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SMC2598

dupilumab 300 mg solution for injection in pre-filled syringe or pre-filled pen (Dupixent®)

Sanofi

12 January 2024

The Scottish Medicines Consortium (SMC) has completed its assessment of the above product and advises NHS Boards and Area Drug and Therapeutic Committees (ADTCs) on its use in NHSScotland. The advice is summarised as follows:

ADVICE: following a full submission assessed under the orphan equivalent medicine process.

dupilumab (Dupixent®) is accepted for use within NHSScotland.

Indication under review: for the treatment of adults with moderate-to-severe prurigo nodularis (PN) who are candidates for systemic therapy.

In two double-blind, randomised, phase III studies, dupilumab treatment resulted in statistically and clinically significant improvements in the severity of pruritus (measured by the reduction in Worst-Itch Numeric Rating Scale [WI-NRS] by ≥4 points from baseline to week 24) in patients with PN, compared with placebo.

This advice applies only in the context of an approved NHSScotland Patient Access Scheme (PAS) arrangement delivering the cost-effectiveness results upon which the decision was based, or a PAS/ list price that is equivalent or lower.

This advice takes account of the views from a Patient and Clinician Engagement (PACE) meeting.

Chair
Scottish Medicines Consortium

1. Clinical Context

1.1. Medicine background

Dupilumab is a recombinant human immunoglobulin (Ig)-G4 monoclonal antibody that inhibits interleukin (IL) -4 and IL-13 signalling; both major drivers of type 2 inflammatory disease. By blocking these pathways, dupilumab decreases many of the mediators of type 2 inflammation.[1-3] SMC has accepted dupilumab for restricted use within NHSScotland for adults and adolescents with other atopic conditions such as severe asthma (SMC2317) and atopic dermatitis (SMC2011, SMC2232).

For prurigo nodularis (PN), the recommended dose of dupilumab for adult patients is an initial dose of 600 mg, followed by 300 mg every other week; all doses are administered subcutaneously. Dupilumab can be used with or without topical corticosteroids. Clinical trial data are available for patients with PN who were treated up to 24 weeks; consideration should be given to stopping dupilumab treatment in patients who have had no response after 24 weeks.[1, 2]

1.2. Disease background

PN is a rare, complex and chronic skin disorder. It is primarily associated with an intense and constant itch (pruritus); the resultant itch-scratch cycle is the main driver for the condition where the physical scratching and rubbing of the skin will cause thicker and more inflamed nerve endings, which worsen the condition. The exact cause of the condition is unknown but it is linked to several neuronal- and immune-mediated mechanisms. As well as driving the disease itself, the pruritus typically results in a significant reduction in quality of life where the constant itching can also result in skin lesions and secondary infections, impaired sleep and psychiatric comorbidities (affecting approximately 70% of patients with chronic pruritus) including anxiety and depression.[3, 4]

There is a strong association between PN and other atopic conditions such as asthma, hay fever and eczema (atopic dermatitis). It is estimated that 20% to 60% of PN patients have either a past or current history of atopic dermatitis or other atopic conditions;[3, 5] however, the British Association of Dermatologists (BAD) suggest that this figure may be closer to 80%.[6]

1.3. Treatment pathway and relevant comparators

Dupilumab is the only systemic therapy with a marketing authorisation for PN. Current treatment comprises a multimodal, stepwise approach of general strategies to control pruritus, treat pruriginous lesions, as well as treat concomitant and potentially pruritogenic diseases. First-line treatment usually involves topical therapies such as topical corticosteroids (TCS) and topical calcineurin inhibitors (TCI), alone or in combination; whilst the continuous use of emollients is recommended throughout the entirety of the disease.[3, 4, 7]

For patients whose PN is uncontrolled by topical therapies, treatment options include ultraviolet phototherapy, oral antihistamines, and corticosteroids (oral or intralesional), whilst other systemic treatment options include off-label immunosuppressants (methotrexate, ciclosporin, azathioprine). Antidepressants and gabapentinoids (pregabalin and gabapentin) can be used as adjunct therapies alongside these systemic treatments, whilst naltrexone and thalidomide can also be considered for the most severe cases of PN.[3, 4, 7]

The submitting company deemed the relevant comparator in this submission to be best supportive care (BSC); defined as a combination of emollients, low to medium potency TCS or TCI, and rescue therapy (defined as higher potency topical or oral corticosteroids or TCI).

