not yet in force
- Resolutions on the benefit assessment according to Section 35a SGB V for the active ingredient dupilumab dated 17 May 2018, 20 February 2020 and 1 July 2021
- 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

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. In particular, the recently updated S3 guideline "Atopic Dermatitis"[2]was taken into account.

Topical glucocorticoids of classes 1 to 3 and the calcineurin inhibitor tacrolimus (0.03%) are available as topical therapy options for a patient-individual optimized therapy regime. Class 4 topical glucocorticoids for children under 12 years of age are not recommended in the guidelines and are only indicated in exceptional cases according to the marketing authorisation, there is a contraindication for children under 3 years of age. Therefore, these are not part of the appropriate comparator therapy.

Class 1 topical glucocorticoids are hereby determined for the first time as options of the appropriate comparator therapy within the framework of a patient-individually optimised treatment regimens. In the course of the written statement procedure, it became clear that class 1 topical glucocorticoids should also be available for children from 6 months to 5 years of age.

According to the S3 guideline "Atopic Dermatitis"[2] it is recommended using topical calcineurin inhibitors in case of non-response or contraindications of topical glucocorticoids. According to the guideline, the use of topical calcineurin inhibitors is particularly recommended for sensitive skin areas where the use of TCS is likely to be associated with side effects, or in areas where side effects from topical glucocorticoids have already occurred. Pimecrolimus is only approved for mild-to-moderate atopic dermatitis. Tacrolimus is only approved for children 2 years and older with moderate-to-severe atopic dermatitis. Thus, there is no approved topical calcineurin inhibitor available for children 6 months to less than 2 years of age with severe atopic dermatitis.

[2] Werfel T. et al. S3 guideline Atopic Dermatitis (AD) [Neurodermitis; atopic eczema]. 2023. [Accessed: 07.09.2023] https://register.awmf.org/assets/guidelines/013-027l_S3_Atopische-Dermatitis-AD-Neurodermitis-atopisches-Ekzem_2023-08.pdf

Tacrolimus has also been used in clinical studies in younger children with moderate-to-severe atopic dermatitis. These indications support the approach to be able to use tacrolimus in younger children with higher disease severity in the present therapeutic indication (severe atopic dermatitis). Therefore, in severely affected children, off-label use of tacrolimus may be a therapeutic alternative in the case of non-response or contraindications to topical glucocorticoids and after a critical benefit/risk assessment, even for children from 6 months to less than 2 years of age. Tacrolimus may therefore be preferable to therapy with topical glucocorticoids, particularly for sensitive skin areas where the use of topical corticosteroids is not an option, even in children from 6 months to under 2 years of age, Section 6, paragraph 2, sentence 3, number 3 Ordinance on the Benefit Assessment of Pharmaceuticals (AM-NutzenV).

The use of antihistamines is not recommended for the treatment of atopic dermatitis.

Systemic glucocorticoids are available as a systemic therapeutic alternative within the framework of an optimised treatment regimen. Such an application is usually done as a short-term flare therapy. Particularly due to the severe side effects, the long-term use of systemic glucocorticoids in children is not recommended, so that they are not determined as part of the appropriate comparator therapy.

Based on the available evidence, phototherapeutic treatment forms are not recommended for children under 12 years of age and are therefore not part of the appropriate comparator therapy.

In the case of the defined appropriate comparator therapy, it is assumed that a patient-individually optimised treatment regimen is used, depending on the manifestation of the disease and taking into account the previous therapy. In case of intolerance, other, alternative active ingredients are used. Particularly as atopic dermatitis is a disease with fluctuating symptomatology - including seasonal - the treatment has to be individually adapted. A specific therapy that is appropriate for all patients cannot be determined.

Therapy adjustment during flares must be distinguished from therapy adjustment during chronic phases. Therapy adjustment during an flare (e.g. short-term administration of systemic glucocorticoids) may be necessary. This would be regarded as a component of the patient-individually optimised treatment regimen within the scope of the therapeutic indication. In addition to the treatment of the flares, it should also be possible to adjust the therapy in the chronic phases.

