Justification

Gemeinsamer Bundesausschuss

to the Resolution of the Federal Joint Committee (G-BA) 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, Adolescent Patients 12 to < 18 Years)

of 20 February 2020

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 statutory health insurance funds,
6. Requirements for a quality-assured application.

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

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

2. Key points of the resolution

The active ingredient 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 1 August 2019, dupilumab received marketing authorisation for a new therapeutic indication classified as a major variation of Type 2 according to Annex 2, number 2a to Regulation (EC) No. 1234/2008 of the Commission from 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 29 August 2019, the pharmaceutical company 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 in due time (i.e. at the latest within four weeks after informing the pharmaceutical company about the approval for a new therapeutic indication).

The G-BA commissioned the IQWiG to carry out the assessment of the dossier. The benefit assessment was published on the website of the G-BA (www.g-ba.de) on 2 December 2019, 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 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 arrived at 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 moderate-to-severe atopic dermatitis (AD) in adolescents 12 years and older who are candidates for systemic therapy.

2.1.2 Appropriate comparator therapy

The appropriate comparator therapy for dupilumab to treat moderate-to-severe atopic dermatitis (AD) in adolescents 12 years and older who are candidates for systemic therapy is as follows.

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

- topical class 2 to 4 glucocorticoids
- tacrolimus (topical)
- cyclosporine

The respective marketing authorisation status of the medicinal product 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 according to 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.

[1] General Methods, Version 5.0 dated 10 July 2017. Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen [Institute for Quality and Efficiency in Health Care], Cologne.

3. As comparator therapy, medicinal products or non-medicinal treatments for which the patient-relevant benefit has already been determined by the Federal Joint Committee shall be preferred.
4. According to the generally recognised state of medical knowledge, the comparator therapy should be part of the appropriate therapy in the therapeutic indication.

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

On 1. In the present therapeutic indication medicinal products with the following active ingredients have been approved: topical class 2 to 4 glucocorticoids, pimecrolimus (moderate atopic eczema), tacrolimus (moderate to severe atopic eczema), systemic glucocorticoids (severe eczema), cyclosporine (severe atopic dermatitis) and antihistamines.

On 2. As non-medicinal treatment, UV therapies (UVA/NB-UVB) can be considered, but not UVA1, as it is not a reimbursable therapy.

On 3. The following resolutions of the G-BA are available in the therapeutic indication under consideration are as follows.

Therapeutic guidelines for tacrolimus (resolution of 4 September 2003) and pimecrolimus (resolution of 4 September 2003).

Resolution on the benefit assessment of the active ingredient dupilumab according to Section 35a SGB V of 17 May 2018:

On 4. The general accepted state of medical knowledge on which the decision of the G-BA is based was illustrated by systematic research for guidelines and reviews of clinical studies in the present indication.

Systematic reviews and the therapeutic guidelines of tacrolimus suggest that pimecrolimus is less effective than tacrolimus. Accordingly, tacrolimus, a topical calcineurin inhibitor, is the medicinal treatment of choice.

Antihistamines are not recommended in the treatment of atopic dermatitis.

Class 2 to 4 topical glucocorticoids and the calcineurin inhibitor tacrolimus can be employed as elements of a patient-individual optimised therapy regime. Topical therapy options are used and recommended for adults as well as for children and adolescents.

Systemic glucocorticoids can be used as a systemic therapy option as part of an optimised therapy regime. Medication of this kind is usually intended as short-term therapy of flares. The severe side effects of systemic glucocorticoids, in particular, mean that they are not recommended for long-term use in adolescents, and they are, thus, not designated as an element of appropriate comparator therapy.

Based on the available evidence, the various forms of phototherapy are not recommended for children, and they are, thus, not designated as an element of appropriate comparator therapy in children over 12 years of age.

Under the terms of authorisation, cyclosporine is exclusively a therapeutic option in adolescents aged 16 and over to treat severe forms of prolonged atopic dermatitis that cannot be adequately treated with conventional therapy. Side effects and contraindications must be observed.

