Gemeinsamer Bundesausschuss

Justification

of the Resolution of the Federal Joint Committee (G-BA) on an Amendment of the Pharmaceuticals Directive:
Annex XII – Benefit Assessment of Medicinal Products with New Active Ingredients according to Section 35a (SGB V)
Dupilumab (new therapeutic indication: treatment of moderate-to-severe prurigo nodularis)

of 5 October 2023

Contents

1. Legal basis

According to Section 35a paragraph 1 German Social Code, Book Five (SGB V), the Federal Joint Committee (G-BA) assesses the benefit of reimbursable medicinal products with new active ingredients. This includes in particular the assessment of the additional benefit and its therapeutic significance. The benefit assessment is carried out on the basis of evidence provided by the pharmaceutical company, which must be submitted to the G-BA electronically, including all clinical trials the pharmaceutical company has conducted or commissioned, at the latest at the time of the first placing on the market as well as the marketing authorisation of new therapeutic indications of the medicinal product, and which must contain the following information in particular:

1. approved therapeutic indications,
2. medical benefit,
3. additional medical benefit in relation to the appropriate comparator therapy,
4. number of patients and patient groups for whom there is a therapeutically significant additional benefit,
5. treatment costs for the statutory health insurance funds,
6. requirements for a quality-assured application.

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

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

2. Key points of the resolution

The active ingredient dupilumab (AM) 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 7 October 2022, the pharmaceutical company submitted an application for postponement of the date for the start of the benefit assessment procedure for dupilumab in the present therapeutic indication "moderate-to-severe prurigo nodularis (PN) in adults who are candidates for systemic therapy" in accordance with Section 35a paragraph 5b SGB V. The pharmaceutical company expected marketing authorisation extensions for the active

ingredient dupilumab within the period specified in Section 35a paragraph 5b SGB V for multiple therapeutic indications at different times.

At its session on 17 November 2022, the G-BA approved the application pursuant to Section 35a paragraph 5b SGB V and postponed the relevant date for the start of the benefit assessment and the submission of a dossier for the benefit assessment for the therapeutic indication in question to four weeks after the marketing authorisation of the last therapeutic indication of the therapeutic indications covered by the application, at the latest six months after the first relevant date. All marketing authorisations for the therapeutic indications covered by the application according to Section 35a paragraph 5b SGB V were granted within the 6-month period.

For the therapeutic indication in question here "moderate-to-severe prurigo nodularis (PN) in adults who are candidates for systemic therapy", dupilumab received the extension of the marketing authorisation as a major type 2 variation as defined according to Annex 2 No. 2 letter a 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, 12.12.2008, p. 7) on 12 December 2022. In accordance with the resolution of 17 November 2022, the benefit assessment of the active ingredient dupilumab in this new therapeutic indication thus began at the latest within four weeks after the last marketing authorisation of dupilumab on 15 March 2023 in the therapeutic indication "severe atopic dermatitis in children 6 months to 5 years of age who are candidates for systemic therapy", i.e. at the latest on 12 April 2023.

On 29 March 2023, the pharmaceutical company has submitted in due time a dossier in accordance with Section 4, paragraph 3, number 3 Ordinance on the Benefit Assessment of Pharmaceuticals (AM-NutzenV) in conjunction with Chapter 5 Section 8, paragraph 2 of the Rules of Procedure (VerfO) of the G-BA on the active ingredient dupilumab with the new therapeutic indication "moderate-to-severe prurigo nodularis (PN) in adults who are candidates for systemic therapy".

The G-BA commissioned the IQWiG to carry out the dossier assessment. The benefit assessment was published on the G-BA website (www.g-ba.de) on 3 July 2023, thus initiating the written statement procedure. In addition, an oral hearing was held.

The G-BA came to a 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, as well of the addendum drawn up by the IQWiG on the benefit assessment. 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 adults with moderate-to-severe prurigo nodularis (PN) who are candidates for systemic therapy.

Therapeutic indication of the resolution (resolution of 05.10.2023):

see the approved therapeutic indication

2.1.2 Appropriate comparator therapy

The appropriate comparator therapy was determined as follows:

Adults with moderate-to-severe prurigo nodularis (PN) who are candidates for systemic therapy

Appropriate comparator therapy for dupilumab:

- Best supportive care

Best supportive care (BSC) is defined as the therapy that provides the best possible, patient-individual, optimised supportive treatment to alleviate symptoms and improve quality of life.

Criteria according to Chapter 5 Section 6 of the Rules of Procedure of the G-BA and Section 6 para. 2 Ordinance on the Benefit Assessment of Pharmaceuticals (AM-NutzenV):

The appropriate comparator therapy must be an appropriate therapy in the therapeutic indication in accordance with the generally recognised state of medical knowledge (Section 12 SGB V), preferably a therapy for which endpoint studies are available and which has proven its worth in practical application unless contradicted by the guidelines under Section 92, paragraph 1 SGB V or the principle of economic efficiency.