In summary, for the treatment of severe atopic dermatitis in children aged 6 months to 5 years of age, a patient-individually optimised treatment regimen, taking into account class 1 to 3 topical glucocorticoids and topical tacrolimus, is determined as the appropriate comparator therapy for dupilumab.

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 dupilumab is assessed as follows:

a) Children from 6 months to 5 years of age with severe atopic dermatitis who are candidates for systemic therapy and whose clinical picture is sufficiently similar to that of adults

For the treatment of severe atopic dermatitis in children aged 6 months to 5 years of age who are eligible for systemic therapy and whose clinical picture is sufficiently similar to that of adults, there is a hint for a non-quantifiable additional benefit of dupilumab compared with the appropriate comparator therapy.

Justification:

The pharmaceutical company submits the studies CHRONOS and PRESCHOOL for the benefit assessment dossier.

The PRESCHOOL study is a 2-part study on dupilumab in patients 6 months to 5 years of age. Part A is an open-label phase II study and is not considered in the present benefit assessment. Part B is a randomised, double-blind, controlled study comparing dupilumab with placebo in children 6 months to 5 years of age with moderate-to-severe atopic dermatitis. In the study, a total of 162 patients were randomised in a 1:1 ratio to a treatment with dupilumab (N = 83) or placebo (N = 79). Patients with chronic dermatitis who had an inadequate response to topical therapies within 6 months prior to enrolment in the study were enrolled. The treatment duration was 16 weeks.

Patients received standardised background therapy with low potent topical glucocorticoids (TCS) on skin sites with active lesions, initiated 14 days prior to initiation of treatment with the study medication. At the doctor's discretion, low potent TCS could also be used 1 time daily on thin skin sites (e.g. skin, face, genital area). With an *Investigator's Global Assessment* (IGA) ≤ 2, the use of the low potent TCS was reduced to 3 times per week. If the skin was free of lesions (corresponding to an IGA = 0), the TCS were discontinued. If lesions reappeared, treatment was re-initiated with medium potent TCS. In the case of an IGA ≥ 3 or intolerable symptomatology under 1-time-daily treatment with low potent TCS, therapy could be escalated. A therapy escalation with medium or highly potent TCS (each 1 time daily), topical calcineurin inhibitors (TCI; at thin skin sites), systemic glucocorticoids as well as systemic non-steroidal immunosuppressants was called rescue therapy in the PRESCHOOL study and was only allowed from day 14.

In the PRESCHOOL study, there are limitations with regard to the implementation of the appropriate comparator therapy:

At the start of the study, no patient-individual decision was planned as to which therapy would have been optimum for the patient in the specific case at the start of the study. In the PRESCHOOL study, all children received a uniform background therapy with low potent TCS at the start of the study; therapy escalation to medium or highly potent TCS or tacrolimus (topical) according to the appropriate comparator therapy was only permitted after day 14 without permanent therapy discontinuation and only if symptomatology is intolerable.

Furthermore, a treatment duration of 16 weeks is insufficient to assess long-term effects of dupilumab on the chronic inflammatory course of atopic dermatitis.

The PRESCHOOL study can therefore not be used to derive an additional benefit. Nevertheless, it is presented additionally, and consistent and large effects in terms of morbidity and quality of life are seen in the dupilumab arm at week 16.

CHRONOS study:

For the present procedure, the results of patients in the age stratum ≥ 18 to < 40 years with moderate-to-severe atopic dermatitis from the CHRONOS study are assessed. The CHRONOS study was already used in the early benefit assessments to assess the additional benefit of dupilumab compared to the appropriate comparator therapy in adults or adolescents with moderate-to-severe atopic dermatitis and children 6 to 11 years old with severe atopic dermatitis for whom systemic therapy is considered. This is a randomised, double-blind, controlled, multicentre phase 3 study comparing dupilumab in combination with TCS versus placebo in combination with TCS in adults. The study compared two different dupilumab doses (300 mg dupilumab 1 time per week (n = 319) or 300 mg dupilumab 1 time every two weeks (n = 106)) versus placebo + TCS (n = 315).

