NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Draft guidance consultation

Nemolizumab for treating moderate to severe atopic dermatitis in people 12 years and over

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

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

The evaluation 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 age, disability, gender reassignment, pregnancy and maternity, race, religion or belief, sex or sexual orientation?

Issue date: March 2025

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- After considering these comments, the committee will prepare the final draft guidance.
- Subject to any appeal by stakeholders, the final draft guidance may be used as the basis for NICE's guidance on using nemolizumab in the NHS in England.

For further details, see NICE's manual on health technology evaluation.

The key dates for this evaluation are:

- Closing date for comments: 17 April 2025
- Second evaluation committee meeting: 07 May 2025
- Details of the evaluation committee are given in section 4

1 Recommendations

1.1 Nemolizumab with topical corticosteroids, calcineurin inhibitors, or both, should not be used to treat moderate to severe atopic dermatitis that is suitable for systemic treatment in people 12 years and over with a body weight of 30 kg or more.

1.2 This recommendation is not intended to affect treatment with nemolizumab 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 healthcare professional consider it appropriate to stop. For young people, this decision should be made jointly by the healthcare professional, the young person, and their parents or carers.

What this means in practice

Nemolizumab is not required to be funded in the NHS in England to treat moderate to severe atopic dermatitis in people 12 years and over. It should not be used routinely in the NHS in England.

This is because the available evidence does not suggest that nemolizumab is value for money.

Why the committee made these recommendations

Usual treatment for moderate to severe atopic dermatitis (eczema) includes emollients, corticosteroids and calcineurin inhibitors applied to the skin (topical treatments). If these treatments are not effective, systemic immunosuppressants (such as ciclosporin and methotrexate) can be added. If these are also not effective, or unsuitable, a Janus kinase (JAK) inhibitor (such as abrocitinib, baricitinib or

upadacitinib) or a biological medicine (such as dupilumab, lebrikizumab or tralokinumab) can be used.

Clinical trial evidence shows that nemolizumab is more effective than placebo at improving the symptoms of atopic dermatitis. It has not been directly compared in a clinical trial with JAK inhibitors or other biological medicines. Indirect comparisons suggest that it may work as well as most of these treatments, but this is uncertain.

There are also uncertainties in the economic model including the assumption around how long people stay on treatment.

The cost-effectiveness estimates are above the range that NICE considers an acceptable use of NHS resources. So, nemolizumab should not be used.

2 Information about nemolizumab

Marketing authorisation indication

2.1 Nemolizumab (Nemluvio, Galderma) is indicated for 'the treatment of moderate-to-severe atopic dermatitis in combination with topical corticosteroids and/or calcineurin inhibitors in adults and adolescents 12 years and older with a body weight of at least 30 kg, who are candidates for systemic therapy'.

Dosage in the marketing authorisation

2.2 The dosage schedule is available in the summary of product characteristics for nemolizumab.

Price

2.3 The list price of nemolizumab is £2,257 per 30 mg unit (company submission).

2.4 The company has a commercial arrangement, which would have applied if nemolizumab had been recommended.

3 Committee discussion

The evaluation committee considered evidence submitted by Galderma, a review of this submission by the external assessment group (EAG), and responses from stakeholders. See the committee papers for full details of the evidence.

The condition

Details of condition and patient perspectives

3.1 Atopic dermatitis (eczema) is a common, chronic and flaring inflammatory skin condition. The exact cause is unknown but involves genetic susceptibility and environmental triggers. Symptoms include dry, flaky and inflamed skin, which can be intensely itchy, and painful lesions typically affecting the hands, eyelids and flexures (skin folds). Patient experts explained that atopic dermatitis is often thought to be a minor condition, but for people with moderate to severe atopic dermatitis, the condition takes over all aspects of life. Symptoms such as the inability to regulate temperature, weeping sores, pain and constant itch substantially impact quality of life. As well as the physical symptoms, another patient expert highlighted the substantial impact on sleep, education and the ability to form relationships. These all substantially impact mental health, leading to anxiety, depression and suicidal thoughts. They added that the effects of the condition can be particularly hard for younger people because of a lack of acceptance among peers and the false expectation that they may grow out of the condition after childhood. There is also a huge sense of responsibility and burden for parents of younger people with the condition. Patient expert submissions described the frustrating, and often unsuccessful, process of 'trial and error' to find a treatment that works. They added that even if a treatment works initially, the effects often wear off over time, resulting in an unmet need for new and effective treatments. A patient expert noted that current treatments can have troubling side effects (such as eye problems) that could be avoided with nemolizumab. Patient experts added that the reduced injection frequency of nemolizumab is also a notable advantage compared with current

treatments. The committee concluded that there is an unmet need for additional effective treatments for atopic dermatitis and that nemolizumab has a reduced administration frequency compared with current treatments.

