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: Chronic Rhinosinusitis with Nasal Polyps)

of 14 May 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 24 October 2019, dupixent received the 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 21 November 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 (chronic rhinosinusitis with nasal polyps) 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 March 2020, 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, 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 assessed 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 as an add-on therapy with intranasal corticosteroids for the treatment of adults with severe CRSwNP for whom therapy with systemic corticosteroids and/or surgery do not provide adequate disease control.

2.1.2 Appropriate comparator therapy

The appropriate comparator therapy was determined as follows:

Adult patients with severe CRSwNP for whom therapy with systemic corticosteroids and/or surgery do not provide adequate disease control

Appropriate comparator therapy:

- A treatment with intranasal corticosteroids (budesonide or mometasone furoate)

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.
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.

[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.

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. Corticosteroids, including budesonide and mometasone furoate as intranasal (topical) corticosteroids (INCS), and (oral) corticosteroids (OCS), are explicitly approved in the therapeutic indication for the treatment of CRSwNP For short-term need intervention, antibiotics and analgesics are included in the marketing authorisation.

On 2. An exclusively non-medicinal treatment is not an option in this therapeutic indication. Surgical measures represent an intervention on demand.

On 3. With regard to chronic rhinosinusitis with nasal polyposis, the G-BA has not passed any resolutions on the benefit assessment of medicinal products with new active ingredients according to § 35a SGB V.

On 4. The generally accepted state of medical knowledge was illustrated by systematic research for guidelines and reviews of clinical studies in this indication. In the overall view, the aggregated evidence suggests a positive recommendation for INCS. INCS are superior to both placebo and “no treatment”. CRSwNP is a chronic disease with a fluctuating course. Patients in whom previous therapies with systemic corticosteroids and/or surgery failed or who have a corresponding contraindication or unsuitability are basically eligible for medicinal therapy with INCS at the time of initiation of dupilumab treatment. Invasive treatment options alone are more likely to be an option in individual cases as needed. The use of saline nasal rinses is also recommended based on evidence.
Although OCS are approved in the therapeutic indication relevant here, the evidence for long-term use of OCS as a standard/maintenance therapy of nasal polyps – especially beyond flare therapy – is to be regarded as rather limited; there are no uniformly positive recommendations for long-term use of OCS based on the aggregated evidence. Rather, national and international guidelines come to the conclusion that systemic glucocorticoids should be considered only as “flare therapy” accompanied by a INCS maintenance therapy. Antibiotics and analgesics are not regarded as standard or maintenance therapy because they are indicated only for short-term treatment (in case of complications or infections).

In summary, the G-BA concludes that for dupilumab as an add-on therapy to intranasal corticosteroids in adult patients with severe CRSwNP that cannot be adequately controlled with systemic corticosteroids and/or surgery a maintenance therapy with intranasal corticosteroids (budesonide or mometasone furoate) is appropriate.

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.

For adult patients with severe CRSwNP for whom therapy with systemic corticosteroids and/or surgery do not provide adequate disease control, there is an indication of a considerable additional benefit for dupilumab as an add-on to intranasal corticosteroids compared with mometasone furoate.

Justification:

The benefit assessment is based on the two double-blind, randomised SINUS-24 and SINUS-52 studies as well as the meta-analysis of both studies at week 24.

The SINUS-24 and SINUS-52 studies are randomised, double-blind Phase III studies comparing dupilumab versus placebo, each with an add-on design in addition to a maintenance treatment with intranasal mometasone furoate. Both studies included adult patients with bilateral nasal polyps who, despite therapy with systemic corticosteroids within the last two years and/or contraindication/intolerance to systemic corticosteroids and/or at least one previous paranasal sinus operation, had a nasal polyp score of ≥ 5 and < 8 as well as at least two persistent symptoms of chronic rhinosinusitis for ≥ 8 weeks before the run-in phase.