In determining the appropriate comparator therapy, the following criteria, in particular, must be taken into account as specified in Chapter 5 Section 6, paragraph 3 VerfO:

1 General Methods, version 6.1 from 24.01.2022. Institute for Quality and Efficiency in Health Care (IQWiG), Cologne.

1. To be considered as a comparator therapy, the medicinal product must, principally, have a marketing authorisation for the therapeutic indication.
2. If a non-medicinal treatment is considered as a comparator therapy, this must be available within the framework of the SHI system.
3. As comparator therapy, medicinal products or non-medicinal treatments for which the patient-relevant benefit has already been determined by the G-BA shall be preferred.
4. According to the generally recognised state of medical knowledge, the comparator therapy should be part of the appropriate therapy in the therapeutic indication.

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

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

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

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

on 1. Apart from dupilumab, no medicinal products are specifically approved at present for the treatment of prurigo nodularis. In principle, however, topical glucocorticoids can be a treatment option for the treatment of inflammatory skin diseases. In addition, the use of a topical basic therapy for skincare is an option for all patients.

on 2. In the present indication, UV phototherapy (NB-UV-B radiations) is a non-medicinal treatment that can be provided within the framework of SHI and is eligible as an appropriate comparator therapy.

on 3. In the therapeutic indication to be considered here, there are no resolutions from the G-BA on the benefit assessment of medicinal products with new active ingredients according to Section 35a SGB V:

on 4. The generally recognised state of medical knowledge was illustrated by a systematic search for guidelines as well as reviews of clinical studies in the present indication and is presented in the "Research and synopsis of the evidence to determine the appropriate comparator therapy according to Section 35a SGB V".

The scientific-medical societies and the Drugs Commission of the German Medical Association (AkdÄ) were also involved in writing on questions relating to the comparator therapy in the present indication according to Section 35a paragraph 7 SGB V (see "Information on Appropriate Comparator Therapy").

Overall, the evidence for the treatment of prurigo nodularis is limited. No medicinal therapies are specifically approved for the treatment of prurigo nodularis, but topical glucocorticoids (TCS) may be an approved treatment option for the treatment of inflammatory skin conditions.

There is agreement that a patient-individual therapeutic approach is recommended for chronic pruritus, which should be based, among others, on the severity of the disease and previous therapies used.

According to the recommendations of the S2k guideline on the diagnosis and therapy of chronic pruritus,[2] skin care with moisturising and hydrating topicals forms the basis of the best possible add-on treatment to alleviate the symptoms of chronic pruritus. Emollients in particular are intended to improve the skin's barrier function.

Furthermore, topical glucocorticoids can also be used in the patient-individual assessment for the therapy of chronic pruritus with inflammatory cutaneous changes; however, they are not recommended for long-term use.

Ciclosporin, methotrexate and azathioprine are also named as possible therapy options for prurigo nodularis. However, as these active ingredients do not have a marketing authorisation for prurigo nodularis or inflammatory skin diseases and no further evidence can be derived for their use, the active ingredients are not named as part of the appropriate comparator therapy.

2 Ständer S. et al. S2k guideline for diagnosis and therapy of chronic pruritus. 2022. [Accessed: 04.08.2023] https://register.awmf.org/assets/guidelines/013-048l_S2k_Diagnostik-Therapie-des-chronischen-Pruritus_2022-09.pdf

As a non-medicinal therapy of chronic pruritus, the above-mentioned S2k guideline recommends[2] the use of UV phototherapy for inflammatory dermatoses and scratch lesions. Compared to the strong recommendation for a basic therapy with emollients and the short-term therapy with topical glucocorticoids in the case of steroid-responsive dermatosis and inflammatory scratch lesions, the guideline recommendation for the use of UV phototherapy becomes weak.

Although UV phototherapy can be used according to the guideline for the treatment of chronic pruritus in inflammatory dermatoses and scratch lesions, its significance in the treatment of prurigo nodularis is unclear in Germany. Furthermore, only limited availability and use of UV phototherapy was discussed in the oral hearing.

In summary, for the treatment of adults with moderate-to-severe prurigo nodularis who are candidates for systemic therapy, best supportive care (BSC) treatment is determined to be the appropriate comparator therapy for dupilumab. Best supportive care (BSC) is defined as the therapy that provides the best possible, patient-individual, optimised supportive treatment to alleviate symptoms and improve quality of life. Topical basic therapy for skin care, topical glucocorticoids and UV-B phototherapy may be used as part of a BSC.