As the therapeutic indication of dupilumab includes treatment of moderate to severe atopic dermatitis, both topical and systemic therapies may be used, depending on the severity of the disease and patient pre-treatment. In determining appropriate comparator therapy, a patient-individual optimised therapy regime is assumed, taking into account the severity of the disease and previous therapy. If a treatment is not tolerated, other, alternative active ingredients are employed. Atopic dermatitis is a disease with fluctuating symptoms, potentially related to seasonal factors, so treatment

needs to be individually tailored to individual patients. There is no specific therapy that is appropriate for all patients.

Therapy adjustment during flares must be differentiated from therapy adjustment in 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 a patient-individual optimised therapy regime in the scope of the intended therapeutic indication. In addition to treatment of flares, it should also be possible to adjust therapy during chronic phases.

In summary, appropriate comparator therapy of moderate to severe atopic dermatitis in adolescent patients from 12 years of age is found to consist of a patient-individual optimised therapy regime comprising topical and systemic medication, including topical class 2 to 4 glucocorticoids, tacrolimus (topical) and cyclosporine, taking into account previous therapy and the severity of the disease.

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

2.1.3 Extent and probability of the additional benefit

In summary, the additional benefit of dupilumab is assessed as follows.

There is a hint for a non-quantifiable additional benefit of dupilumab compared to the appropriate comparator therapy in the treatment of moderate to severe atopic dermatitis in adolescent patients aged 12 to < 18 years who are eligible for systemic therapy.

Justification:

The pharmaceutical company has submitted the study AD-1526 (n=251) as part of the benefit assessment dossier. This is a randomised, controlled, double-blind study comparing dupilumab with placebo in adolescents aged 12 to < 18 years. The study included patients who had suffered from chronic dermatitis for at least one year and who had an inadequate response to topical treatment within the six months prior to study inclusion or for whom topical therapy was not advisable. The duration of the study was 16 weeks.

In addition to a background therapy consisting of emollients, patients in the comparator arm of the study received a medicinal rescue therapy in the event of non-tolerable symptoms, while patients in the intervention arm were administered with dupilumab as sustained specific medicinal therapy. In line with the prescription ladder scheme to treat moderate to severe atopic dermatitis, patients are always provided with a specific medicinal therapy, and it can therefore be assumed that patients in the comparator arm were under-treated. Hence, the G-BA considers that the AD-1526 study is not suitable to determine an additional benefit. Nevertheless, in the dupilumab arm at week 16 there was evidence of a consistent and substantial effect on morbidity and quality of life.

CHRONOS study:

The current assessment draws on findings from the CHRONOS study comprising moderate to severe atopic dermatitis patients aged ≥ 18 to < 40 years.

CHRONOS is a randomised, double-blind, controlled, multi-site phase 3 study (n=740) comparing adults receiving dupilumab in combination with topical corticosteroids (TCS) or placebo in combination with TCS. The study compares two different dupilumab doses (300 mg dupilumab once a week (n=319) or 300 mg dupilumab once every two weeks (n=106)) versus placebo + TCS (n=315).

For a detailed description of the CHRONOS study as already presented, please refer to the justifications in support of the resolution on dupilumab of 17 May 2018.

In atopic dermatitis, as has been stated by the IQWiG in its benefit assessment, appropriating data from adults to the treatment of adolescents is feasible; the pathogenesis and clinical presentation in adolescents and adults are sufficiently similar, no significant effect modification due to age was observed in the CHRONOS study, and consistent and significant effects were observed in the AD-1526 study for the various endpoints in both studies.

On the basis of these arguments, the G-BA considers that appropriating the findings of the ≥ 18 to < 40-year-old age group in the CHRONOS study is justified in the present assessment for adolescent patients.

Extent and probability of the additional benefit

Mortality

No deaths were reported in the two relevant study arms by week 52.

Morbidity

In the present assessment, morbidity includes measures of itching (Peak Pruritus NRS), EASI, SCORAD, sleep disturbances (SCORAD-VAS), the Patient-Oriented Eczema Measure (POEM) and health status (EQ-5D-VAS).

Itching (peak pruritus NRS)

Itching is recorded by means of the peak pruritus NRS scale, a score of 0 corresponding to no itch and a score of 10 to the worst itch imaginable.