For a detailed description of the study characteristics of the already known CHRONOS study, see justification for the resolution on dupilumab of 17 May 2018.[3]

Transferability of data from adults is only possible to children whose clinical picture is sufficiently similar to that of adults. The clinical picture of atopic dermatitis is heterogeneous overall and the clinical presentation of early childhood atopic dermatitis differs from that of adults, particularly with regard to the occurrence of chronic lesions that are characteristic of the adult clinical picture. It is unclear how differences in the chronification and location of lesions affect the two patient populations. Eczema in infants and young children also differs from atopic dermatitis in older children and adults, particularly in terms of a higher remission rate. For this reason, in the present data constellation, a transfer is only possible to those children whose clinical picture is sufficiently similar to that of adults. It is true that there are molecular differences, e.g. in the cytokine concentrations in the blood, compared to adults. However, according to the current state of research, these differences are considered insufficient to fundamentally question the transferability of the results from adults to children from 6 months to 5 years of age. Furthermore, in the present data constellation, the transfer of data from adults to children (whose clinical picture is sufficiently similar to that of adults) is supported by the fact that no significant effect modification by age was observed in the CHRONOS study, and consistent and large effects were observed in the PRESCHOOL study across the different endpoints assessed in both studies (as well as in the studies AD-1526 with 12 to < 18-year-olds and AD-1652 with 6 to < 12-year-olds).

In terms of disease severity, the approved therapeutic indication for dupilumab differs between adults (moderate-to-severe atopic dermatitis) and children from 6 months to 5 years (severe atopic dermatitis). In the present situation, the age stratum ≥ 18 to < 40 years of the CHRONOS study is considered for the assessment, which includes both patients with severe and moderate atopic dermatitis. According to the classification of severity according to Eczema Area and Severity Index (EASI) and Scoring Atopic Dermatitis (SCORAD), the total population and the relevant age stratum of the CHRONOS study were predominantly (> 80%) affected by severe disease according to their own calculations based on mean values and standard deviations assuming a normal distribution. Because the CHRONOS study did not show any meaningful effect modifications by disease severity, the rendering of the results of the age stratum ≥ 18 to < 40 years with moderate to severe atopic dermatitis of the CHRONOS study to the target population of children 6 months to 5 years of age with severe atopic dermatitis, whose clinical picture sufficiently similar to that of adults, is not questioned.

[3] https://www.g-ba.de/downloads/40-268-4986/2018-05-17_AM-RL-XII_Dupilumab_D-328_TrG.pdf

Based on these arguments, the G-BA considers it justified in the present assessment to use the results of the age stratum of ≥ 18- to < 40-year-olds from the CHRONOS study for children aged 6 months to 5 years of age, whose clinical picture is sufficiently similar to that of adults.

Extent and probability of the additional benefit

Mortality

No deaths occurred in either relevant study arms up to week 52.

Morbidity

Morbidity is presented in the present assessment using itching (Peak Pruritus NRS), EASI, SCORAD, sleep disorder (SCORAD-VAS), patient-reported symptomatology (POEM), and health status (EQ-5D-VAS).

Itching (Peak Pruritus NRS)

Itching was assessed using the Peak Pruritus NRS scale, where a score of 0 corresponded to no itching and a score of 10 corresponded to the worst imaginable itching.
An improvement of ≥ 4 points by week 52 was observed. For the endpoint of itching, there was a statistically significant difference in the age stratum of ≥ 18 to < 40 years for the relevant sub-population of the CHRONOS study to the advantage of dupilumab compared to the appropriate comparator therapy.

