

Dupilumab for treating moderate to severe atopic dermatitis

Technology appraisal guidance

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Your responsibility

The recommendations in this guidance represent the view of NICE, arrived at after careful consideration of the evidence available. When exercising their judgement, health professionals are expected to take this guidance fully into account, alongside the individual needs, preferences and values of their patients. The application of the recommendations in this guidance is at the discretion of health professionals and their individual patients and do not override the responsibility of healthcare professionals to make decisions appropriate to the circumstances of the individual patient, in consultation with the patient and/or their carer or guardian.

All problems (adverse events) related to a medicine or medical device used for treatment or in a procedure should be reported to the Medicines and Healthcare products Regulatory Agency using the [Yellow Card Scheme](#).

Commissioners and/or providers have a responsibility to provide the funding required to enable the guidance to be applied when individual health professionals and their patients wish to use it, in accordance with the NHS Constitution. They should do so in light of their duties to have due regard to the need to eliminate unlawful discrimination, to advance equality of opportunity and to reduce health inequalities.

Commissioners and providers have a responsibility to promote an environmentally sustainable health and care system and should [assess and reduce the environmental impact of implementing NICE recommendations](#) wherever possible.

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1 Recommendations

- 1.1 Dupilumab is recommended as an option for treating moderate to severe atopic dermatitis in adults, only if:
- the disease has not responded to at least 1 other systemic therapy, such as ciclosporin, methotrexate, azathioprine and mycophenolate mofetil, or these are contraindicated or not tolerated
 - the company provides dupilumab according to the [commercial arrangement](#).
- 1.2 Stop dupilumab at 16 weeks if the atopic dermatitis has not responded adequately. An adequate response is:
- at least a 50% reduction in the Eczema Area and Severity Index score (EASI 50) from when treatment started and
 - at least a 4-point reduction in the Dermatology Life Quality Index (DLQI) from when treatment started.
- 1.3 When using the EASI, healthcare professionals should take into account skin colour and how this could affect the EASI score, and make the clinical adjustments they consider appropriate.
- 1.4 When using the DLQI, healthcare professionals should take into account any physical, psychological, sensory or learning disabilities, or communication difficulties that could affect the responses to the DLQI, and make any adjustments they consider appropriate.
- 1.5 These recommendations are not intended to affect treatment with dupilumab that was started in the NHS before this guidance was published. People having treatment outside these recommendations 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

ciclosporin, methotrexate, azathioprine and mycophenolate mofetil. Dupilumab would be used after these treatments no longer work, and best supportive care is the only other available option. Dupilumab would likely be offered alongside topical corticosteroids.

The clinical evidence shows that dupilumab is very effective when used in this way. The most plausible cost-effectiveness estimates for dupilumab plus topical corticosteroids compared with best supportive care are within the range that NICE normally considers an acceptable use of NHS resources.

2 Information about dupilumab

Marketing authorisation indication

- 2.1 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

- 2.2 The dosage schedule is available in the [summary of product characteristics](#).

Price

- 2.3 The cost of dupilumab is £1,264.89 per pack of 2×2-ml syringes of 150 mg/1 ml solution (excluding VAT; BNF online accessed March 2018).
- 2.4 The company has a [commercial arrangement](#). This makes dupilumab available to the NHS with a discount. The size of the discount is commercial in confidence. It is the company's responsibility to let relevant NHS organisations know details of the discount.

3 Committee discussion

The [appraisal committee](#) 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 Atopic dermatitis is a chronic, recurrently flaring, generalised skin condition that can be life-limiting, debilitating and isolating. It can affect all aspects of life (physical, psychological, social and financial). Severe disease 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

Symptoms, signs and quality of life determine the severity of atopic dermatitis

- 3.2 The committee understood that there is variability in how clinicians assess severity in atopic dermatitis. They assess severity based on clinical signs and on patient-reported symptoms including effect on sleep and work, and how much patients need to use topical corticosteroids or systemic therapy. 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 POEM is easier to administer in practice than the EASI. The committee

understood that NHS clinicians routinely use the Dermatology Life Quality Index (DLQI) to assess quality of life in other skin conditions. It concluded that the EASI, DLQI and POEM are appropriate for assessing the severity of atopic dermatitis in NHS practice.

Clinical management

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

- 3.3 Although clinicians individualise therapy for patients, a typical treatment pathway involves emollients and topical corticosteroids (first line), topical calcineurin inhibitors (second line), phototherapy (third line) and systemic immunosuppressant therapies (fourth line) including ciclosporin (the only licensed drug), methotrexate, azathioprine and mycophenolate mofetil. These systemic therapies can have serious adverse effects and, if a drug is no longer effective, it will be stopped and another drug will be offered. For people whose disease does not respond to multiple systemic therapies, the only remaining treatment option is best supportive care, which may include education, psychological support, emollients, topical corticosteroids, bandages and hospitalisation. Managing exacerbations (flares) in atopic dermatitis includes using short-term potent topical corticosteroids, oral corticosteroids and systemic therapy.

