National Institute for Health and Care Excellence

Single Technology Appraisal (STA)

Crisaborole for treating mild to moderate atopic dermatitis in people aged 2 years and older ID1195

Response to consultee and commentator comments on the draft remit and draft scope (pre-referral)

Please note: Comments received in the course of consultations carried out by NICE are published in the interests of openness and transparency, and to promote understanding of how recommendations are developed. The comments are published as a record of the submissions that NICE has received, and are not endorsed by NICE, its officers or advisory committees.

Comment 1: the draft remit

Section	Consultee/ Commentator	Comments [sic]	Action
Appropriateness	Pfizer Limited	We believe that it is appropriate for this topic to be referred to NICE for a single technology appraisal (STA). Atopic Dermatitis (AD) is a highly prevalent condition, especially in children, and we consider there to be an unmet clinical need for additional topical therapies, particularly of a non-steroidal nature, for the management of mild to moderate AD.	Comments noted. No action required.
	National Eczema Society	Yes, it would be appropriate to refer this topic to NICE for appraisal	Comment noted. No action required.
Wording	Pfizer Limited	We believe that the draft remit wording adequately reflects the [redacted]	Comment noted. No action required.
	National Eczema Society	Yes, the wording of the remit reflects the issue(s) of clinical and cost effectiveness about this technology.	Comment noted. No action required.

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Timing Issues	Pfizer Limited	Crisaborole, as an efficacious non-steroidal therapy, would offer patients an alternative topical agent for the treatment of mild to moderate AD, for which there is a current unmet need. We therefore believe that the timing for a technology appraisal (TA) is appropriate.	Comment noted. NICE aims to provide draft guidance to the NHS within 6 months from the date when the marketing authorisation for a technology is granted. NICE has scheduled this topic into its work programme. See the NICE website: https://www.nice.org.uk/guidance/proposed/gid-ta10435. No action required.

Comment 2: the draft scope

Section	Consultee/ Commentator	Comments [sic]	Action
Background information	Pfizer Limited	We believe that the wording of the draft scope underestimates the potential impact that mild to moderate AD has on the quality of life (QoL), psychological health, and social functioning of both the individual patient and the caregiver (1).	Comment noted. This section of the scope aims to provide a brief overview of the background for the appraisal; additional details may be considered by the

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		Emerging evidence suggests that individuals with mild AD have reduced quality of life across a number of domains, take significantly more time off work and have impaired sleep compared to counterparts without AD (2, 3). It has also been demonstrated that median EQ-5D index scores at baseline in young adults with mild AD were similar to those for chronic sinusitis and in moderate AD were similar to those for migraine, asthma, upper spinal problems and lower back disorders (4). AD, of which the large majority is mild to moderate, represents a considerable cost burden to patients, their caregivers and society, with an estimated annual cost to the UK economy exceeding £800 million (5, 6). Recently, skin disease, of which the majority was inflammatory in nature, was demonstrated to be the second leading cause of ill health in the UK (7). We suggest that GP consultation data for mild to moderate AD (if available) may be more relevant to the remit and scope than Hospital Episode Statistics, which are likely to be more reflective of severe AD. To avoid misrepresenting NICE TA82, we recommend modifying (see shaded areas) the below sentence from paragraph 3 of 'Background information': Tacrolimus ointment (calcineurin inhibitor) is recommended when moderate to severe atopic dermatitis has not been adequately controlled by use of topical steroids at the maximum strength and potency or where there is a	committee, if appropriate, at the time of the appraisal. Pimecrolimus has been added to the background section.

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		serious risk of important adverse effects from further topical corticosteroid use, particularly irreversible skin atrophy (TA82). Suggest to re-word as follows: *Tacrolimus ointment (calcineurin inhibitor) is recommended [, within its licensed indications, as an option for second line treatment in adults and children aged 2 years and older] when moderate to severe atopic dermatitis has not been adequately controlled by use of topical [cortico]steroids at the maximum strength and potency, or where there is a serious risk of important adverse effects from further topical corticosteroid use, particularly irreversible skin atrophy (TA82).* Furthermore, pimecrolimus should also be included as a relevant treatment in this section, as follows: *Pimecrolimus is recommended, within its licensed indications, as an option for the second-line treatment of moderate atopic eczema on the face and neck in children aged 2 to 16 years that has not been controlled by topical corticosteroids, where there is a serious risk of important adverse effects from further topical corticosteroid use, particularly irreversible skin atrophy (TA82).* Whilst topical therapies (such as topical corticosteroids; TCS, and topical calcineurin inhibitors; TCIs) are recommended for the treatment of AD, they are associated with limitations (8, 9). The long term use of TCS has been associated with skin atrophy, striae formation and systemic side effects (9). TCIs have been associated with application site adverse reactions (8, 9) and	