Eczema Area and Severity Index (EASI 75 and EASI 90 Response)

In the German healthcare context, the EASI represents a standard tool for the classification of severity by doctors and is relevant for the diagnosis and monitoring of disease severity in health care. The EASI is used in conjunction with other tools to determine the severity of atopic dermatitis. The symptoms erythema, oedema/ papule formation, abrasions as well as lichenification of the skin are assessed by the doctor for each of the body regions head and neck, trunk, arms and legs with a score between 0 (absent) and 3 (very severe). The proportion of the body surface area affected is estimated by the principal investigator as a percentage of the total body surface area. Based on the evaluation of the symptoms and the assessment of the affected body surface area, an overall score is obtained. The EASI score can range from 0 (no evidence of atopic dermatitis) to 72.
The operationalisation of the EASI was based on the number of patients, who achieved a 90% (EASI 90) and 75% (EASI 75) improvement in EASI score from the start of the study to week 52, respectively.
An EASI 75 or EASI 90 response is considered patient-relevant. There is a statistically significant difference to the advantage of dupilumab for both response thresholds (EASI 75 and EASI 90) in the age stratum of ≥ 18 to < 40-year-olds.

Scoring Atopic Dermatitis (SCORAD)

The SCORAD is another established tool for assessing the severity of atopic dermatitis. It is made up of three components:

- Assessment of the areal extent of the skin changes by the doctor.
- Assessment of the intensity of skin changes for 6 symptoms (erythema, oedema/ papule formation, oozing/ crusting, skin abrasion, lichenification as well as dryness of non-affected skin) by the doctor
- Patient-reported survey of symptoms of insomnia and itching during the last 3 days or nights, each on a VAS from 0 (no symptoms) to 10 (most severe symptoms)

An overall score is calculated from the three components of the SCORAD. The SCORAD can assume values between 0 and 103.
Operationalisation of SCORAD was based on the number of patients who achieved 90% (SCORAD 90) and 75% (SCORAD 75) improvement in SCORAD score from the start of the study to week 52, respectively. The total score includes the symptoms of insomnia and itching. The evaluations of the SCORAD-VAS scale can be used for the endpoint of insomnia. No separate evaluations are available for the endpoint of itching.

SCORAD 75 and SCORAD 90

A SCORAD 75 or a SCORAD 90 response is considered patient-relevant. There is a statistically significant difference in the age stratum of ≥ 18 to < 40-year-olds for the response threshold SCORAD 75 to the advantage of dupilumab. The response threshold value SCORAD 90 shows no statistically significant difference between the treatment groups.

Sleep disorders (SCORAD-VAS)

Sleep disorders reported by patients are recorded using a visual analogue scale on which the patient assesses his or her sleep disorders at the time of measurement. For the mean change for the patient-relevant endpoint of sleep disorders, there was a statistically significant positive effect to the advantage of dupilumab. This is a clinically relevant effect.

Patient-reported symptomatology (POEM)

The POEM is a tool for recording the symptomatology of patients with atopic dermatitis. The questionnaire records the frequency of occurrence of 7 different symptoms (itching, sleep disorders, bleeding skin, oozing skin, cracked skin, scaly skin, dry/rough skin) within the previous week. The frequency is recorded and the total score is formed (values between 0 and 28). A high value corresponds to severe symptomatology. The mean change in POEM at week 52 compared to the start of the study will be used for the benefit assessment. For the mean change for patient-reported symptomatology, the age stratum of ≥ 18 to < 40-year-olds showed a statistically significant, clinically relevant, positive effect to the advantage of dupilumab + TCS compared with placebo + TCS.

Health status (VAS of EQ-5D)

Health status was assessed using the visual analogue scale (VAS) of the EQ-5D questionnaire. On this, the subject rates their health status on a scale from 0 (worst perceivable health status) to 100 (best perceivable health status). For the endpoint of health status (EQ-5D-VAS), there is no statistically significant difference between the treatment groups for the mean change at week 52 compared to the start of the study.

