NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Draft guidance consultation

Dupilumab for treating moderate to severe prurigo nodularis

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 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: August 2023

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- After considering these comments, the committee will prepare the final draft guidance.
- Subject to any appeal by stakeholders, the final draft guidance may be used as the basis for NICE's guidance on using dupilumab in the NHS in England.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: 14 September 2023
- Second evaluation committee meeting: 4 October 2023
- Details of the evaluation committee are given in section 4.

1 Recommendations

1.1 Dupilumab is not recommended, within its marketing authorisation, for treating moderate to severe prurigo nodularis in adults when systemic treatment 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

There is no standard care for prurigo nodularis, but in the NHS, care usually starts with treatments applied to the skin to relieve symptoms. Other treatments are then added as symptoms get more severe. Dupilumab would be used as an alternative for some of these later treatments.

The clinical trial evidence shows that dupilumab improves symptoms of prurigo nodularis compared with best supportive care. But this care did not include many of the treatments that are usually used in the NHS. So, the trial results are uncertain and may not be generalisable to the NHS.

The results from the economic analysis are uncertain because there are several concerns with the model, including:

- the different utility values applied for dupilumab and best supportive care at the start of treatment for people whose condition has not responded
- the way loss of treatment response is modelled for people having best supportive care.

Because of the concerns with the economic model and the uncertain clinical evidence, the cost-effectiveness estimates are highly uncertain. They are also above

the range that NICE considers to be an acceptable use of NHS resources. So, dupilumab cannot be recommended for routine use in the NHS.

2 Information about dupilumab

Marketing authorisation indication

2.1 Dupilumab (Dupixent, Sanofi) is indicated for 'the treatment of adults with moderate-to-severe prurigo nodularis (PN) 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 dupilumab.

Price

2.3 The list price of dupilumab is £1,264.89 for a 2-pack of 300 mg per 2 ml solution for injection pre-filled syringes or pens (excluding VAT; BNF online accessed August 2023).

2.4 The company has a commercial arrangement. This makes dupilumab available to the NHS with a discount and it would have also applied to this indication if the technology had been recommended. 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 evaluation committee considered evidence submitted by Sanofi, 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

3.1 Prurigo nodularis is a rare, chronic condition that affects the skin. It is characterised by firm, thick nodules (or bumps) on the surface of the skin. The cause of prurigo nodularis is unknown but it is associated with abnormal levels of nerve fibres, neuropeptides, and cytokine-producing immune cells. Prurigo nodularis is associated with an intense and constant itch. The itch often disturbs sleep and can have a major impact on quality of life. The appearance of the nodules can also be distressing for people with prurigo nodularis. The patient experts explained that the disease has a large impact on all aspects of life. They also explained that because the condition is rare, it can be challenging to get a diagnosis. The committee agreed there is an unmet need for quicker diagnosis and treatment for people with moderate to severe prurigo nodularis.

Clinical management

Treatment options

3.2 There is no established standard care for prurigo nodularis. The clinical expert explained that while treatment between centres varies, it usually follows a ‘stepped approach’. This is when treatments that are more potent but have more severe side effects are added to treatment combinations, as the condition gets more severe. The first treatments are emollients, topical corticosteroids and topical calcineurin inhibitors. After these, other treatments include phototherapy, oral corticosteroids and antihistamines. Immunosuppressants, antidepressants, pregabalin and gabapentin may also be considered. Finally, neurokinin-1 receptor (NK1R) antagonists, mu-opioid antagonists and thalidomide may be considered in the most severe cases, although the clinical expert explained that it is difficult to get these treatments prescribed. None of the currently available treatments are licensed for treating prurigo nodularis. The company explained that dupilumab would be used when other systemic treatments

were considered. The committee agreed that the positioning of dupilumab in the treatment pathway was appropriate.

Comparators

3.3 In the company's submission, dupilumab in combination with best supportive care was compared with best supportive care without dupilumab. Best supportive care included topical emollients, topical corticosteroids and topical calcineurin inhibitors. The EAG agreed with the company's exclusion of phototherapy but believed that the exclusion of antihistamines, oral corticosteroids, immunosuppressive therapies and antidepressants did not align with the best supportive care used in the NHS. The company explained that there is no randomised controlled trial evidence to support the effectiveness of these medicines for treating prurigo nodularis. It also said that the use of these treatments in clinical practice was highly variable. The clinical expert explained that antihistamines, oral corticosteroids, immunosuppressive therapies and antidepressants were all part of best supportive care used in the NHS, although oral corticosteroids would not be used long term. They also explained that immunosuppressive therapies would not be used alongside dupilumab and therefore was a relevant comparator. The committee agreed with the clinical expert on what represents best supportive care in the NHS. It also agreed that oral corticosteroids and immunosuppressive therapies are relevant comparators that the company excluded from its decision problem. The committee concluded that antihistamines, oral corticosteroids, immunosuppressive therapies and antidepressants are all part of best supportive care used in the NHS and that oral corticosteroids and immunosuppressive therapies should be included as comparators.

