NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Appraisal consultation document

Crisaborole for treating mild to moderate atopic dermatitis in people 2 years and older

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

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

The appraisal committee is interested in receiving comments on the following:

- Has all of the relevant evidence been taken into account?
- Are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence?
- Are the recommendations sound and a suitable basis for guidance to the NHS?
- Are there any aspects of the recommendations that need particular consideration to ensure we avoid unlawful discrimination against any group of people on the grounds of race, gender, disability, religion or belief, sexual orientation, age, gender reassignment, pregnancy and maternity?

Note that this document is not NICE's final guidance on this technology. The recommendations in section 1 may change after consultation.

After consultation:

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

For further details, see NICE's guide to the processes of technology appraisal.

The key dates for this appraisal are:

Closing date for comments: Friday 2 October 2020

Second appraisal committee meeting: TBC

Details of membership of the appraisal committee are given in section 5.

1 Recommendations

1.1 Crisaborole is not recommended, within its marketing authorisation, for treating mild to moderate atopic dermatitis in people 2 years and older when 40% or less of their body surface area is affected.

1.2 This recommendation is not intended to affect treatment with crisaborole 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. For children and young people, this decision should be made jointly by the clinician and the child or young person, and their parents or carers.

Why the committee made these recommendations

Mild to moderate atopic dermatitis is usually controlled using emollients and topical corticosteroids. Sometimes topical calcineurin inhibitors are used for moderate atopic dermatitis to treat flares and on delicate areas such as the face and neck. Crisaborole is likely to be used for moderate atopic dermatitis, after emollients and topical corticosteroids, or when these cannot be used.

Evidence from clinical trials shows that crisaborole ointment improves the severity of atopic dermatitis compared with unmedicated ointment. However, this is based on assessing atopic dermatitis in a way that:

- is not used in UK clinical practice
- does not capture outcomes that are important to patients
- is a subjective and unreliable way of assessing atopic dermatitis severity.

So, it is not possible to determine whether crisaborole is clinically effective and whether the small improvements seen are clinically relevant. Also, there are no trials directly comparing crisaborole with topical calcineurin inhibitors, and the results from

indirect comparisons are inconsistent and difficult to interpret. So, the efficacy of crisaborole compared with topical calcineurin inhibitors is uncertain.

The cost-effectiveness analysis is unreliable because of the uncertainty about any clinical benefits with crisaborole. Therefore, crisaborole cannot be recommended for mild to moderate atopic dermatitis.

2 Information about crisaborole

Anticipated marketing authorisation indication

2.1 On 30 January 2020, the Committee for Medicinal Products for Human Use adopted a positive opinion recommending the granting of a marketing authorisation for the medicinal product crisaborole (Staquis, Pfizer) for the treatment of 'mild to moderate atopic dermatitis in adults and paediatric patients from 2 years of age with ≤ 40% body surface area (BSA) affected'.

Dosage in the marketing authorisation

2.2 Crisaborole is a topical ointment that is applied as a thin layer twice daily to affected skin areas of up to 40% of the body's surface area. It can be used on all skin areas apart from the scalp for up to 4 weeks. Treatment should be stopped if signs or symptoms on treated areas persist after 3 treatment courses of 4 weeks, or worsen during treatment.

Price

2.3 The company has not confirmed the list price for crisaborole with the Department of Health and Social Care. The proposed list price is considered confidential by the company.

3 Committee discussion

The appraisal committee (section 5) considered evidence submitted by Pfizer, a review of this submission by the evidence review group (ERG), and the technical

report developed through engagement with stakeholders. See the committee papers for full details of the evidence.

The appraisal committee was aware that several issues were resolved or partially resolved during the technical engagement stage:

- The company included in its model the therapies people might use after crisaborole or its alternatives: phototherapy and systemic therapies (methotrexate, azathioprine, mycophenolate, ciclosporin).
- It is appropriate to base the amount of drug use per application in the economic model on data for people with the same body surface area affected as the licensed indication for crisaborole, that is 40% or less.
- It is appropriate to include a health state for severe atopic dermatitis in the economic model.

It recognised that there were remaining areas of uncertainty associated with the analyses presented, and took these into account in its decision making. It discussed the following issues outstanding after the technical engagement stage:

- issue 1: what the relevant comparator is for people with mild atopic dermatitis
- issue 3: whether to assume only a partial response for therapies used after crisaborole or its alternative treatments
- issue 4: how to determine the duration of subsequent therapies
- issue 6: whether company network meta-analyses are appropriate.