Quality of life

Dermatology Life Quality Index (DLQI)-Response

The DLQI is a validated questionnaire for the assessment of disease-specific health-related quality of life in adult patients with dermatological diseases. 10 items for 6 domains are recorded: Symptoms and well-being, daily activities, leisure time, work and school, personal relationships and treatment; the questionnaire is completed by the patient. Each item has 4 response categories ranging from 0 (not at all) to 3 (very strongly). A total score is then formed (values from 0 to 30). The lower the score, the better the health-related quality of life.

For the percentage of patients with a DLQI of 0 or 1, at week 52 there is a statistically significant advantage of dupilumab compared to placebo + TCS.

Side effects

Eye disorders (SOC) and broad CMQ conjunctivitis

For the endpoint of eye disorders, a statistically significant difference to the disadvantage of dupilumab compared to the comparator therapy is shown for the age stratum ≥ 18 to < 40 years.
In addition, broad CMQ conjunctivitis is considered. This endpoint includes 16 preferred terms (PTs) that represent the AE conjunctivitis more comprehensively than the SOC eye disorders. For the endpoint of conjunctivitis (broad CMQ), the results presented additionally for the total population at week 52 show a statistically significant difference to the disadvantage of dupilumab compared to the comparator therapy.
Overall, there is a statistically significant disadvantage of dupilumab compared to the comparator therapy for the endpoint of eye disorders (SOC).

Comments on the results of the PRESCHOOL study

Furthermore, the results of the CHRONOS study are clearly supported by the results of the PRESCHOOL study with children from 6 months to 5 years of age. This study investigates the correct patient population, which is thus covered by the therapeutic indication; however, there are limitations with regard to the implementation of the appropriate comparator therapy and the treatment duration of 16 weeks is inappropriate to assess the long-term effects of dupilumab on the chronic-inflammatory course of atopic dermatitis. However, the results in the verum arm of the study show large effects such as improvement in itching by ≥ 4 points in 53% of patients and improvement in EASI 75 in 64% of patients. The other morbidity endpoints such as SCORAD 75, POEM and the SCORAD VAS sleep disorders also showed consistent positive effects.
The European Medicines Agency based its extension of marketing authorisation for children 6 months to 5 years of age mainly on the PRESCHOOL study. In the context of the early benefit assessment according to Section 35a, this is insufficient in the view of the G-BA, as the treatment duration of the PRESCHOOL study of 16 weeks is too short to assess long-term effects of dupilumab on the chronic-inflammatory course of atopic dermatitis. Despite the heterogeneity in the clinical picture of atopic dermatitis in children 6 months to 5 years of age, it is justified in the view of the G-BA in the present assessment to transfer the results of the age stratum of the ≥ 18 to < 40-year-olds of the CHRONOS study to children 6 months to 5 years of age, whose clinical picture is sufficiently similar to that of adults. Nevertheless, the results of the evidence transfer are supported by the consistent and large effects in the dupilumab arm of the PRESCHOOL study.

Overall assessment

For the benefit assessment of dupilumab for the treatment of severe atopic dermatitis in children 6 months to 5 years of age who are eligible for systemic therapy and whose clinical picture is sufficiently similar to that of adults, mortality, morbidity, quality of life and side effects results are available from the CHRONOS study for the age stratum of ≥ 18 to < 40 years compared to placebo + TCS. A transfer of the evidence to children is possible since no significant effect modification by age was observed in the CHRONOS study, and consistent and large effects across the different endpoints were shown in the PRESCHOOL study at week 16.