Experts consulted by SMC indicated that dupilumab would be a systemic treatment option prior to or after systemic immunosuppressants such as oral corticosteroids, methotrexate, ciclosporin, and azathioprine.

1.4. Category for decision-making process

Eligibility for a PACE meeting
Dupilumab meets SMC orphan equivalent criteria for this indication.

2. Summary of Clinical Evidence

2.1. Evidence for the licensed indication under review

Evidence to support dupilumab for this indication comes from the PRIME and PRIME2 studies. Details are summarised in Table 2.1.

Table 2.1. Overview of relevant studies

Criteria	PRIME and PRIME2[3, 5]
Study design	International, parallel-group, double-blind, randomised, phase III studies.
Eligible patients	• Adults (18 to 80 years of age) with a PN diagnosis from a dermatologist ≥3 months before screening. • Moderate to severe PN, defined as an average WI-NRS score of ≥7 (range: 0 to 10) in the seven days before Day 1. • A total of ≥20 PN lesions on both legs, and/or both arms, and/or trunk, at screening and on Day 1. • Have previously failed a two-week course of medium-to-super potent TCS or TCS were not medically advisable.[a] • Moderate-to-severe AD within 6 months before the screening visit, or from screening to the randomisation visit.
Treatments and randomisation	Patients were randomised equally to receive subcutaneous dupilumab 600 mg on Day 1 followed by 300 mg once every two weeks, or matching placebo, until week 24; this was followed by a 12-week period of untreated follow-up. Background therapies included emollients[b] and low to medium potency TCS or TCI[c]; patients could also be rescued with high potency or superpotent TCS or TCI as needed. Randomisation was stratified according to history of atopy (atopic versus non-atopic), stable use of TCS or TCI (yes or no), and country or territory code.
Primary outcome	Proportion of patients with improvement (reduction) in WI-NRS by ≥4 from baseline to week 24 (PRIME only).[d] Proportion of patients with improvement (reduction) in WI-NRS by ≥4 from baseline to week 12 (PRIME 2 only).
Key Secondary outcomes	• Proportion of patients with improvement (reduction) in WI-NRS by ≥4 from baseline to week 24 (a secondary outcome in PRIME2 only). • Proportion of patients with IGA PN-S 0 or 1 ('clear' or 'almost clear') score at week 24. • Percent change in WI-NRS from baseline at week 24. • Change in HRQoL, as measured by DLQI, from baseline at week 24.
Statistical analysis	Efficacy analyses were performed in the intention to treat (ITT) population, which included all patients who underwent randomisation. A hierarchical statistical testing strategy was applied in

	both studies with no formal testing of outcomes after the first non-significant outcome in the hierarchy. Therefore the results reported for these outcomes are descriptive only and not inferential (no p-values reported).

[a] Treatment failure with medium to superpotent TCS was defined as patients who are unable to achieve and/or maintain remission and low disease activity despite treatment with a daily regimen of medium to superpotent TCS (with or without TCI as appropriate), applied for at least 14 days, or for the maximum duration recommended by the product prescribing information, whichever is shorter.

[b] The application of moisturisers (emollients) once or twice daily was required for patients in both study groups for at least 5 days during the week before the start of the intervention period and continuously until the end of the study (week 36).

[c] Patients on a stable regimen of low to medium potency TCS or TCI at screening could continue their use throughout the study. Patients on stable regimens of high potency or superpotent TCS at screening were to decrease potency to medium potency TCS and continue to apply daily from screening to week 24.

[d] The timing of this primary outcome (PRIME only) was changed from week 12 to week 24 following a protocol amendment.

Abbreviations: AD = atopic dermatitis; DLQI = Dermatology Life Quality Index; HADS = Hospital Anxiety and Depression Scale; HRQoL = health-related quality of life; IGA PN-S = Investigator's Global Assessment for Prurigo Nodularis-Stage score; ITT = intention-to-treat; NRS = Numeric Rating Scale; PN = prurigo nodularis; TCI = topical calcineurin inhibitors; TCS = topical corticosteroids; WI-NRS = The Worst-Itch Numeric Rating Scale.