An improvement by ≥ 4 points by week 52 was considered. For the pruritis endpoint, a statistically significant difference was discovered in favour of dupilumab in the age group ≥ 18 to < 40 years old for the relevant sub-population of the CHRONOS study compared to the appropriate comparator therapy.

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

In the German healthcare context, EASI is a standard instrument for classifying the degree of severity by physicians and is relevant for the diagnosis and monitoring of the severity of the disease in healthcare. EASI is used in conjunction with other instruments to determine the severity of atopic dermatitis. The symptoms erythaema, oedema / papulae formation, abrasions and skin lichenification are each assessed by the physician for 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 affected body surface is estimated by the investigator as a percentage of the total surface area of the body region. An overall score is formed based on the evaluation of the symptoms and the assessment of the affected body surface. The EASI score can range from 0 (no signs of atopic dermatitis) to 72.

The operationalisation of EASI is based on the number of patients who from baseline to week 52 achieved a 90% (EASI 90) or 75% (EASI 75) improvement in EASI score.

Both an EASI 75 and an EASI 90 response are considered to be patient relevant. In the ≥ 18- to < 40-year-old age group, a statistically significant difference was observed in favour of dupilumab for both response thresholds (EASI 75 and EASI 90).

Scoring atopic dermatitis (SCORAD)

SCORAD is another established tool for assessing the severity of atopic dermatitis. It consists of the following three components:

- evaluation of the surface extent of the skin changes by the physician;

- evaluation of the intensity of the skin changes for six symptoms (erythaema, oedema/papulae formation, oozing/crusting, scratch marks, lichenification and dryness of unaffected skin) by the physician; and
- patient reported symptoms of sleep disturbances and itching for the last three days or nights as reported on a VAS of 0 (no symptoms) to 10 (most severe symptoms).

The overall SCORAD score is calculated as the sum of the three components. SCORAD scores can vary from 0 to 103.

SCORAD operationalisation was based on the number of patients who achieved a 90% (SCORAD 90) and a 75% (SCORAD 75) SCORAD score improvement from baseline to week 52. The total score encompasses the sleep disturbances and itching component symptoms. The sleep disturbances endpoint was assessed using the SCORAD visual analogue scale (VAS). No separate assessments of the pruritus endpoint exist.

SCORAD 75 and SCORAD 90

Both a SCORAD 75 and a SCORAD 90 response are considered to be patient relevant. In the ≥ 18- to < 40-year-old age group, a statistically significant difference was observed in favour of dupilumab for the SCORAD 75 response threshold. There was no statistically significant difference between the treatment groups for the SCORAD 90 response threshold.

Sleep disturbances (SCORAD VAS)

Sleep disturbances was self-reported by patients by means of a visual analogue scale. A statistically significant mean improvement was observed for the patient-relevant endpoint sleep disturbances in favour of dupilumab + TCS over placebo + TCS. This is considered to be a clinically relevant effect.

Patient-Oriented Eczema Measure (POEM)

POEM is a patient-based instrument for recording atopic dermatitis symptoms. The questionnaire records the frequency of incidence of seven different symptoms (itching, sleep disturbance, skin haemorrhages, weeping skin, cracked skin, skin flaking, skin dryness/roughness) within the preceding week. The frequency is recorded and an overall score is calculated (scored between 0 and 28). A high score corresponds to severe symptoms. The benefit assessment draws on the mean change in POEM score from baseline to week 52. A statistically significant, clinically relevant, benefit in favour of dupilumab + TCS compared to placebo + TCS was observed in the mean change in patient-reported symptoms for the ≥ 18 to < 40-year-old age group.

Health status (EQ-5D, VAS component)

Health status was assessed using the visual analogue scale (VAS) component of the EQ-5D questionnaire. In this, the patient assesses their state of health on a scale from 0 (worst possible health) to 100 (best possible health). A statistically significant mean difference between the treatment groups for the health status endpoint (EQ-5D-VAS) was observed from baseline to week 52.