Clinical effectiveness

PRIME trials

3.4 The main clinical evidence came from 2 phase 3, randomised, multicentre, double-blind, placebo-controlled trials: PRIME (n=151) and

PRIME2 (n=160). These trials investigated the safety and efficacy of dupilumab in adults with prurigo nodularis that was inadequately controlled with prescribed topical treatments. People were assigned to 1 of 2 treatment groups, dupilumab or placebo. People in both treatment arms were also required to have best supportive care. Both trials had a treatment period of 24 weeks with 12 weeks of untreated follow up. The primary outcome of both trials was a 4-point or more reduction on the Worst Itch-Numerical Rating Scale (WI-NRS). Other outcomes included quality of life data and severity rating score using the Investigator's Global Assessment for Prurigo Nodularis-Stage (IGA-PN-S) tool, which measures the inflammation and number of skin nodules. Both trials were also included in a pooled analysis. The results from both trials and the pooled analysis indicated a statistically significant increase in response for dupilumab compared with the best supportive care provided in the trials. The pooled analysis indicated that people having dupilumab were over 7 times more likely to have a response after 24 weeks of treatment than those having best supportive care. The committee was satisfied that dupilumab provided an effective response.

Generalisability of best supportive care

3.5 The EAG raised concerns that by excluding treatments included in best supportive care used in the NHS (see section 3.3), the results from the PRIME trials would not be representative of practice in the NHS. The EAG's clinical advisers provided estimates of the use of different treatments used in best supportive care for prurigo nodularis in the NHS. The estimates indicated that antihistamines, oral corticosteroids and immunosuppressive therapies were commonly used in the NHS. Methotrexate was considered a key treatment in the NHS, and the EAG's clinical adviser estimated that 50% of people with moderate to severe prurigo nodularis had used it. The company noted that it did a case note review of people with prurigo nodularis who had treatment with systemic therapy in England. This indicated that fewer people had used methotrexate than was estimated, and only a minority of those people had

a response to it (the results of this study are considered academic in confidence by the company and so cannot be reported here). The clinical expert said that best supportive care for people with moderate to severe prurigo nodularis would involve more than just topical treatments (see section 3.3). The committee agreed that best supportive care used in the trials did not reflect best supportive care in clinical practice. It concluded that this may impact the generalisability of the results of the PRIME trials.

Generalisability of the trial populations

3.6 The EAG noted several differences in the trial populations compared with NHS practice. Firstly, the average age of the trial population appeared to be around 10 years younger than the average age of people with prurigo nodularis in the NHS population. The clinical expert said that age should not have an effect on the results from the trials. But, the EAG noted that an older population would generally have a higher average body weight and its clinical advisers would expect that treatment effect could be influenced by body weight. The company provided preplanned analyses that evaluated the impact of weight on efficacy in the clinical trial. The company considers these analyses academic in confidence so the results cannot be reported here. It argued that because prurigo nodularis is a rare condition, subgroup analyses are subject to the effects of small sample sizes. The company provided evidence from studies of dupilumab in atopic dermatitis that showed that body weight did not significantly change effectiveness. The committee did not agree that data from people with atopic dermatitis disproved a change in treatment effect by body weight in people with prurigo nodularis. It concluded that more evidence is needed to prove that body weight does not have an impact on treatment effect.

Economic model

Company's model

3.7 The company developed a decision tree followed by a Markov model. The decision tree was separated into 0 to 12 weeks and 12 to 24 weeks. From

0 to 12 weeks, baseline utility was applied to both treatment arms. Then, from 12 to 24 weeks, different utility values were assigned based on treatment arms, with the dupilumab arm being assigned a higher utility. At the end of the decision tree at 24 weeks, people were assigned a response status, depending on if their condition responded (from now, referred to as 'responder') or if their condition did not respond (from now, referred to as 'non-responder') and transitioned into the appropriate health state in the Markov model. The Markov model had 3 health states: responder, non-responder, and death. People could transition from being a responder to being a non-responder. An all-cause annual discontinuation rate and a probability of loss of sustained response were included. Upon transitioning to non-responder, a person's utility values would gradually decrease over 2 years. The baseline characteristics of the population in the model were based on the population in the pooled PRIME trials. This meant the model population had a starting age of 49.5 years. The committee concluded that the company's model structure was acceptable for decision making but noted it would like to see a scenario that included a starting age of 61 years, which was the average age found in the case note review of people with prurigo nodularis.

