National Institute for Health and Clinical Excellence

Oral alitretinoin for the treatment of severe chronic hand eczema

Comment 1: The draft remit

Section	Consultee	Comment	Action
Appropriateness	Basilea Pharmaceuticals Ltd	This is an appropriate topic for referral because chronic hand eczema (CHE) is associated with significant occupational, psychosocial and healthcare burden. Despite this, there are currently no licensed treatments for severe CHE that is unresponsive to potent topical steroids and no clinical guidelines exist, hence there is wide variation in the use of comparator interventions which may be associated with significant toxicity in the absence of reliable evidence of efficacy. For these reasons, from the perspective of the manufacturer, an STA of alitretinoin would appear more appropriate than an MTA. Refractory CHE suitable for systemic therapy is however at the severest end of the spectrum of hand eczema and is responsible for a relatively small proportion of the total healthcare burden attributable to hand eczema. Feedback from Consultant Dermatologists suggests that more effective management of the broader condition of hand eczema, including skin protective measures, optimal emollient and topical treatment and appropriate GP referral for patch testing would have a greater impact on population health than guidance on the use of a single systemic therapy in the relatively small number of adequately investigated patients currently being referred to consultants in secondary or tertiary care. For these reasons, we would suggest that a valid alternative approach to STA would be the issue of a clinical guideline for the management of chronic hand eczema.	Comments noted. At the scoping workshop discussions were had regarding whether the appraisal should be a STA or MTA. Overall it was felt by the Consultees and Commentators that this appraisal would be suitable for the STA process.
Appropriateness	British Association of Dermatologists	Appropriate but possibly premature as UK Dermatologists have little if any experience of using this drug and therefore the comments which follow are based purely on the limited literature available	Comment noted. NICE aims, where possible, to produce timely guidance in line

			with health technologies receiving their marketing authorisations.
Appropriateness	Centre of Evidence-Based Dermatology	Highly appropirate that NICE should be looking at alitretinoin. Treatment of severe hand eczema is a real problem in clinical practice and alitretinoin is the first 'new' treatment that has come along to help this group of patients who are often refractory to a conventional therapy. But I am aware that alitretinoin has a number of adverse effects and it is likely to be expensive. It is also unclear how alitretinoin compares to current alternative therapy for severe hand eczema such as ciclosporin. All these are good reasons to refer the topic to NICE, especially as its use is likely to become widespread if licensed.	Comments noted.
Wording	Basilea Pharmaceuticals Ltd	It should be specified that the licenced indication will be for the treatment of adult CHE unresponsive to potent topical corticosteroids (thus none of the topical corticosteroids are relevant comparators to alitretinoin, being placed earlier in the treatment algorithm).	Comments noted. The scope has been amended accordingly.
Wording	British Association of Dermatologists	yes	Comment noted
Wording	Centre of Evidence-Based Dermatology	I don't think the wording is a good enough reflection of the clinical problem. I realise that you have to avoid dermatological terms for the wide readership but the basic description of eczema and its classification isnt quite right. In the first paragraph, I suggest : Hand eczema (also known as hand dermatitis) is an itchy inflammatory condition of the skin affecting the hands. The palms, finger, and backs of the hands, and wrists may become involved. Skin inflammation associated with hand eczema	Comments noted. The background of the scope has been amended accordingly. The scoping

		can be acute, characterised by redness, blisters, weeping, crusting, and breaks in the skin, or it may become chronic characterised by thickening, deep cracks (fissures) and scaling. An attempt is usually made to establish the cause of the eczema in an individual. Types of hand eczema include atopic hand eczema and contact dermatitis. Contact dermatitis is itself sub-divided into irritant contact dermatitis (due to exposure to repeated wetting and mild irritants in the workplace for example), and allergic contact dermatitis (representing a specific allergy to a contact substance such as rubber). When the cause of hand eczema is unknown, it is usually referred to as endogenous hand eczema. The term pompholyx eczema simply desctibes large collections of fluid under the thick skin of the palm, as found in endogenous eczema. The next paragraph starting 'Hand eczema is estimated…. chronic form of the disease' reads well. The last paragraph, 'Treatment usually starts….. and retinoids.' isnt quite right. We don't wait until patch tests are done 4-5 weeks after seeing the patient before starting treatment of the acute eczema as this would be cruel. The aim of treatment is to try to restore normal skin as well as reduce symptoms. I am also not aware of use of other retinoids for hand eczema as their drying effect may make it worse. I would suggest the following minor changes : 'Treatment of the acute episode typically involves the use of potent topical corticosteroids and emollients. Patch tests are usually performed when possible to exclude any allergic contact factors. The aims of treatment are to reduce the inflammatory response in order to reduce symptoms and to restore normal function of the skin on the hands. Because the skin of the palms is so thick, potent topical corticosteroids are often used as first line treatment although milder preparations may be used if the eczema is only present on the backs of the hands and fingers. Potent topical steroids and super potent topical corticosteroids are sometimes used polythene occlusion during the initial phases of treatment for severe hand	document only provides a very brief summary of the condition and its management.

