

**NATIONAL INSTITUTE FOR HEALTH AND CARE
EXCELLENCE**

Appraisal consultation document

**Dupilumab for treating moderate to severe
atopic dermatitis**

The Department of Health and Social Care has asked the National Institute for Health and Care Excellence (NICE) to produce guidance on using dupilumab in the NHS in England. The appraisal committee has considered the evidence submitted by the company and the views of non-company consultees and commentators, clinical experts and patient experts.

This document has been prepared for consultation with the consultees. It summarises the evidence and views that have been considered, and sets out the recommendations made by the committee. NICE invites comments from the consultees and commentators for this appraisal and the public. This document should be read along with the evidence (see the [committee papers](#)).

The appraisal committee is interested in receiving comments on the following:

- Has all of the relevant evidence been taken into account?
- Are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence?
- Are the recommendations sound and a suitable basis for guidance to the NHS?
- Are there any aspects of the recommendations that need particular consideration to ensure we avoid unlawful discrimination against any group of people on the grounds of race, gender, disability, religion or belief, sexual orientation, age, gender reassignment, pregnancy and maternity?

Note that this document is not NICE's final guidance on this technology. The recommendations in section 1 may change after consultation.

After consultation:

- The appraisal committee will meet again to consider the evidence, this appraisal consultation document and comments from the consultees.
- At that meeting, the committee will also consider comments made by people who are not consultees.
- After considering these comments, the committee will prepare the final appraisal determination.
- Subject to any appeal by consultees, the final appraisal determination may be used as the basis for NICE's guidance on using dupilumab in the NHS in England.

For further details, see NICE's [guide to the processes of technology appraisal](#).

The key dates for this appraisal are:

Closing date for comments: 24 April 2018

Second appraisal committee meeting: 10 May 2018

Details of membership of the appraisal committee are given in section 5.

1 Recommendations

- 1.1 Dupilumab is not recommended, within its marketing authorisation, for treating moderate to severe atopic dermatitis in adults when systemic therapy is suitable.
- 1.2 This recommendation is not intended to affect treatment with dupilumab that was started in the NHS before this guidance was published. People having treatment outside this recommendation may continue without change to the funding arrangements in place for them before this guidance was published, until they and their NHS clinician consider it appropriate to stop.

Why the committee made these recommendations

Current systemic treatment for moderate to severe atopic dermatitis (eczema) includes oral corticosteroids, ciclosporin, methotrexate, azathioprine and mycophenolate mofetil. Dupilumab plus topical therapy (notably, corticosteroids) would be used after these treatments no longer work, and best supportive care is the only available option.

The clinical evidence shows that dupilumab is effective when used in this way. However, the most plausible cost-effectiveness estimates for dupilumab plus topical corticosteroids compared with best supportive care range from £29,792 to £77,701 per quality-adjusted life year gained. These estimates are higher than those NICE normally considers an acceptable use of NHS resources. It is also likely that when the committee's preferred assumptions are used in the economic model, these estimates will further increase. Therefore, dupilumab does not reflect good use of limited NHS resources.

2 Information about dupilumab

Marketing authorisation indication	Dupilumab (Dupixent, Sanofi Genzyme) is indicated for the 'treatment of moderate to severe atopic dermatitis in adults who are candidates for systemic therapy'.
Dosage in the marketing authorisation	The recommended dose, given by subcutaneous injection, is initially 600 mg (2x300 mg injections), followed by 300 mg given every other week. If the condition shows no response after 16 weeks, treatment should be stopped. If the condition shows partial response, improvement may be seen with continued treatment after 16 weeks.
Price	£1,264.89 per pack of 2x2 ml syringes of 150 mg/1 ml solution (excluding VAT; British national formulary online, accessed March 2018). The company has agreed a patient access scheme with the Department of Health and Social Care. If dupilumab had been recommended, this scheme would provide a simple discount to the list price of dupilumab with the discount applied at the point of purchase or invoice. The level of the discount is commercial in confidence. The Department of Health and Social Care considered that this patient access scheme would not constitute an excessive administrative burden on the NHS.

3 Committee discussion

The appraisal committee (section 5) considered evidence submitted by Sanofi Genzyme and a review of this submission by the evidence review group (ERG). See the [committee papers](#) for full details of the evidence.