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 adults with moderate-to-severe prurigo nodularis who are candidates for systemic therapy, there is a hint for a non-quantifiable additional benefit compared with the appropriate comparator therapy.

Justification:

For the assessment of the additional benefit of dupilumab, the pharmaceutical company submits two multicentre, randomised, double-blind placebo-controlled phase III studies. The PRIME and PRIME2 studies enrolled 151 and 160 patients, respectively, aged 18 to 80 years with prurigo nodularis diagnosed at least 3 months ago. Study participants were treated in a 1:1 ratio with either dupilumab (PRIME: N = 75; PRIME2: N = 78) or placebo (PRIME: N = 76; PRIME2: N = 82), treated in each case in addition to background therapy. In the background therapy, the use of emollients was mandatory, with optional administration of weak to moderate topical glucocorticoids (TCS) or topical calcineurin inhibitors (TCI). TCS or TCI with strong or very strong effect could also be used as short-term emergency therapy. The 24-week treatment phase was followed by a follow-up phase of 12 weeks.

The design of the two studies was very similar, with only the timing of collecting the primary endpoint differing between PRIME and PRIME2. The inclusion and exclusion criteria of the studies were identical and the specifications for concomitant therapy and emergency therapy were also defined in the same way.

In the 7 days before the start of treatment, patients had to have given an average of at least 7 points on the Worst-Itching-Intensity-Numeric-Rating Scale (WI-NRS). In addition, study participants should have a total of at least 20 prurigo nodularis lesions on both legs and/or both arms and/or trunk at screening and on day 1. In addition, at least 2-week therapy with moderate to very strong TCS had to have been unsuccessful in the past or the use of TCS had to be contraindicated.

The primary endpoint of the studies was the number of patients with an improvement of at least 4 points in the WI-NRS. The endpoint was assessed after 24 weeks in the PRIME study and after 12 weeks in PRIME2. Other endpoints were collected, among others, in the categories of morbidity, health-related quality of life, and adverse events (AEs).

Suitability of the study for the benefit assessment: Implementation of the appropriate comparator therapy

The studies submitted by the pharmaceutical company are subject to significant uncertainties with regard to the implementation of the appropriate comparator therapy. Despite these uncertainties, a sufficient approximation to the appropriate comparator therapy is assumed overall, so that the present studies can be used for the benefit assessment.

It cannot be conclusively assessed to what extent the concomitant and emergency medication administered in the studies ensures the best possible, patient-individually optimised, add-on treatment to alleviate symptoms and improve quality of life according to the current state of medical knowledge. The reasons for these uncertainties lie in limitations regarding the use of topical glucocorticoids as well as the non-permitted use of UV-B phototherapy.

As part of the concomitant medication, the use of topical glucocorticoids was limited to preparations with a weak to moderate effect. Strong to very strong TCSs were only allowed to be used as so-called emergency therapy and also escalated - if possible, only 14 days after start of study. Furthermore, dose adjustments of TCS outside of emergency therapy were not planned.

Patients who were not stable on a TCS 14 days prior to start of study had their treatment discontinued, so that a significant percentage of the study participants did not receive TCS therapy. It remains unclear to what extent this can be sufficiently justified by the fact that, according to the inclusion criteria, at least 2-week therapy with moderate to very strong TCS had to have been unsuccessful in the past or the use of TCS had to be contraindicated. However, it can be assumed that for some of these refractory to therapy patients no further TCS therapy was indicated, since the guideline explicitly recommended this only as a short-term treatment option for chronic pruritus in case of steroid-responsive dermatosis and inflammatory scratch lesions.

Furthermore, the prohibition of UV-B phototherapy is to be seen critically as it contradicts the recommendations of the current S2k guideline. This therapy option should not have been excluded from the studies as its efficacy in inflammatory dermatoses has been proven in principle.

With regard to the emollients, initiation of therapy with a prescription emollient or change of emollient during the study was not planned. However, a stable topical basic therapy of prurigo nodularis existing for at least 3 months was a prerequisite for participation in the study and should also be continued as concomitant treatment during the course of the study.

Overall, the add-on treatment methods for patients do not seem to have been fully exhausted, so that doubts exist as to the extent to which the concomitant and emergency medication for the treatment of moderate to severe prurigo nodularis carried out in the studies corresponds to the current therapy standard. Despite these clear uncertainties, the results of the PRIME and PRIME2 studies and the meta-analysis of both studies can be regarded as a sufficient

approximation to the appropriate comparator therapy and can therefore be used for the benefit assessment.

Extent and probability of the additional benefit

Mortality

There were no deaths in the course of both studies.