		eczema. Thick emollients are used liberally when the acute phase of the eczema has subsided, and special precautions need to be taken around the house and workplace to avoid further damage from frequent washing and soaps. Another popular way of maintaing remission in hand eczema is to use potent topical corticosteroids for 2 days each week, ie. weekend therapy – a strategy which has been shown to reduce relapses in previous studies. Topical immunomodulators such as tacrolimus or pimecrolimus are rarely effective when potent topical corticosteroids fail, although they can be used to help prevent relapses when a person becomes dependent on continuous use of topical corticosteroids. For those who fail on topical therapies completely, treatment includes short courses of oral corticosteroids, immunosuppressant drugs such as azathioprine, and ultraviolet light therapy directed towards the hands.'	
Timing Issues	Basilea Pharmaceuticals Ltd	[redacted] It is not clear how alitretinoin will be utilised in the NHS because of the lack of licensed precedents in this disease area, thus the rate at which alitretinoin might replace current anecdote or experience-based intervention cannot be predicted. Technology Appraisal or a broader clinical guideline may be considered urgent from the medical governance perspective however; many of the unlicensed therapies currently used in CHE are associated with significant safety risks including malignancy, which may not be acceptable to all stakeholders once licensed therapy is available. It is not possible to comment on the urgency of these considerations relative to other NHS priorities.	Comments noted.
Timing Issues	British Association of Dermatologists	See above	Comments noted.
Timing Issues	Centre of Evidence-Based Dermatology	Timing is perfect as there is likely to be a lot of pressure on UK GPs and dermatologists to prescribe this new treatment.	Comment noted.

Comment 2: The draft scope

Section	Consultee	Comment	Action
Background information	Basilea Pharmaceuticals Ltd	Paragraph 1: Hand eczema is sometimes classified by the primary cause in the individual, roughly divided into exogenous causes (allergic or more commonly irritant forms of contact eczema) and endogenous (atopic) eczema. Most authorities would agree that accurate classification by primary cause, aided by patch testing, is desirable because it can guide initial attempts to avoid disease triggers but unfortunately this is often not possible in severe ,refractory disease.There is frequently overlapping aetiology in the same patient with CHE eg. suspected or proven irritant contact eczema in a patient who also has an atopic history. Furthermore, factors that may have been responsible for triggering hand eczema (eg contact allergens identified by patch testing) may cease to be relevant to perpetuation of the disease in its chronic phase. Pompholyx is not part of this aetiological classification, being part of a second, morphological classification (which includes hyperkeratotic, erythemosquamatous, discoid and other types). A third classification of hand eczema is by its localisation (eg palmar, fingertip, fingerweb, wrist). In clinical practice, a mixed classification tends to be used reflecting the limitations of any individual system. Paragraph 2: Basilea would suggest that the wording of last sentence is amended to state: Approximately 7% of people with hand eczema are estimated to have a severe, chronic form of the disease, with one third to one half of this subgroup estimated to be refractory to potent topical corticosteroids (Diepgen, Contact Dermatitis 2007:57:203-210) Paragraph 3, sentence 1: Basilea would suggest replacing with: "Treatment usually starts when an identified allergen or irritant cannot be removed" Basilea	Comments noted. The background of the scope has been amended accordingly. The scoping document only provides a very brief summary of the condition and its management.