Experience of people with atopic dermatitis

Atopic dermatitis affects all aspects of a person's life

- 3.1 The clinical experts explained that atopic dermatitis is a chronic, recurrently flaring, generalised skin condition starting in childhood. People with severe atopic dermatitis may need hospitalisation for treatment. Feedback from patient and professional organisations highlighted that the condition is life-limiting, debilitating and isolating, affecting all aspects of life (physical, psychological, social and financial). They emphasised that, if

the condition is severe, it is associated with intolerable itch that disrupts sleep, and there is a higher risk of depression and suicide. The committee noted that having treatments that improve the condition and which are associated with few or manageable adverse effects is important to people with atopic dermatitis.

Assessing severity of atopic dermatitis

Clinical experts consider that signs, symptoms and quality of life determine the severity of atopic dermatitis

3.2 The committee understood that clinicians have many tools to rate the severity of atopic dermatitis, but no 1 tool captures all the key aspects of the condition. The clinical experts explained that, in NHS practice other than in specialist centres, atopic dermatitis-specific assessment tools are not commonly used. Instead, clinicians assess severity based on patient-reported symptoms including effect on sleep and work, and how much patients need to use topical corticosteroids or systemic therapy. One clinical expert highlighted that the consensus-based Harmonising Outcome Measures for Eczema ([HOME](#)) initiative recommends using the Eczema Area and Severity Index (EASI) to assess signs (for example, skin lesions) and the Patient Oriented Eczema Measure (POEM) to assess symptoms (for example, itch). The clinical experts explained that the EASI uses well-defined, measurable criteria, is reasonably objective and correlates well with the Investigators' Global Assessment (IGA) score. However, the EASI has several limitations; for example, it does not capture itch well, nor does it always characterise the full extent of some types of eczema lesions. The clinical experts explained that NHS clinicians routinely use the Dermatology Life Quality Index (DLQI) that assesses quality of life in other skin conditions. The committee concluded that the EASI, DLQI and POEM are appropriate for assessing the severity of atopic dermatitis in NHS practice.

Minimal clinically important differences are 6 points for the EASI and 4 points for the DLQI, but clinicians use a holistic approach for clinical effectiveness

3.3 The clinical experts explained that it is difficult to define a minimal clinically important difference in atopic dermatitis. For the EASI and DLQI, this difference is generally a 6-point and 4-point improvement respectively. However, there are several factors that determine whether changes are clinically meaningful in practice, such as the baseline scores, the need for concomitant corticosteroids, and the ability to sleep well and work. It also depends on the toxicity of treatment; the minimal important difference for a treatment such as ciclosporin may be higher to justify its use given its toxicity. The committee understood that, in practice, clinicians use a holistic approach to assessing the effectiveness of treatment.

Clinical management

Atopic dermatitis can be treated with topical therapies, phototherapy and systemic immunosuppressant therapies

3.4 Although clinicians individualise therapy for patients, a typical treatment pathway involves:

- emollients and topical corticosteroids as first-line treatment
- topical calcineurin inhibitors such as tacrolimus as second-line treatment
- phototherapy as third-line treatment, although this is used variably across centres and mainly for moderate rather than severe atopic dermatitis
- systemic immunosuppressant therapies including oral corticosteroids, ciclosporin (licensed), methotrexate, azathioprine and mycophenolate mofetil as fourth-line treatment
- best supportive care including emollients and topical corticosteroids when other treatments do not control the condition.

Treating atopic dermatitis includes managing exacerbations (flares) with short-term potent topical corticosteroids and systemic therapy. The clinical experts further explained that:

- Tacrolimus is generally poorly tolerated and, for a few people who can take it, it is used for body parts such as the face that are particularly prone to corticosteroid-associated side effects (for example, skin thinning).
- Systemic therapies can have serious adverse effects and are normally used for short periods or with topical corticosteroids to reduce the doses needed; if a drug is no longer effective, it will be stopped and another drug will be offered.
- Best supportive care may include education, psychological support, emollients, topical corticosteroids, bandages, and hospitalisations for 1 week to 2 weeks to intensify treatment and provide respite for people having to apply topical medications. The clinical experts had different views on whether phototherapy and systemic therapy are included in best supportive care.