In summary, the data presented show a statistically significant advantage in favour of dupilumab + TCS over placebo + TCS under the endpoint category of morbidity for symptoms of itching and sleep disorders, patient-reported symptomatology, and improvement in EASI score by 75% and 90%, respectively, and improvement in SCORAD score by 75%.
Similarly, in the endpoint category of quality of life, achieving a DLQI of 0 or 1 results in a statistically significant benefit to the advantage of dupilumab + TCS over placebo + TCS.
In the relevant age stratum, a negative effect is shown in the endpoint category of side effects, which is caused by the endpoint of eye disorders. This negative effect was not seen in the PRESCHOOL study presented additionally with patients of the target population. Overall, the negative effect in the endpoint of eye disorders in the relevant age stratum of the CHRONOS study does not call into question the positive effects of dupilumab. Thus, there are positive effects for morbidity and quality of life as well as a negative effect with regard to side effects. However, these negative effects do not call into question the positive effects of dupilumab.
Furthermore, these advantages of dupilumab shown in the age stratum of patients from ≥ 18 to < 40 years in the CHRONOS study are clearly supported by the results of the PRESCHOOL study.
In summary, for children aged 6 months to 5 years of age with severe atopic dermatitis who are eligible for systemic therapy and whose clinical picture is sufficiently similar to that of adults, there is a hint for a non-quantifiable additional benefit of dupilumab compared with the appropriate comparator therapy.

Reliability of data (probability of additional benefit)

The results of the age stratum ≥ 18 to < 40 years of the CHRONOS study were used for the assessment of the additional benefit in the patient group of children 6 months to 5 years of age with severe atopic dermatitis. Due to the limitations of the available evidence as well as the evidence transfer, a hint for a non-quantifiable additional benefit can be derived with regard to the reliability of data.

b) Children from 6 months to 5 years of age with severe atopic dermatitis who are candidates for systemic therapy and whose clinical picture is not sufficiently similar to that of adults

For the treatment of severe atopic dermatitis in children 6 months to 5 years of age who are eligible for systemic therapy and whose clinical picture is not sufficiently similar to that of adults, the additional benefit is not proven.

Justification:

For children from 6 months to 5 years of age with severe atopic dermatitis who are eligible for systemic therapy and whose clinical picture is not sufficiently similar to that of adults, transfer of the CHRONOS study results is not possible (see study description for patient population a). The clinical picture of atopic dermatitis is heterogeneous overall and the clinical presentation of early childhood atopic dermatitis differs from that of adults, particularly with regard to the occurrence of chronic lesions that are characteristic of the adult clinical picture. Eczema in infants and young children also differs from atopic dermatitis in older children and adults, particularly in terms of a higher remission rate. In the PRESCHOOL study, only about 7% of the children were younger than 2 years at the start of the study. In addition, the duration of disease was at least 3 years in 65% of the children enrolled. It can therefore be assumed that the majority of the study population already had chronic atopic dermatitis or chronic lesions.

However, there were also children with atopic dermatitis that had only been present for a short time (duration of disease 0 years), in whom the illness had not yet become chronic. It is unclear how high this percentage is. In contrast, only adults with chronic atopic dermatitis were enrolled in the CHRONOS study. It is unclear how differences in the chronification and location of lesions affect the two patient populations. For this reason, in the present data constellation, a transfer is only possible to those children whose clinical picture is sufficiently similar to that of adults. For children from 6 months to 5 years of age with severe atopic dermatitis who are eligible for systemic therapy and whose clinical picture is not sufficiently similar to that of adults, an additional benefit of dupilumab is thus 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 dupilumab. The therapeutic indication assessed here is as follows: "Treatment of severe atopic dermatitis in children 6 months to 5 years of age who are eligible for systemic therapy."

In the therapeutic indication under consideration, two patient groups were distinguished, depending on the comparability of the clinical picture with that of adults. As appropriate comparator therapy, the G-BA determined a patient-individually optimised treatment regimen, depending on the manifestation of the disease and under consideration of the previous therapy, under selection of topical glucocorticoids of the classes 1 to 3 and tacrolimus (topical). For the assessment of additional benefit, results from the CHRONOS study (age range ≥ 18 to < 40 years), supported by the results from the dupilumab arm of the PRESCHOOL study (children 5 months to 6 years of age) are available.