Positioning of dupilumab in the treatment pathway

Dupilumab would be used after existing systemic therapies

- 3.4 The marketing authorisation for dupilumab is for 'moderate to severe atopic dermatitis in adults who are candidates for systemic therapy'. The company only submitted evidence for dupilumab as a fifth-line treatment, after systemic immunosuppressant therapies, as an alternative to best supportive care. The clinical experts explained that people are likely to have had at least 1 systemic

therapy before dupilumab in clinical practice. The committee concluded that it would appraise dupilumab for moderate to severe atopic dermatitis, compared with best supportive care.

Comparators

The company's revised definition of best supportive care is appropriate for decision-making

- 3.5 The company defined best supportive care in its economic model as 'emollients, low-to-mid potency topical corticosteroids, and rescue therapy with higher potency topical or oral corticosteroids or topical calcineurin inhibitors'; it also included phototherapy and psychological support in its revised model, submitted in response to the appraisal consultation document. However, it excluded bandages because these were captured within 'day case' treatment and education because no reliable data were available. The ERG agreed with the company's revised approach in defining best supportive care. The committee concluded that the company's revised definition of best supportive care was adequate for decision-making.

Clinical evidence

The CAFÉ and CHRONOS trials provide the key clinical evidence for dupilumab

- 3.6 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 as needed (CAFÉ and CHRONOS). All patients had best supportive care. The clinical experts explained that dupilumab is likely to be offered alongside topical corticosteroids. The committee therefore agreed to focus on the evidence on dupilumab 'combination therapy' with topical corticosteroids. CAFÉ and CHRONOS were randomised double-blind trials that included a total of 1,065 patients who had had 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. The trials compared 2 doses of dupilumab (300 mg every week [unlicensed] or 300 mg every other week [licensed]) with placebo. The committee agreed to focus only on the data for the licensed dose of dupilumab. The primary endpoints were assessed at the end of the 'induction period' (that is, 16 weeks after starting treatment):

- CHRONOS (co-primary endpoints):
 - at least a 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 Investigators' Global Assessment, and at least a 2-point improvement from baseline.
- CAFÉ: EASI 75.

Patients in CHRONOS had an additional 36 weeks of treatment.

The open-label extension study provides long-term clinical evidence for dupilumab

- 3.7 In response to the appraisal consultation document, the company provided data for up to 100 weeks from the start of an ongoing, open-label extension study. It included patients from previous dupilumab trials who had not had any adverse effects that led them to stop the trial, or patients screened for the SOLO studies but unable to enter them because of closure of the trials. Patients had weekly dupilumab (unlicensed dose) and could also use topical medications as needed. The company provided data for 2 subgroups: patients who had not had dupilumab before the study ('dupilumab-naive') or patients who had previously had dupilumab but with treatment gaps ranging from less than 6 weeks to more than 13 weeks ('dupilumab-exposed'). The committee concluded that evidence from this extension study, particularly that from the 'dupilumab-exposed' subgroup, would help in the understanding of dupilumab's long-term clinical effectiveness and to inform the assumptions in the economic model (see [section](#)

3.15 and section 3.17).

Company's revised base case

The base case focuses on a subgroup of patients from CAFÉ and CHRONOS, 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 therapies, it focused its base case on a subgroup of 299 patients from CAFÉ and CHRONOS 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 concluded that the subgroup was sufficiently large to provide reliable estimates of clinical effectiveness.

Clinical experts advise that the population in the company's subgroup is similar to patients in the NHS who would have dupilumab

- 3.9 The subgroup identified by the company included patients who were on average 38 years old; 60% were men and 91% were 'white'. Patients had atopic dermatitis for an average of 29 years, which covered an average of 58% of their body, and they had average scores of 34 on the EASI, 20 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 population generally reflected people who would be treated with dupilumab in NHS clinical practice.

Analyses that consider patients to be 'non-responders' if they have rescue therapy are appropriate

- 3.10 In its revised base case, the company presented results from 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. The committee concluded that these analyses were 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 combination of EASI 50 plus an improvement in the DLQI of at least 4 is an appropriate outcome for decision-making

- 3.11 To model the cost effectiveness of dupilumab, the company defined a clinical benefit in its base case of an EASI 50 (at least a 50% reduction in the EASI score from when treatment started) plus an improvement in the DLQI of at least 4. The clinical experts explained that EASI 50 and an improvement in the DLQI of at least 4 are sensitive to changes in treatment outcomes and more clinically relevant than an EASI 75 (at least a 75% reduction in the EASI score from when treatment started). The committee concluded that the composite endpoint of an EASI 50 plus an improvement in the DLQI of at least 4 was appropriate for decision-making.