Positioning of dupilumab in the treatment pathway

Clinical experts advise that dupilumab would be used after existing systemic therapies

3.5 The marketing authorisation for dupilumab is for ‘moderate to severe atopic dermatitis in adults who are candidates for systemic therapy’. The company positioned dupilumab as a fifth-line treatment, after systemic immunosuppressant therapies (for example, ciclosporin), as an alternative to best supportive care. Two clinical experts confirmed that this is a point at which NHS clinicians would use dupilumab, for both moderate and severe atopic dermatitis. However, 1 expert explained that, in practice, dupilumab may be an option as a fourth-line treatment because the toxicity risks of systemic therapies (see section 3.4) are such that it is unlikely that people would be offered every fourth-line treatment option

available before being offered dupilumab. However, people are likely to have had at least 1 systemic therapy. The committee concluded that it would appraise dupilumab for moderate to severe atopic dermatitis, compared with best supportive care, after other systemic therapies.

Comparators

The company's definition of best supportive care is appropriate but does not include all the elements likely to be offered in clinical practice

3.6 The company defined best supportive care in its model as 'emollients, low-to-mid potency topical corticosteroids, and rescue therapy of higher potency topical or oral corticosteroids or topical calcineurin inhibitors'. The clinical experts explained that this reflected some elements of best supportive care in clinical practice, although it excluded education, psychological support, bandages and hospitalisation (see section 3.4). The committee concluded that the company's definition of best supportive care included some, but not all, elements of care likely to be offered in clinical practice.

Clinical evidence

The SOLO-1, SOLO-2, CAFÉ and CHRONOS trials provide the key clinical evidence for dupilumab

3.7 The main evidence for dupilumab came from 4 trials; 2 on dupilumab monotherapy (SOLO-1 and SOLO-2) and 2 on dupilumab plus topical corticosteroids (CAFÉ and CHRONOS). Patients in all trial arms had background best supportive care. The trials were randomised and double-blind, and included a total of 2,444 patients with chronic moderate to severe atopic dermatitis for at least 3 years that had not been controlled with topical medications for at least 6 months. Patients may or may not have had immunosuppressant therapy (including ciclosporin). The trials compared 2 doses of dupilumab (300 mg every week [unlicensed] or 300 mg every other week [licensed]) with placebo. The committee agreed

that it would focus only on the data for the licensed dose of dupilumab. The primary endpoints included the EASI, IGA or both (co-primary endpoints) assessed at the end of the 'induction period' (that is, 16 weeks after starting treatment), as follows:

- SOLO-1, SOLO-2 and CHRONOS:
 - at least 75% reduction in the EASI score from when treatment started (EASI 75) and
 - a rating of 'clear' (score of 0) or 'almost clear' (score of 1) on the IGA, and at least a 2-point improvement from baseline.
- CAFÉ: EASI 75.

Patients in CHRONOS had an additional 36 weeks of treatment. In SOLO-1 and SOLO-2, patients initially randomised to dupilumab whose condition met the co-primary endpoints were re-randomised in an extension study (SOLO-CONTINUE) to 1 of 4 different doses of dupilumab or placebo for a further 36 weeks. The company explained that additional long-term data on dupilumab were available from an open-label study with 2 to 3 years of follow-up. These data were not available at the time of the submission, and so were not presented to the committee. The committee concluded that evidence from this study would be useful to understand the long-term effectiveness of dupilumab and inform the modelling.

Company's base case

The base case focuses on a subgroup of patients from the 4 trials and data from placebo groups to represent best supportive care

- 3.8 Because the company considered that dupilumab would be used as a fifth-line treatment, after systemic immunosuppressant therapies, it focused its base case on a subgroup of 491 patients who had the licensed dose of dupilumab and placebo, compiled from:

- SOLO-1 and SOLO-2: a subgroup of 192 patients defined post hoc who had previously had immunosuppressants (commonly ciclosporin) before enrolling in the trials
- CAFÉ: 215 patients who could not have ciclosporin, or whose condition had not responded to ciclosporin
- CHRONOS: a subgroup of 84 patients defined post hoc who could not have ciclosporin or whose condition had not responded to ciclosporin.

