NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Final draft guidance

Dupilumab for treating moderate to severe prurigo nodularis

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 in the trials, 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 of several concerns with the model, including:

- that different utility values were applied for dupilumab and for best supportive care after 24 weeks of treatment for people whose condition had not responded
- the way that loss of treatment response is modelled for people having best supportive care.

The cost-effectiveness estimates are uncertain because of the concerns about the economic model, and because the clinical evidence is uncertain. The estimates 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 October 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 unusual 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 effect on quality of life. The appearance of the nodules can also be distressing for people with prurigo nodularis. The patient experts explained that prurigo nodularis has a large effect on all aspects of life. They noted the effect of it on their physical, mental and social health. They also explained that because the condition is rare, it can be challenging to get a diagnosis. The committee agreed that 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. But the clinical expert explained that it is difficult to get these treatments prescribed and none of the currently available treatments are licensed for treating prurigo nodularis. The patient experts explained that the side effects of the more potent treatments have a strong negative effect on their quality of life. The patient experts also noted that dupilumab is the first treatment to target the cause of prurigo nodularis, and so they felt that the side effects would be less severe than other treatments. The company explained that dupilumab would be used when other systemic treatments were being 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 it believed that the exclusion of antihistamines, oral corticosteroids, immunosuppressants 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, immunosuppressants and antidepressants were all part of best supportive care used in the NHS, but oral corticosteroids would not be used long term. They also explained that immunosuppressants would not be used alongside dupilumab, so they are 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 immunosuppressants are relevant comparators that the company excluded from its decision problem. The committee

concluded that antihistamines, oral corticosteroids, immunosuppressants and antidepressants are all part of best supportive care used in the NHS, and that oral corticosteroids and immunosuppressants should be included as comparators in the decision problem.

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 also needed 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 (improvement) on the Worst Itch-Numerical Rating Scale (WI-NRS). Other outcomes included quality of life data and a severity rating score using the Investigator's Global Assessment for Prurigo Nodularis-Stage (IGA PN-S) tool, which measures the inflammation and the 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 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 noted that the PRIME trials excluded treatments that are usually included in the best supportive care that is used in the NHS (see section 3.3). So, it raised concerns that the results from the 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 immunosuppressants 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 had done a case-note review of people with prurigo nodularis who had been treated with systemic therapy in England. This indicated that fewer people had used methotrexate than was estimated by the EAG, 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). In its response to the draft guidance, the company provided results from a survey of 5 UK consultant dermatologists who had experience of using dupilumab in atopic dermatitis, and, in some cases, prurigo nodularis. The dermatologists who were surveyed noted that not all the options for best supportive care that are used in the NHS were included in the PRIME trials. But they believed that the outcomes for people having best supportive care would be unchanged if those treatments were given, because those treatments are largely ineffective. They considered that the best supportive care treatments used in the trials were acceptable for decision making. The EAG considered that it was unlikely that the excluded treatments are largely ineffective, because they are used in the NHS, which indicates that they are regarded by clinicians to be effective to some extent. It noted that it was unclear why the treatments were excluded from the trials if they are ineffective. At the second committee meeting, the clinical experts noted that the treatments included by the company are universally accepted as the base of supportive care for prurigo nodularis, but other treatments would be added to these. They noted large variability in the other additional treatments. They believed that the other treatments have limited effectiveness, but they would still

provide some clinical benefit. The committee concluded that best supportive care used in the trials did not reflect best supportive care in NHS clinical practice. It concluded that this may affect the generalisability of the results of the PRIME trials and added uncertainty to the clinical and cost-effectiveness results.

