NICE National Institute for Health and Care Excellence

NICE guidance

Baricitinib 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.

Contents

1 Recommendations

1.1 Baricitinib 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 systemic immunosuppressant, such as ciclosporin, methotrexate, azathioprine and mycophenolate mofetil, or these are not suitable, and
- the company provides it according to the commercial arrangement.

1.2 Assess response from 8 weeks and stop baricitinib if there has not been an adequate response at 16 weeks, defined as a reduction of at least:

- 50% in the Eczema Area and Severity Index score (EASI 50) from when treatment started and
- 4 points in the Dermatology Life Quality Index (DLQI) from when treatment started.

1.3 When using the EASI, take into account skin colour and how this could affect the EASI score, and make appropriate clinical adjustments.

1.4 When using the DLQI, take into account any physical, psychological, sensory or learning disabilities, or communication difficulties that could affect the responses to the DLQI, and make any appropriate adjustments.

1.5 These recommendations are not intended to affect treatment with baricitinib 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

People with moderate to severe atopic dermatitis that has not responded to at least 1 systemic immunosuppressant are usually offered either dupilumab or best supportive

care. Dupilumab does not always work, and some people stop taking it because of side effects. Baricitinib is an alternative to dupilumab and best supportive care. It is likely to be offered alongside topical corticosteroids.

Clinical trial results show that baricitinib reduces the severity and symptoms of atopic dermatitis compared with placebo. Baricitinib has not been directly compared with dupilumab. The results of an indirect comparison suggest that baricitinib is less effective than dupilumab.

The most likely cost-effectiveness estimates for baricitinib are within what NICE considers an acceptable use of NHS resources. Therefore, baricitinib is recommended as an option for moderate to severe atopic dermatitis when at least 1 systemic immunosuppressant has not worked or is not suitable.

2 Information about baricitinib

Marketing authorisation indication

2.1 Baricitinib (Olumiant, Eli Lilly) is 'indicated for the treatment of moderate to severe atopic dermatitis in adult patients 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 A 28-pack of 4-mg tablets costs £805.56 (excluding VAT, BNF online, accessed December 2020). The company has a commercial arrangement. This makes baricitinib 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 Eli Lilly, a review of this submission by the evidence review group (ERG), NICE's technical report, and responses from stakeholders. See the committee papers for full details of the evidence.

The appraisal committee was aware that several issues were resolved during the technical engagement stage, and agreed that:

- The drug acquisition cost for best supportive care should be removed from the model, to avoid duplication with the costs for concomitant medications.
- Baricitinib should be assumed to have no benefit over best supportive care in reducing flare frequency in the model.
- The costs of bathing products should be removed from the model.
- There would be 9 doses of dupilumab given during induction.
- There should be 4 annual full blood tests assumed for baricitinib in the model.
- The company's 'secondary' censoring rule better reflected clinical practice. Under secondary censoring, the disease was considered to have not responded after people stopped treatment or started systemic rescue therapies.

The appraisal committee recognised that there were remaining areas of uncertainty (see technical report pages 2 to 17), and took these into account in its decision making. It discussed the following issues, which were outstanding after the technical engagement stage:

- the positioning of baricitinib in the treatment pathway (issue 1, see technical report, page 2)
- whether systemic immunosuppressant therapy is a relevant comparator for baricitinib (issue 2, see technical report, page 2)
- whether a 50% reduction in Eczema Area and Severity Index score (EASI 50) plus an improvement in the Dermatology Life Quality Index (DLQI) of at least 4, or a 75% reduction in EASI score (EASI 75), is more appropriate to define an adequate response

to baricitinib (issue 4, see technical report, page 5)

- when response to baricitinib would be assessed in clinical practice (issue 5, see technical report, page 5)
- whether baricitinib and dupilumab are likely to be used in a sequence, and how cost-effectiveness analyses for treatment sequences should be considered in decision making (issue 6, see technical report, page 6)
- what proportion of patients having best supportive care would lose the quality-of-life benefit over time in clinical practice (issue 7, see technical report, page 7)
- whether the stopping rate between week 16 and week 52 in the model should be based on loss of response, or stopping treatment for any reason (issue 8, see technical report, page 9)
- whether it was appropriate to assume that a proportion of patients having baricitinib or dupilumab lose the quality-of-life benefit from treatment over time (issue 9, see technical report, page 12)
- which utility values were most appropriate for decision making (issue 10, see technical report, page 2)
- whether it was appropriate to include the data from people of Japanese family origin in the baricitinib clinical trials, given that this may not be generalisable to the UK population (issue 11, see technical report, page 14)
- whether the results of the indirect treatment comparison were suitable for decision making (issue 12, see technical report, page 16).

