NICE National Institute for Health and Care Excellence

NICE guidance

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

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 Lebrikizumab is recommended as an option for treating moderate to severe atopic dermatitis that is suitable for systemic treatment in people 12 years and over with a body weight of 40 kg or more, only if:

- the atopic dermatitis has not responded to at least 1 systemic immunosuppressant or these treatments are not suitable, and
- dupilumab or tralokinumab would otherwise be offered, and
- the company provides it according to the commercial arrangement.

1.2 Stop lebrikizumab after 16 weeks if the atopic dermatitis has not responded adequately. An adequate response is:

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

1.3 Take into account how skin colour could affect the EASI score and make any clinical adjustments needed.

1.4 Take into account any physical, sensory or learning disabilities, or communication difficulties that could affect the responses to the DLQI, and make any clinical adjustments needed.

1.5 If people with the condition and their healthcare professionals consider lebrikizumab to be 1 of a range of suitable treatments, after discussing the advantages and disadvantages of all the options, the least expensive should be used. Administration costs, dosage, price per dose and commercial arrangements should all be taken into account.

1.6 These recommendations are not intended to affect treatment with lebrikizumab 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 healthcare professional consider it appropriate to stop. For young people, this decision should be made jointly by the healthcare professional, the young person, and their parents or carers.

Why the committee made these recommendations

Standard treatment for moderate to severe atopic dermatitis (eczema) includes topical emollients and corticosteroids (treatments applied to the skin). If these treatments are not effective, systemic immunosuppressant treatments such as ciclosporin and methotrexate can be added. If there is an inadequate response after at least 1 of these systemic treatments, or if these are unsuitable, a Janus kinase (JAK) inhibitor (abrocitinib, baricitinib or upadacitinib) or a biological medicine (dupilumab or tralokinumab) can be used.

For this evaluation, the company asked for lebrikizumab to be considered only for people who have had at least 1 systemic immunosuppressant treatment. This does not include everyone who it is licensed for.

Clinical trial evidence shows that lebrikizumab is more effective than placebo at improving the symptoms of atopic dermatitis. It has not been directly compared in a clinical trial with standard treatments. But indirect comparisons with JAK inhibitors and biological medicines suggest that it is broadly likely to work as well as these.

The cost-effectiveness estimates for lebrikizumab are within the range that NICE normally considers an acceptable use of NHS resources when compared with other biological medicines (dupilumab or tralokinumab), but not when compared with JAK inhibitors. So, lebrikizumab is only recommended when dupilumab or tralokinumab would otherwise be offered.

2 Information about lebrikizumab

Marketing authorisation indication

2.1 Lebrikizumab (Ebglyss, Almirall) is indicated for 'the treatment of moderate-to-severe atopic dermatitis in adults and adolescents 12 years of age and older with a body weight of at least 40 kg who are candidates for systemic therapy'.

Dosage in the marketing authorisation

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

Price

2.3 The list price for lebrikizumab is £2,271.26 per 2-pack of 250 mg/2 ml solution for injection prefilled pens or syringes (excluding VAT; company submission, accessed April 2024).

2.4 The company has a commercial arrangement. This makes lebrikizumab available to the NHS with a discount. The size of the discount is commercial in confidence.

3 Committee discussion

The evaluation committee considered evidence submitted by Almirall, 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 the condition and effect on quality of life

3.1 Atopic dermatitis is a chronic, recurrently flaring, generalised skin condition that affects children, young people and adults. Symptoms of atopic dermatitis include dry, flaky and inflamed skin that can be intensely itchy. The patient experts explained that the condition is often misunderstood and dismissed, but that the itching can have a severe impact on quality of life, including causing sleep disturbance. The patient experts further explained that the condition is debilitating and isolating, and affects all aspects of life (physical, psychological, social and financial). The clinical experts noted that there is evidence of higher rates of mental health conditions (including depression, anxiety and suicide) in adults with atopic dermatitis than in the general population. They explained that atopic dermatitis is a heterogeneous disease and having a variety of treatment options, including additional biological medicines such as lebrikizumab, is useful. The clinical and patient experts expressed concerns about the side effects of some current systemic treatments. They noted that there is an unmet need for additional biological medicines that are effective and have less side effects than some current systemic treatments. The committee concluded that there is an unmet need for additional effective treatments for atopic dermatitis that have better safety profiles.