The company used data from the placebo groups to represent best supportive care in its economic model. The committee noted that the subgroups for dupilumab monotherapy (192 SOLO patients) and combination therapy with topical corticosteroids (299 CAFÉ and CHRONOS patients) were sufficiently large to provide reliable estimates of effectiveness. It concluded that the company's chosen population reflected people at the stage in therapy at which dupilumab would likely be offered in clinical practice (see section 3.5).

Clinical experts advise that the populations in the company's subgroups are similar to patients in the NHS who would have dupilumab

3.9 The subgroups identified by the company included patients who were on average 38 years old, 63% were men and 81% were white. Patients had atopic dermatitis for an average of 29 years, which covered an average of 59% of their body and they had average scores of 35 on the EASI, 3.6 on the IGA, 21 on the POEM and 15 on the DLQI. The clinical experts confirmed that the baseline characteristics of these patients were similar to those likely to be seen in the NHS. The committee concluded that the trial subgroup populations generally reflected people who would be treated with dupilumab in NHS clinical practice.

The comparison of dupilumab plus topical corticosteroids with placebo plus topical corticosteroids is the most relevant for decision-making

3.10 The company presented 2 separate analyses of dupilumab compared with placebo: 'monotherapy' (a subgroup of SOLO-1 and SOLO-2) and

'combination therapy' (a subgroup of CAFÉ and CHRONOS). The clinical experts explained that, similar to other current systemic therapies (see section 3.4), dupilumab is likely to be offered alongside short-term topical corticosteroids. The committee concluded that it would focus on the evidence on dupilumab 'combination therapy' (the CAFÉ and CHRONOS subgroup).

Analyses that consider patients to be 'non-responders' if they had rescue therapy are preferable

3.11 The company used data from all patients, even if they had rescue therapy (that is, treatment for flares) or had withdrawn from the study ('all observed' analyses). It also presented results from separate analyses that considered patients to be 'non-responders' if they had not provided data at week 16, or if they had rescue therapy or withdrew from the study ('primary' analyses). The company's base case used data from the 'all observed' analyses. However, the committee concluded that the 'primary' analyses were more appropriate because the clinical experts stated that systemic treatments are usually stopped when they are no longer effective at controlling the condition and patients need rescue therapy.

The base case uses a composite endpoint of EASI 50 plus an improvement in the DLQI of at least 4, which is different from the trials

3.12 To model the cost effectiveness of dupilumab, the company defined a clinical benefit in its base case as an EASI 50 (at least 50% reduction in the EASI score from when treatment started) plus an improvement in the DLQI of at least 4. The committee queried why the company chose different clinical endpoints for its trials and for its economic base-case analysis. The company explained that it chose a composite endpoint for the economic analysis based on what clinicians consider to be clinically meaningful changes in outcomes, while the trial endpoints were dictated by the requirements of regulatory agencies. The clinical experts explained that EASI 75 and IGA 0/1, the endpoints of the trials, are difficult to achieve in practice, and that the EASI 50 and an improvement in the DLQI

of at least 4 are more sensitive to changes in treatment outcomes and more clinically relevant. The committee concluded that the composite endpoint of EASI 50 plus an improvement in the DLQI of at least 4 was appropriate for decision-making, although it would have also liked to have seen the proportion of patients whose condition met each endpoint.

Dupilumab with or without topical corticosteroids is more clinically effective than placebo

3.13 In the analysis including ‘all observed’ patients (that is, those who had or did not have rescue therapy), the committee noted that patients randomised to dupilumab plus topical corticosteroids were more likely to have EASI 75, and EASI 50 plus an improvement in the DLQI of at least 4 at week 16 compared with placebo plus topical corticosteroids (see table 1). The differences were statistically significant and clinically meaningful. Dupilumab without topical corticosteroids was also more effective than placebo without topical corticosteroids. The committee concluded that dupilumab was more clinically effective than placebo, although it would have preferred to have seen the results of the ‘primary’ analyses (see section 3.11).