Morbidity

Morbidity is presented in the present assessment using itching (WI-NRS), skin pain (skin pain NRS), sleep quality (sleep quality NRS), lesions, anxiety and depressive symptomatology, and health status (PGIC, EQ-5D-VAS *and PGIS*).

Symptomatology – itching, skin pain and sleep quality using Worst Itching Intensity Numerical Rating Scale (WI-NRS), skin pain NRS and sleep quality NRS

The WI-NRS, skin pain NRS and sleep quality NRS are self-reporting tools to determine worst itching, maximum skin pain and the worst possible sleep quality within the last 24 hours, respectively. The assessment is done using a numerical scale from 0 to 10. For the WI-NRS and skin pain NRS, 0 means no itching or pain and 10 means worst perceivable itching or pain. For the sleep quality NRS, in contrast, 0 means worst possible sleep and 10 best possible sleep.

For the endpoints of itching (improvement by ≥ 4 points), skin pain (improvement by ≥ 1.5 points) and sleep quality (improvement by ≥ 1.5 points), no usable data are available for the meta-analysis. Considering the PRIME study alone, there is a statistically significant advantage of dupilumab over placebo for all 3 endpoints listed when looking at the improvement up to week 24.

Symptomatology – Lesions using Prurigo Activity Score (PAS)

The PAS is a tool for the medical assessment of prurigo nodularis-lesions, which consists of 5 items. The type as well as the estimated number of lesions, the distribution over the body areas, the exact number of lesions in a representative body area, and the crusting and healing of the lesions are assessed. For the present assessment, the percentage of patients with 100% healed lesions at week 24 is used. Such complete healing of the external signs represents a patient-relevant endpoint.

For the endpoint of lesions (100% healed lesions), the meta-analysis of the PRIME and PRIME2 studies showed a statistically significant difference in favour of dupilumab.

Anxiety symptomatology and depressive symptomatology using the Hospital Anxiety and Depression Scale (HADS)

The HADS is a patient-reported instrument to assess the severity of anxiety and depressive symptomatology during the past week. The scale consists of 14 questions that are grouped into 2 subscales (anxiety symptomatology [HADS-A] and depressive symptomatology [HADS-

D]) with 7 items each. The questions are answered on scales from 0 to 3, with 0 indicating normal state and 3 indicating the highest level of anxiety or depression. The HADS subscales can each take values from 0 to 21 points. A score of 0 to 7 points is interpreted as a normal state, 8 to 10 points give an indication of anxiety or depression, and scores ≥ 11 indicate the probable presence of these disorders.

For the endpoints of anxiety symptomatology (improvement by ≥ 3.15 points) and depressive symptomatology (improvement by ≥ 3.15 points), the meta-analysis of the data at week 24 showed statistically significant advantages of dupilumab over the appropriate comparator therapy.

Health status using Patient Global Impression of Change (PGIC), Patient Global Impression of Severity (PGIS) and visual analogue scale of the EQ-5D questionnaire (EQ-5D VAS)

Health status was assessed in both studies using PGIC, EQ-5D VAS and PGIS.

The PGIC consists of a single question directed at the study participants to assess the overall change in disease since the start of treatment. The assessment is made on a 7-point scale with indications ranging from "very much better" to "very much worse". For the present assessment, the results on the percentage of patients who assessed their health status at week 24 as "very much better" or "much better" compared to the start of treatment are used.

The PGIS also consists of only one question asking patients to rate their severity of disease within the last week on a 4-point scale (1 = "none" to 4 = "severe"). The PGIS was collected at screening and at weeks 0, 4, 8, 12 and 24. The change in the PGIS at week 24 is used since the aim of the therapy in the present indication is an improvement in the health status.

Using EQ-5D VAS, the study participants rate their health status on a scale from 0 (worst perceivable health status) to 100 (best perceivable health status).

In the meta-analysis, the PGIC, PGIS and EQ-5D VAS evaluations at week 24 from baseline each showed statistically significant advantages of dupilumab over placebo.

<u>Quality of life</u>

Dermatology Life Quality Index (DLQI)

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 comprising values from 0 (not at all) to 3 (very strong). A total score is then formed (values from 0 to 30). The lower the score, the better is the health-related quality of life.

For the percentage of patients with a DLQI of 0 or 1, the meta-analysis of the PRIME and PRIME2 studies showed a statistically significant advantage of dupilumab over placebo.

Side effects

SAEs and eye disorders (SOC, AEs)

For the assessed population, the meta-analysis of the PRIME and PRIME2 studies did not show any statistically significant differences between the treatment groups in the evaluation of the endpoints of SAEs and eye disorders (SOC, AEs).

Discontinuation due to AEs

For the endpoint of discontinuation due to AEs, the meta-analysis showed a statistically significant difference in favour of dupilumab over placebo.