Experience of people with atopic dermatitis

Atopic dermatitis affects all aspects of a person's life

3.1 The clinical experts explained that atopic dermatitis is a chronic, recurrently flaring, generalised skin condition starting in childhood and continuing into adulthood for most people. People with severe atopic dermatitis may need hospitalisation for treatment. Feedback from patient and professional organisations highlighted that the condition is debilitating and isolating, affecting all aspects of life (physical,

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

Clinical management

People with moderate to severe atopic dermatitis would welcome a new oral treatment option with a different mechanism of action

3.2 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). Fourth-line treatments include ciclosporin (the only systemic immunosuppressant with a marketing authorisation for atopic dermatitis), methotrexate, azathioprine and mycophenolate mofetil. The committee heard that patients often have difficulty adhering to topical corticosteroids, and would welcome a new treatment option that reduces topical corticosteroid use. Clinical experts also explained that systemic immunosuppressants need frequent blood monitoring tests and may have serious adverse effects. Also, ciclosporin is only used for short periods because of toxicity concerns. If a systemic immunosuppressant is no longer effective, it will be stopped and another immunosuppressant may be offered. Dupilumab is recommended as an option if the atopic dermatitis has not responded to at least 1 other systemic therapy (fifth-line). However, atopic dermatitis does not always respond to dupilumab, and some people must stop treatment because of adverse effects. For people whose disease has not responded to all available systemic therapies, the only remaining treatment option is best supportive care. This may include education, psychological support, emollients, topical corticosteroids, bandages and hospitalisation. Exacerbations (flares) in atopic dermatitis are managed using short-term high-potency topical corticosteroids, oral corticosteroids and systemic therapy. The committee concluded that patients and clinicians would

welcome a well-tolerated oral treatment with a different mechanism of action, that could potentially reduce topical corticosteroid use.

Positioning in the treatment pathway, comparators and sequencing

Baricitinib would be used after at least 1 systemic immunosuppressant

3.3 The marketing authorisation for baricitinib is 'for the treatment of moderate to severe atopic dermatitis in adult patients who are candidates for systemic therapy'. The company positioned baricitinib as a fifth-line treatment, after at least 1 systemic immunosuppressant, as an alternative to dupilumab and best supportive care. Clinical experts agreed that they would prefer to offer baricitinib as an alternative to systemic immunosuppressants, because it needs less monitoring. However, they acknowledged that in clinical practice people are likely to have had at least 1 systemic immunosuppressant before having baricitinib. The committee concluded that it would appraise baricitinib for moderate to severe atopic dermatitis after at least 1 systemic immunosuppressant, in the same position as dupilumab.

Dupilumab and best supportive care are the most appropriate comparators for baricitinib

3.4 The company suggested that systemic immunosuppressants are not a relevant comparator in people who have had at least 1 systemic immunosuppressant. For these people, the only remaining treatment options are dupilumab or best supportive care. The clinical experts agreed that in clinical practice some patients have a second systemic immunosuppressant before dupilumab, but most patients have dupilumab after only 1 systemic immunosuppressant. At technical engagement, the company attempted an indirect treatment comparison of baricitinib with ciclosporin, in the absence of direct evidence. However, the ERG and company agreed that the results of the indirect comparison were not reliable because of difficulties in matching the

patient populations and outcomes between trials. The committee concluded that systemic immunosuppressants were a relevant comparator for baricitinib in some people, but that dupilumab and best supportive care were the most appropriate comparators. This was because most patients have dupilumab at the point in the treatment pathway where the company had positioned baricitinib, and there was a lack of data to compare baricitinib with systemic immunosuppressants.