Experience of people with atopic dermatitis

Atopic dermatitis affects all aspects of a person's life

3.1 Atopic dermatitis is a chronic, recurrently flaring, generalised skin condition that can be life-limiting, debilitating and isolating. It can affect all aspects of life (physical, psychological, social and financial). Severe disease is associated with intolerable itch that disrupts sleep, and there is a higher risk of depression and suicide. The committee concluded that having treatments that improve the condition, and which are associated

with few or manageable adverse effects, is important to people with atopic dermatitis.

Assessing atopic dermatitis severity

Symptoms, signs and quality of life determine the severity of atopic dermatitis

3.2 Clinicians assess the severity of atopic dermatitis based on clinical signs and on patient-reported symptoms. These included its effect on sleep and work, and how much topical corticosteroids or systemic therapy people use. The consensus-based Harmonising Outcome Measures for Eczema (HOME) initiative recommends using the Eczema Area and Severity Index (EASI) to assess signs (for example, skin lesions) and the Patient Oriented Eczema Measure (POEM) to assess symptoms (for example, itch). The clinical experts explained that POEM is easier than EASI to administer in practice. NHS clinicians routinely use the Dermatology Life Quality Index (DLQI) to assess quality of life in other skin conditions. However, they do not use the Investigator's Static Global Assessment (ISGA) score, which formed the basis of the company's trials (see section 3.5). The committee concluded that the EASI, DLQI and POEM are appropriate for assessing the severity of atopic dermatitis in NHS practice.

Positioning of crisaborole in the treatment pathway

Crisaborole would be used after emollients and topical corticosteroids

3.3 The marketing authorisation for crisaborole is for mild to moderate atopic dermatitis in people 2 years and older when 40% or less of their body surface area is affected. The company positioned crisaborole as a second-line treatment for people with mild to moderate atopic dermatitis that has not been controlled by topical corticosteroids, or when there is a serious risk of adverse effects from topical corticosteroid use. The clinical experts explained that there is not a group of people with mild atopic dermatitis for whom topical corticosteroids are contraindicated or not

effective, and that mild disease can be adequately controlled using emollients and topical corticosteroids. There are several different strengths of topical corticosteroids that people can use safely, and which are effective with the right education. The committee concluded that crisaborole would not be used as a treatment for mild disease or for first-line treatment. The committee further concluded that the appropriate place in the treatment pathway for crisaborole would be for adults and children with moderate atopic dermatitis that is not controlled with optimised treatment with emollients and topical corticosteroids.

Comparators

Topical calcineurin inhibitors are a relevant comparator in the NHS for crisaborole in people with moderate atopic dermatitis

3.4 The company indirectly compared crisaborole with the topical calcineurin inhibitors pimecrolimus and tacrolimus. NICE's technology appraisal guidance on pimecrolimus and tacrolimus for atopic eczema recommends both drugs for moderate disease. The clinical experts explained that topical calcineurin inhibitors are rarely used for mild to moderate atopic dermatitis, and are used only to prevent flares or on delicate areas such as the face. The committee concluded that topical calcineurin inhibitors are a relevant comparator for crisaborole in people with moderate atopic dermatitis on delicate areas such as the face or to prevent flares. It further concluded that crisaborole would be used in a similar way to topical calcineurin inhibitors.

Clinical evidence

The key clinical evidence for crisaborole in AD-301 and AD-302 is not generalisable to UK practice

3.5 The company provided evidence from 2 double-blind randomised vehicle-controlled trials for the efficacy of crisaborole: AD-301 and AD-302. The trials compared topical crisaborole in vehicle with topical vehicle alone.

Both trials were carried out in the US, lasted 4 weeks and included people 2 years and older with an ISGA score of 2 (mild atopic dermatitis) or 3 (moderate atopic dermatitis) and dermatitis affecting 5% or more of the body surface area. The primary outcome was the proportion of people in whom ISGA was defined as a 'success', that is, a score of 0 (clear) or 1 (almost clear) and at least a 2-grade improvement from baseline at day 29. ISGA success occurred in a higher proportion of people randomised to crisaborole (AD-301 33%, AD-302 31%) than vehicle (AD-301 25%, AD-302 18%). The clinical experts explained that clinicians in the UK do not use ISGA scores to assess atopic dermatitis. They consider it to be an unreliable subjective measure because results can vary widely depending on the investigator. The committee recalled having heard (see section 3.2) that EASI and POEM are the most appropriate tools for assessing severity in atopic dermatitis. This is because they incorporate quality of life and symptoms, and are the most widely used in UK clinical practice. Therefore, although the clinical trials reported a marginal improvement in ISGA severity with crisaborole in vehicle compared with the vehicle alone, it was not possible to tell whether the results were clinically significant to clinical practice in the UK. Furthermore, the population of the trials was not generalisable to the company's proposed population because only 43% had had previous treatment for atopic dermatitis. The committee concluded that the trial population and results were not generalisable to UK clinical practice.