Overall assessment

For the assessment of the additional benefit of dupilumab, evaluations of the two double-blind, randomised, placebo-controlled phase III studies PRIME and PRIME2 (each in addition to a background therapy of emollients and, if necessary, topical glucocorticoids and topical calcineurin inhibitors) as well as the meta-analysis of both studies at week 24 are available. The implementation of the appropriate comparator therapy is subject to considerable uncertainties; nevertheless, the therapy in the comparator arm can be regarded as a sufficient approximation to the appropriate comparator therapy BSC. Therefore, the two studies PRIME and PRIME2, as well as the meta-analysis, are used for the benefit assessment.

In summary, in the morbidity category at week 24, there are exclusively statistically significant, clinically relevant effects in favour of dupilumab over placebo. In the meta-analysis, dupilumab showed a statistically significant improvement in the disease symptom of lesions (assessed by PAS) and the anxiety symptomatology or depressive symptomatology (assessed by HADS) compared to placebo. When looking at the PRIME study alone, statistically significant advantages of dupilumab over placebo were also shown for the disease symptoms of itching (assessed by WI-NRS), skin pain (assessed by skin pain NRS) and sleep quality (assessed by sleep quality NRS).

Furthermore, there are statistically significant advantages of dupilumab over placebo for the endpoints of health status (assessed by EQ-5D VAS, PGIC and PGIS) and health-related quality of life (assessed by DLQI) in the meta-analysis, whereby the observed advantages are also to be classified as clinically relevant.

In the category of side effects, there were no statistically significant differences between the treatment groups when looking at the results for SAEs and in detail for AEs in the SOC eye disorders. For the endpoint of discontinuation due to AEs, a statistically significant advantage of dupilumab over placebo was observed in the meta-analysis.

In the overall assessment, there were only statistically significant, positive effects for dupilumab compared to placebo at week 24. The advantages in the categories of morbidity and health-related quality of life are not offset by any disadvantages from the categories of mortality and side effects. Overall, however, these advantages cannot be quantified to the

extent due to uncertainties regarding the implementation of the appropriate comparator therapy.

Reliability of data (probability of additional benefit)

The PRIME and PRIME2 studies and the meta-analysis of both studies were used to assess the additional benefit.

Due to high and discrepant percentages of substituted values between the treatment arms, the risk of bias for the results on the endpoints of morbidity and health-related quality of life in the PRIME study is rated as high. The risk of bias is also estimated to be high for the other endpoints recorded in the PRIME study and the only separately evaluable endpoint of the PRIME2 study.

At the level of the meta-analysis, the uncertainties regarding the high percentages of substituted values, which differ between the treatment groups, also arise. Consequently, the reliability of data for all endpoints of the meta-analysis is also considered limited.

Against the background of these uncertainties, the reliability of data is rated in "hint" category.

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 "Dupixent is indicated for the treatment of adults with moderate-to-severe prurigo nodularis (PN) who are candidates for systemic therapy".

"Best supportive care" with the treatment options of topical basic therapy for skin care, topical glucocorticoids and UV-B phototherapy was determined by the G-BA as an appropriate comparator therapy.

For this patient group, the pharmaceutical company presents results of the two double-blind, randomised, placebo-controlled phase III studies PRIME and PRIME2 and their meta-analysis, in which dupilumab was compared with placebo (in each case in addition to background therapy) over a period of 24 weeks.

There were no deaths in both studies.

In the morbidity category, there were only statistically significant effects in favour of dupilumab over placebo. In the studies, statistically significant improvements were observed in the disease symptom of lesions (PAS), anxiety symptomatology or depressive symptomatology (HADS) and the disease symptoms of itching (WI-NRS), skin pain (skin pain NRS) and sleep quality (sleep quality NRS) of dupilumab compared to placebo. For the endpoints of health status (EQ-5D VAS, PGIC and PGIS) and health-related quality of life (DLQI), dupilumab showed statistically significant advantages compared to placebo.

In the category of side effects, there were no statistically significant differences between the treatment groups for the SAEs or AEs of the SOC eye disorders. For the endpoint of

discontinuation due to AEs, a statistically significant advantage of dupilumab over placebo was observed.

Overall, however, these advantages cannot be quantified to the extent due to uncertainties regarding the implementation of the appropriate comparator therapy.

The significance of the evidence is rated in the hint category, as uncertainties arise with regard to high and different percentages of substituted values between treatment groups.

In the overall assessment, a hint for a non-quantifiable additional benefit of dupilumab is identified.

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

The information on the number of patients is based on the target population in statutory health insurance (SHI).

The G-BA bases its resolution on the patient numbers from the dossier submitted by the pharmaceutical company.