Clinical management

Treatment pathway

3.2 Moderate to severe atopic dermatitis is initially treated with emollients, topical corticosteroids and topical calcineurin inhibitors. When the condition has not responded adequately to topical treatment, first-line systemic immunosuppressants may be offered. These include azathioprine, ciclosporin, methotrexate and mycophenolate mofetil. If the condition does not respond to first-line systemic immunosuppressants, or if these are not tolerated or not suitable, then a biological medicine (dupilumab, lebrikizumab or tralokinumab) or a Janus kinase (JAK) inhibitor (abrocitinib, baricitinib or upadacitinib) can be offered. The company positioned nemolizumab after first-line systemic treatments or if these treatments are not suitable. The clinical experts agreed with the company's positioning. The committee concluded that nemolizumab was appropriately positioned. The committee added that, in practice, adults would likely have biological medicines such as nemolizumab as a second-line systemic treatment after first-line systemic immunosuppressants, but young people would likely have these at first line. This is because typical first-line systemic options in adults are not suitable for young people.

Comparators

3.3 Comparators to nemolizumab in the company's model included the JAK inhibitors abrocitinib, baricitinib or upadacitinib, and the biological medicines dupilumab, lebrikizumab or tralokinumab, but not first-line systemic treatments such as ciclosporin or methotrexate. In its submission, the company noted that the previous NICE technology appraisal recommendations for baricitinib, dupilumab and tralokinumab

were for adults only, so the company did not initially include these treatments as comparators for young people. The EAG highlighted in its report that the marketing authorisations for dupilumab and tralokinumab have since been extended (to people 6 months and over for dupilumab and 12 years and over for tralokinumab). Clinical advice to the EAG was that both dupilumab and tralokinumab are used in young people so these should also be included as comparators. The company updated its model at clarification stage to include dupilumab and tralokinumab for young people. A clinical expert at the committee meeting explained that treatment choice is highly individual. Comorbidities, the safety profiles of treatments, individual preference for an injection or oral medicine, and how fast a response is needed all impact treatment choice. The clinical expert added that JAK inhibitors may be used by people who prefer an oral medicine. JAK inhibitors are also faster acting than biological medicines. But JAK inhibitors may not be suitable for everyone because they have a higher risk of venous thromboembolism and cardiovascular events. The committee concluded that both JAK inhibitors and biological medicines were relevant comparators and noted that this was in line with previous appraisals of biological medicines for moderate to severe atopic dermatitis.

Clinical effectiveness

Clinical trials

3.4 The clinical evidence for nemolizumab came from the ARCADIA 1 (n=941), ARCADIA 2 (n=787) and ARCADIA-CYCLO (n=276) trials. ARCADIA 1 and ARCADIA 2 were phase 3, double-blind, randomised controlled trials comparing nemolizumab with placebo in adults and young people over 12 years with moderate to severe atopic dermatitis. ARCADIA-CYCLO was a phase 3b, double-blind, randomised controlled trial comparing nemolizumab with placebo in adults whose condition was not adequately controlled with ciclosporin or for whom ciclosporin was unsuitable. In all trials, best supportive care with treatments such as