<u>Quality of life</u>

Dermatology Life Quality Index (DLQI) Response

The DLQI instrument is a validated questionnaire used to determine disease-specific health-related quality of life in adult patients with dermatological diseases. Ten items in six domains are surveyed: symptoms and well-being, daily activities, leisure, work, and school, personal relationships, and treatment. The questionnaire is completed by the patient. Each item has four response categories ranging from 0 (not at all) to 3 (very strong). A total score is then calculated (values from 0 to 30). The lower the score, the better the health-related quality of life.

Patients with a DLQI of 0 or 1 experienced a statistically significant benefit in favour of dupilumab compared to placebo + TCS at week 52.

Side effects

Specific AEs

Eye disorders (SOC) and all instances of conjunctivitis and blepharitis

A statistically significant difference in the eye disorders endpoint for the ≥ 18 to < 40 years age group was observed to the detriment of dupilumab compared to the comparator therapy.

In addition, the endpoint all instances of conjunctivitis or blepharitis (PT) is evaluated for the ≥ 18 to < 40 years age group. This endpoint includes any PTs related to conjunctivitis or blepharitis that occurred during the study. A statistically significant difference to the detriment of dupilumab compared to the comparator therapy was also found.

Comments on the findings of the AD-1526 study

The results of the AD-1526 study in adolescent patients clearly support the findings of the CHRONOS study. AD-1526 investigates the correct patient population and thus the patient population covered by the therapeutic indication. However, the G-BA considers patients in the comparator arm to have been under-treated and, thus, the findings of AD-1526 are not comparable. Nevertheless, the results in the verum arm reveal significant effects such as improvement of itching and EASI 75 in 45% of patients. The other morbidity endpoints such as SCORAD 75, POEM and SCORAD VAS sleep disturbances also reveal consistent beneficial effects. 24.4% of patients reported a health-related quality of life DLQI score of 0 or 1.

The European Medicines Agency bases its authorisation extension for adolescents aged 12 years and older chiefly on the AD-1526 study. In the context of the earlier benefit assessment in accordance with Section 35 a, however, the G-BA considers appropriation of the evidence from the findings from the adult group (18 to ≤ 40 years) to the adolescent group is necessary, as in the AD-1526 study involving adolescent patients the appropriate comparator therapy was poorly implemented. The findings of the evidence appropriation are nevertheless supported by the consistent and significant effects in the dupilumab arm of study AD-1526.

Overall assessment

The benefit assessment of dupilumab for the treatment of moderate-to-severe atopic dermatitis in adolescents 12 years and older who are candidates for systemic therapy draws on mortality, morbidity, quality of life and side effects findings from the CHRONOS study for the ≥ 18 to < 40-year-old age group compared to placebo + TCS. Appropriating evidence from this to the adolescent group is feasible because the pathogenesis and clinical presentation are sufficiently similar in adolescents and adults, no significant effect modification by age was observed in the CHRONOS study, and consistent and significant effects in the various endpoints were observed in the AD-1526 study at week 16.

In summary, based on the data presented in the morbidity endpoint category for the symptoms itching and sleep disturbance, the self-reported symptoms of patients, the improvements in EASI score of 75% and/or 90%, and the 75% improvement in SCORAD score, a statistically significant benefit in favour of dupilumab + TCS has been demonstrated compared to placebo + TCS.

Similarly, in the quality of life endpoint category, achievement of a DLQI score of 0 or 1 indicates a statistically significant benefit in favour of dupilumab + TCS over placebo + TCS.

In the side-effects category, dupilumab treatment was found to be detrimental to the eye disorder endpoint, including conjunctivitis.

Thus, beneficial effects on morbidity and quality of life and detrimental effects on side effects have been shown. However, these detrimental effects do not outweigh the beneficial effects of dupilumab.

In addition, the beneficial effects of dupilumab demonstrated in the CHRONOS study in patients aged ≥ 18 to < 40 years are clearly supported by the findings of the AD-1526 study.