The design of both studies included a 4-week run-in phase prior to randomisation followed by a 24-week (SINUS-24) or 52-week (SINUS-52) blinded treatment phase followed by a follow-up phase (SINUS-24: 24 weeks; SINUS-52: 12 weeks).Prior to randomisation, both studies had a 4-week run-in phase in which the suitability of the patients for inclusion in the study was assessed and maintenance therapy was started with 400 µg of intranasal mometasone furoate daily (2 puffs of 50 µg per nostril twice daily). Following the run-in phase, only those patients who, in addition to meeting the inclusion criteria, exhibited at least 2 symptoms (including nasal congestion/obstruction of medium or severe severity as well as loss of sense of smell or anterior/posterior rhinorrhoea) for a total of at least 12 weeks (at least 8 weeks before and 4 weeks during the run-in phase) could be randomised to the treatment arms. In both studies, the administration of intranasal mometasone furoate was continued at stable doses in all study arms during the treatment phase. In addition to the study medication to be investigated and maintenance therapy with intranasal mometasone furoate, emergency treatment was allowed in the case of deterioration of (endoscopic/radiological) signs (SINUS-24, SINUS-52) and/or symptomatology (SINUS-52). In both studies, treatment with intranasal mometasone furoate at stable doses was continued in the follow-up phase, or treatment was changed at the investigator's discretion.

In the SINUS-24 study, 276 patients were randomised to 24-week treatment with dupilumab 300 mg every 2 weeks (N = 143) or with placebo (N = 133). In the SINUS-52 study, 448 patients were randomised to 3 treatment arms. The patients received either dupilumab (300 mg) every 2 weeks for 52 weeks (N = 150) (Arm A) or dupilumab (300 mg) every 2 weeks for 24 weeks and then dupilumab (300 mg) every 4 weeks until Week 52 (N = 145) (arm B) or placebo for 52 weeks (N = 153). The primary endpoints of both studies were changes in nasal congestion/obstruction and nasal polyp score at Week 24. Further patient-relevant endpoints were overall mortality as well as endpoints in the endpoint categories morbidity and side effects.

For the benefit assessment, the total population of each study is considered. Because of the similarity of the studies, all dupilumab treatment arms of the two studies are considered for a meta-analysis at Week 24 for this benefit assessment. In addition to the meta-analytical summary of the SINUS studies at Week 24, the results of the SINUS-52 study at Week 52 are presented and used for the benefit assessment to compare dupilumab + mometasone furoate (dosage compliant with marketing authorisation, arm A) with placebo + mometasone furoate.

Extent and probability of the additional benefit

Mortality

In the SINUS-24 and SINUS-52 studies, no deaths occurred until Week 24 and Week 52, respectively.

Morbidity

SNOT-22 (symptomatology and social/emotional consequences of rhinosinusitis; here: Improvement of ≥ 8.9 points in the SNOT-22 overall score)

In the two SINUS studies, the symptomatology and social/emotional consequences of rhinosinusitis were assessed using SNOT-22. This is a disease-specific, patient-reported questionnaire with 22 individual questions to assess the severity and frequency of occurrence of symptoms and social/emotional consequences of rhinosinusitis. Each question is answered on a scale of 0 (no problems) to 5 (worst possible problems). An overall score (0 to 110) is formed from the individual scores for each question. Lower scores correspond to less impairment. Because this questionnaire is used mainly to assess impairments caused by symptoms (e.g. congested nose, runny nose, post-nasal secretion, diminished sense of smell/taste), it is assigned to morbidity. In this benefit assessment, the pre-specified operationalisation via the proportion of patients with a patient-relevant improvement of ≥ 8.9 points is included in the overall score.

For the SNOT-22 endpoint, a statistically significant advantage of dupilumab + mometasone furoate compared with placebo + mometasone furoate was shown for the proportion of patients with a relevant improvement of the overall score by ≥ 8.9 points in the meta-analysis of the SINUS-24 and SINUS-52 studies at Week 24.

This statistically significant, considerable advantage for dupilumab as an add-on to mometasone furoate is maintained at Week 52 (SINUS-52 study) in a comparable magnitude.