Table 1. Proportion of patients with a score of EASI 75 and of EASI 50 plus an improvement in the DLQI of at least 4 at week 16 in monotherapy (SOLO-1 and SOLO-2) and combination therapy (CAFÉ and CHRONOS) subgroups

	Monotherapy		Combination therapy	
	Dupilumab (n=104)	Placebo (n=88)	Dupilumab plus topical corticosteroids (n=169)	Placebo plus topical corticosteroids (n=130)
EASI 75	45%	17%	67%	30%
EASI 50 plus an improvement in the DLQI of at least 4	59%	24%	73%	28%
Abbreviations: DLQI, Dermatology Life Quality Index; EASI, Eczema Area and Severity Index.				

Patients in the trials had a relatively high ‘placebo response’

3.14 The committee queried the high response rates seen in the placebo groups (see table 1). One clinical expert explained that this was likely because nurses in the trials closely supervised topical therapy regimens, which can improve adherence and maximise effectiveness. While this level of supervision is feasible in a short-term trial, it is not sustainable for prolonged periods (after 6 months), so any ‘placebo response’ is likely to decline over time. The committee agreed that any benefit from supervision should have been applied equally to both the dupilumab and placebo groups, which should not have affected how the treatments performed relative to one another in the trial. The company noted that, in CAFÉ, there was a higher reduction in topical corticosteroid use in the dupilumab arm than the placebo arm (51% reduction compared with 17% reduction). The committee concluded that the ‘placebo response’ in the trials was unlikely to have affected the treatment effect of dupilumab relative to placebo.

Adverse events

Patients on dupilumab and placebo experienced low rates of adverse events

3.15 The committee noted that the rates of serious adverse events were generally low in the dupilumab and placebo groups of the trial populations across all studies. It concluded that patients were likely to tolerate dupilumab.

Company’s economic model

The model combines a decision tree and Markov state transition

3.16 The company’s model consisted of 2 components:

- Decision tree up to 52 weeks: people entered the model either in the ‘dupilumab 300 mg every other week’ or the ‘best supportive care’ arm. Based on trial data, this part of the model evaluated treatment

response at 2 time points, 16 weeks and 52 weeks after starting treatment. The company defined response as EASI 50 plus an improvement in the DLQI of at least 4 in its base case (see section 3.12).

- At week 16 after starting treatment, people in the ‘dupilumab 300 mg every other week’ arm whose condition had responded continued to have dupilumab for a further 36 weeks (that is, up to week 52 after starting treatment). People whose condition had not responded, switched to best supportive care for the remaining 36 weeks, in line with the marketing authorisation. The clinical experts confirmed that this stopping rule reflects clinical practice. Everyone in ‘best supportive care’ remained in this arm whether their condition had responded or not.
- At week 52 after starting treatment, people in the ‘dupilumab 300 mg every other week’ arm whose condition continued to respond moved into the ‘maintenance’ Markov state of the model; people whose condition had lost response moved into the ‘best supportive care’ Markov state. Everyone who had best supportive care moved into the ‘best supportive care’ Markov state.
- Markov state transition with annual cycles from year 2 onwards: this component modelled long-term treatment (up to 61 years) of atopic dermatitis and included 3 states; maintenance on dupilumab, best supportive care and death. People having dupilumab maintenance therapy could stop dupilumab for any reason (loss of response, adverse effects, patient or physician preference) and move into the ‘best supportive care’ Markov state. Anyone could die at any time.

In its combined decision tree and Markov state transition model, the company assumed that dupilumab improved quality of life, but did not extend length of life, compared with best supportive care. The committee had concerns that the model split ‘responders’ and ‘non-responders’ into different states for dupilumab, but not for best supportive care. Because

the best supportive care group had a high 'placebo response' in the trial (see sections 3.13 and 3.14), the committee concluded that the current model structure oversimplified the treatment pathway in people who have best supportive care.

Assumptions in the economic model

Stopping rates should be based on all available trial data and reflect the proportion of patients needing rescue therapy

3.17 The company assumed that 3.7% of people having dupilumab plus topical corticosteroids as maintenance therapy stop treatment every year for any reason, and move onto best supportive care. This reflected the proportion of people in CHRONOS whose condition responded to treatment (EASI 50 plus an improvement in the DLQI of at least 4) at 16 weeks who withdrew from the trial by 52 weeks. The clinical experts advised that 3.7% seemed low but that they had not treated people with dupilumab long enough to establish an accurate stopping rate. The company's estimate did not take into account patients who had rescue therapy in CHRONOS, although in clinical practice, people who have such therapy would stop systemic treatment (see section 3.11). Furthermore, the company applied the stopping rate, estimated at week 52, across the entire horizon, up to 61 years after starting treatment. The committee agreed that this was a source of uncertainty. It would have preferred the stopping rate to be based on longer-term data from its open-label study (see section 3.7), and also see a range of sensitivity analyses to test this assumption.