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		prescribing information from the EMA includes a warning for both Protopic/Protopy (tacrolimus) and Elidel (pimecrolimus) for a theoretical increased risk of malignancy (10). The Committee for Medicinal Products for Human Use (CHMP) could not, on the basis of the available data, neither prove nor disprove that Protopic/Protopy or Elidel were associated with the reported cancers and lymphomas (10). They state that 'prescribers and patients need to be aware of the need to monitor patients being treated for AD and that suspected adverse reactions including tumours should be reported'. https://www.ema.europa.eu/en/medicines/human/referrals/elidel (10) As a result of the limitations associated with currently available topical therapies, an efficacious and safe alternative topical therapy is needed for the treatment of AD (9)	
	National Eczema Society	The background information appears to be accurate and complete.	Comment noted. No action required.
The technology/ intervention	Pfizer Limited	The brand name for crisaborole in the draft scope, i.e. Eucrisa, reflects the name of the product in the US market. This should be changed to [redacted] to reflect the name for the UK market. The description of the technology and the cytokine pathways affected by crisaborole are not fully accurate or comprehensive in the draft scope, e.g. IL-12 and IL-23 are not thought to be key cytokines affected by crisaborole. Regarding the boron moiety, [redacted] We ask that the description of crisaborole and its mode of action be updated as follows (from the draft SmPC): [redacted]	Comment noted. This section of the scope aims to provide a brief overview of the technology for the appraisal; additional details may be considered by the committee, if appropriate, at the time of the appraisal. This section has been

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		[redacted] This section indicates that crisaborole has been compared, in phase III clinical trials, with placebo. We would like to emphasise that in the phase III clinical trials (AD301 and AD302) the comparator was vehicle treatment (9). It should be noted that vehicle treatments in different trials are formulated with different emollient properties and in some older trials included excipients that could be irritating and induce dermatitis (11). Vehicle treatments should efficiently deliver, release and sustain the drug substance in the target tissue for pharmacological effect, and be acceptable to the patient (12). Properties of vehicle formulations may influence drug delivery, efficacy, and tolerance profiles of topical medications (13-15). Therefore, we believe that vehicle comparators should not be referred to as typical placebo treatments, and we recommend that a qualification statement for what constitutes placebo should be applied to the scope.	updated to reflect the suggested changes.
	National Eczema Society	Yes, as far as we are aware.	Comment noted. No action required.
Population	Pfizer Limited	The population is defined appropriately [redacted]. Broadly, we believe that adult and child populations, and mild and moderate AD populations should be considered separately (see section below, 'Other considerations', for further detail).	Comment noted. These subgroups have been added in the 'Other considerations' section.

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	National Eczema Society	Yes, the population is defined appropriately. We don't think there are groups within this population that shoulod be considered separately.	Comment noted. No action required.
Comparators	Pfizer Limited	Standard NHS comparators would largely be reflected in the NICE Eczema pathway For mild AD, comparators should comprise: • Mild potency TCS For moderate AD, comparators should comprise: • Moderately potent TCS and TCIs (tacrolimus in patients ≥2 years; and, pimecrolimus for face and neck atopic eczema in patients 2-16 years, as per NICE TA82) We believe that Best Supportive Care is not a relevant comparator based on the anticipated position of crisaborole in the treatment pathway, as an alternative to mild/moderate potency TCS and TCIs.	Comments noted. This section has been updated based on feedback from the scoping workshop.
	National Eczema Society	We are unsure whether oral steroid treatment should be compared against Crisaborole, and consider the alternative topical treatments listed to be fairer and more applicable comparators.	Comment noted. This section has been updated based on feedback from the scoping workshop.
Outcomes	Pfizer Limited	Yes, the outcomes will capture the most important health related benefits and harms. It is noteworthy that there is a lack of consistency in the AD clinical literature with respect to the definition of a 'flare' (16), which may limit the comparative interpretation of long-term disease control in AD clinical trials. A 'flare' can be treatment defined, behaviourally defined or more frequently have an arbitrary	Comments noted. No action required.

