Dupilumab (prurigo nodularis)

Benefit assessment according to §35a SGB V[1]

EXTRACT

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[2] Table numbers start with “2” as numbering follows that of the full dossier assessment.

I List of abbreviations

Abbreviation	Meaning
ACT	appropriate comparator therapy
AE	adverse event
BSC	best supportive care
G-BA	Gemeinsamer Bundesausschuss (Federal Joint Committee)
IQWiG	Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen (Institute for Quality and Efficiency in Health Care)
RCT	randomized controlled trial
SGB	Sozialgesetzbuch (Social Code Book)
TCI	topical calcineurin inhibitor
TCS	topical corticosteroids
UVB	ultraviolet B radiation
WI-NRS	Worst Itch Numeric Rating Scale

I 1 Executive summary of the benefit assessment

Background

In accordance with §35a Social Code Book V, the Federal Joint Committee (G-BA) commissioned the Institute for Quality and Efficiency in Health Care (IQWiG) to assess the benefit of the drug dupilumab. The assessment is based on a dossier compiled by the pharmaceutical company (hereinafter referred to as the "company"). The dossier was sent to IQWiG on 31 March 2023.

Research question

The aim of the present report is to assess the added benefit of dupilumab in comparison with best supportive care (BSC) as appropriate comparator therapy (ACT) in the treatment of moderate-to-severe prurigo nodularis in adults who are candidates for systemic therapy.

The research question presented in Table 2 results from the ACT specified by the G-BA.

Table 2: Research question of the benefit assessment of dupilumab

Therapeutic indication	**ACT**[a]
Moderate-to-severe prurigo nodularis in adults who are candidates for systemic therapy	BSC[b, c]

a. Presented is the ACT specified by the G-BA.
b. BSC refers to the therapy that provides the patient with the best possible, individually optimized, supportive treatment to alleviate symptoms and improve the quality of life. BSC may include the use of topical basic skin care therapy, topical corticosteroids, and UVB phototherapy. If treatment needs to be adjusted for the patients (e.g. different dosages of topical corticosteroids), such adjustments should be made.
c. In the present case, the drugs recommended in guidelines or used in clinical practice, that have no or no explicit approval for the present therapeutic indication, cannot be considered as ACT in the narrower sense within the meaning of §2 para 1 S. 3, §12 SGB V (BSG judgment of 22 February 2023, reference number: B 3 KR 14/21 R).

ACT: appropriate comparator therapy; BSC: best supportive care; BSG: Federal Social Court; G-BA: Federal Joint Committee.; SGB: Social Code Book; UVB: ultraviolet B radiation

On 13 April 2023, 2 months after the company submitted the dossier (31 March 2023), the G-BA modified the ACT as shown in Table 2. The original ACT of 12 July 2022 was individualized therapy taking into account the respective prior therapies and the severity of the symptoms. The company claimed to have followed the ACT specified by the G-BA. The information provided by the company in the dossier relates to the original ACT, however.

The present benefit assessment is based on the adjusted ACT.

The assessment is conducted by means of patient-relevant outcomes on the basis of the data provided by the company in the dossier. Randomized controlled trials (RCTs) with a minimum duration of 24 weeks are used for the derivation of added benefit.

Results

No relevant study was identified from the check of the information retrieval.

In contrast, the company identified the RCTs LIBERTY-PN PRIME and LIBERTY-PN PRIME2, referred to as “PRIME” and “PRIME2” in the dossier and in the rest of this report, and used them to assess the added benefit of dupilumab.

The data presented by the company are unsuitable for drawing conclusions on the added benefit of dupilumab in comparison with the ACT. This is justified below.

Evidence presented by the company – studies PRIME and PRIME2

The studies PRIME and PRIME2 are double-blind RCTs comparing dupilumab with placebo. The 2 studies were planned and conducted analogously. The inclusion and exclusion criteria of both studies were identical, as was the definition of the concomitant therapy permitted and prohibited by the study protocol and of the specifications for rescue treatment.