Utility values in the economic model

Utility values specific for people whose condition does not respond to dupilumab are preferable to those for people having best supportive care

3.18 The company adjusted the utility values multiplicatively for the impact of aging on health-related quality of life, which the committee agreed was

appropriate. The company assumed that if atopic dermatitis did not respond to dupilumab plus topical corticosteroids at week 16 after starting treatment or beyond, people accrue the average utility value of everyone having best supportive care ('responders' and 'non-responders') at week 16 (0.81). The committee did not agree with this assumption because:

- It implied that there was no systematic difference between patients who had best supportive care from the outset, and those who started on dupilumab and subsequently moved to best supportive care because the condition had not responded to treatment. For example, dupilumab 'non-responders' may have a more severe condition than the average patient who starts treatment with best supportive care. The committee queried whether there were any baseline characteristics that predicted whether atopic dermatitis would respond to treatment or not, but the company stated that it had not identify any.
- The 'placebo response' was higher in the trials than would likely be seen in people who have best supportive care in clinical practice because of the more rigorous medical oversight delivered in a trial setting (see section 3.14).

The ERG noted that the utility values for dupilumab 'non-responders' and patients initially randomised to best supportive care were similar. However, the committee concluded that it was more appropriate to use the utility value specific to people whose condition had not responded to dupilumab plus topical corticosteroids at 16 weeks than the utility value from everyone having best supportive care. Over time, however, the committee agreed that everyone would have equal utility, whether they started on dupilumab then moved to best supportive care following loss of response, or had best supportive care from the beginning.

Using data rather than opinion is preferable for estimating the decline in quality of life for patients after dupilumab or best supportive care

3.19 The company assumed in both treatment states that from year 2 after starting treatment onwards, part of the clinical benefit of treatment (as determined at week 52 of the trials), and the associated utility benefit, were lost:

- In the dupilumab maintenance state, the company assumed that 2% of the benefit would be lost in year 2, 5% in year 3, 7% in year 4, and 8% in year 5 and beyond. It used these estimates to adjust down the proportion of people who continued to have dupilumab (that is, those who lost the benefit of dupilumab moved to the best supportive care state and then accrued the utility associated with that state).
- In the best supportive care state, the company assumed that 63% of the benefit would be lost in year 2, 91% in year 3, and 100% in year 4 and beyond. It used these estimates to adjust down the utility value applied over time, by applying in each year the average of the utility value for best supportive care during the trials (0.81), and the baseline utility value (0.66), weighted by the proportion of people who were assigned each utility value. Therefore, by the end of year 4, everyone in the best supportive care state returned to the baseline utility (0.66) for the remainder of their time in the model.

The company based the quality of life waning assumptions on feedback from the experience of 5 dupilumab trial investigators. Because the benefit of treatment on quality of life, rather than length of life, determines the quality-adjusted life year (QALY) difference between treatments in the model (see section 3.16), the committee preferred that evidence from the open-label study (see section 3.7) is used to support the waning assumptions.

The quality of life waning assumptions for best supportive care are a source of uncertainty

3.20 The committee questioned whether the quality of life waning assumptions for best supportive care (see section 3.19) were realistic, that is, whether so many people would lose benefit so quickly (91% in year 3) and whether no one would maintain benefit after 3 years. It considered the possibility that, because patients are recruited to trials when their condition is most severe (that is, quality of life is poor), their condition would naturally return to less severe levels over time (that is, quality of life would improve). However, the company explained that best supportive care had been optimised for all patients before they were enrolled into the trials. So, any observed benefit during the trial is because of the stringent treatment monitoring, and is unlikely to continue after the trial follow-up. One clinical expert advised that, in practice, quality of life improves for 2 to 3 months in patients supported for short periods, but that this improvement is only rarely sustained after 6 months. In general, the experts explained that it was a realistic expectation that all patients having best supportive care would return to baseline utility values after 3 years, given the chronic nature of the condition. However, another clinical expert considered that no sustained best supportive care benefit in year 4 and beyond seemed too low. The committee noted the conflicting views of the clinical experts, which it took to reflect the uncertainty about the decline in the utility benefit of the best supportive care offered during the trials. The committee concluded that the effect of best supportive was likely to wane fairly rapidly but how rapidly was uncertain.