Reliability of data (probability of additional benefit)

The evaluation of the additional benefit in the patient group 12 to < 18 years with moderate to severe atopic dermatitis drew on the findings for the age group ≥ 18 to < 40 years of the CHRONOS study. Due to the limitations of the available evidence and the appropriation of evidence, the G-BA considers that the reliability of the evidence is sufficient to support the conclusion of a hint for a non-quantifiable additional benefit.

2.1.4 Summary of the assessment

The present assessment concerns the benefit assessment of a new therapeutic indication for the active ingredient dupilumab. The therapeutic indication assessed here is as follows:

Treatment of moderate-to-severe atopic dermatitis (AD) in adolescents 12 years and older who are candidates for systemic therapy.

The appropriate comparator therapy as designated by the G-BA was found to consist of a patient-individual optimised therapy regime comprising topical and systemic medication, including topical class 2 to 4 glucocorticoids, tacrolimus (topical) and cyclosporine, taking into account previous therapy and the severity of the disease. The respective marketing authorisation status of the medicinal product must be taken into account.

The evaluation of the additional benefit in the patient group 12 to < 18 years with moderate to severe atopic dermatitis drew on the findings of the age group ≥ 18 to < 40 years of the CHRONOS study. Hence, findings are available for dupilumab + TCS compared to placebo + TCS on mortality, morbidity, quality of life and side effects. No deaths were reported in the two relevant study arms by week 52.

In summary, based on the data presented in the morbidity endpoint category for the symptoms itching and sleep disturbance, the self-reported symptoms of patients, the improvements in EASI score of 75% and/or 90%, and the 75% improvement in SCORAD score, a statistically significant benefit in favour of dupilumab + TCS has been demonstrated compared to placebo + TCS.

Similarly, in the quality of life endpoint category, achievement of a DLQI score of 0 or 1 indicates a statistically significant benefit in favour of dupilumab + TCS over placebo + TCS.

In the side-effects category, dupilumab treatment was found to be detrimental to the eye disorder endpoint, including conjunctivitis.

The benefits of dupilumab identified in the CHRONOS study in the ≥ 18 to < 40-year-old patient population are, furthermore, clearly supported by findings of the AD-1526 study submitted by the pharmaceutical company.

Overall, the beneficial findings of the studies for dupilumab regarding morbidity and quality of life outweigh the detrimental findings regarding side effects. Hence, dupilumab is judged to have a hint for a non-quantifiable additional benefit.

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

The number of patients is the target population in the statutory health insurance (SHI). These are based on the data from the pharmaceutical company's dossier. The number of patients in the entire 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: 25 November 2019):
https://www.ema.europa.eu/documents/product-information/dupixent-epar-product-information_en.pdf

In patients who do not respond 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: 1 February 2020).

Treatment duration:

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 employed in calculating the "number of treatments/patient/year", time intervals between individual treatments and for the maximum treatment duration, if specified in the product information.

Topical therapy options are employed on a patient-individual basis depending on the severity and site of the disease. Treatment, in particular, is adapted to patient-individual incidences of flares, with the result that treatment duration is patient-individual.

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	every 14 days	26.1	1	26.1
Appropriate comparator therapy				
Topical therapy				
Hydrocortisone butyrate	2 x daily for 8 weeks	Different for each individual patient		
Methyl prednisolone	1 x daily for 6 weeks	Different for each individual patient		
Clobetasol	1 x daily for 2 weeks	Different for each individual patient		
Tacrolimus	2 × weekly	Different for each individual patient		
Systemic therapy				
Cyclosporine	2 × daily	Different for each individual patient		

Usage and consumption:

In principle, the G-BA does not base the calculation of the consumption of weight-dependent medicinal products to be dispensed on indication-specific average weights. Body weight (BW) is therefore based on the average weight of the German population from the official representative statistics “Mikrozensus 2017 - Körpermaße der Bevölkerung” [Microcensus 2017 - Body measurements of the population][2]. The average body weight of 12-year-old children is 47.1 kg; the average body weight of 17-year-old children is 67 kg.