The submitting company presented results from the primary analyses of PRIME (data cut-off August 2021) and PRIME2 (data cut-off November 2021); the results from these data indicate statistically significant increases in response, after 24 weeks, for dupilumab compared with placebo. Additionally data from both studies were also included in a prespecified pooled efficacy analysis of the intention-to-treat (ITT) populations, the results of which are descriptive only; these results favoured dupilumab over placebo. Detailed results are in Table 2.2.

Table 2.2: Results of primary and secondary outcomes from the PRIME and PRIME2 studies, and the pooled efficacy data from the ITT populations of these studies.[3, 5]

	PRIME		**PRIME2**		**Pooled data for the ITT populations from both studies**	
	Dupilumab (n=75)	**Placebo (n=76)**	**Dupilumab (n=78)**	**Placebo (n=82)**	**Dupilumab (n=153)**	**Placebo (n=158)**
Primary outcome in PRIME2: Proportion of patients with improvement (reduction) in WI-NRS by ≥4 points from baseline at week 12[a]						
Responders, %	44%	16%	37%	22%	41%	19%
Difference for dupilumab versus placebo (95% CI)	29% (14 to 44)[b]		17% (2.3 to 31) p=0.022		23% (12 to 33)	
Primary outcome in PRIME: Proportion of patients with improvement (reduction) in WI-NRS by ≥4 points from baseline at week 24[c]						
Responders, %	60%	18%	58%	20%	59%	19%
Difference for dupilumab versus placebo (95% CI)	43% (28 to 58) p<0.001		43% (29 to 56) p<0.001		43% (33 to 53)	

Secondary outcome: Proportion of patients with IGA PN-S score of 0 or 1 ('clear' or 'almost clear') at week 24.						
Responders, %	48%	18%	45%	16%	46%	17%
Difference for dupilumab versus placebo (95% CI)	28% (13 to 43) p<0.001		31% (16 to 45) p<0.001		30% (19 to 40)	
Secondary outcome: Percent change in WI-NRS from baseline to week 24.						
LS mean (SE)	-48.9 (5.6)	-22.2 (5.7)	-59.3 (6.4)	-36.2 (6.2)	-53.4 (4.3)	-28.0 (4.2)
Difference for dupilumab versus placebo (95% CI)	-26.7 (-38.4 to -14.9) p<0.001		-23.2 (-33.8 to -12.5) p<0.001		-25.5 (-33.4 to -17.5)	
Secondary outcome: Change in DLQI from baseline to week 24.						
LS mean (SE)	-12.0 (1.0)	-5.8 (1.0)	-13.2 (1.2)	-6.8 (1.2)	-12.6 (0.8)	-6.3 (0.8)
Difference for dupilumab versus placebo (95% CI)	-6.2 (-8.3 to -4.1) p<0.001		-6.4 (-8.4 to -4.4) p<0.001		-6.3 (-7.8 to -4.8)	

[a] Primary outcome in PRIME2; changed to a secondary outcome in PRIME following a protocol amendment.
[b] Outcome was not multiplicity controlled in PRIME, therefore no p-value is reported.
[c] Primary outcome in PRIME; secondary outcome in PRIME2.

A low score indicates a good outcome for WI-NRS (range 0 to 10), IGA PN-S (range 0 to 4), and DLQI (range 0 to 30).

Abbreviations: CI = confidence interval; DLQI = Dermatology Life Quality Index; IGA PN-S = Investigator's Global Assessment for Prurigo Nodularis-Stage score; ITT = intention-to-treat; LS = least squares; NRS = Numeric Rating Scale; SE = standard error; WI-NRS = Worst-Itch Numeric Rating Scale.