Dupilumab with topical corticosteroids as needed is substantially more clinically effective than placebo

- 3.12 The committee noted that patients having dupilumab plus topical corticosteroids as needed had a clinically and statistically significantly higher response rate in the EASI 50 plus an improvement in the DLQI of at least 4 at week 16 (73% of 130 patients) than patients having placebo plus topical corticosteroids as needed (28% of 169 patients). The committee noted that these results also included patients who had rescue therapy. It concluded that dupilumab was substantially more clinically effective than placebo, although it would have preferred to have seen the results of the analyses in which patients who had rescue therapy were

considered to be 'non-responders' (see [section 3.10](#)).

Patients in the trials had a relatively high 'placebo response'

3.13 The committee queried the high response rate seen in the placebo group (see section 3.12). 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. The committee concluded that the 'placebo response' in the trials was unlikely to have affected the treatment effect of dupilumab relative to placebo.

Company's revised economic model

The model combines a decision tree and Markov state transition

- 3.14 The company's model consisted of 2 components:
- Decision tree up to 52 weeks: people entered the model either in the 'dupilumab' 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.
 - At week 16 after starting treatment, people in the 'dupilumab' 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 and split according to treatment response into 'responders' or 'non-responders'.

- At week 52 after starting treatment, people in the 'dupilumab' 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 and split according to treatment response into 'responders' or 'non-responders'.
- 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 concluded that the revised model structure was appropriate.

Assumptions in the revised economic model

A yearly stopping rate of 3.7% for people having dupilumab plus topical corticosteroids is plausible based on data from the open-label extension study

- 3.15 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 at 16 weeks who withdrew from the trial by 52 weeks. In response to the appraisal consultation document,

the company provided sensitivity analyses on a range of stopping rates based on data from its open-label extension study, ranging from 2.1% in 'responders' at week 24 to 6.4% in the whole population at 52 weeks. The ERG agreed that the original stopping rate appear reasonable and consistent with the available data. The committee noted that the different stopping rates had minimal impact on the cost-effectiveness estimates, and agreed that the company's original stopping rate of 3.7% is plausible.

Utility values in the revised economic model

Utility values specific for people whose condition does not respond to dupilumab are appropriate

3.16 In its revised model, the company assumed that, if atopic dermatitis did not respond to dupilumab plus topical corticosteroids:

- at week 16 after starting treatment, people accrued the average utility value of dupilumab 'non-responders' and best supportive care 'non-responders' (0.82)
- from week 52 onwards, people accrued the utility value of best supportive care 'non-responders' (0.77).

The ERG agreed that the company's revised approach to modelling utility values for dupilumab 'non-responders' was appropriate. These revisions had a minimal effect on the cost-effectiveness estimates. However, the committee agreed that it was appropriate to use the utility value specific to people whose condition had not responded to dupilumab plus topical corticosteroids at 16 weeks rather than the utility value from everyone having best supportive care (0.81), as the company had done in its original model.

Assumptions on loss of utility benefit should be based on data from the open-label extension study and CHRONOS

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

- 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). The company based these assumptions for dupilumab on feedback from the experience of 5 dupilumab trial investigators, supported by evidence from its open-label extension study that showed a sustained treatment effect.
- In the best supportive care state, the company assumed that 25% of the benefit would be lost in year 2, 50% in year 3, 75% in year 4, and 100% in year 5 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 (0.80), 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 5, everyone in the best supportive care arm returned to the baseline utility (0.66) for the remainder of their time in the model.

The company also provided analyses in which it changed its assumptions on the decline in quality of life (see table 1).