Patient group a):

For the benefit assessment of dupilumab for the treatment of severe atopic dermatitis in children 6 months to 5 years of age who are eligible for systemic therapy and whose clinical picture is sufficiently similar to that of adults, mortality, morbidity, quality of life and side effects results are available from the CHRONOS study for the age stratum of ≥ 18 to < 40-year-olds compared to placebo + TCS. A transfer of the evidence to children, whose clinical picture is sufficiently similar to that of adults, is possible since no significant effect modification by age was observed in the CHRONOS study, and consistent and large effects across the different endpoints were shown in the PRESCHOOL study at week 16.
In the morbidity endpoint category, there was a statistically significant advantage in favour of dupilumab for symptoms of itching and sleep disorders, patient-reported symptomatology and improvement in EASI score by 75% and 90%, respectively, and improvement in SCORAD score by 75%. In terms of quality of life, there is also a statistically significant advantage in favour of dupilumab when a DLQI of 0 or 1 is achieved. In contrast, there is a disadvantageous effect with regard to side effects. However, these negative effects do not call into question the positive effects of dupilumab.
Furthermore, these advantages of dupilumab shown in the age stratum of patients from ≥ 18 to < 40 years in the CHRONOS study are clearly supported by the results of the PRESCHOOL study.
In summary, for children aged 6 months to 5 years of age with severe atopic dermatitis who are eligible for systemic therapy and whose clinical picture is sufficiently similar to that of adults, there is a hint for a non-quantifiable additional benefit of dupilumab compared with the appropriate comparator therapy.

Patient group b):

For children from 6 months to 5 years of age with severe atopic dermatitis who are eligible for systemic therapy and whose clinical picture is not sufficiently similar to that of adults, transfer of the CHRONOS study results is not possible. The clinical picture of atopic dermatitis is heterogeneous overall and the clinical presentation of early childhood atopic dermatitis differs from that of adults, particularly with regard to the occurrence of chronic lesions that are characteristic of the adult clinical picture. Eczema in infants and young children also differs from atopic dermatitis in older children and adults, particularly in terms of a higher remission rate. In the PRESCHOOL study, only about 7% of the children were younger than 2 years at the start of the study. In addition, the duration of disease was at least 3 years in 65% of the children enrolled. It can therefore be assumed that the majority of the study population already had chronic atopic dermatitis or chronic lesions. However, there were also children with atopic dermatitis that had only been present for a short time in whom the illness had not yet become chronic. It is unclear how high this percentage is. In contrast, only adults with chronic atopic dermatitis were enrolled in the CHRONOS study. It is unclear how differences in the chronification and location of lesions affect the two patient populations. For this reason, in the present data constellation, a transfer is only possible to those children whose clinical picture is sufficiently similar to that of adults. For children from 6 months to 5 years of age with severe atopic dermatitis who are eligible for systemic therapy and whose clinical picture is not sufficiently similar to that of adults, an additional benefit of dupilumab is thus not proven.

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

The number of patients is the target population in statutory health insurance (SHI). The information is based on data provided by the pharmaceutical company in the dossier. The number of patients in the SHI target population is subject to uncertainties, especially due to the operationalisation of the severity, but is in a plausible order of magnitude.

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 Dupixent (active ingredient: dupilumab) at the following publicly accessible link (last access: 7 September 2023):

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

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 September 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.

Only proprietary prescription medicinal products were included in the cost representation. In the topical treatment with glucocorticoids frequently formulations are used which have not been considered here.

Topical therapy options are used on a patient-individual basis depending on the manifestation and localisation of the disease. In particular, the therapy is adapted to the patient-individual occurrence of the flares, so that the treatment duration is patient-individual.

As an example, one active ingredient each of the topical glucocorticoids class I (prednisolone), class II (hydrocortisone butyrate) and class III (methylprednisolone) is presented.