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 affect 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. In its response to the draft guidance, the company provided further evidence on this issue. It noted that pharmacokinetic data suggested that weight has an effect on exposure to dupilumab but that it was not a big enough effect to result in a need for dose adjustment. The dermatologists in the company's survey (see section 3.5) said that they had not seen a relationship between body weight and the effect of dupilumab. The company also produced an analysis that matched people from the PRIME trials with people from the company's case-note review, by age and body mass index (BMI). The company said that this smaller matched population was more reflective of

the population seen in the NHS. The company noted that this population had a higher percentage of people whose condition responded to dupilumab and a lower percentage of people whose condition responded to best supportive care. It said that this suggested that dupilumab would have at least equal effectiveness in the NHS population as it had in the trial population. The company also produced an analysis of the PRIME trials that included an additional weight category, which indicated no statistically significant effect of weight on treatment effect. The EAG believed the new analyses were less valid than the original analyses. It noted that the new analyses had smaller sample sizes and had used a post-hoc outcome of a WI-NRS score improvement (reduction) of 4 or more points and an improvement (reduction) in IGA PN-S score of 1 or more point. At the second committee meeting, the clinical experts believed that dupilumab may have a reduced effect in people who weigh over 90 kg. But they noted that prurigo nodularis is not linked to obesity and that a minority of people with prurigo nodularis would weigh over 90 kg. The committee concluded that the effectiveness of dupilumab is likely reduced for people who weigh over 90 kg but that the effect of this may be limited in the population of people with prurigo nodularis.

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. This depended on if their condition responded to treatment (from now, referred to as 'responder') or if their condition did not respond to treatment (from now, referred to as 'non-responder'). Then they 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 it 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 points on the WI-NRS and an improvement in IGA PN-S score 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 score 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 points on the WI-NRS and an IGA PN-S score of 0 or 1 to measure response. The company responded that reaching an IGA PN-S score of 0 to 1 in 24 weeks was unrealistic. The clinical expert noted that response in prurigo nodularis is usually slower than progression. The company also noted that a trial endpoint was not necessarily a good response criteria for a model. The patient experts noted that reducing nodules is important, but 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 effective treatments that are used in NHS practice were excluded from best supportive care in the trials (see section 3.5), which may have affected the level and duration of response. It considered only using the probability of sustained response, and thought that this resulted in a reasonable 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. In its response to the draft guidance, the company provided comments related to loss of response to best supportive care from its consultant dermatologist survey (see section 3.5). The dermatologists who were surveyed believed that including only loss of sustained response meant that response to best supportive care lasted longer than what would be expected in NHS practice. The company produced a new base case with a lower response rate for people having best supportive care than the previous loss of response. It also removed the discontinuation rate for best supportive care from its base case. The committee considered that the numbers that were used for loss of response to best supportive care were arbitrary and very uncertain. It concluded that the EAG's preference for only including the original loss of sustained response was preferable for decision making, because of the level of uncertainty.

Utility values in the Markov model

3.10 In the model, utility values were derived from the PRIME trials at 3 time points (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 prespecified variables to derive utility values instead of an automatic algorithm. The EAG raised concerns about the utility values used at the start of the Markov model (the week-24 values). 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 (improvement) on the WI-NRS, which is an important factor in quality of life. At the first committee meeting the committee noted that there were not statistically significant and clinically meaningful differences in utility values between treatment arms in the trials. So, the committee agreed with the EAG that 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. In its response to the draft guidance, the company provided an analysis of the change from baseline WI-NRS and Dermatology Life Quality Index scores. There was a statistically significant difference for these scores in non-responders between treatment arms. The company also highlighted that the change from baseline WI-NRS score in the dupilumab arm was above the minimal clinically important difference identified by Riepe et al. (2019). But in the best supportive care arm it was not. The EAG believed

there was limited clinical justification for the difference in week-24 utility values between treatment arms in non-responders. This was especially so, considering the much lower difference in week-24 utility values between treatment arms for responders. The company also provided 2 scenarios examining alternative regression models. The first scenario included only treatment and response status variables, while the second scenario also included baseline characteristic variables. The committee noted that in both alternative models, treatment arm was not a statistically significant variable. It also noted that in both alternative models, the effect of the treatment arm on the regression was limited when combined with the effect of response status and treatment arm together. The committee concluded that there was not enough evidence to support different utility values for non-responders at week 24 and preferred using pooled utility values because of the uncertainty.