The studies included patients 18 to 80 years of age with prurigo nodularis diagnosed for at least 3 months. According to the study protocol, patients had to have an average score of at least 7 on the Worst Itch Numeric Rating Scale (WI-NRS) in the 7 days prior to treatment start. Furthermore, patients had to have a minimum of 20 prurigo nodularis lesions in total on both legs, and/or both arms and/or trunk, at screening visit and on day 1. According to the inclusion criteria, they also had to have a history of failing an at least 2-week course of medium-to-superpotent topical corticosteroids (TCS), or the use of TCS was not medically advisable.

In the PRIME study, a total of 151 patients were randomized in a 1:1 ratio, 75 to the dupilumab arm and 76 to the placebo arm. The PRIME2 study included 160 patients; 78 were allocated to the dupilumab arm and 82 to the placebo arm.

During the 24-week treatment phase, patients were treated with dupilumab in compliance with the Summary of Product Characteristics (SPC) or received a placebo. In both study arms, patients additionally received background therapy. The 24-week treatment phase was followed by a 12-week follow-up phase.

The primary outcome was defined as the number of patients with WI-NRS improvement by at least 4 points, recorded after 24 weeks in the PRIME study, and after 12 weeks in the PRIME2 study. Patient-relevant secondary outcomes were surveyed in the categories of mortality, morbidity, health-related quality of life, and adverse events (AEs).

Appropriate comparator therapy not implemented in the studies PRIME and PRIME2

The G-BA specified BSC as the ACT for dupilumab in the treatment of moderate-to-severe prurigo nodularis in adults who are candidates for systemic therapy. BSC refers to the therapy that provides the patient with the best possible, individually optimized, supportive treatment to alleviate symptoms and improve the quality of life. BSC may include the use of topical basic skin care therapy, TCS, and ultraviolet B radiation (UVB) phototherapy. If treatment needs to be adjusted for the patients (e.g. different dosages of TCS), such adjustments should be made.

In the PRIME and PRIME2 studies presented by the company, patients in both study arms received background therapy, which included the mandatory use of emollients and the optional continuation of stable treatment with low to medium potency TCS or topical calcineurin inhibitors (TCIs). If escalation was needed throughout the study, rescue treatment with high potency or superpotent TCS or TCIs could be initiated.

Even though the measures of background and rescue treatment in the PRIME and PRIME2 studies contain components of the ACT BSC specified by the G-BA, this ACT was not implemented due to the restrictions contained in the study protocols. This is explained below.

Restriction of the background therapy with TCS

Patients on stable TCS therapy at screening could continue this therapy during the entire study duration. However, background therapy with TCS was restricted to low to medium potency preparations, so that high potency to superpotent TCS had to be decreased in potency before study start. Furthermore, continued treatment with TCS throughout the study was only allowed if this treatment had been stable for at least 14 days before study start. The preparation applied, the dosage or the frequency were not allowed to be changed during the study. According to the study protocols, treatment in both studies could only be adjusted, e.g. with regard to the dosing listed in the notes on the ACT, by initiating rescue treatment. Overall, about 60.9% of patients in the PRIME study and 56.3% in PRIME2 were receiving stable background therapy with TCS or TCIs at screening.

Rescue therapy is not an adequate implementation of the appropriate comparator therapy

In both studies, high potency and superpotent TCS or TCIs could be used for rescue therapy. According to the study protocol, rescue therapy was indicated in case of intolerable symptoms, for example, and should be started, if possible, at least 14 days after initiation of treatment. Continuation of the study treatment was allowed.

The study report shows that 21.1% of patients in the placebo arm in the PRIME study, and 24.4% in PRIME2 received rescue therapy. In the dupilumab arm, the proportion was notably lower, at 6.7% (PRIME) and 7.7% (PRIME2).

Considering background and rescue therapy, TCS of any potency and TCIs were available in the studies, but rescue therapy is not an adequate therapy in the sense of BSC.