In both studies, patients in both treatment groups were followed up for 12 weeks after study treatment discontinuation at week 24. The proportion of patients in the dupilumab group with an improvement in Worst-Itch Numeric Rating Scale (WI-NRS) by ≥4 points from baseline decreased from 59% (90/153) at week 24, to 47% (48/102) at week 36. Conversely, the number of responders in the placebo group increased from 19% (at week 24) to 28% (at week 36). Additionally, the proportion of patients in the dupilumab group with an Investigator's Global Assessment 0 or 1 score for Prurigo Nodularis-Stage score (IGA PN-S) of 0 ('clear') or 1 ('almost clear') from baseline decreased from 46% (at week 24) to 39% (at week 36).[3]

2.2. Health-related quality of life outcomes

The effect of dupilumab on Health-Related Quality of Life (HRQoL) was measured by the change in Dermatology Life Quality Index (DLQI) from baseline to week 24; this was one of the hierarchically tested secondary outcomes in both the PRIME and PRIME2 studies. In both studies, dupilumab treatment resulted in statistically significant reductions (improvements) in DLQI compared to placebo.[3, 5]

2.3 Indirect evidence to support clinical and cost-effectiveness comparisons

The submitting company conducted a feasibility assessment of indirect treatment comparisons (ITCs) between dupilumab and other systemic treatments for PN. Following a systematic literature review, the company concluded that it was not feasible to conduct an ITC for dupilumab against systemic immunosuppressant such as methotrexate and ciclosporin, based on the limited

identified evidence for these off-label uses (low quality non-randomised, uncontrolled, retrospective studies with small sample sizes).

3. Summary of Safety Evidence

The safety profile of dupilumab observed in patients with PN was consistent with those observed in other licensed indications such as asthma and atopic dermatitis.[3]

Safety data are available for 24 weeks from the PRIME (data cut-off August 2021) and PRIME2 (data cut-off November 2021) studies. In the pooled safety analysis of both these studies, 149/152 (98%) and 116/157 (74%) of patients completed the 24-week study intervention period in the dupilumab and placebo groups respectively. A lower percentage of patients discontinued study treatment before week 24 in the dupilumab group compared with the placebo group (2.0% and 26%, respectively); the main reasons for permanent medicine discontinuation prior to week 24 were withdrawal by patient (0.7% and 12%, respectively) and lack of efficacy (0.7% and 10%, respectively). None of the premature intervention discontinuation in the dupilumab group was due to an AE.[3]

In the dupilumab and placebo groups, a serious adverse event (AE) was reported by 4.6% and 7.6% of patients respectively; all serious AEs in the dupilumab group were deemed to be unrelated to the medicine. Injection site reactions were reported less frequently in the dupilumab group (3.9%) than the placebo group (5.7%); these were generally of short duration and all recovered without corrective treatment.[3]

Although it was only reported by 2.0% (dupilumab group) and 0.6% (placebo group) in the pooled safety analysis of both PRIME and PRIME2, conjunctivitis (as well as dry eye and keratitis-related events) have been reported with dupilumab and are listed in the Summary of Product Characteristics (SPC) as a special warning. Patients are advised to be aware of any new signs or worsening eye symptoms whilst on dupilumab treatment.[1, 2]

4. Summary of Clinical Effectiveness Considerations

4.1. Key strengths

- PRIME and PRIME2 were phase III studies which appear to have been well-conducted, with stratification and most baseline characteristics were balanced between the two treatment groups; this makes it likely that there is a low risk of bias, and provides reassurance about the internal validity of the study.
- In the PRIME and PRIME2 studies, when compared with placebo, dupilumab treatment resulted in statistically significant and clinically meaningful improvements for clinical outcomes including changes in WI-NRS (measure of itch)[3, 5]; and changes in IGA PN-S (measure of PN lesions)[3, 5], where achieving an absolute score of 1 to 2 out of possible score of 4 is deemed a clinically significant response by the BAD.[8]
- In the PRIME and PRIME2 studies, when compared with placebo, dupilumab treatment resulted in statistically significant and clinically meaningful improvements in the HRQoL outcome, change in DLQI from baseline to week 24 in PRIME and PRIME2.[3, 5]