Baricitinib and dupilumab are likely to be used in a sequence, but the reliability of sequencing analyses is uncertain

3.5 The company did not consider the sequence of baricitinib followed by dupilumab, or dupilumab followed by baricitinib. This was because the company positioned baricitinib as an alternative to dupilumab (see section 3.3), and there was a lack of data on the effectiveness of baricitinib in a sequence with dupilumab. The ERG considered it likely that in clinical practice baricitinib and dupilumab will be used in a sequence. The clinical experts explained that because dupilumab is likely to be more effective than baricitinib (see section 3.11), it would usually be used first in a sequence. However, treatment decisions are individualised, and there would likely be no 'standard' sequence of dupilumab and baricitinib. The committee understood that atopic dermatitis is a lifelong disease, and that most patients would need to stop treatment with dupilumab eventually. The committee considered that cost-effectiveness analyses for sequences of baricitinib and dupilumab should be taken into account in decision making. But, it acknowledged the uncertainty because of the lack of clinical data on sequential effectiveness.

Clinical evidence

The JAIN (BREEZE-AD4) and JAIY (BREEZE-AD7) trials provide the key clinical evidence for baricitinib

3.6 The evidence for baricitinib came from 5 trials: 2 on baricitinib monotherapy (JAHL [BREEZE-AD1] and JAHM [BREEZE-AD2]), 2 on baricitinib plus background topical corticosteroids (JAIN [BREEZE-AD4] and JAIY [BREEZE-AD7]), and a long-term extension study (JAHN

[BREEZE-AD3]) for patients completing JAHL, JAHM or JAIY. The clinical experts explained that baricitinib is likely to be offered alongside topical corticosteroids. The committee therefore agreed to focus on the evidence of baricitinib 'combination therapy' with topical corticosteroids from JAIN and JAIY. Both were randomised double-blind trials including patients who had moderate to severe atopic dermatitis for at least 12 months. Moderate to severe atopic dermatitis was defined as an EASI score of 16 or more, an Investigator's Global Assessment (IGA) score of 3 or more, and body surface area involvement of 10% or more. The disease must have responded inadequately to topical corticosteroids. In JAIN, ciclosporin had to be contraindicated or not tolerated, or the disease uncontrolled on ciclosporin. The trials compared 3 doses of baricitinib (1 mg, 2 mg, or 4 mg once daily) with placebo. However, the committee agreed that it would focus only on the 4 mg dose because it was the licensed dose relevant for most patients. The primary end points were assessed at 16 weeks after the 'induction' period:

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

  Patients in JAIN had an additional 36 weeks of treatment, followed by a long-term extension study. The committee understood that data from the JAIN extension study were not available at the time of the submission. The committee concluded that the JAIN and JAIY trials provided the key clinical evidence for baricitinib.

Baricitinib with topical corticosteroids is more clinically effective than placebo

3.7 In the analysis of the trial data using secondary censoring, patients having baricitinib plus topical corticosteroids in JAIN and JAIY were statistically significantly more likely to achieve EASI 50, EASI 75, and have an IGA score of 0 or 1 at week 16 than patients having placebo. Baricitinib also produced statistically significant reductions in itch and skin pain at week 16, as well as quality-of-life improvements based on

the DLQI and EQ-5D. The committee noted that the data showed a peak response to baricitinib at, or before, week 12 for many outcomes. However, by week 24 in JAIN baricitinib was no longer statistically significantly more effective than placebo for EASI 75 or an IGA score of 0 or 1. The committee concluded that baricitinib was more clinically effective than placebo at week 16, but that this appeared to wane over time.

The data from JAIN and the JAIN-like subgroup of patients from JAIY represents who would have baricitinib in the NHS

3.8 The company's base case was based on a pooled population of patients from JAIN and a subgroup of patients from JAIY for whom ciclosporin was contraindicated or not tolerated, or whose disease was uncontrolled on ciclosporin (the 'JAIN-like' subgroup). The ERG noted that the mean EASI score for these patients was within the published definition of severe atopic dermatitis (21.1 to 50), and that they therefore represented more severe disease. The clinical experts agreed that the patients in JAIN and JAIY had severe disease, but considered that they were representative of patients who would likely have baricitinib in the NHS. The committee concluded that the pooled JAIN plus JAIN-like subgroup from JAIY generally reflected people who would have baricitinib in NHS clinical practice.