Prohibition of UVB phototherapy

In the PRIME and PRIME2 studies, phototherapy was prohibited in both study arms within 4 weeks before screening and during the entire study duration. Receiving phototherapy during the study led to discontinuation of the study medication. Compared with TCS, there is a weakened but consistent recommendation for UVB phototherapy in guidelines. As described in the G-BA's notes, it should be possible to use UVB phototherapy as part of BSC.

Stable use of emollients

According to the study protocol, emollients had to be applied once or twice daily for at least 5 out of the 7 consecutive days before treatment start. With the exception of the use of products with itch-relieving ingredients, all types of emollients were basically allowed. Prescription emollients and emollients containing additives such as ceramide, hyaluronic acid, urea, menthol, polidocanol, or filaggrin degradation products could only be used if already used at stable doses before screening. Changing emollients was not allowed during the study.

Summary

In the placebo-controlled RCTs PRIME and PRIME2 presented by the company, the allowed concomitant treatments were restricted by the study protocol. High potency to superpotent TCS could not be used outside rescue therapy, and dose adjustment of the TCS therapy was also not allowed. The use of UVB phototherapy was also prohibited. Thus, key components of the ACT BSC were not allowed in the studies, or their use was restricted. The restrictions of regular care in the studies are also reflected in a high proportion of patients with rescue therapy in the placebo arms.

The ACT BSC was therefore not implemented in the PRIME and PRIME2 studies presented, and no data suitable for answering the research question of this benefit assessment are available.

Results on added benefit

Since no relevant study is available for the benefit assessment, there is no hint of an added benefit of dupilumab in comparison with the ACT; an added benefit is therefore not proven.

Probability and extent of added benefit, patient groups with therapeutically important added benefit[3]

Table 3 shows a summary of probability and extent of the added benefit of dupilumab.

Table 3: Dupilumab – probability and extent of added benefit

Therapeutic indication	ACT[a]	Probability and extent of added benefit
Moderate-to-severe prurigo nodularis in adults who are candidates for systemic therapy	BSC[b, c]	Added benefit not proven

a. Presented is the ACT specified by the G-BA.
b. BSC refers to the therapy that provides the patient with the best possible, individually optimized, supportive treatment to alleviate symptoms and improve the quality of life. BSC may include the use of topical basic skin care therapy, topical corticosteroids, and UVB phototherapy. If treatment needs to be adjusted for the patients (e.g. different dosages of topical corticosteroids), such adjustments should be made.
c. In the present case, the drugs recommended in guidelines or used in clinical practice, that have no or no explicit approval for the present therapeutic indication, cannot be considered as ACT in the narrower sense within the meaning of §2 para 1 S. 3, §12 SGB V (BSG judgment of 22 February 2023, reference number: B 3 KR 14/21 R).

ACT: appropriate comparator therapy; BSC: best supportive care; BSG: Federal Social Court; G-BA: Federal Joint Committee.; SGB: Social Code Book; UVB: ultraviolet B radiation

The G-BA decides on the added benefit.

[3] On the basis of the scientific data analysed, IQWiG draws conclusions on the (added) benefit or harm of an intervention for each patient-relevant outcome. Depending on the number of studies analysed, the certainty of their results, and the direction and statistical significance of treatment effects, conclusions on the probability of (added) benefit or harm are graded into 4 categories: (1) “proof”, (2) “indication”, (3) “hint”, or (4) none of the first 3 categories applies (i.e., no data available or conclusions 1 to 3 cannot be drawn from the available data). The extent of added benefit or harm is graded into 3 categories: (1) major, (2) considerable, (3) minor (in addition, 3 further categories may apply: non-quantifiable extent of added benefit, added benefit not proven, or less benefit). For further details see [1,2].

I 2 Research question

The aim of the present report is to assess the added benefit of dupilumab in comparison with BSC as ACT in the treatment of moderate-to-severe prurigo nodularis in adults who are candidates for systemic therapy.

The research question presented in Table 4 results from the ACT specified by the G-BA.