Due to the partly inconsistent definition and terminology of the disease prurigo nodularis, the number given by the pharmaceutical company for the upper and lower limits is subject to uncertainty. Due to differences in the operationalisation of the severity levels in the studies presented compared to the SHI routine data analysis, it is particularly unclear to what extent adults with milder severity levels were also included in the estimation. In addition, some patients may not have been assigned ICD-10 code L28.1 for *prurigo nodularis* but ICD-10 diagnosis L28.2 for *other prurigo*.

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: 26 June 2023):

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

2.4 Treatment costs

The treatment costs are based on the requirements in the product information and the information listed in the LAUER-TAXE® (last revised: 15 September 2023).

In order to improve comparability, the costs of the medicinal products were approximated both on the basis of the pharmacy sales price level and also deducting the statutory rebates

in accordance with Section 130 and Section 130a SGB V. To calculate the annual treatment costs, the required number of packs of a particular potency was first determined on the basis of consumption. Having determined the number of packs of a particular potency, the costs of the medicinal products were then calculated on the basis of the costs per pack after deduction of the statutory rebates.

The treatment costs for best supportive care are different from patient to patient. Because best supportive care has been determined as an appropriate comparator therapy, this is also reflected in the medicinal product to be assessed. The type and scope of best supportive care can vary depending on the medicinal product to be assessed and the comparator therapy.

Treatment period:

If no maximum treatment duration is specified in the product information, the treatment duration is assumed to be one year (365 days), even if the actual treatment duration varies from patient to patient and/or is shorter on average. The time unit "days" is used to calculate the "number of treatments/ patient/ year", time intervals between individual treatments and for the maximum treatment duration, if specified in the product information.

Designation of the therapy	Treatment mode	Number of treatments/ patient/ year	Treatment duration/ treatment (days)	Treatment days/ patient/ year
Medicinal product to be assessed				
Dupilumab	Continuously, 1 x every 14 days	26.1	1	26.1
Best supportive care	Different from patient to patient			
Appropriate comparator therapy				
Best supportive care	Different from patient to patient			

Consumption:

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

In general, initial induction regimens are not taken into account for the cost representation, since the present indication is a chronic disease with a continuous need for therapy and, as a rule, no new titration or dose adjustment is required after initial titration.

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 x 300 mg	26.1	26.1 x 300 mg
Best supportive care	Different from patient to patient				
Appropriate comparator therapy					
Best supportive care	Different from patient to patient				

Costs:

Costs of the medicinal products:

Designation of the therapy	Packaging size	Costs (pharmacy sales price)	Rebate Section 130 SGB V	Rebate Section 130a SGB V	Costs after deduction of statutory rebates
Medicinal product to be assessed					
Dupilumab 300 mg	6 SFI	€ 3,990.65	€ 2.00	€ 385.05	€ 3,603.60
Best supportive care	Different from patient to patient				
Appropriate comparator therapy					
Best supportive care	Different from patient to patient				
Abbreviations: SFI = solution for injection in pre-filled pen					

LAUER-TAXE® last revised: 15 September 2023

Costs for additionally required SHI services:

Only costs directly related to the use of the medicinal product are taken into account. If there are regular differences in the necessary use of medical treatment or in the prescription of other services in the use of the medicinal product to be evaluated and the appropriate comparator therapy in accordance with the product information, the costs incurred for this must be taken into account as costs for additionally required SHI services.

Medical treatment costs, medical fee services, and costs incurred for routine examinations (e.g. regular laboratory services such as blood count tests) that do not exceed the standard expenditure in the course of the treatment are not shown.

Because there are no regular differences in the necessary use of medical treatment or in the prescription of other services in the use of the medicinal product to be evaluated and the

appropriate comparator therapy in accordance with the product information, no costs for additionally required SHI services need to be taken into account.

2.5 Designation of medicinal products with new active ingredients according to Section 35a, paragraph 3, sentence 4 SGB V that can be used in a combination therapy with the assessed medicinal product

According to Section 35a, paragraph 3, sentence 4, the G-BA designates all medicinal products with new active ingredients that can be used in a combination therapy with the assessed medicinal product for the therapeutic indication to be assessed on the basis of the marketing authorisation under Medicinal Products Act.

Basic principles of the assessed medicinal product

A designation in accordance with Section 35a, paragraph 3, sentence 4 SGB V requires that it is examined based on the product information for the assessed medicinal product whether it can be used in a combination therapy with other medicinal products in the assessed therapeutic indication. In the first step, the examination is carried out on the basis of all sections of the currently valid product information for the assessed medicinal product.

If the assessed medicinal product contains an active ingredient or a fixed combination of active ingredients in the therapeutic indication of the resolution (assessed therapeutic indication) and is approved exclusively for use in monotherapy, a combination therapy is not considered due to the marketing authorisation under Medicinal Products Act, which is why no designation is made.