A composite end point of EASI 50 plus an improvement in the DLQI of at least 4 is most relevant for decision making

3.9 In its original model, the company defined a clinical benefit using the composite end point of EASI 50 plus an improvement in the DLQI of at least 4. This was for consistency with NICE's technology appraisal guidance on dupilumab for treating moderate to severe atopic dermatitis (from now, TA534). At technical engagement, the company updated its model to define a clinical benefit using EASI 75. This was because the composite end point was not associated with a quality-of-life improvement in the baricitinib clinical trials. The company noted a move towards using EASI 75 in clinical practice, and that an EASI 75 response correlated better with a quality-of-life improvement in the baricitinib clinical trials. In addition, EASI 75 at week 16 was the primary end point in

JAIN, and a key secondary end point in JAIY. The committee heard from clinical experts that the composite end point was widely used in clinical practice. Also, the EASI without the DLQI would fail to capture important patient-reported quality-of-life improvements, such as reduced itching. The committee recognised that the composite end point of EASI 50 plus an improvement in the DLQI of at least 4 was widely used in clinical practice, included patient-reported quality of life, and was consistent for comparing baricitinib with dupilumab. Therefore, it concluded that this is the most relevant end point for decision making and should be used to define response.

Indirect treatment comparison

The company's indirect treatment comparison with dupilumab is acceptable for decision making

3.10 There was no direct evidence comparing baricitinib with dupilumab for atopic dermatitis, so the company did an indirect treatment comparison. For baricitinib, the company pooled the data from JAIN plus the JAIN-like subgroup from JAIY. For dupilumab, the company pooled the data from the CAFÉ trial and a subgroup of patients from the CHRONOS trial for whom ciclosporin was contraindicated or not tolerated, or whose disease was uncontrolled on ciclosporin (the 'CAFÉ-like' subgroup). The ERG noted several differences between the baricitinib and dupilumab trials included in the indirect comparison, which may reduce the reliability of the results:

- There was a higher proportion of people of Asian family origin in JAIN and JAIY compared with CAFÉ and CHRONOS.
- Baseline EASI scores were higher in CAFÉ and CHRONOS, indicating patients had more severe atopic dermatitis.
- Unlike CAFÉ and CHRONOS, patients in JAIN and JAIY had a 2-week washout period when they could not use topical treatments for their atopic dermatitis. Patients in CAFÉ and CHRONOS may therefore have experienced fewer flares immediately after entering the trial than those in JAIN or JAIY.

- Data from patients who had rescue therapy or stopped study treatment in CAFÉ and CHRONOS were used, whereas data from JAIN and JAIY were subject to secondary censoring. This potentially favours dupilumab, because patients having systemic rescue treatment would not have been censored as having atopic dermatitis that did not respond to treatment.

  The clinical experts agreed that the differences in the washout period and censoring rules between the trials likely favoured dupilumab. The committee concluded that, despite its limitations, the company's indirect treatment comparison with dupilumab was acceptable for decision making.

The results of the indirect treatment comparison suggest that baricitinib is less effective than dupilumab

3.11 The proportion of patients achieving EASI 50 plus an improvement in the DLQI of at least 4 compared with placebo was statistically significantly greater for patients having dupilumab compared with patients having baricitinib. At technical engagement the company updated the indirect comparison using EASI 75, to reflect that they had changed the definition of response in the model (see section 3.9). The direction of the results was similar to the indirect comparison using the composite end point. The committee recalled its earlier conclusion that baricitinib was more clinically effective than placebo, but concluded that baricitinib is likely to be less effective than dupilumab.

Adverse events

Patients on baricitinib generally experience few serious adverse events

3.12 The committee noted that the rates of serious adverse events were generally low in the baricitinib and placebo groups of the trial populations across all studies. Although the proportion of baricitinib patients in JAIN who experienced 1 or more treatment-emergent adverse event was higher than placebo, the committee concluded that patients were likely to tolerate baricitinib.

Company's economic model

The structure of the company's model is similar to that in TA534, and appropriate for decision making

3.13 The company originally submitted a Markov model with 4 health states: induction, maintenance, non-response, and death. Patients entered the model in the 'induction' state, during which they could not stop treatment. At week 16, people in the baricitinib or dupilumab arms whose disease had not responded to treatment switched to best supportive care. People whose disease had responded to treatment moved into the 'maintenance' state, where they continued to have baricitinib or dupilumab until their disease stopped responding (up to week 52) or they stopped treatment for any reason (from year 2 onwards). At this point patients switched to best supportive care. People having best supportive care entered the 'non-response' state if their disease had either not responded at week 16 or stopped responding by week 52, or they stopped treatment for any reason from year 2 onwards. Patients in the 'non-response' state could not transition back into previous states. Patients could move into the 'death' state at any time. The committee noted that the company's model was generally similar to that of TA534. It concluded that, despite some uncertainties around how the loss of quality-of-life benefit of treatment over time was modelled (see section 3.17 and section 3.18), the structure of the company's model was appropriate for decision making.