[2] German Federal Office For Statistics, Wiesbaden 2017: www.gbe-bund.de

Designation of the therapy		Dosage/ application	Dosage/patient/treatment days	Consumption by potency/treatment day	Treatment days/ patient/ year	Average annual consumption by potency
Medicinal product to be assessed						
Dupilumab	< 60 kg BW	200 mg	200 mg	200 mg	26.1	26.1 × 200 mg
	< 60 kg BW	300 mg	300 mg	300 mg	26.1	26.1 × 300 mg
Appropriate comparator therapy						
Topical therapy						
Hydrocortisone		Different for each individual patient				
Methyl prednisolone		Different for each individual patient				
Clobetasol		Different for each individual patient				
Tacrolimus		Different for each individual patient				
Systemic therapy						
Cyclosporine		2.5 – 5 mg/kg BW	Different for each individual 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 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.

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

The cost presentation only drew on the costs of proprietary prescription medicinal products. Topical treatment with glucocorticoids often involves the use of formulations that were not taken into account in the present calculation.

Costs of the medicinal product:

Designation of the therapy		Package 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	€ 4,645.00	€ 1.77	€ 262.00	€ 4,381.23
	300 mg	6 SFI	€ 4,645.00	€ 1.77	€ 262.00	€ 4,381.23
Appropriate comparator therapy						
Topical therapies						
Hydrocortisone butyrate 0.1 %[3]		100 g	€ 26.74	€ 1.77	€ 1.24	€ 23.73
Methyl prednisolone 0.1 %[4]		100 g	€ 26.74	€ 1.77	€ 1.24	€ 23.73
Clobetasol 0.05 %[4]		50 g	€ 19.00	€ 1.77	€ 0.63	€ 16.60
Tacrolimus 0.03 %		60 g	€ 86.13	€ 1.77	€ 4.32	€ 80.04
Tacrolimus 0.1 %		60 g	€ 80.75	€ 1.77	€ 3.31	€ 75.67
Systemic therapies						
Cyclosporine 10 mg[4]		100 SCA	€ 48.66	€ 1.77	€ 0.00	€ 46.89
Cyclosporine 25 mg[4]		100 SCA	€ 105.91	€ 1.77	€ 7.50	€ 96.64
Cyclosporine 50 mg[4]		100 SCA	€ 202.10	€ 1.77	€ 15.11	€ 185.22
Cyclosporine 100 mg[4]		100 SCA	€ 395.77	€ 1.77	€ 30.43	€ 363.57
Acronyms: SCI = solution for injection, SC = soft capsules						

Pharmaceutical retail price (LAUER-TAXE®) as last revised: 1 February 2020

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 medical treatment or the prescription of other services when using the medicinal product to be assessed and the appropriate comparator therapy according to the product information, no costs for additionally required SHI services had to be taken into account.

3. Bureaucratic costs

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.

[3] Fixed reimbursement rate

4. Process sequence

The Subcommittee on Medicinal Products determined the appropriate comparator therapy at its session on 29 January 2019.

On 29 August 2019, 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 29 August 2019 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 November 2019, and the written statement procedure was initiated with publication on the website of the G-BA on 2 December 2019. The deadline for submitting written statements was 23 December 2019.

The oral hearing was held on 6 January 2020.

By letter dated 6 January 2020, the IQWiG was commissioned with a supplementary assessment of data submitted in the written statement procedure. The addendum prepared by IQWiG was submitted to the G-BA on 30 January 2020.

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 11 February 2020, and the proposed resolution was approved.

At its session on 20 February 2020, the plenum adopted a resolution to amend the Pharmaceuticals Directive.

Chronological course of consultation

Session	Date	Subject of consultation
Subcommittee Medicinal Products	29 January 2019	Determination of the appropriate comparator therapy
Subcommittee Medicinal Products	6 January 2020	Conduct of the oral hearing, Commissioning of the IQWiG with the supplementary assessment of documents
Working group Section 35a	14 January 2020 4 February 2020	Consultation on the dossier evaluation by the IQWiG, evaluation of the written statement procedure
Subcommittee Medicinal Products	11 February 2020	Concluding discussion of the draft resolution
Plenum	20 February 2020	Adoption of the resolution on the amendment of Annex XII of the AM-RL

Berlin, 20 February 2020

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

Prof. Hecken