Nasal congestion/obstruction

Nasal congestion/obstruction is a patient-relevant symptom of the disease in this indication. In the SINUS-24 and SINUS-52 studies, the severity of this symptom was assessed once daily (in the morning) using an electronic symptom diary; each symptom was rated on a scale of 0 (no symptoms) to 3 (severe symptoms), taking into account the past 24 hours. The evaluations based on non-specified MIDs were not considered.

For the endpoint nasal congestion/obstruction, the meta-analysis of the SINUS studies at Week 24 showed a statistically significant difference to the advantage of dupilumab + mometasone furoate compared with placebo + mometasone furoate based on the mean change. The 95% confidence interval (CI) of the standardised mean difference (Hedges' g) is completely outside the irrelevance range. A clinically relevant difference is therefore assumed.

The effect in favour of dupilumab as an add-on to mometasone furoate is also confirmed in the supplementary analysis of the SINUS 52 study at Week 52.

Loss of the sense of smell

In this indication, the loss of the sense of smell is considered patient-relevant. The meta-analysis of the SINUS-24 and SINUS-52 studies at Week 24 showed a statistically significant difference in favour of dupilumab + mometasone furoate compared with placebo + mometasone furoate for the endpoint loss of the sense of smell – surveyed by means of an electronic patient diary analogous to nasal congestion/obstruction. Because the 95% CI of the standardised mean difference (Hedges' g) is completely outside the irrelevant range, a clinically relevant difference is assumed.

Also at Week 52 of the SINUS-52 study, this effect remains in favour of dupilumab + mometasone furoate compared with placebo + mometasone furoate.

Rhinorrhoea (anterior/posterior)

Rhinorrhoea is also considered a patient-relevant symptom in this indication. Analogous to the loss of the sense of smell and nasal obstruction/congestion, this was reported daily using an electronic patient diary. For the endpoint rhinorrhoea (anterior/posterior), the meta-analysis of the SINUS studies at Week 24 also showed a statistically significant effect in favour of dupilumab + mometasone furoate compared with placebo + mometasone furoate based on the mean change. This advantage is considered a clinically relevant difference because of the 95% CI of the standardised mean difference (Hedges' g), which is completely outside the irrelevant range.

Also at Week 52, the analyses of the SINUS-52 study confirmed a long-lasting difference in favour of dupilumab + mometasone furoate compared with placebo + mometasone furoate.

Rhinosinusitis VAS

In the SINUS-24 and SINUS-52 studies, general symptom severity was assessed using the rhinosinusitis VAS. Patients were asked to indicate on a 10-cm VAS how stressful they perceived the symptoms of their rhinosinusitis to be. A value of 0 corresponds to symptoms that are "not at all stressful", and a value of 10 corresponds to symptoms that are "very stressful". The pre-specified responder analyses on the proportion of patients with an improvement in rhinosinusitis symptoms from > 7 to ≤ 7 are not considered in this benefit assessment. The evaluations of the mean change, which in contrast to the responder analysis not only records positive disease progressions but also allows conclusions to be drawn about negative or neutral symptom changes, are considered to be more adequate and are used for the benefit assessment.

For the endpoint VAS rhinosinusitis, the meta-analysis of the two SINUS studies at Week 24 showed a statistically significant difference for the mean change to the advantage of dupilumab + mometasone furoate compared with placebo + mometasone furoate. The 95% CI of the standardised mean difference (Hedges' g) is completely outside the irrelevance range. A clinically relevant difference is therefore assumed.

The statistically significant effect in favour of dupilumab + mometasone furoate in the rhinosinusitis VAS was maintained at Week 52 (SINUS-52 study).

Health status (EQ-5D VAS)

In the SINUS-24 and SINUS-52 studies, the health status was surveyed via the EQ-5D using a VAS from 0 to 100 on which patients answers question regarding their health status at the time of measurement. Here 0 stands for the worst imaginable health status and 100 for the best imaginable health status.

For the endpoint health status (EQ-5D VAS), the meta-analysis of the SINUS-24 und SINUS-52 studies at Week 24 showed a statistically significant difference to the advantage of dupilumab + mometasone furoate compared with placebo + mometasone furoate. The 95% CI of the standardised mean difference (Hedges' g) is completely outside the irrelevance range. A clinically relevant difference is therefore assumed.