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		definition (16). A 2016 systematic review (17) described the difficulties in assessing long-term control and highlighted the need for harmonised long term outcome measures in AD clinical trials.	
	National Eczema Society	Yes, these outcome measures will capture the most important health related benefits (and harms) of Crisaborole.	Comment noted. No action required.
Economic analysis	Pfizer Limited	The economic analyses will follow the NICE reference case methodology.	Comment noted. No action required.
Equality and Diversity	Pfizer Limited	The appraisal committee for the recent TA for dupilumab for treating moderate to severe atopic dermatitis (TA534) (18) highlighted potential equality issues relating to the use of the Eczema Area and Severity Index (EASI) and the Dermatology Life Quality Index (DLQI) as outcome assessments. Specifically, it was noted that the EASI clinical assessment may underestimate the severity of AD in patients with darker skin and that the DLQI may preclude assessment of anxiety and depression. The TA guidance recommended that these potential equality issues be taken account of by healthcare professionals, and for adjustments to be made as considered appropriate. The phase III crisaborole studies (9) included patients with an Investigators Static Global Assessment (ISGA) of 2 (mild AD) or 3 (moderate AD), and assessed ISGA success as the primary efficacy endpoint. DLQI was also assessed as a validated measure of QoL (19). Given the presence of signs such as erythema, which were part of the ISGA assessments (and which could be affected by skin colour), and the assessments of DLQI in the pivotal studies, the potential equality issues identified in NICE TA534 may also apply to any appraisal of crisaborole.	Comments noted. In line with other technology appraisals in atopic dermatitis, these equality issues will be considered by the committee during the appraisal. No action required.

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	National Eczema Society	We don't think the proposed remit and scope require changing	Comment noted. No action required.
Other considerations	Pfizer Limited	As indicated previously, additional sub-groups that could be considered (if evidence allows) are as follows: • Adults and children • Child sub-groups (2-6 years; 7-11 years; 12-17 years; 18+ years) • Mild and moderate AD • Sensitive skin areas and non-sensitive skin areas	Comment noted. Attendees at the scoping workshop attendees agreed with these subgroups except for the different child subgroups, based on age.
Innovation	Pfizer Limited	It is possible that some health related benefits of crisaborole may not be captured in the QALY calculation, i.e. potential health benefits to a parent and/or carer.	Comments noted. The company will have an opportunity to provide evidence on the innovative nature of its product in its submission. No action required.
	National Eczema Society	Yes, we consider the technology to be innovative in its potential to make a significant and substantial impact on health-related benefits for people with eczema, and how it might improve the way that current need is met. At present, the only topical treatments for eczema are emollients, topical corticosteroids of different potencies and topical calcineurin inhibitors.	Comment noted. The appraisal committee will discuss the potentially innovative nature of this technology. No action required.

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		Adherence to current treatments is often sub-optimal. Many people are reluctant to use topical corticosteroids – even those of mild and moderate potencies – because of concerns about steroids' potential to thin the skin (some 72.5% of respondents in a study said they worried about using topical corticosteroids on their own or their child's skin – Charman C.R., Morris A.D. & Williams H.C. (2000) 'Topical corticosteroid phobia in patients with atopic eczema', British Journal of Dermatology 142(5):931-6). While these patient concerns are not evidence-based, they nevertheless affect patient behaviour and compliance. Some people have concerns about topical calcineurin inhibitors due to their potential association with an increased risk of skin cancer. Crisaborole, as a non-steroidal topical treatment, is likely to be more acceptable to many people than topical corticosteroids. Crisaborole also does not have a potential association with skin cancer risk, like topical calcineurin inhibitors. Crisaborole can be used on both eczema that is flaring and as part of a longer-term disease control/maintenance regime. Unlike topical corticosteroids, Crisaborole may be safe to use on a long-term, continuous basis. This would make it easier to use than topical corticosteroids, as people wouldn't have to remember to stop the treatment for specific lengths of time. The introduction of Crisaborole wouldn't necessarily lead to a 'step-change' in the management of eczema. Nevertheless, its existence would broaden patient choice, which is vital given the limited treatment options for the condition at present, and increase the likelihood that people with mild to	

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		moderate eczema would find a treatment that is effective for them and to which they would be willing to adhere. We don't consider that the use of the technology would result in any potential significant and substantial health-related benefits that are unlikely to be included in the QALY calculation.	