4.2. Key uncertainties

- Efficacy data are only available for patients with PN treated with dupilumab for up to 24 weeks in PRIME and PRIME2.[3, 5] In both studies, there was evidence of recurrence of signs and symptoms of PN within the 12-week non-treatment follow-up period. Evidence on the longer-term efficacy and safety of dupilumab for the treatment of PN is currently lacking.[1-3] The submitting company has advised that no further analyses or extension studies are planned, and the marketing authorisation recommends that consideration should be given to stopping dupilumab treatment in patients with PN who have shown no response after 24 weeks.[1, 2]
- There was no requirement for patients to have treatment-failure with previous systemic therapy in the PRIME studies. Few patients in the pooled ITT populations (in the dupilumab and placebo groups respectively) had prior exposure to methotrexate and ciclosporin.[3, 5]
- In both PRIME studies, patients on stable regimens of high potency or super potent TCS at screening were required to decrease to medium potency TCS to become eligible for inclusion to the study.[3] Although patients were allowed to use high potency or super potent TCS as 'rescue therapy' in the study, not allowing them to continue on their pre-trial doses of TCS throughout the study may have destabilised disease control in some patients. Clinical experts contacted by SMC indicated that high potency or super potent TCS would be continued until the efficacy of systemic therapy has been established, then these could be reduced to medium potency TCS. This study requirement may affect the generalisability of study results to patients who would continue with high or super potent steroids in clinical practice until systemic therapy was established. In the pooled efficacy analysis of both studies, there were some differences (around 3% to 4%) between the treatment groups in terms of concomitant emollient and TCS use and compliance, which collectively might have favoured dupilumab over placebo.[3]

4.3. Clinical expert input

Experts consulted by SMC considered dupilumab to be a therapeutic advancement and fulfil an unmet need for this patient population, since it represents the only on-label treatment option for this condition.

4.4. Service implications

No significant service implications are anticipated.

*Other data were also assessed but remain confidential.**

5. Summary of Patient and Carer Involvement

A patient and clinician engagement (PACE) meeting with patient group representatives and clinical specialists was held to consider the added value of dupilumab (Dupixent®), as an orphan equivalent medicine, in the context of treatments currently available in NHSScotland.

The key points expressed by the group were:

- Prurigo nodularis (PN) is a chronic skin disorder that is 'totally devastating' for those affected. A lack of awareness of the condition can lead to significant delays in diagnosis, meaning

families are subjected to various appointments and various empirical treatment options with limited efficacy, that are all taxing on their time and resources.

- The condition itself is associated with an 'intense' and 'excruciating' itch. In PN patients, both the lesions and unaffected skin can be excruciatingly itchy, which can perpetuate an itch-scratch cycle. The lesions are often deemed to be 'unsightly', causing patients to feel shame, patients are often stigmatised and become reclusive, often avoiding social interactions and being unable to establish and maintain intimate relationships. Scratching can 'break' the skin and cause a greater susceptibility to infections which require attendance at a GP and/or hospital.

- The constant itching for some patients can also be associated with pain and considerable sleep loss is very common in PN patients, meaning many people with PN suffer from significant fatigue. The severe disease burden, including a constant itch, lesions, lack of sleep and socio-economic impact, in combination with a lack of targeted and effective treatment can lead to depression. Patients often have no quality of life and suffer from severe psychological distress. Many families and carers feel helpless due to being unable to help alleviate these symptoms. The severity of the symptoms can impact the ability of their work, which can have drastic effects on family income and well-being.

- There are currently no licensed treatments for PN. Current off-label treatments used (such as potent topical corticosteroids or systemic immunosuppressive agents like ciclosporin and methotrexate) have a very limited to no efficacy, as well as various side effects and potential consequences (i.e. osteoporosis due to prolonged oral steroid use); some patients may also not be suitable for these medicines due to other co-morbidities. Phototherapy is also used but this is quite resource intensive, there are long waiting lists across most centres in Scotland, and any benefit is usually short-term. and it is also not known to help all patients.

- In two phase III studies, dupilumab plus best supportive care showed statistically significant and clinically meaningful improvements for clinical outcomes that measured itch and the number of lesions. If realised, these clinical benefits would result in improved sleep and mood, reduced itch, pain, and improved skin appearance; all drastically improving the quality of life of these patients.

- Improving the quality of life for patients with PN will improve family life as patients are no longer burdened by their skin condition. Additionally, the improvement in sleep quality would be another huge benefit to family and carers if PN is treated effectively. This also means that patients could partake more in family life and attend work.

- There is expected to be minimal, if any, service impact since there is already a well-established treatment pathway for dupilumab for those with moderate to severe atopic dermatitis pathway. Once patients are established on dupilumab treatment, blood monitoring tests can be done twice a year. Once patients have been stable for at least a year, patient can choose to stop treatment or to reduce frequency of injection.