There are no head-to-head studies comparing crisaborole with relevant treatments

3.6 The key trials compared crisaborole dissolved in vehicle ointment with vehicle ointment alone. The vehicle was not a true placebo because some of the individual ingredients had emollient properties, which could have improved atopic dermatitis. Also, the ingredients in the vehicles for crisaborole and topical calcineurin inhibitors differ, so their emollient benefits may differ. The company did a network meta-analysis to estimate the efficacy of crisaborole compared with the topical calcineurin inhibitors

pimecrolimus and tacrolimus. All trials in the network compared active treatment in vehicle with vehicle ointment alone, and used different vehicles. Therefore, the company adjusted its network meta-analysis for the size of the response to vehicle treatment alone. The ERG explained that, by adjusting for a vehicle effect in a network meta-analysis, the assumption is that the vehicles are the same. These alternative approaches were also considered:

- The ERG presented a simple unadjusted network meta-analysis.
- The company presented a matching adjusted indirect comparison (MAIC).

The ERG explained that, if the vehicles are different, any network meta-analysis would be disconnected, so the MAIC should have been used for the company's base case instead. The committee acknowledged that it was difficult to determine whether one of the network meta-analyses or the MAIC was the most appropriate. However, it considered that, even if the vehicles in the trials were different, the network meta-analyses may have been valid if:

- the effectiveness of the active drugs (crisaborole or topical calcineurin inhibitors) and vehicle combined was the same as the sum of the effectiveness of active drug and vehicle individually
- there was some interaction between the vehicle and active ingredient (meaning that it was more or less effective when combined than if the benefits were additive), but the baseline risk was adjusted for.

The company's network meta-analysis adjusted for baseline risk of atopic dermatitis in the control arm of each trial (because of a placebo effect or other differences between the studies), and used an average baseline risk across the trials in the economic model. However, the ERG noted that, because different vehicles were used for the different treatments, using an average baseline risk for each treatment was not

appropriate. Although there seemed to be some evidence that models adjusting for baseline risk fitted the data better, this was uncertain because there were few datapoints (that is, trials on which to base the adjustment). The committee recognised that there are several methodological limitations with a MAIC because it is not possible to tell if all confounding factors have been adjusted for. It also recognised that the results of the analyses (based on network meta-analyses or the MAIC) may have been biased either in favour of crisaborole or in favour of calcineurin inhibitors, whichever approach was taken. The committee concluded that it was not possible to tell whether crisaborole was more effective than topical calcineurin inhibitors based on the evidence.

There are uncertainties associated with the clinical-effectiveness evidence

3.7 The committee recognised that there were issues with the clinical evidence about whether crisaborole was more or less effective than current options in the NHS. These included that:

- no trial directly compared crisaborole with drugs used in the NHS (see sections 3.5 and 3.6)
- outcomes of the main crisaborole trial were not reliable or relevant to UK clinical practice (see section 3.5)
- only 43% of people in the main crisaborole trial reflected the relevant population, in that they had had previous treatment for atopic dermatitis (see section 3.5)
- there was a high degree of uncertainty in the relative effect estimates of crisaborole compared with calcineurin inhibitors produced by the network meta-analysis and MAIC (see section 3.6).

Overall, the committee was concerned about the quality of the available evidence in both the vehicle-controlled crisaborole trials. This was because neither the comparator nor the outcome measures were relevant to clinical practice. It was also concerned about methodological issues when indirectly comparing crisaborole with

calcineurin inhibitors (see section 3.6). This meant that it could not recommend crisaborole as an effective treatment for the NHS.

Cost effectiveness

The structure of the cost-effectiveness model is suitable

3.8 The company revised its Markov model in response to technical engagement. The model included 5 health states: controlled (ISGA score 0 or 1), mild flare (ISGA score 2), moderate flare (ISGA score 3), severe flare (ISGA score of 4) and death. Disease could resolve in a proportion of children. The committee agreed that the structure of the model was appropriate for decision making. However, it concluded that there were problems in how the model dealt with sequencing of subsequent therapies after second-line treatment (see section 3.9).

Therapies third line and beyond are a large driver of cost effectiveness in the company's model and are not modelled adequately

3.9 The committee recognised that subsequent treatments after second-line treatment with crisaborole or calcineurin inhibitors were a large driver of cost effectiveness in the model. If a person's atopic dermatitis responded to treatment at 4 weeks in the model, the company assumed no further treatment was needed. However, if it did not respond to treatment, people had subsequent therapy with phototherapy followed by systemic treatment. Using the company's preferred network meta-analysis comparing crisaborole with topical calcineurin inhibitors adjusted for differences in baseline risk (the prevalence and severity in the vehicle only arm of the trials), the model predicted that crisaborole would reduce the cost of treatment by avoiding the need for subsequent therapy. The ERG explained that the company had not adequately modelled subsequent therapies. This was because the model estimated that a high proportion of people with mild and moderate disease go on to have treatment with multiple lines of treatment with long-term systemic therapy, despite their condition not responding when they had previously had systemic therapy.

