Annex 2 to agenda item 6.1.4

Gemeinsamer Bundesausschuss

Justification

of the Resolution of the Federal Joint Committee on an Amendment of the Pharmaceuticals Directive (AM-RL): Annex XII – Benefit Assessment of Medicinal Products with New Active Ingredients according to Section 35a SGB V Dupilumab (New Therapeutic Indication: atopic dermatitis, 6 to 11 years of age)

of 1 July 2021

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:

1st Approved therapeutic indications,

2nd Medical benefit,

3rd Additional medical benefit in relation to the appropriate comparator therapy,

4th Number of patients and patient groups for whom there is a therapeutically significant additional benefit,

5th Treatment costs for statutory health insurance funds,

6th 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 online 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 25 November 2020, 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 December 2008, p. 7).

On 16 December 2020, 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 "Dupixent is indicated for the treatment of severe atopic dermatitis in children 6 to 11 years old 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 assessment of the dossier. The benefit assessment was published on 1 April 2021 on the G-BA website (www.g-ba.de), thus initiating the written statement procedure. In addition, an oral hearing was also 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, the statements submitted in the written statement and oral hearing procedure, and the addenda to the benefit assessment prepared by the IQWiG. 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 to 11 years old who are candidates for systemic therapy.

Therapeutic indication of the resolution (resolution of 1 July 2021):

see new therapeutic indication according to marketing authorisation

2.1.2 Appropriate comparator therapy

The appropriate comparator therapy was determined as follows:

Children 6 to 11 years of age with severe atopic dermatitis who are candidates for systemic therapy

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

- Topical glucocorticoids of classes 2 to 3
- Tacrolimus (topical)

[1] General Methods, version 6.0 of 5.11.2020. Institute for Quality and Efficiency in Health Care (IQWiG), Cologne.

The authorisation status of the medicinal products must be taken into account.

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

- Topical glucocorticoids of classes 2 to 4
- pimecrolimus (moderate atopic dermatitis) and
- tacrolimus (moderate to severe atopic dermatitis)
- systemic glucocorticoids (severe dermatitis)
- 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)
- Resolution 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 systemical reviews and the therapy information of tacrolimus there are disadvantages regarding the efficacy of pimecrolimus compared to tacrolimus. Accordingly, the application of tacrolimus from the product classes of the topical calcineurin inhibitors is preferably recommended.

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

Topical glucocorticoids of classes 2 to 3 and the calcineurin inhibitor tacrolimus (0.03%) are available as topical therapy options for a patient-individual optimised therapy regime. Topical class 4 glucocorticoids are not recommended in the guidelines for children under 12 years of age and are only indicated in exceptional cases according to the marketing authorisation. Therefore, these are not part of the appropriate comparator therapy.

Systemic glucocorticoids are available as a systemic therapy option within an optimised therapy regime. Such an application is usually carried out 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 comparative 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 comparative therapy.

In the case of the defined appropriate comparative therapy, it is assumed that a therapy regime patient-individual optimised is used, depending on the severity 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 a flare (e.g. short-term administration of systemic glucocorticoids) may be necessary. This would be regarded as a component of the patient-individual optimised therapy regime 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 to 11 years, a patient-individual optimised therapy regime taking into account topical glucocorticoids of classes 2 to 3 and topical tacrolimus is determined as the appropriate comparative therapy for dupilumab.

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 dupilumab is assessed as follows:

For the treatment of severe atopic dermatitis in children aged 6 to 11 years who are eligible for systemic therapy, there is hint of a non-quantifiable additional benefit of dupilumab compared with the appropriate comparator therapy.

Justification:

The pharmaceutical company submits the studies CHRONOS and AD-1652 for the benefit assessment.

Study AD-1652 (n=367) is a randomised, controlled, double-blind study comparing dupilumab with placebo in children aged 6 to 11 years with severe atopic dermatitis. The study included patients with chronic dermatitis for at least one year who had an inadequate response to topical therapies within 6 months prior to time of enrolment. The treatment duration was 16 weeks.

Patients received standardised background therapy with moderately potent topical glucocorticoids (TCS) on skin sites with active lesions, initiated 14 days prior to initiation of treatment with the study medication. At the discretion of the physician, low potency TCS could be used 1 time daily on areas with thin skin (e.g., skin, face, genital area) or on areas where continuous treatment with medium potency TCS is considered unsafe. Topical treatment with tacrolimus was not allowed during treatment with the study medication. With an *Investigator's global assessment* (IGA) ≤ 2, the use of medium potency TCS was reduced to 3 times per week. When the skin was free of lesions (corresponding to an IGA = 0), TCS were discontinued. If lesions reappeared, treatment was reinitiated with medium potent TCS. In the case of an IGA = 4 or intolerable symptomatology under 1-times-daily treatment with medium potent TCS, therapy could be escalated. An escalation of therapy with highly potent TCS (1 time daily each), systemic glucocorticoids as well as systemic non-steroidal immunosuppressants were called rescue therapy in the AD-1652 study.