Assumptions in the economic model

The stopping rate from week 16 to week 52 should be based on stopping treatment for any reason

3.14 The company assumed that 6.1% of people having dupilumab plus topical corticosteroids as maintenance therapy stop treatment in the first year and then have best supportive care. This reflected the proportion of people in CHRONOS whose condition responded to treatment at 16 weeks (EASI 50 plus an improvement in the DLQI of at least 4), but

was no longer responding to treatment at 52 weeks. For people having baricitinib plus topical corticosteroids, the company based the stopping rate in the first year on the 52-week data from JAIN. The company's assumption reflected the proportion of people in JAIN whose condition responded to treatment at 16 weeks, but was no longer responding to treatment at 52 weeks. The ERG disagreed with deriving stopping rates in the first year from loss of response at 52 weeks, conditional on response at 16 weeks. This was because stopping treatment depends not only on loss of efficacy but also other factors such as adverse events. The ERG preferred to base the stopping rates on the all-cause stopping rate in JAIN (and CHRONOS, for dupilumab) for people whose condition responded to treatment at 16 weeks, but who withdrew from the trial by 52 weeks. The committee concluded that, on balance, the ERG's approach was more appropriate.

Treatment response to baricitinib should be assessed by 16 weeks, with an earlier assessment likely to improve baricitinib's cost effectiveness

3.15 The committee understood from the summary of product characteristics for baricitinib that 'consideration should be given to discontinuing treatment in patients who show no evidence of therapeutic benefit after 8 weeks of treatment'. The committee was aware that a 16-week 'induction' phase was implemented in the clinical trials (see section 3.6) and in the company's economic model, which was consistent with TA534. However, the results from JAIN showed a peak response at 12 weeks or earlier across many outcomes. In clinical practice, response to baricitinib may be assessed earlier than 16 weeks (although this scenario was not modelled by the company or the ERG), which would likely improve the cost effectiveness of baricitinib. This was because response rates would be similar, but patients whose disease did not respond would accrue fewer treatment costs. The committee concluded that response to baricitinib should be assessed from 8 weeks, and baricitinib stopped if the atopic dermatitis does not respond adequately by 16 weeks.

Utility values in the economic model

The utility values from TA534 are preferable when response is defined as EASI 50 plus an improvement in the DLQI of at least 4

3.16 The company's original model, when response was defined using EASI 50 plus an improvement in the DLQI of at least 4, used 2 utility values. A utility value of 0.78 was assigned to people in the 'maintenance' state, and a utility value of 0.5979 was assigned to people in the 'induction' and 'non-response' states. These were derived from the pooled data from JAIN plus the JAIN-like subgroup from JAIY, and were the same regardless of treatment arm in the model (baricitinib, dupilumab or best supportive care). The ERG had several concerns with the company's utilities. The pooled data from JAIN plus the JAIN-like subgroup from JAIY showed that patients whose disease responded to treatment based on the composite end point had a lower utility gain from baseline (0.1821) than those whose disease had not responded to treatment (0.2042). However, the company only applied the utility increase for people whose disease responded to treatment in the model, and assigned the baseline utility to those whose disease did not respond. The ERG found this approach to be flawed, and likely confounded by regression to the mean effects. It also questioned why the company had also not included the data from the 'JAIN-like' subgroups from JAHL and JAHM when deriving the utilities. In addition, the ERG considered that using only 2 utility values was overly simplistic and failed to capture magnitude of response. It preferred to use the utility values from TA534, which were treatment-specific and had previously been accepted by the committee. The committee considered which utility values were more appropriate for the composite end point. It noted the flaws in the company's original approach, and acknowledged the ERG's concern that the 'maintenance' health state was not associated with a utility gain. However, it heard from clinical experts that patients achieving EASI 50 plus an improvement in the DLQI of at least 4 were likely to have an improvement in quality of life, even if this had not been shown in the pivotal trials. The committee also understood that the EQ-5D often fails to capture quality-of-life improvements for people with skin conditions. The committee concluded that, given the flaws with the company's utility values, the utility values

from TA534 were preferable.