Clinical management

Treatment options and comparators

3.2 The committee understood that the severity of atopic dermatitis is assessed by clinicians based on symptoms of the condition and areas of the body affected. Two commonly used assessment tools include the Eczema Area and Severity Index (EASI) and Dermatology Life Quality Index (DLQI). Higher assessment scores indicate more severe atopic dermatitis. The clinical experts noted that moderate to severe atopic dermatitis can be initially treated with emollients, topical corticosteroids and topical calcineurin inhibitors. Phototherapy is offered after this, although the clinical experts explained that this is not widely available in the NHS. They noted that people 12 years and over whose condition has not responded adequately to topical treatment and phototherapy can be considered for first-line systemic immunosuppressants. These include ciclosporin, methotrexate, azathioprine and mycophenolate mofetil, but only ciclosporin is licensed for atopic dermatitis. If there is a further inadequate response or intolerance to at least 1 systemic treatment, a biological medicine (dupilumab or tralokinumab) or a Janus kinase (JAK) inhibitor (abrocitinib, upadacitinib or baricitinib) is offered. Baricitinib is only available for people 18 years and over. The company positioned lebrikizumab as an alternative treatment for people who have had at least 1 systemic treatment. The clinical experts confirmed that the company's positioning of lebrikizumab was appropriate. The committee concluded that lebrikizumab was appropriately positioned as an alternative treatment for people who have had at least 1 systemic treatment.

Treatment sequencing and switching

3.3 There are multiple treatment options available for people 12 years and over with atopic dermatitis who have had at least 1 systemic treatment (see section 3.2). The committee asked the clinical experts how, in clinical practice, a decision is made on what treatment to use. The clinical experts explained that a joint decision-making process is usually used, in which clinical evidence and the person's preferences are both considered. The clinical experts explained that JAK inhibitors tend to be faster acting than biological medicines for atopic dermatitis.

JAK inhibitors are also oral treatments that are useful for people who prefer not to have injections. But, they are associated with some side effects and cannot be used in people 65 years and over, people with a history of smoking, or people with a history or risk of cardiovascular disease or cancer. The clinical experts noted that biological medicines are usually suitable for longer-term use. The clinical experts considered lebrikizumab an alternative treatment to the other biological medicines. The committee asked the clinical experts whether switching treatments has any benefit when there is a loss of response or an inadequate response to a treatment. The clinical experts highlighted that there is some emerging real-world evidence suggesting that switching between treatment class (for example, from a JAK inhibitor to a biological medicine) and switching within treatment class (for example, from 1 biological medicine to another) is reasonable. Although the evidence is limited, treatment switching can be used when there is no response to a treatment or when an initial response has not been maintained. The committee was not given data that showed how treatment switching to a different medicine with the same mechanism of action would provide different efficacy. So, it considered this to be an uncertainty. It concluded that there is uncertainty about the exact treatment sequence for second-line systemic treatments, but that lebrikizumab is an appropriate alternative to the other biological medicines.

Clinical effectiveness

Clinical trials

3.4 The company's pivotal clinical trials were ADvocate 1, ADvocate 2, ADhere and ADvantage. These were phase 3, double-blind, randomised controlled trials comparing lebrikizumab with placebo in adults and young people (that is, from age 12 years) with moderate to severe atopic dermatitis. ADvantage only included people whose condition was not adequately controlled with ciclosporin or for whom ciclosporin was unsuitable. The EAG highlighted that ADhere and ADvantage were more relevant to clinical practice. This was because people could use their treatment in combination with topical corticosteroids, while the ADvocate trials were monotherapy trials. The committee noted that the company used clinical-effectiveness results from ADhere and ADvocate to inform its base

case. The common primary outcome from the trials was EASI 75 at week 16 (that is, a reduction of at least 75% from the baseline EASI score). The results showed that lebrikizumab met the primary outcome in both the monotherapy and combination treatment trials. That is, it was statistically significantly more effective than placebo at achieving EASI 75 at week 16. But these trials did not include comparisons with biological medicines or JAK inhibitors (see section 3.3). The committee concluded that the relevant trials were the combination trials ADhere and ADvantage, which included treatment with topical corticosteroids. They showed that lebrikizumab is more effective than placebo at achieving EASI 75, but did not include comparators relevant to NHS practice (see section 3.3).