In the AD-1652 study, there are limitations with regard to the implementation of the appropriate comparator therapy:

At the beginning of the study, no patient-individual decision was made as to which therapy would have been optimal for the individual patient at the start of the study. Furthermore, topical treatment with tacrolimus as part of the appropriate comparator therapy was not allowed during treatment with the study medication.

Additionally, a treatment duration of 16 weeks is not suitable to make statements on the additional benefit of Dupilumab as long-term treatment in the chronically running as well as seasonally fluctuating atopical dermatitis.

Therefore, in the view of the G-BA, the AD-1652 study cannot be used to determine an additional benefit. Nevertheless, it is presented in a complementary fashion, 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 evaluated.

The CHRONOS study (n=740) is a randomised, double-blind, controlled, multicentre phase 3 study comparing dupilumab in combination TCS versus placebo in combination TCS in adults. The study will compare 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.[2]

As IQWiG also states in its benefit assessment, transferability of the data from adults to children is possible in the therapeutic indication of atopic dermatitis, as pathogenesis and disease onset are sufficiently similar in children and adults, no significant effect modification by age was observed in the CHRONOS study, and consistent and large effects were observed across the different endpoints assessed in both studies in the AD-1652 study.

In terms of disease severity, the approved therapeutic indication for dupilumab differs between adults (moderate to severe atopic dermatitis) and children 6 to 11 years of age (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 overall 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 to 11 years with severe atopic dermatitis is not questioned.

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 to 11 years.

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 pruritus (Peak Pruritus NRS), EASI, SCORAD, sleep disorder (SCORAD-VAS), patient-reported symptomatology (POEM), and health status (EQ-5D-VAS).

Pruritus (Peak Pruritus NRS)

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

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

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

In the German health care context, the EASI represents a standard instrument 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 instruments to determine the severity of atopic dermatitis. The symptoms erythema, oedema / papule formation, abrasions as well as lichenification of the skin are evaluated by the physician for each of the body regions head and neck, trunk, arms and legs with a score between 0 (not present) 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, 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 baseline to week 52, respectively. An EASI 75 or EASI 90 response is considered patient-relevant. There is a statistically significant difference in favour 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 physician
- 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 baseline 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 insomnia. No separate evaluations are available for the endpoint 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 in favour of dupilumab. The response threshold SCORAD 90 shows no statistically significant difference between the treatment groups.

Sleep disorders (SCORAD-VAS)

Sleep disorders are recorded patient-reported by means of a visual analogue scale on which the patient assesses his sleep disorders at the time of measurement. For the mean change in the patient-relevant endpoint Sleep disturbance, there was a statistically significant positive effect in favour of dupilumab + TCS compared to placebo + TCS. This is a clinically relevant effect.

Patient reported symptomatology (POEM)

The POEM is an instrument for recording the symptoms of patients with atopic dermatitis. The questionnaire records the frequency of occurrence of 7 different symptoms (itching, sleep disturbances, 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 symptoms. The mean change in POEM at week 52 compared to baseline 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 in favour 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 person rates their state of health on a scale from 0 (worst conceivable health status) to 100 (best conceivable health status). For the endpoint Health status (EQ-5D-VAS), there is no statistically significant difference between the treatment groups for the mean change at week 52 compared to start of study.

<u>Quality of life</u>

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

Side effects

Eye disorders (SOC) and Narrow CMQ conjunctivitis

For the endpoint Ocular diseases, there was a statistically significant difference to the disadvantage of dupilumab compared to comparator therapy for the age stratum ≥ 18 to < 40 years.
Narrow CMQ conjunctivitis of the total population is observed additionally. This endpoint includes 5 preferred terms (PTs) that represent the AE Conjunctivitis more comprehensively than SOC Eye disorders. For the endpoint Conjunctivitis (narrow CMQ), the supplemental results for the overall population at week 52 show no statistically significant difference between treatment arms.
Overall, there is a statistically significant disadvantage of dupilumab compared to the comparator therapy for the endpoint Eye disorders (SOC).