The ERG considered that this lacked face validity. The committee also noted that the model did not include dupilumab after systemic treatment, despite a NICE technology appraisal recommending dupilumab for moderate atopic dermatitis that has not responded to a systemic therapy. The committee concluded that the costs in the model were unlikely to be accurate. It added that it was important that subsequent therapies were modelled accurately because they had driven the differences in costs.

The economic results are sensitive to changes in the data source

3.10 Differences in the clinical effectiveness of crisaborole compared with calcineurin inhibitors from the network meta-analyses and MAIC determined the movement of people through the modelled health states. Because response to treatment was determined by the ISGA, which is not used in the UK (see section 3.7), the committee was unable to determine whether gains in the quality-adjusted life years (QALYs) predicted by the model would apply to clinical practice. Modelled differences in the costs and QALYs for crisaborole compared with calcineurin inhibitors were very small. The results were sensitive to changes in the model assumptions, for example, the dosing regimen of crisaborole compared with calcineurin inhibitors. The cost-effectiveness results varied depending on how they were calculated. Crisaborole dominated calcineurin inhibitors (that is, cost less and was more effective) using the company's adjusted network meta-analysis or MAIC. Calcineurin inhibitors dominated crisaborole in scenarios that used the ERG's simple (unadjusted) network meta-analysis. The committee concluded that crisaborole was not a cost-effective treatment option compared with calcineurin inhibitors.

Crisaborole cannot be recommended as a cost-effective use of NHS resources

3.11 The committee recognised the clinical uncertainty in the clinical benefit of crisaborole compared with the vehicle ointment in the pivotal clinical trials (see section 3.5), and of crisaborole compared with topical calcineurin inhibitors in the indirect comparisons (see section 3.10). Also, the cost-effectiveness results of the model were particularly sensitive to the

method used for indirectly comparing the clinical-effectiveness data. Differences in the incremental costs and QALYs for crisaborole were small, making the incremental cost-effectiveness ratio (ICER) sensitive to changes in the model assumptions (for example, the dosing regimen for crisaborole compared with calcineurin inhibitors). Also, the ICERs for crisaborole compared with topical calcineurin inhibitors varied widely, reflecting the high degree of uncertainty in crisaborole's clinical effectiveness compared with treatments currently offered in the NHS. The committee stated that it would need more evidence of the clinical benefit of crisaborole because having crisaborole as another treatment option would delay patient access to dupilumab. This is particularly important because NICE's technology appraisal guidance on dupilumab recommends that the drug has proven efficacy as an option for treating moderate to severe atopic dermatitis if the disease has not responded to at least 1 other systemic therapy. The committee acknowledged that it is unlikely that these uncertainties would be reduced through revised modelling because the uncertainties caused by trial data would remain. The committee agreed that the current cost-effectiveness results were unreliable because of the clinical uncertainty, so it could not identify a most plausible ICER for crisaborole. It concluded that crisaborole could not be recommended as a cost-effective use of NHS resources.

Innovation

Crisaborole is not innovative

3.12 The committee was aware that crisaborole is a non-steroidal compound and is a first-in-class topical PDE4 inhibitor. Also, it has not been associated with the serious adverse events reported with oral PDE4 inhibitors, such as nausea, vomiting, emesis and headache. However, the committee did not consider this relevant because oral PDE4 inhibitors are not second-line treatment options for moderate atopic dermatitis. The company noted that trials showed that crisaborole improves pruritus, a symptom of atopic dermatitis responsible for a significant proportion of

disease burden. However, this was not adequately captured by the EQ-5D results. Also, the committee did not see evidence for pruritis as an outcome when comparing crisaborole with calcineurin inhibitors. It concluded that crisaborole is not innovative, but that there may be some benefits of treatment that were not adequately captured by the QALY.

4 Proposed date for review of guidance

4.1 NICE proposes that the guidance on this technology is considered for review by the guidance executive 3 years after publication of the guidance. NICE welcomes comment on this proposed date. The guidance executive will decide whether the technology should be reviewed based on information gathered by NICE, and in consultation with consultees and commentators.

Amanda Adler
Chair, appraisal committee
July 2020

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 that 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.

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.

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.

Jessica Cronshaw
Technical lead

Ellie Donegan
Technical adviser

Jeremy Powell
Project manager

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