In support of the EQ-5D VAS analyses, it should also be noted that Week 52 data from SINUS-52 confirmed the statistically significant, clinically relevant advantages of the meta-analysis in favour of dupilumab + mometasone furoate.

Quality of life

In the SINUS-24 and SINUS-52 studies, no data on health-related quality of life suitable for the benefit assessment was collected. The pharmaceutical company assigned individual domains of the SNOT-22 symptom questionnaire to health-related quality of life but did not consider them when deriving the additional benefit. From the perspective of the G-BA, all SNOT-22 items are assigned to the category morbidity and taken into account accordingly.

Side effects

AE, SAE, discontinuation because of AE

In the evaluations of the SINUS studies on AE, there are also events that can be assigned to both the side effects category and the symptomatology of the disease (morbidity). Because this affects a large proportion of patients, the data on the AEs cannot be used to derive the additional benefit. Similarly, for the endpoints SAE and discontinuation because of AE, no usable data are available from either the SINUS-24 or SINUS-52 study.

For the patients in whom SAE occurred, the complete list of SAEs at the SOC/PT level in the respective study reports shows that in most cases, only one event per patient occurred. For AEs that lead to therapy discontinuation, one event per patient is usually also recorded. If the total rates of SAE and AE leading to discontinuation of therapy are subtracted from the total rates of SAE and AE leading to discontinuation of therapy for patients with an event that can also be attributed to the symptoms, there are still no increased rates of SAE and AE leading to discontinuation of therapy for dupilumab as an add-on to maintenance therapy with mometasone furoate compared to therapy with mometasone furoate alone.

Overall, when considering the results on SAE and discontinuations because of AE – also considering the low number of events – it can be assumed that there is no disadvantage for dupilumab + mometasone furoate compared with placebo + mometasone furoate.

<u>Overall assessment</u>

For the assessment of the additional benefit of dupilumab, evaluations of the two double-blind, randomised, placebo-controlled Phase III SINUS-24 and SINUS-52 studies (each in an add-on design to a maintenance treatment with intranasal mometasone furoate) as well as the meta-analysis of both studies at Week 24 are available. The benefit assessment is based on the results at Week 24 (meta-analysis) as well as the evaluations of the SINUS-52 study at Week 52.

In summary, in the morbidity category, there are only statistically significant, clinically relevant effects in favour of dupilumab + mometasone furoate compared with placebo + mometasone furoate at both Week 24 and Week 52. Compared with placebo + mometasone furoate,

dupilumab + mometasone furoate showed a statistically significant and considerable improvement regarding symptomatology and social/emotional consequences of rhinosinusitis (assessed by SNOT-22) both in the meta-analysis at Week 24 and the SINUS-52 study at Week 52. The meta-analysis at Week 24 also shows that dupilumab + mometasone furoate has statistically significant advantages compared with placebo + mometasone furoate regarding the endpoints "loss of the sense of smell", "rhinosinusitis VAS", "nasal congestion/obstruction", "rhinorrhoea (anterior/posterior)" and "health status (assessed by EQ-5D VAS)"; these effects can be classified as clinically relevant and are also confirmed in the evaluations of the SINUS 52 study in all endpoints at Week 52.

In the health-related quality of life category, no data suitable for the benefit assessment were presented. The evaluations of the SNOT-22 symptom questionnaire were considered in the morbidity category in this benefit assessment.

In the side effects category, when considering the results on SAE and discontinuations because of AE – also considering the low number of events – it can be overall assumed that there is no disadvantage for dupilumab + mometasone furoate compared with the appropriate comparator therapy placebo + mometasone furoate.

In the overall view, only statistically significant, positive effects for dupilumab + mometasone furoate compared with placebo + mometasone furoate were observed at Week 24 and Week 52. These morbidity advantages are not offset by disadvantages from other categories.