Comments on the results of the AD-1652 study

Furthermore, the results of the CHRONOS study are clearly supported by the results of the AD-1652 study with children aged 6 to 11 years. In this study, the correct patient population, which is thus covered by the therapeutic indication, is investigated; however, there are limitations with regard to the implementation of the appropriate comparative therapy and the treatment duration of 16 weeks is inappropriate to make statements on the additional benefit of dupilumab as a long-term treatment in chronic and seasonally fluctuating atopic dermatitis. However, the results in the verum arm of the study show large effects such as improvement in itching in 62% of patients and improvement in EASI 75 in 72% of patients. The other morbidity endpoints such as SCORAD 75, POEM and the SCORAD VAS sleep disorders also showed consistent positive effects. In health-related quality of life measured by CDLQI, 30% of patients score 0 or 1.
The European Medicines Agency based its extension of marketing authorisation for children aged 6 to 11 years mainly on the AD-1652 study. In the context of the early benefit assessment according to Section 35a, this is not sufficient in the view of the G-BA, as the treatment duration of the study AD-1652 of 16 weeks is too short to assess long-term effects of dupilumab on the chronic-inflammatory course of atopic dermatitis. Due to the comparability of the pathogenesis and disease onset of atopic dermatitis in adults and children aged 6 to 11 years, the G-BA considers it justified 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 aged 6 to 11 years. Nevertheless, the results of the evidence transfer are supported by the consistent and large effects in the dupilumab arm of the AD-1652 study.

Overall assessment

For the benefit assessment of dupilumab for the treatment of severe atopic dermatitis in children 6 to 11 years of age who are eligible for systemic therapy, 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 with placebo + TCS. A transfer of the evidence to children is possible, because pathogenesis and disease onset are sufficiently similar in children and adults, 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 AD-1652 study at week 16.
In summary, the data presented show a statistically significant benefit in favour of dupilumab + TCS over placebo + TCS under the endpoint category Morbidity for symptoms of pruritus

and sleep disorders, patient-reported symptoms, and improvement in EASI score by 75% and 90%, respectively, and improvement in SCORAD score by 75%.
Similarly, in the endpoint category Quality of life, achieving a DLQI of 0 or 1 results in a statistically significant benefit in favour of dupilumab + TCS over placebo + TCS.
In the relevant age stratum, a negative effect is shown in the endpoint category Side effects, which is caused by the endpoint Eye disorders. This negative effect was not seen in the supplementary study AD-1652 with patients of the target population. Overall, the negative effect in the endpoint Ocular 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 benefits 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 AD-1652 study.
In summary, for children aged 6 to 11 years with severe atopic dermatitis eligible for systemic therapy, there is evidence of 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 to assess the additional benefit in the patient group 12 to < 18 years of age with moderate to 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.

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 to 11 years of age who are candidates for systemic therapy.

As appropriate comparator therapy, the G-BA determined a patient-individual optimised therapy regime consisting of topical and systemic therapy depending on the severity of the disease and under consideration of the previous therapy, under selection of topical glucocorticoids of the classes 2 to 3 and tacrolimus (topical). The authorisation status of the medicinal products must be taken into account.

The results of the age stratum ≥ 18 to < 40 years of the already known CHRONOS study were used for the assessment of the additional benefit in the patient group 6 to 11 years with severe atopic dermatitis. Thus, results are available for dupilumab + TCS compared to placebo + TCS on mortality, morbidity, quality of life and side effects. No deaths occurred in either relevant study arms up to week 52.

In summary, the data presented show a statistically significant benefit in favour of dupilumab + TCS over placebo + TCS under the endpoint category Morbidity for symptoms of pruritus and sleep disorders, patient-reported symptoms, and improvement in EASI score by 75% and 90%, respectively, and improvement in SCORAD score by 75%.

Similarly, in the endpoint category Quality of life, achieving a DLQI of 0 or 1 results in a statistically significant benefit in favour of dupilumab + TCS over placebo + TCS.

In the category of side effects, there are disadvantages for the treatment with dupilumab with regard to the endpoint Eye disorders, which, however, is not shown in the supplementary study AD-1652 with patients of the target population.

The benefits of dupilumab shown in the age stratum of patients from ≥ 18- to < 40 years in the CHRONOS study continue to be clearly supported by results from the AD-1652 study submitted by the pharmaceutical company.

In the overall view of the study results, the positive effects of dupilumab on morbidity and quality of life outweigh the disadvantage in side effects, which is why a hint for a non-quantifiable additional benefit is determined for dupilumab.