emollients, topical corticosteroids and topical calcineurin inhibitors was used alongside nemolizumab or placebo. The primary outcomes in ARCADIA 1 and ARCADIA 2 were assessed at week 16. These included EASI 75 response (a reduction of at least 75% from baseline Eczema Area and Severity Index [EASI] score) and Investigator's Global Assessment (IGA) success (defined as an IGA of 0 [clear] or 1 [almost clear], and at least a 2-point reduction from baseline). The primary outcomes in ARCADIA-CYCLO were EASI 75 and Peak Pruritus Numerical Rating Scale (PP-NRS), a measure of itch intensity. In ARCADIA 1 and ARCADIA 2 there was a statistically significantly greater proportion of people with EASI 75 response for nemolizumab compared with placebo at week 16 (ARCADIA 1, 43.5% versus 29.0%; ARCADIA 2, 42.1% versus 30.2%). This response was continued in the pooled maintenance period up to week 48. Similarly, there was a statistically significantly greater proportion of people with IGA success for nemolizumab compared with placebo at week 16 (ARCADIA 1, 35.6% versus 24.6%; ARCADIA 2, 37.7% versus 26.0%). This was continued in the pooled maintenance period up to week 48. Results of ARCADIA-CYCLO are considered confidential by the company so cannot be reported here. The committee concluded that nemolizumab was more effective than placebo.

Network meta-analysis

3.5 There were no clinical trials directly comparing nemolizumab with the relevant comparators (see section 3.3). So, the company did a network meta-analysis (NMA) for a range of efficacy, quality of life and adverse event outcomes. EASI 75 response at week 16 was the efficacy outcome used in the economic model (see section 3.7). Separate NMAs were done for:

- adults (18 years or over), second-line treatment (ciclosporin-experienced)
- young people (12 to 17 years), first-line treatment (ciclosporin-naive).

The company's NMA results for the second-line adult population did not show a statistically significant difference in the odds of EASI 75 response for nemolizumab compared with the biological medicines (dupilumab, lebrikizumab and tralokinumab) or JAK inhibitors (abrocitinib, baricitinib and 15 mg upadacitinib). But results did show a statistically significant difference in favour of 30 mg upadacitinib. The company's NMA results for the first-line young people population did not show a statistically significant difference in odds of EASI 75 response for nemolizumab compared with abrocitinib, lebrikizumab or 15 mg upadacitinib. The company's NMA in the first-line young people population showed a statistically significant difference in favour of 30 mg upadacitinib, but this was not a comparator for young people. The exact odds ratios from the NMA are considered confidential by the company so cannot be reported here. The EAG did its own NMA to validate the company's NMA and to correct minor methodological issues. Results of the EAG's NMA were similar to the company's for both populations. The committee noted the uncertainty in the company's NMA results, as shown by wide confidence intervals around odds ratios.

Clinical equivalence assumption

3.6 Where results of the company's NMA did not show a statistically significant difference between nemolizumab and each of the comparators (see section 3.5), the company assumed clinical equivalence. That is, the company assumed that each of the comparators had the same efficacy as nemolizumab, by applying an odds ratio of 1 in its economic model. The EAG did not agree with the company's approach. It preferred to use point estimates for the odds ratios based on the EAG's own NMA in its cost-utility base case (EAG base case 2). The EAG also presented a cost-comparison base case (EAG base case 1) assuming the efficacy of all the biological medicines was identical. The EAG noted that if nemolizumab could be assumed to have the same efficacy as biological medicines, then it could potentially be recommended based on a comparison of costs alone. Clinical experts considered whether all the biological medicines

could be assumed to have the same efficacy. One clinical expert explained that they each have different mechanisms of action, which is likely to result in them having different efficacy and tolerability profiles. But, the expert explained that the current biological medicines target the same immune pathway. They also noted that nemolizumab may improve symptoms of itching more than other biologics because of its unique mechanism of action. The committee noted that point estimates from the NMA showed quite substantial differences between treatments (odds ratios not close to 1). It added that the wide credible intervals suggested high uncertainty around the relative benefits. The committee noted that not finding a statistically significant difference in efficacy between treatments is not the same as the treatments being clinically equivalent. The committee concluded that it could not assume equal efficacy across all the biological medicines in either adults or young people. The committee concluded that it preferred a cost-utility analysis, using the EAG's approach (in base case 2) with point estimates of odds ratios from the EAG's NMA, rather than assuming clinical equivalence.