A designation is also not considered if the G-BA has decided on an exemption as a reserve antibiotic for the assessed medicinal product in accordance with Section 35a, paragraph 1c, sentence 1 SGB V. The additional benefit is deemed to be proven if the G-BA has decided on an exemption for a reserve antibiotic in accordance with Section 35a, paragraph 1c, sentence 1 SGB V; the extent of the additional benefit and its therapeutic significance are not to be assessed by the G-BA. Due to the lack of an assessment mandate by the G-BA following the resolution on an exemption according to Section 35a, paragraph 1c, sentence 1 SGB V with regard to the extent of the additional benefit and the therapeutic significance of the reserve antibiotic to be assessed, there is a limitation due to the procedural privileging of the pharmaceutical companies to the effect that neither the proof of an existing nor an expected at least considerable additional benefit is possible for exempted reserve antibiotics in the procedures according to Section 35a paragraph 1 or 6 SGB V and Section 35a paragraph 1d SGB V. The procedural privileging of the reserve antibiotics exempted according to Section 35a, paragraph 1c, sentence 1 SGB V must therefore also be taken into account at the level of designation according to Section 35a, paragraph 3, sentence 4 SGB V in order to avoid valuation contradictions.

With regard to the further examination steps, a differentiation is made between a "determined" or "undetermined" combination, which may also be the basis for a designation.

A "determined combination" exists if one or more individual active ingredients which can be used in combination with the assessed medicinal product in the assessed therapeutic indication are specifically named.

An "undetermined combination" exists if there is information on a combination therapy, but no specific active ingredients are named. An undetermined combination may be present if the information on a combination therapy:

- names a product class or group from which some active ingredients not specified in detail can be used in combination therapy with the assessed medicinal product, or
- does not name any active ingredients, product classes or groups, but the assessed medicinal product is used in addition to a therapeutic indication described in more detail in the relevant product information, which, however, does not include information on active ingredients within the scope of this therapeutic indication.

In the case of information on "determined" or "undetermined" combinations, the assessed medicinal product can be used in a combination therapy according to this information on the basis of the marketing authorisation under Medicinal Products Act. For the designation, the G-BA, within the scope of its legislative discretion, uses the constellation of a "determined" or an "undetermined" combination as a justifiable interpretation variant.

If a designation as a so-called determined or as a so-called indetermined combination is omitted due to the lack of information on a combination therapy in the product information of the assessed medicinal product, the non-designation in the resolution according to Section 35a, paragraph 3, sentence 1 SGB V does not affect the possibility that the assessed medicinal product can be used in an open-label combination under marketing authorisation regulations.

Concomitant active ingredient:

The concomitant active ingredient is a medicinal product with new active ingredients that can be used in combination therapy with the assessed medicinal product for the therapeutic indication to be assessed.

For a medicinal product to be considered as a concomitant active ingredient, it must be classified as a medicinal product with new active ingredients according to Section 2 paragraph 1 Ordinance on the Benefit Assessment of Pharmaceuticals (AM-NutzenV) in conjunction with the corresponding regulations in Chapter 5 of the Rules of Procedure of the G-BA as of the date of the present resolution. In addition, the medicinal product must be approved in the assessed therapeutic indication, whereby a marketing authorisation is sufficient only for a sub-area of the assessed therapeutic indication.

Based on an "undetermined combination", the concomitant active ingredient must be attributable to the information on the product class or group or the therapeutic indication according to the product information of the assessed medicinal product in the assessed therapeutic indication, whereby the definition of a product class or group is based on the corresponding information in the product information of the assessed medicinal product.

In addition, there must be no reasons for exclusion of the concomitant active ingredient from a combination therapy with the assessed medicinal product, in particular no exclusive marketing authorisation as monotherapy.

In addition, all sections of the currently valid product information of the eligible concomitant active ingredient are checked to see whether there is any information that excludes its use in combination therapy with the assessed medicinal product in the assessed therapeutic

indication under marketing authorisation regulations. Corresponding information can be, for example, dosage information or warnings. In the event that the medicinal product is used as part of a determined or undetermined combination which does not include the assessed medicinal product, a combination with the assessed medicinal product shall be excluded.

Furthermore, the product information of the assessed medicinal product must not contain any specific information that excludes its use in combination therapy with the eligible concomitant active ingredient in the assessed therapeutic indication under marketing authorisation regulations.

Medicinal products with new active ingredients for which the G-BA has decided on an exemption as a reserve antibiotic in accordance with Section 35a, paragraph 1c, sentence 1 SGB V are ineligible as concomitant active ingredients. The procedural privileging of the reserve antibiotics exempted according to Section 35a, paragraph 1c, sentence 1 SGB V also applies accordingly to the medicinal product eligible as a concomitant active ingredient.