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 total SHI target population is 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 Dupixent (active ingredient: dupilumab) at the following publicly accessible link (last access: 4 May 2021):
https://www.ema.europa.eu/documents/product-information/dupixent-epar-product-information_de.pdf

In patients in whom no therapeutic benefit can be demonstrated after 16 weeks of treatment, discontinuation of treatment should be considered. Some patients with an initial partial response may benefit from continued treatment 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 June 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.

Only proprietary prescription medicinal products were included in the cost presentation. 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 severity 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 class II (hydrocortisone butyrate) and class III (methylprednisolone) of the topical glucocorticoids are presented.

Treatment duration:

Designation of the therapy	Treatment mode	Number of treatments/patient/year	Treatment duration/treatment (days)	Days of treatment/patient/year
Medicinal product to be assessed				
Dupilumab	Once every 14 or 28 days	13 – 26.1	1	13 – 26.1
Appropriate comparator therapy				
Topical glucocorticoids of classes 2 to 3				
Hydrocortisone butyrate	2 x day for 2 weeks	Patient-individual		
Methylprednisolone	1 x day for 3 weeks	Patient-individual		
Tacrolimus (topical)				
Tacrolimus	2 x daily - 2 x weekly	Patient-individual		

Consumption:

For dosages depending on body weight, the average body measurements from the official representative statistics "Microcensus 2017 – body measurements of the population" were applied (average body weight of 6-year-old 23.6 kg and of 11-year-old 42.1 kg).[3]

Designation of the therapy	Dosage/ application	Dosage/patient/days of treatment	Usage by potency/day of treatment	Treatment days/ patient/ year	Average annual consumption by potency
Medicinal product to be assessed					
Dupilumab	300 mg	300 mg	300 mg	13 -	13 x 300 mg -
	200 mg	200 mg	200 mg	26.1	26.1 x 200 mg
Appropriate comparator therapy					
Topical glucocorticoids of classes 2 to 3					
Hydrocortisone butyrate	1 mg	Patient-individual			
Methyl-prednisolone	1 mg	Patient-individual			
Tacrolimus (topical)					
Tacrolimus	0.31 mg	Patient-individual			

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 Sections 130 and 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.

Cost of medicinal product:

[3] Statistisches Bundesamt (Federal Statistic Office), Wiesbaden 2018: http://www.gbe-bund.de/

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 ILO	€ 4,337.01	€ 1.77	€ 244.41	€ 4,090.83
Dupilumab 300 mg	6 ILO	€ 4,337.01	€ 1.77	€ 244.41	€ 4,090.83
Appropriate comparator therapy					
Hydrocortisone 0.1%[4] (topical)	100 g CRE	€ 26.74	€ 1.77	€ 1.24	€ 23.73
Methylprednisolone 0.1%[4] (topical)	100 g CRE	€ 26.74	€ 1.77	€ 1.24	€ 23.73
Tacrolimus 0.03% (topical)	60 g OIN	€ 86.13	€ 1.77	€ 4.16	€ 80.20
Abbreviations: SFI = solution for injection; CRE = cream; OIN = ointment					

Last revised LAUER-TAXE®: 15 June 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 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 25 February 2020, the Subcommittee on Medicinal Products determined the appropriate comparator therapy.

[4]fixed reimbursement rate

On 16 December 2020, 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, sentence 2 VerfO.

By letter dated 16 December 2020 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 30 March 2021, and the written statement procedure was initiated with publication on the G-BA website on 1 April 2021. The deadline for submitting written statements was 22 April 2021.

The oral hearing was held on 10 May 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 were discussed at the session of the subcommittee on 22 June 2021, and the draft resolution was approved.

At its session on 1 July 2021, the plenum adopted a resolution to amend the Pharmaceuticals Directive.

Chronological course of consultation

Session	Date	Subject of consultation
Subcommittee Medicinal products	25 February 2020	Implementation of the appropriate comparator therapy
Working group Section 35a	5 May 2021	Information on written statements received; preparation of the oral hearing
Subcommittee Medicinal products	10 May 2021	Conduct of the oral hearing
Working group Section 35a	19 May 2021 2 June 2021 16 June 2021	Consultation on the dossier evaluation by the IQWiG and evaluation of the written statement procedure
Subcommittee Medicinal products	22 June 2021	Concluding discussion of the draft resolution
Plenum	1 July 2021	Adoption of the resolution on the amendment of Annex XII AM-RL

Berlin, 1 July 2021

Federal Joint Committee
in accordance with Section 91 SGB V
The Chair

Prof. Hecken