Economic model

Company's modelling approach

3.7 The company's economic model was a hybrid model that consisted of a short-term (1-year) decision tree followed by a long-term Markov model (year 2 onwards). At baseline, people in the model had nemolizumab or comparators for a 16-week induction period. People whose condition had responded to treatment at week 16 were described as 'responders', and were able to continue having maintenance treatment with nemolizumab or a comparator up to week 52. 'Non-responders' were people who initially had a treatment response at week 16 that was then lost, or people who stopped treatment for any reason including side effects by week 52. After week 52, responders and non-responders entered different phases of the long-term Markov model. The long-term Markov model included 3 mutually exclusive health states: maintained response, no response,

and dead. Transitions between health states were informed by probabilities of losing response, discontinuation and death. For the long-term Markov model, an annual cycle length with a half-cycle correction was applied. The model assumed a time horizon of 60 years and applied an annual discount rate of 3.5% for costs and quality-adjusted life years (QALYs). The company's model base case assumed clinical equivalence between treatments where NMA results were not statistically significantly different (see section 3.5). This meant that the QALY gain for nemolizumab in the company's model was small and resulted from nemolizumab having a better side effect profile and lower probability of flare-ups. The EAG corrected several model programming errors and other minor issues with the company's model, including increasing the time horizon to cover an entire life time. The committee concluded that the corrected model was suitable for decision making.

Discontinuation probability

3.8 The company initially used data from ARCADIA 1 and ARCADIA 2 to calculate the discontinuation probability for nemolizumab between week 16 and week 52. This probability was also used to determine the annual long-term discontinuation probability in the model. The EAG noted an error in the company's calculation, which the company corrected at clarification stage. This resulted in a different discontinuation probability for nemolizumab. The exact probability is confidential so cannot be reported here. The company stated that the recalculated probability was different to the discontinuation probability assumed for other biological medicines in previous NICE technology appraisals and so it preferred to use the probability from TA986. In TA986, discontinuation probabilities were applied according to treatment class (3.9% for biological medicines and 10.0% for JAK inhibitors). One clinical expert at the committee meeting could not think of a reason why discontinuation for nemolizumab should be different to that of other biological medicines, particularly because nemolizumab appeared to be better tolerated. Another clinical expert explained that the different probability may be because of the

increased number of alternative treatment options currently available for this condition compared with when biological medicines were first recommended. The company added the discontinuation rate in ARCADIA 1 and ARCADIA 2 may have been impacted because the trials were done during the COVID-19 pandemic. The EAG used the discontinuation probability from TA986 in its base case and explored a scenario analysis using the discontinuation probability from ARCADIA 1 and ARCADIA 2. The EAG's scenario analysis had a large impact on the cost-effectiveness results. When assuming the TA986 probability, nemolizumab was cost effective compared with the other biological medicines. But when assuming the trial probability, nemolizumab was not cost effective compared with the other biological medicines. The committee noted that the different mechanism of action of nemolizumab compared with other biological medicines could result in differences in discontinuation. It further noted that, given nemolizumab was generally better tolerated with lower rates of adverse events, it was unclear why discontinuation should be different for nemolizumab compared with other biological medicines. In the absence of further information on why discontinuation probabilities in ARCADIA 1 and 2 were different to those assumed for other biological medicines, the committee opted to use the value from the trials. But the committee noted that more information from the company would be helpful, including but not limited to:

- discontinuation probabilities for the ARCADIA 1, ARCADIA 2 and ARCADIA-CYCLO trials separately with any differences explained
- corresponding discontinuation probabilities for the placebo arm
- the reasons for discontinuation of treatment in all trials across both treatment arms
- examples of other trials or treatments that have shown a trend for increased discontinuation because of the COVID-19 pandemic, for example, trials for nemolizumab in other indications
- if feasible, discontinuation rates from trials of other biological medicines

- if feasible, an NMA for discontinuation of nemolizumab compared with other biological medicines for the initial 16-week treatment period.

Utility values

3.9 Health state utility values in the company's and EAG's models for responders (in years 1 and 2) and non-responders were based on the EQ-5D-3L data from ARCADIA 1 and ARCADIA 2 (for both adults and young people) and ARCADIA-CYCLO (for adults only). The health state utility value for responders (in year 3 and beyond) was based on a long-term extension study. The committee noted that some of the utility values seemed implausibly high when compared with general population utility values, and also higher than those used in TA986. The committee preferred to cap health state utility values in the model at general population levels.