Response criteria

3.8 The response criteria used in the model was a composite of an improvement of 4 or more on the WI-NRS and an improvement in IGA-PN-S of 1 point or more. The EAG agreed with using a composite measure of response. But the EAG noted that an improvement in IGA-PN-S of 1 point or more was not a key outcome in the trial. It noted that an IGA-PN-S score of 0 or 1 was a key outcome. It preferred using a composite of an improvement of 4 or more on the WI-NRS and an IGA-PN-S score of 0 or 1 to measure response. The company responded that achieving an IGA-PN-S score of 0 to 1 was unrealistic in 24 weeks. The clinical expert noted that response in prurigo nodularis is usually slower than progression. The company also noted that a trial end point was not necessarily a good response criteria for a model. The patient

experts noted that while reducing nodules is important, reducing itch is likely to be the most important factor to people with prurigo nodularis. The committee concluded that both the EAG's and the company's preferred criteria were suitable for measuring response.

Loss of response

3.9 The company's model included both an all-cause annual discontinuation rate and a probability of loss of sustained response. Both factors applied to responders, increasing the rate of transition from response to non-response. The EAG noted that both factors were much higher in the best supportive care arm than the dupilumab arm. It noted that the number of responders in the best supportive care arm rapidly reduced to 0. It believed that including both factors meant that people in the best supportive care arm lost response too quickly. The EAG's preferred assumption was to only include loss of sustained response. The company argued that conditions in the trials meant that people who had best supportive care in the trials would be more likely to have a response than people in NHS practice. The clinical expert noted that response is usually linked to adherence to treatment, which would be higher in clinical trials. The committee noted that excluding effective treatments that are used in NHS practice from best supportive care in the trials (see section 3.5) may have impacted the level and duration of response. It considered only using the probability of sustained response and thought that this resulted in a fairly rapid loss of response in the best supportive care arm. It also concluded that the company's rationale for including 2 separate loss of response parameters was unclear. It concluded that the EAG's preference for only including loss of sustained response was preferable.

Baseline utility values in the Markov model

3.10 In the model, utility values were derived from the PRIME trials at 3 timepoints (baseline, week 12 and week 24) using regression analysis of EQ-5D-5L responses mapped to the EQ-5D-3L, including several covariates. The committee noted that the regression analysis that was

used to derive the utility values, used forward selection. It noted that it preferred using pre-specified variables to derive utility values instead of an automatic algorithm. The EAG raised concerns about the baseline utility values used in the Markov model. In the company's base case, dupilumab non-responders had a higher initial utility value when starting the Markov model than best supportive care non-responders. The EAG noted that in both treatment arms, non-responders would have best supportive care, so their utility values should be the same. The EAG's preferred assumption was for a pooled non-responder utility value to be used for both treatment arms at the start of the Markov model. The company argued that in the dupilumab arm there would be more partial responders, so the average utility of non-responders would be higher. It also noted that in the trial, non-responders to dupilumab had a greater reduction on the WI-NRS, which is an important factor in quality of life. The committee agreed with the EAG, that in the absence of statistically significant and clinically meaningful differences in utility values between treatment arms in the trials, a pooled utility value for non-responders should be used in the model. It requested analyses from the company using only treatment arm and response status to prove a statistically significant difference in utilities at week 24.

Utility value waning

3.11 The EAG was also concerned with how waning of utilities was applied to non-responders. In the company's base case, the utilities applied to non-responders decreased over 2 years. But the EAG noted that this appears inconsistent with the results from the 12 week follow up which suggests that the treatment effect for dupilumab diminishes without rebound when it is stopped. The EAG's preferred assumption was for utility to hold for the first 6 months after non-response (with the initial utility to depend on whether the person was a responder at week 24), then return to baseline utility. The company argued that the follow up was not powered to evaluate maintenance of response. It also noted potential for bias in the population of the follow-up studies. The EAG also noted that in the original

company base case, responders to dupilumab at 24 weeks who later became non-responders, kept a small utility benefit over responders to best supportive care at 24 weeks, who later became non-responders for the entirety of the model. The company responded that it did scenario analyses, which applied the same percentage utility benefit to responders to best supportive care at 24 weeks who later became non-responders, although this meant that there was still a very small difference in utility values. The company reported that this implementation was now part of its base case. The committee strongly agreed that for people who initially had a response and later became non-responders, final utility should be the same in each arm and noted that the small difference in utilities that still remained should be removed. It requested further evidence of the time and speed of utility decline in non-responders. Because of uncertainties surrounding the implementation of utilities in the model, the committee concluded that the model was not currently suitable for decision making.