Based on these considerations, the information in the dossier, and the results of the benefit assessment, the G-BA considers the additional benefit of dupilumab as an add-on to intranasal corticosteroids compared with the appropriate comparator therapy for the treatment of adults with severe CRSwNP for whom therapy with systemic corticosteroids and/or surgery do not provide adequate disease control to be a significant improvement of the therapy-relevant benefit not yet achieved and classifies the extent of the additional benefit as considerable.

Reliability of data (probability of additional benefit)

In the SINUS-24 and SINUS-52 studies, the additional benefit is assessed on the basis of two randomised, double-blind, and directly comparative Phase III studies (each in add-on design to a maintenance treatment with intranasal mometasone furoate).

The risk of bias at the study level is classified as low. At the endpoint level, the risk of bias for the results of the endpoints in the endpoint categories mortality and morbidity is assessed as low in each case; the risk of bias for the non-usable data on side effects cannot be assessed.

Notwithstanding the low risk of bias, there are uncertainties regarding the suitability of sub-populations of the study population presented for the question of benefit assessment. Nearly all patients underwent at least one sinus operation during the 2 years preceding the study, and/or received treatment with systemic corticosteroids, and had at least 2 moderate to severe rhinosinusitis symptoms persisting for 12 weeks at the time of randomisation. However, an analgesic intolerance syndrome (NSAID-ERD) was also present as a comorbidity in about 25 to 30% of the patients included. Overall, concerns remain as to whether patients with NSAID-ERD have been adequately treated in advance as well as within the framework of the SINUS studies.

Overall, the reliability of the statement is classified as an "indication".

2.1.4 Summary of the assessment

This assessment refers to the benefit assessment of a new therapeutic indication for the active ingredient dupilumab. The therapeutic indication assessed here is as follows:
“as an add-on therapy with intranasal corticosteroids for the treatment of adults with severe CRSwNP for whom therapy with systemic corticosteroids and/or surgery do not provide adequate disease control”.

The G-BA determined that a treatment with intranasal corticosteroids (INCS; budesonide or mometasone furoate) was an appropriate comparator therapy.

For the assessment of the additional benefit of dupilumab, the two double-blind, randomised, placebo-controlled Phase III SINUS-24 and SINUS-52 studies (each in add-on design to a maintenance treatment with intranasal mometasone furoate) as well as the meta-analysis of both studies at Week 24 were submitted. The benefit assessment is thus based on the results at Week 24 (meta-analysis) as well as the evaluations of the SINUS-52 study at Week 52.

Hence, findings are available for dupilumab + mometasone furoate compared with placebo + mometasone furoate on mortality, morbidity, quality of life, and side effects. In both studies, no deaths occurred in any study arms up to Week 24 and 52, respectively. In summary, based on the data presented, in the morbidity category, there are only statistically significant, clinically relevant effects in favour of dupilumab + mometasone furoate compared with placebo + mometasone furoate at both Week 24 and Week 52. In the health-related quality of life category, no data suitable for the benefit assessment were presented. In the side effects category, when considering the results on SAE and discontinuations because of AE – also considering the low number of events – it can be assumed overall that there is no disadvantage for dupilumab + mometasone furoate compared with the appropriate comparator therapy placebo + mometasone furoate.

In the overall view, dupilumab as an add-on to mometasone furoate has only positive effects in morbidity; these are not offset by negative effects in other categories. Consequently, for adult patients with severe CRSwNP for whom therapy with systemic corticosteroids and/or surgery do not provide adequate disease control, there is an indication of a considerable additional benefit for dupilumab as an add-on to intranasal corticosteroids compared with the appropriate comparator therapy.

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). The G-BA bases the resolution on the estimate of the number of patients derived by the pharmaceutical company in the dossier. However, the patient numbers specified are subject to uncertainties because the pharmaceutical company considered only patients who had already been prescribed INCS and assumed a time interval of 4 quarters between the last documented diagnosis and a previous sinus operation. In the overall view, there is an underestimate.

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: 3 April 2020):
https://www.ema.europa.eu/en/documents/product-information/dupixent-epar-product-information_en.pdf

For patients who do not respond to CRSwNP treatment after 24 weeks, discontinuation of treatment should be considered. Some patients with an initial partial response may benefit from continued treatment beyond 24 weeks.