Generalisability of network meta-analysis

3.5 There were no clinical trials directly comparing lebrikizumab with its relevant comparators. So, the company did a network meta-analysis (NMA) to get response rate odds, which were calculated from various lebrikizumab and comparator combination (with topical corticosteroid) trials. The NMA results suggested that the odds of achieving EASI 75 were significantly higher with lebrikizumab compared with baricitinib, whereas the odds were lower compared with upadacitinib 30 mg. There was no statistically significant difference between lebrikizumab and abrocitinib, dupilumab, tralokinumab or upadacitinib 15 mg. The EAG noted that the trials included in the NMA had different eligibility criteria. These criteria did not fully represent people with atopic dermatitis in NHS clinical practice and may have biased the NMA results. These differences included use of previous treatment, suitability of systemic treatment and prior treatment response. The EAG was concerned that including people who had not had a systemic treatment could potentially have affected the treatment response rates. But it did not expect this to have markedly affected the model results. It also acknowledged that the company's NMA represented the available evidence. The committee was concerned that some lebrikizumab trials included people who had had biological medicines. So, it questioned the effect of this on the efficacy results. One of the clinical experts responded that people who had had treatment with a biological medicine were likely to have more severe atopic dermatitis, which was less likely to respond to additional treatment. The committee considered that doing an appropriate baseline-adjusted NMA would adjust for the

treatment effect associated with previous use of biological medicines. The company responded that subgroup analysis of the key lebrikizumab trials showed that response rates did not differ between people who had had systemic treatment and people who had not. The committee also recalled that JAK inhibitors have a faster onset of action than biological medicines (see section 3.3). So, it highlighted that the NMA results based on response at week 16 may potentially have favoured the JAK inhibitors. It concluded that, because the effect of previous treatments and different populations on the NMA results had not been appropriately examined, the results of the NMA were uncertain.

Relevant outcome

3.6 Previous NICE technology appraisal guidance on abrocitinib, tralokinumab or upadacitinib for treating moderate to severe atopic dermatitis (from now, TA814) and on baricitinib for treating moderate to severe atopic dermatitis) highlighted that EASI 75 alone may not sufficiently capture:

- quality-of-life improvements
- clinically meaningful improvements in symptoms of atopic dermatitis.

So, a composite outcome consisting of EASI 50 plus an improvement in DLQI of at least 4 was the preferred outcome for decision making. This composite outcome was not collected in the lebrikizumab trials, but the company did post-hoc analyses to derive this data. The company did not use the results of the post-hoc analyses in its base case, but it indirectly derived response rates using EASI 75 results from the NMA (see section 3.5). The company explained that it had taken this approach because results for the composite outcome were not publicly available for all the comparator treatments. It considered that EASI 75 had the closest relative response to the composite outcome. The EAG questioned the similarity of EASI 75 and the composite outcome. But it acknowledged that the company's general approach may have been reasonable in the absence of further data. The clinical experts noted that the EASI 75 is harder to achieve than the composite outcome. They explained that a reduction in DLQI would closely match a decrease in EASI score, so the relative effect would likely be the same. The committee

was satisfied that in the absence of results for the composite outcome, using EASI 75 to indirectly inform treatment response was appropriate.

Economic model

Company's modelling approach

3.7 The company submitted a hybrid model that consisted of a short-term (1 year) decision tree capturing treatment induction and a long-term Markov model (year 2 onwards). For the long-term Markov model, an annual cycle length with a half-cycle correction was applied. The model assumed a lifetime horizon (up to 100 years), and applied a discount rate of 3.5% for costs and quality-adjusted life years (QALYs). At baseline, people started treatment with either lebrikizumab or its comparators. People whose condition responded to treatment could continue to have lebrikizumab or its comparators, but people whose condition did not respond proceeded to have best supportive care (topical treatment or phototherapy). The committee concluded that the company's model was suitable for decision making.