Quality of life waning assumptions for dupilumab should be based on all available data and consider the relative use of topical corticosteroids in trials

3.21 The committee was aware that patients in both arms of the trials had best supportive care. However, it considered that the company did not assume that the effect of best supportive care on quality of life wanes in the same way in both arms. Instead, it assumed that there would be a much more

rapid loss of this effect in the best supportive care arm than the dupilumab arm, which the committee agreed was not appropriate. None of the company's or ERG's sensitivity analyses explored larger, and more rapid declines in quality of life in the dupilumab arm than the base case. The committee recalled that in CAFÉ, patients who had dupilumab reduced their topical corticosteroids use by 51% compared with 17% in patients who had best supportive care (see section 3.14). The committee considered this to be a good proxy for the relative effect of best supportive care on health-related quality of life in each arm. The same assumption about the waning effect of best supportive care could then be applied to different proportions of people in each arm, based on the relative use of topical corticosteroids in that arm in CAFÉ, or in the company's long-term study (see section 3.7), which the committee is yet to see evidence from. The committee concluded that using this method and data from the open-label study would reflect a more evidence-based approach to modelling the waning of the quality of life benefit.

Costs in the economic model

The long-term costs of best supportive care are likely to be over-estimated

3.22 The committee noted that there was a structural link between the assumptions concerning clinical benefit (that is, quality of life) and costs. As the quality of life estimates were adjusted over time, more people having best supportive care were assumed to be 'non-responders' (see section 3.19). Hence, over time, more people, and eventually everyone having best supportive care were assumed to be 'non-responders' and incurred the higher resource use and costs associated with 'non-response' (see section 3.23). The committee considered that this would have over-estimated the longer-term costs of best supportive care. Because of this, the committee reiterated that it is important to model objective and plausible assumptions about the decline in clinical effectiveness and quality of life benefits (see sections 3.19–3.21).

The average resource use from all patients having best supportive care could be used instead of the resource use associated with ‘non-responders’

3.23 The company derived some of its data on resource use from a review of the secondary care notes of 30 patients with atopic dermatitis, not controlled with systemic therapy. It applied resource use estimates depending on whether the person had dupilumab or best supportive care, and whether the condition responded to treatment or not. The company explained that there were additional data available from 60 people in total; the committee would have preferred to have had resource use estimates from the larger sample. In its exploratory analyses, the ERG used additional data available in the company submission on the secondary care notes review; these resulted in estimates that were generally higher for ‘responders’ than the company’s estimates. One clinical expert explained that, in practice, patients on systemic therapy would generally be seen 3 to 4 times per year by dermatologists and probably more often by GPs, but that the frequency would likely depend on whether the condition was moderate or severe. Another expert explained that patients on new drugs such as dupilumab would have more frequent monitoring than patients on older drugs. Because the company’s model is likely to over-estimate the long-term costs of best supportive care (see section 3.22), the committee concluded that a reasonable alternative scenario would be to use the average resource use from all patients rather than assuming everyone is a ‘non-responder’.

Different models of costs associated with adverse events are preferable

3.24 In its model, the company included the costs of 4 adverse events: injection site reactions, allergic conjunctivitis, infectious conjunctivitis and oral herpes. It assumed that injection site reactions occurred only once and used annual rates for the other adverse events. The clinical experts confirmed that injection site reactions are not one-time events. The committee would have preferred the company to have applied an annual rate for injection site reactions. The company also estimated that an

accident and emergency visit costs £137.82, which the committee considered to be too low.