Modelling of best supportive care

The loss of quality-of-life benefit on best supportive care over time is likely to be between the base cases of the company and ERG

3.17 At technical engagement, the company used the same approach as the ERG by removing best supportive care discontinuation. 'Discontinuing' best supportive care meant that patients moved permanently into the 'non-response' state, with a lower utility value and higher costs than the 'maintenance' state (see section 3.13). The ERG's approach was consistent with the 52-week placebo arm data from CHRONOS. This data suggested that people having best supportive care fluctuated between periods of good and bad disease control, and that for every patient losing disease control, another had an improvement. In both the company's and ERG's base cases, costs were therefore a weighted average of people whose disease responded to treatment and those whose disease did not respond. However, the company considered that quality of life for patients having best supportive care would return to baseline over time, despite costs not increasing. The company thought it implausible that the effectiveness of best supportive care would be maintained after the trial, when there is decreased treatment adherence. Therefore, it explored the 2 committee-preferred sensitivity analyses from TA534 in its updated base cases. These modelled 2 trajectories of the proportion of patients losing the quality-of-life benefit of best supportive care over time, based on the data from CHRONOS. The ERG considered that the company's revised approach was methodologically flawed, because it separated utilities from costs within the model. It was also based on a selective analysis of the clinical trials, in that the placebo arm data were disregarded as being unrealistic, while the data from the baricitinib and dupilumab arms were treated as generalisable to clinical practice. The clinical experts explained that patients are monitored closely in clinical trials, and that only a minority of patients having best supportive care would retain long-term disease control. The committee acknowledged that the ERG's approach represented different patients

moving in and out of disease control over time. Even so, the committee considered that it overestimated the quality of life of patients having best supportive care, because it was implausible that there would be no loss of quality-of-life benefit over time on average. However, the committee also found that the company's 2 quality-of-life waning approaches underestimated the likely quality of life of patients having best supportive care. The committee concluded that the proportion of patients having best supportive care losing the quality-of-life benefit over time was likely to be somewhere between the base cases of the company and ERG.

Quality-of-life waning for baricitinib and dupilumab

Applying quality-of-life waning assumptions for baricitinib and dupilumab has minimal impact on the ICERs

3.18 At technical engagement, the company also applied the committee-preferred quality-of-life waning assumptions for dupilumab from TA534, for consistency with that appraisal. The company assumed that the following proportion of patients would lose the quality-of-life benefit from treatment over time: year 2: 2%, year 3: 5%, year 4: 7%, year 5 and beyond: 8%. The company applied the same assumptions for both baricitinib and dupilumab. The ERG had similar criticisms of the company's approach as described in section 3.17, in that it separated costs from utilities in the model. The committee concluded that the degree of quality-of-life waning for patients having baricitinib or dupilumab was uncertain, but noted that it had minimal impact on the incremental cost-effectiveness ratios (ICERs).

Cost-effectiveness results

Baricitinib is cost effective compared with dupilumab based on the pairwise ICERs for the committee's preferred scenarios

3.19 The committee initially focused on the pairwise ICERs for baricitinib compared with dupilumab. The company and ERG's deterministic base cases included the confidential patient access scheme discounts for both baricitinib and dupilumab. These showed that baricitinib resulted in cost savings and a quality-adjusted life year (QALY) loss compared with dupilumab, producing ICERs that reflected savings per QALY lost. In situations when an ICER is derived from a technology that is less effective and less costly than its comparator, the commonly assumed decision rule of accepting ICERs below a given threshold is reversed. So, the higher the ICER, the more cost effective a treatment becomes. The ERG's base case included the committee's preferred assumptions:

- using EASI 50 plus an improvement in the DLQI of at least 4 to define response (see section 3.9)
- using the utility values from TA534 (see section 3.16)
- stopping rates from week 16 to week 52 based on stopping treatment for any reason, rather than only loss of response (see section 3.14).

The ERG's base case assumed no loss of quality-of-life benefit over time on average for patients having best supportive care. The committee recalled that there was considerable uncertainty about this assumption (see section 3.17). However, the committee noted that in the ERG's base case both with and without quality-of-life waning on best supportive care, the ICERs for baricitinib compared with dupilumab were within what NICE considers an acceptable use of NHS resources. Because of a confidential commercial arrangement for dupilumab, the cost-effectiveness results cannot be reported here.