Designation

The medicinal products which have been determined as concomitant active ingredients in accordance with the above points of examination are named by indicating the relevant active ingredient and the invented name. The designation may include several active ingredients, provided that several medicinal products with new active ingredients may be used in the same combination therapy with the assessed medicinal product or different combinations with different medicinal products with new active ingredients form the basis of the designation.

If the present resolution on the assessed medicinal product in the assessed therapeutic indication contains several patient groups, the designation of concomitant active ingredients shall be made separately for each of the patient groups.

Exception to the designation

The designation excludes combination therapies for which - patient group-related - a considerable or major additional benefit has been determined by resolution according to Section 35a, paragraph 3, sentence 1 SGB V or it has been determined according to Section 35a, paragraph 1d, sentence 1 SGB V that at least considerable additional benefit of the combination can be expected. In this context, the combination therapy that is excluded from the designation must, as a rule, be identical to the combination therapy on which the preceding findings were based.

In the case of designations based on undetermined combinations, only those concomitant active ingredients - based on a resolution according to Section 35a, paragraph 3, sentence 1 SGB V on the assessed medicinal product in which a considerable or major additional benefit had been determined - which were approved at the time of this resolution are excluded from the designation.

Legal effects of the designation

The designation of combinations is carried out in accordance with the legal requirements according to Section 35a, paragraph 3, sentence 4 and is used exclusively to implement the combination discount according to Section 130e SGB V between health insurance funds and

pharmaceutical companies. The designation is not associated with a statement as to the extent to which a therapy with the assessed medicinal products in combination with the designated medicinal products corresponds to the generally recognised state of medical knowledge. The examination was carried out exclusively on the basis of the possibility under Medicinal Products Act to use the medicinal products in combination therapy in the assessed therapeutic indication based on the product information; the generally recognised state of medical knowledge or the use of the medicinal products in the reality of care were not the subject of the examination due to the lack of an assessment mandate of the G-BA within the framework of Section 35a, paragraph 3, sentence 4 SGBV.

The findings made neither restrict the scope of treatment required to fulfil the medical treatment mandate, nor do they make statements about expediency or economic feasibility.

Justification for the findings on designation in the present resolution:

Adults with moderate-to-severe prurigo nodularis (PN) who are candidates for systemic therapy

No medicinal product with new active ingredients that can be used in a combination therapy and fulfils the requirements of Section 35a, paragraph 3, sentence 4 SGB V.

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 10 May 2022, the Subcommittee on Medicinal Products determined the appropriate comparator therapy.

A review of the appropriate comparator therapy took place once the positive opinion was granted. The Subcommittee on Medicinal Products determined the appropriate comparator therapy at its session on 13 April 2023.

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

By letter dated 31 March 2023 in conjunction with the resolution of the G-BA of 1 August 2011 concerning the commissioning of the IQWiG to assess the benefits of medicinal products with new active ingredients in accordance with Section 35a SGB V, the G-BA commissioned the IQWiG to assess the dossier concerning the active ingredient dupilumab.

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

The oral hearing was held on 8 August 2023.

By letter dated 8 August 2023, the IQWiG was commissioned with a supplementary assessment. The addendum prepared by IQWiG was submitted to the G-BA on 14 September 2023.

In order to prepare a recommendation for a resolution, the Subcommittee on Medicinal Products commissioned a working group (Section 35a) consisting of the members nominated by the leading organisations of the care providers, the members nominated by the SHI umbrella organisation, and representatives of the patient organisations. Representatives of the IQWiG also participate in the sessions.

The evaluation of the written statements received and the oral hearing was discussed at the session of the subcommittee on 26 September 2023, and the proposed resolution was approved.

At its session on 5 October 2023, the plenum adopted a resolution to amend the Pharmaceuticals Directive.

Chronological course of consultation

Session	Date	Subject of consultation
Subcommittee Medicinal products	10 May 2022	Determination of the appropriate comparator therapy
Subcommittee Medicinal products	13 April 2023	New implementation of the appropriate comparator therapy
Working group Section 35a	1 August 2023	Information on written statements received; preparation of the oral hearing
Subcommittee Medicinal products	8 August 2023	Conduct of the oral hearing, Commissioning of the IQWiG with the supplementary assessment of documents
Working group Section 35a	15 August 2023; 19 September 2023	Consultation on the dossier assessment by the IQWiG, evaluation of the written statement procedure
Subcommittee Medicinal products	26 September 2023	Concluding discussion of the draft resolution
Plenum	5 October 2023	Adoption of the resolution on the amendment of the AM-RL

Berlin, 5 October 2023

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

Prof. Hecken