Cost-effectiveness estimate

There are no analyses that include the committee's preferred assumptions

3.25 The committee recalled its concerns about the company's base-case analyses, which were that they:

- included only part of the best supportive care likely to be offered in NHS practice (see sections 3.4 and 3.6)
- used data that included patients who had rescue therapy ('all observed' analyses; see section 3.11)
- pooled 'responders' and 'non-responders' in best supportive care (see section 3.16)
- applied a constant annual stopping rate of 3.7%, which appeared low (see section 3.17)
- generalised the utility value for 'responders' and 'non-responders' in the best supportive care arm to dupilumab 'non-responders' (see section 3.18)
- applied different assumptions for the decline in the clinical and utility benefits of best supportive care in the dupilumab and best supportive care arms (see sections 3.19, 3.20 and 3.21)
- overestimated the long-term costs of best supportive care (see sections 3.22 and 3.23)
- underestimated the cost of injection site reactions, and accident and emergency visits (see section 3.24).

Cost-effectiveness estimates for dupilumab compared with best supportive care are too high to consider it a good use of NHS resources

3.26 The committee did not see analyses that brought together all its preferred assumptions. The incremental cost-effectiveness ratios (ICERs) for dupilumab plus topical corticosteroids compared with best supportive care

alone in the company's base case and relevant sensitivity analyses ranged from £29,792 to £41,838 per QALY gained. The ICERs in the ERG's exploratory analyses ranged from £39,293 to £77,701 per QALY gained. The committee noted that the ICERs were sensitive to small changes in the proportion of people continuing to benefit from best supportive care. It considered that modelling using its preferences (see section 3.25) may further increase the ICER for dupilumab compared with best supportive care, and concluded that dupilumab does not reflect a good use of NHS resources.

Other factors

An equality issue is that the EASI and DLQI may not be appropriate for all people with atopic dermatitis

3.27 The committee noted potential equality issues, namely, that:

- the EASI might underestimate the severity of atopic dermatitis in people with darker skin
- the DLQI may miss anxiety and depression.

The committee concluded that, when using the EASI, healthcare professionals should take into account skin colour and how this could affect the EASI score. Also, it concluded that, when using the DLQI, healthcare professionals should take into account any physical, psychological, sensory or learning disabilities, or difficulties in communication that could affect a person's response to the DLQI. However, because the committee did not recommend dupilumab, there was no need to reflect these issues in the preliminary recommendations.

Another equality issue is that certain ethnic groups have different cytokine pathways

3.28 Feedback from patient and professional organisations highlighted that there are specific cytokine pathways in atopic dermatitis in different ethnic groups; for example, interleukin-4 and interleukin-13 cytokines

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predominate in most populations whereas, in some Asian populations, interleukin-17 cytokines predominate. The committee understood that there is insufficient evidence to determine the extent to which different cytokine pathways modify treatment effect. Therefore, it did not consider that it needed to account for the variation in cytokine expression in different ethnic groups.

Dupilumab is an innovative treatment

3.29 Patient and professional feedback highlighted the significant and substantial health-related benefits associated with treatment with dupilumab. The committee agreed that dupilumab is innovative and a step change in managing atopic dermatitis, and acknowledged the stigma that can be associated with the condition. However, it did not hear that there were any additional gains in health-related quality of life over those already included in the QALY calculations.

4 Proposed date for review of guidance

4.1 NICE proposes that the guidance on this technology is considered for review by the guidance executive 3 years after publication of the guidance. NICE welcomes comment on this proposed date. The guidance executive will decide whether the technology should be reviewed based on information gathered by NICE, and in consultation with consultees and commentators.

Amanda Adler
Chair, Appraisal Committee
March 2018

5 Appraisal committee members and NICE project team

Appraisal committee members

The 4 technology appraisal committees are standing advisory committees of NICE. This topic was considered by [committee B](#).

Committee members are asked to declare any interests in the technology to be appraised. If it is considered there is a conflict of interest, the member is excluded from participating further in that appraisal.

The [minutes](#) of each appraisal committee meeting, which include the names of the members who attended and their declarations of interests, are posted on the NICE website.

NICE project team

Each technology appraisal is assigned to a team consisting of 1 or more health technology analysts (who act as technical leads for the appraisal), a technical adviser and a project manager.

Sharlene Ting

Technical Lead

Ahmed Elsada

Technical Adviser

Jeremy Powell

Project Manager

ISBN: **[to be added at publication]**