Cost-effectiveness estimates

Acceptable ICER

3.12 NICE's manual for health technology evaluations notes that judgements about the acceptability of a technology as an effective use of NHS resources will take into account the degree of certainty around the incremental cost-effectiveness ratio (ICER). The committee will be more cautious about recommending a technology if it is less certain about the ICERs presented.

The committee noted concerns around the high level of uncertainty, specifically:

- the exclusion of comparators from the decision problem (see section 3.3) and the clinical trials (see section 3.5)
- the discontinuation rate and probability of loss of sustained response in the model for people having best supportive care (see section 3.9)

- baseline utility values for people entering the Markov model as non-responders (see section 3.10)
- the application of utility waning for non-responders in the Markov model (see section 3.11).

Because of the high level of uncertainty in the clinical and economic evidence, the committee agreed that an acceptable ICER should be towards the lower end of the range normally considered a cost-effective use of NHS resources (£20,000 to £30,000 per quality-adjusted life year [QALY] gained). To reduce the uncertainty in the cost-effectiveness estimates, the committee requested the following:

- further analysis of the effect of body weight on treatment effect
- a scenario in which the starting age in the model is 61 (the average age of people with prurigo nodularis in the NHS)
- further analysis to assess whether a difference in starting utility, based on treatment arm at 24 weeks, is suitable for non-responders.

3.13 The company's preferred base case included the following assumptions:

- a composite response criteria of a WI-NRS improvement of 4 or more and an IGA-PN-S reduction of 1 or more (see section 3.8)
- including both an all-cause annual discontinuation rate and a probability of loss of sustained response (see section 3.9)
- separate initial utility values for non-responders based on treatment arm (see section 3.10)
- utility waning for non-responders applied for 2 years after loss of response (see section 3.11).

When taking into account the confidential discount for dupilumab, the company's base case ICER was £28,900 per QALY gained.

3.14 The EAG's preferred base case included the following assumptions:

- a composite response criteria of a WI-NRS improvement of 4 or more and an IGA-PN-S of 0 or 1 (see section 3.8)
- inclusion of only probability of loss of sustained response (see section 3.9)
- pooled initial utility values for non-responders (see section 3.10)
- utility values hold for 6 months after treatment, then revert to baseline (see section 3.11).

When taking into account the confidential discount for dupilumab, the EAG's base case ICER was £37,300 per QALY gained.

3.15 The committee preferred the EAG's assumptions, with the exception of its response criteria, for which it considered that the company's preference was also plausible. Applying the company's preferred response criteria to the EAG's base case gave an ICER of £35,600 per QALY gained.

Other factors

Equality

3.16 The committee considered evidence that prevalence of prurigo nodularis may be higher in some groups of people. These include:

- a study in the US that reported a higher prevalence of prurigo nodularis in people from Black African and Caribbean family backgrounds
- clinical expert statements that suggest prurigo nodularis is more prevalent in people from South Asian and East Asian family backgrounds in the UK
- clinical expert statements that suggest prurigo nodularis is more common in women.

The committee also considered the perspective of 1 of the patient experts that people with brown or black skin may wait longer for a prurigo nodularis diagnosis. Race and sex are protected characteristics under the Equality Act 2010. But because the committee's

recommendation does not restrict access to treatment for some people over others, it agreed that these were not potential equality issues.

Innovation

3.17 The committee considered if dupilumab was innovative. It did not identify additional benefits of dupilumab not captured in the economic modelling. So, the committee concluded that all additional benefits of dupilumab had already been taken into account.

Conclusion

Recommendation

3.18 Because of the uncertainties in the economic modelling and clinical data, and the high cost-effectiveness estimates, the committee concluded that it could not recommend dupilumab for treating moderate to severe prurigo nodularis.

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

Dr 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), and a project manager.

George Millington

Technical lead

Leena Issa and Vonda Murray

Project managers

ISBN: [to be added at publication]