Utility value waning

3.11 The EAG was also concerned about how waning of utility values were 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 appeared inconsistent with the results from the 12-week follow up that suggest 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 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. This benefit remained for the entirety of the model. The company responded that it had done scenario analyses that applied the same percentage utility benefit to responders to best supportive care at

24 weeks who later became non-responders. But 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. The committee noted that the small difference in utilities that remained should be removed. It requested further evidence of the time and rate of utility decline in non-responders. In its response to the draft guidance, the company confirmed its preference for utilities to wane over 2 years. It also included the remaining utility benefit for responders who later became non-responders. But the company also provided a scenario in which this benefit was removed. The company noted that the dermatologists it had surveyed (see section 3.5) believed that a difference in utilities for people who had previously responded was reasonable and would persist for a while. The EAG noted that the company's justification for including the residual benefit was that people would retain learned behaviours from the more structured trial environment. It believed that this would not occur in real-world practice. At the second committee meeting, the clinical expert noted that people whose condition had previously responded may have different behaviours to people whose condition had never responded. The committee reiterated that there should be no difference in utilities between treatment arms after 2 years. It considered that the scenario that removed remaining benefits for people who had previously responded was still highly uncertain because of the lack of empirical evidence to support it. The committee concluded that the approach of utilities returning to baseline values 6 months after loss of response was the most appropriate for decision making.

Additional costs for non-responders

3.12 In its response to the draft guidance, the company noted that 1 of the dermatologists it surveyed believed that additional costs should be included for non-responders. The dermatologist said that this would account for the costs of best supportive care treatment failure. The

company estimated the extra costs by considering usage by drug class from the case-notes review. The drug classes included antihistamines, gabapentinoids, immunosuppressants and systemic corticosteroids. The company estimated that the additional cost would be £439 per year. The committee noted that no benefits were applied to these additional treatments. The committee concluded that these additional costs for non-responders should not be included, and scenarios including them were not plausible or appropriate.

Cost-effectiveness estimates

Acceptable ICER

3.13 NICE's health technology evaluations manual notes that decisions 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 level of uncertainty, specifically the:

- exclusion of comparators from the decision problem (see section 3.3) and the clinical trials (see section 3.5)
- 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)
- application of utility waning for non-responders in the Markov model (see section 3.11).

Because of the 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).

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

- a composite measure of response of a WI-NRS score improvement of 4 or more points and an IGA PN-S score improvement of 1 or more points (see section 3.8)
- a probability of loss of sustained response that decreased faster than in the original model (see section 3.9)
- different 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, with people who had previously been responders but later became non-responders, retaining some residual benefit (see section 3.11)
- additional costs applied to non-responders to account for the cost of treatment failure (see section 3.12).

When taking into account the confidential discount for dupilumab, the company's base-case ICER was £28,200 per QALY gained.

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

- a composite measure of response of a WI-NRS score improvement of 4 or more points and an IGA PN-S score of 0 or 1 (see section 3.8)
- only including the original model's probability of loss of sustained response (see section 3.9)
- pooled initial utility values for non-responders (see section 3.10)
- utility values held for 6 months after treatment, then reverting to baseline (see section 3.11)
- no additional costs applied to non-responders to account for the cost of treatment failure (see section 3.12).

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

3.16 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 £35,400 per QALY gained. The committee noted that all the scenarios produced ICERs that were above the range it considered acceptable (see section 3.13). It also noted that all the scenarios that excluded the additional costs for non-responders (see section 3.12) produced an ICER above £30,000 per QALY gained.

Other factors

Equality

3.17 The committee considered evidence that the prevalence of prurigo nodularis may be higher in some groups of people. This evidence includes:

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

3.18 The committee considered dupilumab was innovative, but it did not identify any additional benefits of dupilumab that were not captured in the

economic modelling. So, the committee concluded that all additional benefits of dupilumab had already been taken into account.

Conclusion

Recommendation

3.19 The committee concluded that all the cost-effectiveness estimates were higher than the range that NICE considers to be an acceptable use of NHS resources. The committee also concluded that there were many uncertainties in the economic modelling and clinical data. So, 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), a technical adviser and a project manager.

George Millington

Technical lead

Alan Moore

Technical adviser

Leena Issa and Vonda Murray

Project managers

ISBN: [to be added at publication]