Table 4: Research question of the benefit assessment of dupilumab

Therapeutic indication	**ACT[a]**
Moderate-to-severe prurigo nodularis in adults who are candidates for systemic therapy	BSC[b, c]

a. Presented is the ACT specified by the G-BA.
b. BSC refers to the therapy that provides the patient with the best possible, individually optimized, supportive treatment to alleviate symptoms and improve the quality of life. BSC may include the use of topical basic skin care therapy, topical corticosteroids, and UVB phototherapy. If treatment needs to be adjusted for the patients (e.g. different dosages of topical corticosteroids), such adjustments should be made.
c. In the present case, the drugs recommended in guidelines or used in clinical practice, that have no or no explicit approval for the present therapeutic indication, cannot be considered as ACT in the narrower sense within the meaning of §2 para 1 S. 3, §12 SGB V (BSG judgment of 22 February 2023, reference number: B 3 KR 14/21 R).

ACT: appropriate comparator therapy; BSC: best supportive care; BSG: Federal Social Court; G-BA: Federal Joint Committee.; SGB: Social Code Book; UVB: ultraviolet B radiation

On 13 April 2023, 2 months after the company submitted the dossier (31 March 2023), the G-BA modified the ACT as shown in Table 4. The original ACT of 12 July 2022 was individualized therapy taking into account the respective prior therapies and the severity of the symptoms. The company claimed to have followed the ACT specified by the G-BA. The information provided by the company in the dossier relates to the original ACT, however.

The present benefit assessment is based on the adjusted ACT.

The assessment is conducted by means of patient-relevant outcomes on the basis of the data provided by the company in the dossier. RCTs with a minimum duration of 24 weeks are used for the derivation of added benefit. This concurs with the company's inclusion criteria.

I 3 Information retrieval and study pool

The study pool of the assessment was compiled on the basis of the following information:

Sources of the company in the dossier:

- study list on dupilumab (status: 16 January 2023)
- bibliographical literature search on dupilumab (last search on 16 January 2023)
- search in trial registries/trial results databases for studies on dupilumab (last search on 17 January 2023)
- search on the G-BA website for dupilumab (last search on 17 January 2023)

To check the completeness of the study pool:

- search in trial registries for studies on dupilumab (last search on 18 April 2023); for search strategies, see I Appendix A of the full dossier assessment

No relevant study was identified from the check.

In contrast, the company identified the RCTs LIBERTY-PN PRIME [3] and LIBERTY-PN PRIME2 [4], referred to as “PRIME” and “PRIME2” in the dossier and in the rest of this report, and used them to assess the added benefit of dupilumab.

The data presented by the company are unsuitable for drawing conclusions on the added benefit of dupilumab in comparison with the ACT. This is justified below.

Evidence presented by the company – studies PRIME and PRIME2

The studies PRIME and PRIME2 are double-blind RCTs comparing dupilumab with placebo. The 2 studies were planned and conducted analogously. The inclusion and exclusion criteria of both studies were identical, as was the definition of the concomitant therapy permitted and prohibited by the study protocol and of the specifications for rescue treatment.

The studies included patients 18 to 80 years of age with prurigo nodularis diagnosed for at least 3 months. According to the study protocol, patients had to have an average score of at least 7 on the WI-NRS in the 7 days prior to treatment start. Furthermore, patients had to have a minimum of 20 prurigo nodularis lesions in total on both legs, and/or both arms and/or trunk, at screening visit and on day 1. According to the inclusion criteria, they also had to have a history of failing an at least 2-week course of medium-to-superpotent TCS, or the use of TCS was not medically advisable. However, a failed treatment attempt with TCS in the past does not mean that further treatment with TCS is no longer an option for these patients.

In the PRIME study, a total of 151 patients were randomized in a 1:1 ratio, 75 to the dupilumab arm and 76 to the placebo arm. The PRIME2 study included 160 patients; 78 were allocated to the dupilumab arm and 82 to the placebo arm. Randomization in each case was stratified by history of atopy (atopic or non-atopic), stable use of TCS or TCIs (yes or no), and country/territory code.