- PACE participants also shared experiences from patients who have PN and have received dupilumab treatment, including from members of Prurigo Nodularis International. Feedback

from these patients has been overwhelmingly positive regarding the efficacy of dupilumab with it being described as 'life-changing' by many. Dupilumab has the potential to dramatically improve the physical, emotional, and mental wellbeing of patients with moderate to severe PN.

Additional Patient and Carer Involvement

We received a patient group submission from Prurigo Nodularis International, which is a patient support group. Prurigo Nodularis International has not received any pharmaceutical company funding in the past two years. A representative from Prurigo Nodularis International participated in the PACE meeting. The key points of their submission have been included in the full PACE statement considered by SMC.

6. Summary of Comparative Health Economic Evidence

6.1. Economic case

Table 6.1 Description of economic analysis

Criteria	Overview
Analysis type	The submitting company presented a cost-utility analysis.
Time horizon	The time horizon was a lifetime horizon, which translated to 50 years in the model.
Population	Adult population with moderate-to-severe prurigo nodularis (PN) who are candidates for systemic therapy.
Comparators	The comparator was best supportive care (BSC). BSC was defined as a combination of emollients, low-to-medium potency topical corticosteroids (TCS)/ topical calcineurin inhibitors (TCI) and rescue therapy (such as higher potency topical or oral corticosteroids or TCIs).
Model description	The submitting company provided a two-part model comprising of a 24-week decision tree model, representing the trial study length and a lifetime Markov model, representing the remaining time span. Health states in both parts of the model were "response" and "no response" for both treatment arms. At the end of the 24 weeks in the decision trees, patients entered the Markov model in their current health state at that point. The number of patients in these health states in the decision tree is determined by the response criteria from the PRIME studies. Discontinuation rates from the trials were applied as transition probabilities when patients entered the Markov model.
Clinical data	Evidence to support dupilumab for this indication came from the PRIME and PRIME2 studies. Response rates for the decision tree part of the economic modelling were based on the pooled PRIME and PRIME2 data using a composite of the primary outcome from the studies (proportion of patients with improvement (reduction) in Worst-Itch Numeric Rating Scale (WI-NRS) by ≥ 4 from baseline to week 24 and week 12, respectively) and the key secondary endpoint, IGA-PN-S reduction ≥1.
Extrapolation	As the clinical data only covered the length of the decision tree model, the submitting company predicted long-term effects of BSC and dupilumab in terms of maintenance of a sustained response by using previous NICE submissions and Structured Expert Elicitation (SEE). BSC's real-world effectiveness was expected to decline due to adherence and behavioural challenges, while dupilumab's effects, supported by the dupilumab Atopic Dermatitis Open Label Extension (AD OLE) study, was anticipated to persist. SEE revealed a swift BSC efficacy drop and stable dupilumab impacts. Annual discontinuation rates for dupilumab and BSC were taken from pooled PRIME data were used as transition probabilities from the "response" to "no response" state in the Markov model.
Quality of life	Health benefits were measured during PRIME and PRIME2 using the EQ-5D-5L and valued using the UK tariff. These were collected at baseline, week 12 and week 24. The company used regression models to estimate utility values for use in the economic model. Responder and non-responder

	utility values in the Markov model were higher for dupilumab than for BSC. No AE disutilities were included in the base case as the company argued the AEs arising from treatment during the trial programme were generally mild and transient. Utilities were age-adjusted. Effect waning assumptions were assumed to apply to the utility gains for any patient who discontinued treatment, based on the SEE, such that patients were assumed to maintain some benefit for a period after treatment cessation. These residual benefits were maintained at higher levels for patients discontinuing dupilumab than patients discontinuing BSC.
Costs and resource use	Medicine costs included were acquisition costs, administration costs, rescue medication costs and background medication costs. Other costs included in the model were healthcare resource use and adverse event costs. The administration cost for dupilumab consisted of the self-injection training assumed to take place once by a hospital nurse and last for one hour.
PAS	A Patient Access Scheme (PAS) was submitted by the company and assessed by the Patient Access Scheme Assessment Group (PASAG) as acceptable for implementation in NHSScotland. Under the PAS, a discount was offered on the list price.

6.2. Results

Base case results provided by the submitting company showed a cost per quality adjusted life year (QALY) of £ 26,393 with the PAS.