Severity

3.10 NICE's methods on conditions with a high degree of severity did not apply.

Cost-effectiveness estimates

Acceptable ICER

3.11 NICE's manual on health technology evaluations notes that, above a most plausible incremental cost-effectiveness ratio (ICER) of £20,000 per QALY gained, judgements about the acceptability of a technology as an effective use of NHS resources will take into account the degree of certainty around the ICER. The committee will be more cautious about recommending a technology if it is less certain about the ICERs presented. But it will also take into account other aspects including uncaptured health benefits. The committee noted the high level of uncertainty resulting from the company's NMA (see section 3.5). But it also recalled the potential benefit of nemolizumab's novel mechanism of action in reducing itch (see section 3.6) as well as the psychological

impact of the condition, particularly on young people (see section 3.1). But it noted that, on balance, elements of these were already factored into the QALY calculation. It also noted nemolizumab's reduced administration frequency compared with other biological medicines (see section 3.1). So, the committee concluded that an acceptable ICER would be around the middle of the range NICE considers a cost-effective use of NHS resources (£20,000 to £30,000 per QALY gained), for both adults and young people.

Company and EAG cost-effectiveness estimates

3.12 Because of confidential discounts for nemolizumab and the comparators, the company's and EAG's cost-effectiveness results are confidential and cannot be reported here. The EAG presented results using a fully incremental analysis for all comparators (JAK inhibitors and biological medicines) and also calculated pairwise net monetary benefit for each comparator individually. Net monetary benefit was presented because the cost-effectiveness results spanned all quadrants of the cost-effectiveness plane. The EAG corrected minor errors and issues in the company's base case and also used point estimates for odds ratios (see section 3.6). The committee preferred the EAG's base case. In addition to this, the committee preferred using the discontinuation probability from ARCADIA 1 and ARCADIA 2 as in the EAG's scenario analysis (see section 3.8) and capping utility values at general population values (see section 3.9). The committee understood that nemolizumab would not be cost effective against any of the comparators in either adults or young people using its preferred assumptions.

Equality

3.13 Stakeholders highlighted that moderate to severe atopic dermatitis may be more common in people from Black or Asian ethnicities, or in people living in deprived or urban areas. The committee concluded that issues related to differences in prevalence or incidence of a disease cannot be addressed in a technology appraisal. Stakeholders also highlighted that measures such as EASI are part of the inclusion criteria for many clinical

trials for atopic dermatitis, including the trials for nemolizumab. Because erythema (redness of the skin) is one of the clinical signs used to determine EASI score, severity can be underestimated in people with black or brown skin. This could lead to undertreatment or exclusion from clinical trials. They explained that inflammation may also have a greater impact on people with black or brown skin because it may result in long-term pigmentation changes. Race is a protected characteristic under the Equality Act 2010. The committee noted that if it had recommended nemolizumab, it would have taken into account how skin colour could affect the measurement of severity of disease. Stakeholders also noted that some neurodiverse children may struggle with using certain treatments because of sensory issues. Stakeholders also highlighted that the Dermatology Life Quality Index (DLQI) may not adequately capture impact in older people or those not in a relationship, and may capture anxiety and depression poorly. Stakeholders also highlighted that lower socioeconomic groups may have difficulties accessing JAK inhibitors and that some treatments may not be suitable for people who are unable to store their treatment in the right conditions. Age and disability are a protected characteristics under the Equality Act 2010. The committee considered all the potential equality issues raised by stakeholders but concluded that its recommendation would not differentially impact anyone on the basis of any protected characteristic.

Conclusion

3.14 The committee concluded that the cost-effectiveness estimates for nemolizumab are above the range that NICE normally considers an acceptable use of NHS resources. So, nemolizumab should not be used.

4 Evaluation committee members and NICE project team

Evaluation 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 being evaluated. If it is considered there is a conflict of interest, the member is excluded from participating further in that evaluation.

The minutes of each evaluation committee meeting, which include the names of the members who attended and their declarations of interests, are posted on the NICE website.

Chair

Charles Crawley

Chair, technology appraisal committee B.

NICE project team

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

Anna Willis and Beth Crompton

Technical leads

Rufaro Kausi

Technical adviser

Jeremy Powell

Project manager

Christian Griffiths

Principal technical adviser and acting associate director

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