During the 24-week treatment phase, patients were treated with dupilumab in compliance with the SPC [5] or received a placebo. In both study arms, patients additionally received background therapy (see section on the implementation of the ACT below). The 24-week treatment phase was followed by a 12-week follow-up phase.

The primary outcome was defined as the number of patients with WI-NRS improvement by at least 4 points, recorded after 24 weeks in the PRIME study, and after 12 weeks in the PRIME2 study. Patient-relevant secondary outcomes were surveyed in the categories of mortality, morbidity, health-related quality of life, and AEs.

Appropriate comparator therapy not implemented in the studies PRIME and PRIME2

The G-BA specified BSC as the ACT for dupilumab in the treatment of moderate-to-severe prurigo nodularis in adults who are candidates for systemic therapy. BSC refers to the therapy that provides the patient with the best possible, individually optimized, supportive treatment to alleviate symptoms and improve the quality of life. BSC may include the use of topical basic skin care therapy, TCS, and UVB phototherapy. If treatment needs to be adjusted for the patients (e.g. different dosages of TCS), such adjustments should be made.

In accordance with international guidelines [6,7], The German S2k guideline on the diagnosis and treatment of chronic pruritus [8] recommends a stepwise approach to symptomatic therapy, depending on the severity of pruritus, comorbidity, expected side effects, comedications, and the patient's general condition. Recommendations include basic lipid-replenishing and hydrating therapy with emollients alone or in combination with specific topical or systemic drugs and/or UV phototherapy.

In the PRIME and PRIME2 studies presented by the company, patients in both study arms received background therapy, which included the mandatory use of emollients and the optional continuation of stable treatment with low to medium potency TCS or TCIs. If escalation was needed throughout the study, rescue treatment with high potency or superpotent TCS or TCIs could be initiated.

Even though the measures of background and rescue treatment in the PRIME and PRIME2 studies contain components of the ACT BSC specified by the G-BA, this ACT was not implemented due to the restrictions contained in the study protocols. This is explained below.

Restriction of the background therapy with TCS

Patients on stable TCS therapy at screening could continue this therapy during the entire study duration. However, background therapy with TCS was restricted to low to medium potency preparations, so that high potency to superpotent TCS had to be decreased in potency before study start. However, the guideline recommendations do not impose any restriction with regard to potency, or they even explicitly include those with higher potency [6-8]. Furthermore, continued treatment with TCS throughout the study was only allowed if this treatment had been stable for at least 14 days before study start. The preparation applied, the dosage or the frequency were not allowed to be changed during the study. Only if lesions had already resolved, the application of the TCS to those sites could be stopped. According to the study protocols, treatment in both studies could only be adjusted, e.g. with regard to the dosing listed in the notes on the ACT, by initiating rescue treatment. Overall, about 60.9% of patients in the PRIME study and 56.3% in PRIME2 were receiving stable background therapy with TCS or TCIs at screening, with TCIs being used only sporadically in fewer than 10% of patients throughout the study period.

Rescue therapy is not an adequate implementation of the appropriate comparator therapy

In both studies, high potency and superpotent TCS or TCIs could be used for rescue therapy, but TCIs were only an option for patients who were not already receiving TCIs as background therapy. According to the study protocol, rescue therapy was indicated in case of intolerable symptoms, for example, and should be started, if possible, at least 14 days after initiation of treatment. Continuation of the study treatment was allowed.

The study report shows that 21.1% of patients in the placebo arm in the PRIME study, and 24.4% in PRIME2 received rescue therapy. In the dupilumab arm, the proportion was notably lower, at 6.7% (PRIME) and 7.7% (PRIME2).

Considering background and rescue therapy, TCS of any potency and TCIs were available in the studies, but rescue therapy is not an adequate therapy in the sense of BSC.