Table 1 Assumptions in proportion of patients losing quality-of-life benefit in each time period for dupilumab and best supportive care in the company's revised base case and sensitivity analyses

Treatment	Dupilumab				Best supportive care			
	Year 2	Year 3	Year 4	Year 5 and beyond	Year 2	Year 3	Year 4	Year 5 and beyond
Revised base case	2%	5%	7%	8%	25%	50%	75%	100%

Treatment	Dupilumab				Best supportive care			
Year	Year 2	Year 3	Year 4	Year 5 and beyond	Year 2	Year 3	Year 4	Year 5 and beyond
Sensitivity analysis 1: Best supportive care – CHRONOS 'time to rescue therapy/stopping study' projections using Weibull curve fit	2%	5%	7%	8%	82%	90%	94%	96%
Sensitivity analysis 2: Best supportive care – CHRONOS 'time to rescue therapy/stopping study' annual rate	2%	5%	7%	8%	57%	82%	92%	97%
Sensitivity analysis 3: Dupilumab – relative decline based on topical corticosteroid use in CAFÉ, 38.4%	10%	19%	29%	38%	25%	50%	75%	100%

The committee agreed that the data from the open-label extension study provided supporting evidence for the sustained effect of dupilumab in the revised base case. The ERG expressed concerns about sensitivity analyses 1 and 2 for best supportive care; it was unclear whether the data were from 'responders' only. It also did not consider the use of rescue therapy to be a good indication of loss of utility benefit because it formed part of best supportive care, which could improve quality of life. The committee agreed that there was uncertainty surrounding the assumptions on loss of utility benefit for best supportive care. It noted that sensitivity analyses 1 and 2 resulted in some patients maintaining benefit from year 5 and beyond, which it considered to be more plausible than no patients maintaining any benefit at all (revised base case and sensitivity analysis 3). Therefore, the committee concluded that sensitivity analyses 1 and 2 were the most plausible analyses for decision-making.

Costs in the economic model

The costs associated with adverse events are appropriate

3.18 In its revised model, the company included the costs of 4 adverse events: injection site reactions, allergic conjunctivitis, infectious conjunctivitis and oral herpes. It used annual rates for injection site reactions. The company also revised its accident and emergency visit costs from £137.82 to £159.78. The ERG agreed with the company's changes. The committee accepted these changes but noted that these changes had a minor effect on the cost-effectiveness estimates.

Cost-effectiveness estimate

Dupilumab is cost effective in people for whom best supportive care is the only option

- 3.19 The incremental cost-effectiveness ratios for dupilumab plus topical corticosteroids as needed compared with best supportive care alone in the company's revised base case and plausible sensitivity analyses (see [section 3.17](#)) ranged from £27,410 to £28,495 per quality-adjusted life year (QALY) gained. The committee concluded that dupilumab plus topical corticosteroids is a cost-effective use of NHS resources for treating atopic dermatitis that has not responded to other systemic therapies, such as ciclosporin, methotrexate, azathioprine and mycophenolate mofetil, or when these options are contraindicated or not tolerated.

Dupilumab should be stopped after 16 weeks if treatment response is inadequate

- 3.20 The committee understood from the [summary of product characteristics](#) that 'consideration should be given to discontinuing treatment in patients who have shown no response after 16 weeks of treatment'. The committee was aware that a similar 'induction' phase was implemented in the clinical trials (see [section 3.6](#)) and applied by the company in the economic model. An adequate response is defined as at least a 50% reduction in the EASI score and at least a 4-point reduction in DLQI from when treatment started in the economic model. The committee agreed that it would be appropriate to stop treatment with dupilumab after 16 weeks if treatment response is inadequate.

Other factors

There is a lack of evidence on the effect of moderate to severe atopic dermatitis on the quality of life of carers

- 3.21 The committee noted comments from stakeholders that the effect of moderate to severe atopic dermatitis on the quality of life of families and carers should be taken into account. Although the committee acknowledged that there could potentially be an effect on the quality of life of families and carers, it agreed that it had not seen any evidence to support this.

EASI and DLQI may not be appropriate for all people with atopic dermatitis

- 3.22 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.

Certain ethnic groups have different cytokine pathways

- 3.23 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 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

- 3.24 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. 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 Implementation

- 4.1 Section 7 of the National Institute for Health and Care Excellence (Constitution and Functions) and the Health and Social Care Information Centre (Functions) Regulations 2013 requires integrated care boards, NHS England and, with respect to their public health functions, local authorities to comply with the recommendations in this evaluation within 3 months of its date of publication. Because dupilumab has been available through the early access to medicines scheme, NHS England and integrated care boards have agreed to provide funding to implement this guidance 30 days after publication.
- 4.2 The Welsh ministers have issued directions to the NHS in Wales on implementing NICE technology appraisal guidance. When a NICE technology appraisal guidance recommends the use of a drug or treatment, or other technology, the NHS in Wales must usually provide funding and resources for it within 2 months of the first publication of the final draft guidance.
- 4.3 When NICE recommends a treatment 'as an option', the NHS must make sure it is available within the period set out in the paragraphs above. This means that, if a patient has atopic dermatitis and the healthcare professional responsible for their care thinks that dupilumab is the right treatment, it should be available for use, in line with NICE's recommendations.

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.

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