2.4 Treatment costs

The treatment costs are based on the contents of the product information and the information listed in the LAUER-TAXE® (last revised: 15 April 2020).

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 between individual treatments, and for maximum treatment duration if specified in the product information.

Treatment duration:

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	1 × every 14 days	26.1	1	26.1
Intranasal corticosteroids				
Budesonide	2 × daily	365	1	365
Mometasone	1 × daily	365	1	365
Appropriate comparator therapy				
Intranasal corticosteroids				
Budesonide	2 × daily	365	1	365
Mometasone	1 × daily	365	1	365

Usage and consumption:

Designation of the therapy	Dosage/ application	Dose/patient/treatment days	Consumption by potency/treatment day	Treatment days/ patient/ year	Average annual consumption by potency
Medicinal product to be assessed					
Dupilumab	300 mg	300 mg	1 × 300 mg	26.1	26.1 × 300 mg
Intranasal corticosteroids					
Budesonide	0.1 mg – 0.2 mg	0.2 mg – 0.4 mg	4 × 0.05 mg – 8 × 0.05 mg	365	1460 puffs of 0.05 mg – 2920 puffs of 0.05 mg
Mometasone	0.1 mg – 0.4 mg	0.1 mg – 0.4 mg	2 × 0.05 mg – 8 × 0.05 mg	365	730 puffs of 0.05 mg – 2920 puffs of 0.05 mg
Appropriate comparator therapy					
Intranasal corticosteroids					
Budesonide	0.1 mg – 0.2 mg	0.2 mg – 0.4 mg	4 × 0.05 mg – 8 × 0.05 mg	365	1460 puffs of 0.05 mg – 2920 puffs of 0.05 mg
Mometasone	0.1 mg – 0.4 mg	0.1 mg – 0.4 mg	2 × 0.05 mg – 8 × 0.05 mg	365	730 puffs of 0.05 mg – 2920 puffs of 0.05 mg

Costs:

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

Costs of the medicinal 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	6 SFI	€ 4,645.00	€ 1.77	€ 262.00	€ 4,381.23
Budesonide[2]	400 puffs	€ 30.59	€ 1.77	€ 1.55	€ 27.27
Mometasone[2]	280 puffs	€ 26.06	€ 1.77	€ 1.19	€ 23.10
Appropriate comparator therapy					
Budesonide[2]	400 puffs	€ 30.59	€ 1.77	€ 1.55	€ 27.27
Mometasone[2]	280 puffs	€ 26.06	€ 1.77	€ 1.19	€ 23.10
Abbreviations: SFI = solution for injection					

Pharmaceutical retail price (LAUER-TAXE®) as last revised: 15 April 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 assessed 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.

[2] Fixed reimbursement rate

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.

4. Process sequence

The Subcommittee on Medicinal Products determined the appropriate comparator therapy at its session on 25 June 2019.

On 21 November 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 1, sentence 2 VerfO.

By letter dated 21 November 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 27 February 2020, and the written statement procedure was initiated with publication on the website of the G-BA on 2 March 2020. The deadline for submitting written statements was 23 March 2020.

The oral hearing was held on 6 April 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 5 May 2020, and the proposed resolution was approved.

At its session on 14 May 2020, the plenum adopted a resolution to amend the Pharmaceuticals Directive.

Chronological course of consultation

Session	Date	Subject of consultation
Subcommittee Medicinal Products	25 June 2019	Determination of the appropriate comparator therapy
Working group Section 35a	31 March 2020	Information on written statements received; preparation of the oral hearing
Subcommittee Medicinal Products	6 April 2020	Conduct of the oral hearing
Working group Section 35a	14 April 2020 29 April 2020	Consultation on the dossier assessment by the IQWiG, evaluation of the written statement procedure
Subcommittee Medicinal Products	5 May 2020	Concluding discussion of the draft resolution

Plenum	14 May 2020	Adoption of the resolution on the amendment of Annex XII of the AM-RL

Berlin, 14 May 2020

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

Prof. Hecken