Prohibition of UVB phototherapy

In the PRIME and PRIME2 studies, phototherapy was prohibited in both study arms within 4 weeks before screening and during the entire study duration. Receiving phototherapy during the study led to discontinuation of the study medication. In the dossier, the company justified the prohibition of phototherapy with the only very weak evidence as well as a lack of efficacy, time-intensive treatment, and an increased risk of photocarcinogenesis following long-term treatment. According to the company, there is an unfavourable benefit-risk ratio, particularly for older patients. In contrast to the argumentation by the company, guidelines recommend UVB phototherapy – albeit with a lower grade of recommendation compared with TCS [6-8].

As described in the G-BA's notes, it should be possible to use UVB phototherapy as part of BSC.

Stable use of emollients

According to the study protocol, emollients had to be applied once or twice daily for at least 5 out of the 7 consecutive days before treatment start. With the exception of the use of products with itch-relieving ingredients, all types of emollients were basically allowed. Prescription emollients and emollients containing certain additives (such as ceramide, hyaluronic acid, urea, menthol, polidocanol, or filaggrin degradation products, for example) could only be used if already used at stable doses before screening, however. Changing emollients was not allowed during the study.

Summary

In the placebo-controlled RCTs PRIME and PRIME2 presented by the company, the allowed concomitant treatments were restricted by the study protocol. High potency to superpotent TCS could not be used outside rescue therapy, and dose adjustment of an already existing TCS therapy was also not allowed. The use of UVB phototherapy was also prohibited. Thus, key components of the ACT BSC were not allowed in the studies, or their use was restricted. Besides the high proportion of patients with rescue therapy in the placebo arms, the restrictions of regular care in the studies are also reflected in the use of medications prohibited in the studies: In the PRIME study, 17.1% of patients received prohibited medication in the placebo arm, compared with 5.3% in the dupilumab arm. In the PRIME2 study, the proportion was 11.0% (placebo) versus 3.8% (dupilumab). In the placebo arms, mainly systemic immunosuppressants or immunomodulators were used.

The ACT BSC was therefore not implemented in the PRIME and PRIME2 studies presented, and no data suitable for answering the research question of this benefit assessment are available.

I 4 Results on added benefit

No suitable data are available to assess the added benefit of dupilumab in comparison with the ACT in the treatment of moderate-to-severe prurigo nodularis in adults who are candidates for systemic therapy. There is no hint of an added benefit of dupilumab in comparison with the ACT; an added benefit is therefore not proven.

I 5 Probability and extent of added benefit

The result of the assessment of the added benefit of dupilumab in comparison with the ACT is summarized in Table 5.

Table 5: Dupilumab – probability and extent of added benefit

Therapeutic indication	**ACT[a]**	**Probability and extent of added benefit**
Moderate-to-severe prurigo nodularis in adults who are candidates for systemic therapy	BSC[b, c]	Added benefit not proven

a. Presented is the ACT specified by the G-BA.
b. BSC refers to the therapy that provides the patient with the best possible, individually optimized, supportive treatment to alleviate symptoms and improve the quality of life. BSC may include the use of topical basic skin care therapy, topical corticosteroids, and UVB phototherapy. If treatment needs to be adjusted for the patients (e.g. different dosages of topical corticosteroids), such adjustments should be made.
c. In the present case, the drugs recommended in guidelines or used in clinical practice, that have no or no explicit approval for the present therapeutic indication, cannot be considered as ACT in the narrower sense within the meaning of §2 para 1 S. 3, §12 SGB V (BSG judgment of 22 February 2023, reference number: B 3 KR 14/21 R).

ACT: appropriate comparator therapy; BSC: best supportive care; BSG: Federal Social Court; G-BA: Federal Joint Committee.; SGB: Social Code Book; UVB: ultraviolet B radiation

The assessment described above departs from that by the company, which derived proof of major added benefit based on the results of the studies PRIME and PRIME2.

The G-BA decides on the added benefit.

I 6 References for English extract

Please see full dossier assessment for full reference list.

The reference list contains citations provided by the company in which bibliographical information may be missing.

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The full report (German version) is published under https://www.iqwig.de/en/projects/a23-24.html.