Short-term discontinuation probability (within 1 year)

3.8 The company's model used discontinuation data to inform whether people continued to have maintenance treatment with lebrikizumab and its comparators or switched to best supportive care (topical treatments and phototherapy). At baseline, people had lebrikizumab or its comparators for a 16-week induction period. People whose condition had responded to treatment at week 16 were described as 'responders'. They were able to continue having maintenance treatment with lebrikizumab or a comparator up to week 52. 'Non-responders' were people who:

- initially had a response at week 16 but in whom the treatment response was lost
- stopped treatment for any reason, including side effects, by week 52.

After week 52, responders and non-responders entered different phases of the long-term Markov model (see section 3.7). The treatment discontinuation data between week 16 and week 52 was used by the company for modelling the probability of discontinuation at 52 weeks (short-term discontinuation).

The EAG noted that the company had used the average discontinuation rate in its model for lebrikizumab and its comparators without a clear explanation why. The EAG preferred to use individual treatment-specific discontinuation rates when available, to align with TA814. The company considered that using treatment-specific rates was unsuitable. This was because the data was from trial populations that differed (for example, in their previous use of systemic treatments, see section 3.5), and adjustments had not been made to account for the differences. It also noted that the discontinuation data was not based on the same outcomes (for example, EASI 50 plus DLQI improvement of at least 4, see section 3.6) and may have been flawed.

The EAG raised further concerns about the company's short-term discontinuation rate for lebrikizumab because it considered it was too high in comparison with the other biological medicines. The exact discontinuation rate cannot be reported here because it is considered confidential by the company. In response, the company explained that it had identified an error in the way that it had calculated the lebrikizumab discontinuation rate and submitted a corrected lower rate (6.25%). The EAG was unclear about how the company's updated lebrikizumab discontinuation rate was derived, but noted that the updated discontinuation rate did not change its cost-effectiveness conclusion. The clinical experts highlighted that the company's updated discontinuation rate for lebrikizumab (6.25%) appeared more plausible than the higher rate in the original submission. They explained that they would expect the discontinuation rates for treatments within a specific treatment class to be similar. They suggested that a short-term discontinuation rate of about 10% for JAK inhibitors was appropriate and that the average rate for the biological medicines (3.9%) was plausible. The committee acknowledged the clinical experts' opinions. It concluded that short-term discontinuation rates should be applied according to treatment class (that is, biological medicines or JAK inhibitors) using the estimates suggested by the clinical experts.

Long-term discontinuation probability

3.9 The company noted in its submission that long-term discontinuation data (from year 2 onwards) was not available for lebrikizumab and its comparators. To model long-term discontinuation, it converted the average discontinuation data used to model short-term discontinuation (see section 3.8) to an annual rate and applied this for lebrikizumab and its comparators. The EAG highlighted that using equal discontinuation rates for all the treatments was not plausible. It noted that the JAK inhibitors (abrocitinib, baricitinib and upadacitinib) have more safety concerns than the biological medicines (dupilumab and tralokinumab). So, it preferred to use class-specific discontinuation rates that would reflect the difference in safety profiles between each class of treatment. The committee noted that a consistent approach for modelling short-term and long-term discontinuation probability was reasonable. So, it concluded that long-term discontinuation probability should be modelled according to treatment class using the annualised estimates for short-term discontinuation (see section 3.8).

Utility values

3.10 Utility values applied in the company's model were sourced from the ADhere trial. The company mapped EQ-5D-5L data at week 16 to EQ-5D-3L using methods described by Hernandez-Alava et al. in the NICE Decision Support Unit's Technical Support Document 22. Utilities from the lebrikizumab arm of the ADhere trial were applied for lebrikizumab and its comparators. Data from the placebo arm of the trial was applied for topical treatments and phototherapy (modelled as best supportive care). For both groups, the utility values were further subdivided based on health states (that is, response and non-response). The company highlighted that it had taken this approach because outcomes for people differed based on treatment arm in ADhere. The clinical experts explained that it was reasonable to have response utilities that differed for each trial arm. The committee was aware that the committee for TA814 decided that:

- Using arm-specific utility introduced unnecessary complexity
- utilities based on overall health state were preferred (that is, baseline, response and non-response).

The EAG preferred to use the weighted average utility values for lebrikizumab and best supportive care, applied to overall health state, which was consistent with TA814. The committee explored whether the size of the difference in treatment side effects could be so large that it would justify a difference in utilities for response in both treatment arms. The EAG noted that utility decrements related to adverse events were already incorporated into the model. The committee concluded that it preferred to use overall health state utilities because treatment arm-specific utilities introduced complexity and uncertainty in this particular model.