6.3. Sensitivity analyses

A number of sensitivity analyses were provided, and key scenarios are summarised in Table 6.3.1.

Additional scenarios provided upon request are presented in Table 6.3.2.

Table 6.3.1. Scenario analyses (with PAS)

	Scenario	Base case	ICER incremental (£/QALY)
	Base case	-	26,393
1	**Response criteria: WI-NRS improvement ≥4**	WI-NRS improvement ≥4 and IGA-PN-S reduction ≥1	28,072
2	**No response waning applied**	The OLE for AD data applied for response waning	27,818
3	**Response waning AD Dermatologist survey + NICE estimates**	The OLE for AD data applied for response waning	27,426
4	**Response waning AD OLE study + SEE**	The OLE for AD data applied for response waning	26,119
5	**HCRU – AD micro-costing**	Clinician estimates, BOI study, TA534	25,267
6	**HCRU-TA814**	Clinician estimates, BOI study, TA534	26,606
7	**HCRU-TA534**	Clinician estimates, BOI study, TA534	24,352
8	**AD discontinuation rate**	PRIME2 and PRIME pooled data	26,169

Table 6.3.2. Additional scenario analyses (with PAS)

	Scenario	ICER incremental (£/QALY)
	Base case	26,393
1	**Scenario analysis in which all non-responder patients have baseline quality of life after 6 months**	29,265
2	**Combined scenario:** **- Adverse event disutilities included** **- Sustained response is equal to 0% in both arms after 5 years** **- Antihistamines are included in BSC (this was only included in non-response health states by the submitting company and they omitted other medicines for this scenario)** **- Non responder utility value in the Markov model is equal across treatment arms (The submitting company only adjusted this to happen after 6 months)**	32,446
3	**Time horizon of 10 years**	29,560
4	**Time horizon of 15 years**	28,153

6.4. Key strengths

- In the PRIME and PRIME2 studies, when compared with placebo, dupilumab treatment resulted in statistically and clinically significant greater reductions in the severity of pruritus, PN lesions and improvements in the HRQoL outcome.

6.5. Key uncertainties

- Given the lack of long-term data following the time period of the clinical trials, the Markov model component of the economic analysis is mostly based on assumptions, expert opinion and findings from the use of dupilumab in atopic dermatitis. This means there is uncertainty associated with the results, as shown by sensitivity analysis which varies the waning assumptions or from assuming no sustained response after 5 years.
- There is a large difference in utility value between the baseline and non-responder utility at week 24. The difference in the non-responder utility by treatment arm is not appropriate. An equal non-responder utility between treatment arm is preferred. A scenario for this was requested, resulting in an ICER of £29,913.
- Statistician feedback noted uncertainty with the face validity of the set of utility values used to inform the cost-effectiveness model, suspecting that the final utility values could lead to an over-estimation of the quality-adjusted life-year (QALY) gain for dupilumab. Furthermore, in relation to the regression used to estimate utility values, it was not clear how the company accounted for repeated measures in the utility regression given the inclusion of DLQI (a different quality of life measure) as a predictor of EQ-5D. However, issues with the resulting set of utility values were set against supportive contextual comments from the PACE statement regarding the magnitude of quality of life benefits that patients could experience upon response.
- In both PRIME studies, patients on stable regimens of high potency or super potent TCS at screening were required to decrease to medium potency TCS to become eligible for inclusion

to the study. This may affect the generalisability of study results to patients who are able to continue with high potency steroids in clinical practice.

- There is a lack of data against all comparators identified in Scottish practice by SMC experts (including oral corticosteroids, methotrexate, ciclosporin and azathioprine), however, on balance the Committee felt the comparator used was appropriate.
- Expert insights, especially from SEE should be considered with caution due to potential biases and limited diversity in perspectives as the rarity of PN and specific selection criteria led to a small pool of experts, raising concerns about the comprehensiveness of the insights gathered.

*Other data were also assessed but remain confidential.**

7. Conclusion

The Committee considered the benefits of dupilumab in the context of the SMC decision modifiers that can be applied when encountering high cost-effectiveness ratios and agreed that as dupilumab is an orphan equivalent medicine, SMC can accept greater uncertainty in the economic case.

After considering all the available evidence and the output from the PACE process, the Committee accepted dupilumab for use in NHSScotland.