Baricitinib is likely to be cost effective compared with best supportive care based on the pairwise ICERs

3.20 The committee considered the pairwise ICERs for baricitinib compared

with best supportive care. The company's and ERG's base cases showed that baricitinib resulted in greater costs and a QALY gain. As such, the standard decision rule of accepting ICERs below a given threshold was applied. The company's deterministic base case showed that baricitinib was associated with ICERs of £27,037 and £28,396 per QALY gained compared with best supportive care, for the best supportive care quality-of-life waning scenarios 1 and 2 respectively (see section 3.17). In the ERG's base case (with no quality-of-life waning on best supportive care) the ICER was £70,825 per QALY gained. However, with quality-of-life waning on best supportive care only this decreased to £26,987 per QALY gained. The committee concluded that there was uncertainty related to the ICER compared with best supportive care, depending on the quality-of-life waning assumptions. But, it was likely to be at the upper end of what NICE normally considers an acceptable use of NHS resources. The committee concluded that baricitinib is likely to be cost effective compared with best supportive care.

Although uncertain, incremental analyses support the cost effectiveness of baricitinib when used before or after dupilumab

3.21 The committee also considered incremental analyses that included sequences of baricitinib and dupilumab. In the ERG's base case both with and without quality-of-life waning on best supportive care, baricitinib followed by dupilumab had a similar incremental net monetary benefit (when the benefit is expressed in monetary terms, minus the costs) to dupilumab followed by best supportive care, at both thresholds of £20,000 and £30,000 per QALY gained. The same applied for the sequence of dupilumab followed by baricitinib. The committee understood that in the sequencing analyses the efficacy of baricitinib and dupilumab was assumed to be unaffected by their position in the sequence. It recalled its uncertainty around treatment sequences (see section 3.5), but concluded that the analyses supported the cost effectiveness of baricitinib when used before or after dupilumab.

Other factors

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 dark skin
- the DLQI may not account for 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.

It is not possible to establish the efficacy of baricitinib in patients with dark skin

3.23 The ERG noted that no subgroup data were reported for patients with dark skin in the baricitinib clinical trials, and so it was not possible to establish the efficacy of baricitinib in this population. Feedback from clinical experts highlighted that the pattern of atopic dermatitis is different in people of African family origin, but that interleukin-4 and interleukin-13 cytokines predominate in most populations. The committee understood that there is insufficient evidence to determine the efficacy of baricitinib in patients with dark skin. Therefore, it could not account for potential differences during decision making.

Baricitinib is not a 'step change' in the same way as dupilumab

3.24 The company considered baricitinib to be an innovative treatment. It has a novel, targeted mechanism of action, and is an oral treatment not associated with the adverse events experienced by patients having dupilumab. The committee considered that baricitinib was not a 'step change' in the same way as dupilumab. However, having a new oral treatment option would be appreciated by some patients. The committee heard and concluded that there were no additional gains in health-

related quality of life associated with baricitinib over those already included in the QALY calculations.

Conclusion

Baricitinib is recommended in people when at least 1 systemic immunosuppressant has not worked or is not suitable

3.25 The committee noted that there was considerable uncertainty around the loss of quality-of-life benefit over time for patients having best supportive care, which had a large impact on the ICERs. However, in the scenarios with the committee's preferred assumptions and quality-of-life waning on best supportive care, the pairwise ICERs suggested that baricitinib was cost effective compared with both dupilumab and best supportive care. Incremental analyses supported the cost effectiveness of baricitinib when used before or after dupilumab, despite uncertainty. Also, the summary of product characteristics states that response to baricitinib may be assessed from 8 weeks rather than the 16 weeks used in the model. This would likely improve the cost effectiveness of baricitinib. The committee concluded that baricitinib is a cost-effective use of NHS resources and could be recommended as an option for people with moderate to severe atopic dermatitis when at least 1 systemic immunosuppressant has not worked or is not suitable. Given the QALY losses for baricitinib compared with dupilumab, treatment choice should be a decision made between the doctor and the patient.

4 Implementation

4.1 Section 7(6) of the National Institute for Health and Care Excellence (Constitution and Functions) and the Health and Social Care Information Centre (Functions) Regulations 2013 requires clinical commissioning groups, NHS England and, with respect to their public health functions, local authorities to comply with the recommendations in this appraisal within 3 months of its date of 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 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 appraisal document.

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 moderate to severe atopic dermatitis and the doctor responsible for their care thinks that baricitinib 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.

Charlie Hewitt
Technical lead

Eleanor Donegan
Technical adviser

Jeremy Powell
Project manager

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