Cost-effectiveness estimates

Acceptable ICER

3.11 NICE's manual on health technology evaluations notes that, above a most plausible incremental cost-effectiveness ratio (ICER) of £20,000 per QALY gained, judgements about the acceptability of a technology as an effective use of NHS resources will take into account the degree of certainty around the ICER. The committee will be more cautious about recommending a technology if it is less certain about the ICERs presented. But it will also take into account other aspects including uncaptured health benefits. The committee recalled the comments from the patient and clinical experts about the severity of the condition and that an additional treatment option would be welcomed (see section 3.1). The committee noted that there remained unresolved uncertainty about the methods used in the NMA (see section 3.5). There was also uncertainty around how the relevant treatment outcome was derived (see section 3.6). The committee concluded that an acceptable ICER would be below £20,000 per QALY gained.

Company and EAG cost-effectiveness estimates

3.12 The committee considered the results of the cost-effectiveness analysis for lebrikizumab using its preferred assumptions, which included:

- treatment class-specific short-term discontinuation rates (see section 3.8)
- treatment class-specific long-term discontinuation rates (see section 3.9)
- utilities based on overall health state and calculated using the weighted average utility values (see section 3.10).

The company and EAG both presented their results using a fully incremental analysis that included the JAK inhibitors (abrocitinib, upadacitinib and baricitinib) and biological medicines (tralokinumab and dupilumab). The committee noted that, in the fully incremental analysis, using its preferred assumptions, lebrikizumab was not cost effective. The exact ICERs are confidential and cannot be reported. The committee recalled its earlier conclusions that:

- lebrikizumab is an appropriate alternative to the biological medicines
- JAK inhibitors are not suitable for all people with moderate to severe atopic dermatitis (see section 3.3).

So, the committee considered the pairwise results using its preferred assumptions. When compared with the biological medicines (tralokinumab and dupilumab) lebrikizumab was cost effective. When compared with the JAK inhibitors (abrocitinib, upadacitinib and baricitinib) lebrikizumab remained not cost effective. The exact ICERs are confidential and cannot be reported here.

Equality

3.13 The committee noted the following potential equality issues:

- the EASI might underestimate the severity of atopic dermatitis in people with brown or black skin, which could lead to undertreatment in people with brown or black skin
- physical, sensory or learning disabilities, or communication difficulties could affect responses to the DLQI.

Race and disability are protected characterises under the Equality Act 2010. The committee took this into account in its decision making. It concluded that, when using the EASI, healthcare professionals should take into account skin colour and how this could affect the EASI score, and make any clinical adjustments needed. It also concluded that, when using the DLQI, healthcare professionals should take into account any physical, sensory or learning disabilities, or communication difficulties that could affect a person's response to the DLQI, and make any clinical adjustments needed.

Conclusion

Recommendation

3.14 The committee concluded that the cost-effectiveness estimates for lebrikizumab compared with current biological medicines (dupilumab or tralokinumab) were within the range that NICE considers a cost-effective use of NHS resources. So, it recommended lebrikizumab for treating moderate to severe atopic dermatitis that is suitable for systemic treatment in people 12 years and over with a body weight of 40 kg or more, only if:

- the atopic dermatitis has not responded to at least 1 systemic immunosuppressant or these treatments are not suitable, and
- dupilumab or tralokinumab would otherwise be offered.

4 Implementation

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

4.2 The Welsh ministers have issued directions to the NHS in Wales on implementing NICE technology appraisal guidance. When a NICE technology appraisal guidance recommends the use of a drug or treatment, or other technology, the NHS in Wales must usually provide funding and resources for it within 2 months of the first publication of the final draft guidance.

4.3 When NICE recommends a treatment 'as an option', the NHS must make sure it is available within the period set out in the paragraphs above. This means that, if a patient has moderate to severe atopic dermatitis and the healthcare professional responsible for their care thinks that lebrikizumab is the right treatment, it should be available for use, in line with NICE's recommendations.

5 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

Baljit Singh
Vice 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.

Raphael Egbu
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