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				
Dupilumab	Continuously, 1 x every 28 days	13.0	1	13.0
Appropriate comparator therapy				
Topical glucocorticoids of classes 1 to 3 or tacrolimus (topical)				
Prednisolone	1 x daily for 2 weeks		Different from patient to patient	
Hydrocortisone butyrate	1-2 x daily for 1-2 weeks		Different from patient to patient	
Methylprednisolone	1 x daily for 2 weeks		Different from patient to patient	
Tacrolimus	1 x daily – 2 x weekly		Different from patient to patient	

Consumption:

For dosages depending on body weight, the average body measurements from the official representative statistics "Microcensus 2017 – body measurements of the population"[4] were applied (average body weight of 7.6 kg for children below one year of age and of 20.8 kg for 5-year-old children).

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					
Dupilumab	< 15 kg: 200 mg	200 mg	1 x 200 mg	13.0	13 x 200 mg
	> 15 kg: 300 mg	300 mg	1 x 300 mg	13.0	13 x 300 mg
Appropriate comparator therapy					
Topical glucocorticoids of classes 1 to 3 or tacrolimus (topical)					
Prednisolone		Different from patient to patient			
Hydrocortisone butyrate		Different from patient to patient			
Methylprednisolone		Different from patient to patient			
Tacrolimus		Different from patient to patient			

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.

[4] Federal Statistical Office, Wiesbaden 2018: http://www.gbe-bund.de/

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					
Dupilumab 200 mg	6 SFI	€ 3,990.65	€ 2.00	€ 385.05	€ 3,603.60
Dupilumab 300 mg	6 SFI	€ 3,990.65	€ 2.00	€ 385.05	€ 3,603.60
Appropriate comparator therapy					
Prednisolone[5]	100 CRE	€ 20.49	€ 2.00	€ 0.73	€ 17.76
0.1% hydrocortisone butyrate (topical)[5]	100 CRE	€ 27.01	€ 2.00	€ 1.24	€ 23.77
0.1% methylprednisolone (topical)[5]	100 EMU	€ 27.01	€ 2.00	€ 1.24	€ 23.77
0.03% tacrolimus (topical)	60 SAL	€ 94.41	€ 2.00	€ 7.89	€ 84.52
Abbreviations: CRE = cream; EMU= emulsion; SFI = solution for injection; UNG = unguentum (ointment)					

LAUER-TAXE® last revised: 1 September 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.

[5] Fixed reimbursement rate

2.5 Designation of 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 the assessed medicinal product

According to Section 35a, paragraph 3, sentence 4, the G-BA designates 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 30 March 2022, the Subcommittee on Medicinal Products determined the appropriate comparator therapy.

On 29 March 2023, the pharmaceutical company submitted a dossier for the benefit assessment of dupilumab to the G-BA in due time in accordance with Chapter 5 Section 8, paragraph 1, number 2 VerfO.

By letter dated 30 March 2023 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 dupilumab.

The dossier assessment by the IQWiG was submitted to the G-BA on 28 June 2023, and the written statement procedure was initiated with publication on the G-BA website on 3 July 2023. The deadline for submitting statements was 24 July 2023.

The oral hearing was held on 8 August 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 12 September 2023, and the proposed resolution was approved.

At its session on 21 September 2023, the plenum adopted a resolution to amend the Pharmaceuticals Directive.

Chronological course of consultation

Session	Date	Subject of consultation
Subcommittee Medicinal products	30 March 2022	Determination of the appropriate comparator therapy
Working group Section 35a	1 August 2023	Information on written statements received; preparation of the oral hearing
Subcommittee Medicinal products	8 August 2023	Conduct of the oral hearing
Working group Section 35a	15 August 2023 5 September 2023	Consultation on the dossier assessment by the IQWiG, evaluation of the written statement procedure
Subcommittee Medicinal products	12 September 2023	Concluding discussion of the draft resolution
Plenum	21 September 2023	Adoption of the resolution on the amendment of the AM-RL

Berlin, 21 September 2023

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

Prof. Hecken