8. Guidelines and Protocols

In 2020, the International Forum for the Study of Itch (IFSI) published a guideline on chronic prurigo including PN.[7]

9. Additional Information

9.1. Product availability date

14 February 2023

Table 9.1 List price of medicine under review

Medicine	Dose regimen	Cost per year (£)
Dupilumab 300 mg solution for injection	600 mg then 300 mg every other week by subcutaneous injection. Treatment should be reviewed if there is no response after 24 weeks.	17,708

Costs from BNF online on 04 October 2023. Costs calculated using the full cost of vials/ampoules assuming wastage. Costs do not take any patient access schemes into consideration.

10. Company Estimate of Eligible Population and Estimated Budget Impact

The submitting company estimated there would be 157 patients eligible for treatment with dupilumab in year 1, increasing to 170 patients in year 5, to which confidential estimates of treatment uptake were applied. SMC clinical expert responses suggest that the company estimates may be underestimated.

The submitting company assume that patients treated with dupilumab will continue to receive TCS/TCI as best supportive care and therefore these were not included as displaced medicines in the budget impact model.

SMC is unable to publish the with PAS budget impact due to commercial in confidence issues. A budget impact template is provided in confidence to NHS health boards to enable them to estimate the predicted budget with the PAS.

*Other data were also assessed but remain confidential.**

References

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3. European Medicines Agency (EMA). European Public Assessment Report. Dupilumab (Dupixent®). EMEA/H/C/004390/II/0063. First Published: 22 February 2023. Available at: https://www.ema.europa.eu/en/medicines/human/EPAR/dupixent [Accessed: 19 September 2023].
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7. Ständer S, Pereira MP, Berger T, Zeidler C, Augustin M, Bobko S, et al. IFSI-guideline on chronic prurigo including prurigo nodularis. Itch. 2020;5(4):e42. doi: 10.1097/itx.0000000000000042.
8. British Association of Dermatologists (BAD). Response to the Single Technology Appraisal for NICE - Dupilumab for treating prurigo nodularis [ID4054] - Professional organisation submission. Available from: http://badmainstage.wpengine.com/wp-content/uploads/2023/03/Response-to-STA-dupilumab-for-PN-ID4054-6-Feb-2023.pdf [Accessed: 05 October 2023].

This assessment is based on data submitted by the applicant company up to and including 20 November 2023.

**Agreement between the Association of the British Pharmaceutical Industry (ABPI) and the SMC on guidelines for the release of company data into the public domain during a health technology appraisal:*https://www.scottishmedicines.org.uk/about-us/policies-publications/

Medicine prices are those available at the time the papers were issued to SMC for consideration. SMC is aware that for some hospital-only products national or local contracts may be in place for comparator products that can significantly reduce the acquisition cost to Health Boards. These contract prices are commercial in confidence and cannot be put in the public domain, including via the SMC Detailed Advice Document. Area Drug and Therapeutics Committees and NHS Boards are therefore asked to consider contract pricing when reviewing advice on medicines accepted by SMC.

Patient access schemes: A patient access scheme is a scheme proposed by a pharmaceutical company in order to improve the cost-effectiveness of a medicine and enable patients to receive access to cost-effective innovative medicines. A Patient Access Scheme Assessment Group (PASAG), established under the auspices of NHS National Services Scotland reviews and advises

NHSScotland on the feasibility of proposed schemes for implementation. The PASAG operates separately from SMC in order to maintain the integrity and independence of the assessment process of the SMC. When SMC accepts a medicine for use in NHSScotland on the basis of a patient access scheme that has been considered feasible by PASAG, a set of guidance notes on the operation of the scheme will be circulated to Area Drug and Therapeutics Committees and NHS Boards prior to publication of SMC advice.

Advice context:

No part of this advice may be used without the whole of the advice being quoted in full.

This advice represents the view of the Scottish Medicines Consortium and was arrived at after careful consideration and evaluation of the available evidence. It is provided to inform the considerations of Area Drug & Therapeutics Committees and NHS Boards in Scotland in determining medicines for local use or local formulary inclusion. This advice does not override the individual responsibility of health professionals to make decisions in the exercise of their clinical judgement in the circumstances of the individual patient, in consultation with the patient and/or guardian or carer.