		would further suggest that treatment aims are broader than stated in sentence 2, including the improvement of hand function (because of its relevance to occupation) and improving cosmetic appearance (because of its role in social functioning and self esteem) but would respectfully refer NICE to clinicians and patient representatives to provide their perspective.	
Background information	British Association of Dermatologists	para 1 Classification: more useful to divide into a) constitutional eg atopic eczema and b) contact eg allergic or irritant para 3 Treatment: Omit first sentence as treatment would normally begin whether causative agent removed or not. Causative agent may be irritant and not allergic therefore remove "allergic" before "inflammatory response"	Comments noted. The background of the scope has been amended accordingly.
Background information	Centre of Evidence-Based Dermatology	Same comments relating to background described in remit. Reference should be made to the economic burden of chronic hand eczema, dur to inability to work.	Comment noted. The NICE reference case specifies that costs and benefits will be considered from a NHS and PSS perspective.
The technology/intervention	Basilea Pharmaceuticals Ltd	Sentence 1: Datiros is no longer the proposed proprietary name for alitretinoin; the proprietary name is awaiting approval therefore the product should be referred to as oral Alitretinoin throughout. Please note that although the Marketing Authorisation Holder will be Basilea Medical Ltd as stated, the name of the company making an appraisal submission would be Basilea Pharmaceuticals Ltd. Basilea would suggest that the remainder of sentence 1 be replaced with: "The mechanism of action of alitretinoin in the treatment of CHE is unknown. Alitretinoin has been described as panagonist of retinoid receptors because it	Comment noted. The technology section of the scope has been amended accordingly.

		activates RAR receptors and RXR receptors. Binding to and activation of the various retinoid receptors might be responsible for certain biological effects of alitretinoin. However, no precise link has been shown between patterns of receptor binding and therapeutic activity in CHE. The activity of alitretinoin in skin inflammatory processes has been investigated in animal models and human trials. Results demonstrate that alitretinoin has antiinflamatory and immunomodulatory effects relevant for treating chemical-induced irritant and hapten-induced skin inflammation, including: - Suppression of the production of chemokines involved in recruitment of leucocytes to sites of skin inflammation - Suppression of the expansion of cytokine-activated leucocytes and antigen-presenting cells involved in the immune response" [redacted] Sentence 3: Because of potential ambiguity in the term "monotherapy", Basilea would suggest that this is amended to state: "Alitretinoin has been studied in combination with standard supportive and emollient care but without the use of concomitant corticosteroids or other pharmacologically active treatment"	
The technology/intervention	British Association of Dermatologists	Yes	Comment noted.
The technology/intervention	Centre of Evidence-Based Dermatology	Maybe you need to specifiy the dose? The very large study of alitretinoin looked at 10mgs and 30mgs. I am not sure whether the proposal is to market it at both of these strengths.	Comment noted. Dosage is not an issue normally discussed at the scoping stage.

Population	Basilea Pharmaceuticals Ltd	. Yes-no additional considerations	Comment noted
Population	British Association of Dermatologists	Yes In terms of cost effectiveness it may be helpful to consider group with occupational dermatitis separately	Comment noted At the scoping workshop it was agreed that no subgroups could be pre-defined.
Population	Centre of Evidence-Based Dermatology	This sounds appropriate, but you will need to be a lot clearer what you mean by 'refractory to topical corticosteroids'. Which topical corticosteroids? Used for how long? Used properly? Should they be new refractory cases or chronic refractory cases?	Comment noted. This will be defined during the appraisal and will be informed by the trial data used to gain marketing authorisation of the technology.
Comparators	Basilea Pharmaceuticals Ltd	None of the therapies listed below are licensed for treatment of CHE and there is limited published evidence to guide clinical choice (EDEN survey BJD 2004; 151:446-451) PUVA should be listed as a standard comparator because it is probably the most widely used intervention in CHE unresponsive to potent topical steroids, although there is limited evidence for its efficacy in this condition. PUVA with oral or topical psoralen is suggested as best alternative care. Systemic immunosuppressive therapies:	Comment noted. It was agreed at the scoping workshop that PUVA and immunosuppressive therapies (azathioprine and ciclosporin) were the most

		Ciclosporin is the most widely used of the systemic agents in the treatment of CHE that is unresponsive to topical steroids and should be included as a standard comparator. The other systemic immunosuppressants mycophenolate, azathioprine and methotrexate (not listed) are only occasionally used. Alternative retinoid therapies: It should be noted that individual retinoids differ in their pharmacological effects and therefore therapeutic application. Acitretin is licensed for severe extensive refractory psoriasis and is occasionally used for the treatment of CHE on the basis that it may reduce hyperkeratinisation but should not be included as a standard comparator. Acitretin therapy tends to be restricted to males and post menopausal females because a long elimination half life dictates two years pregnancy prevention measures after cessation of therapy. Oral isotretinoin is licenced for the treatment of acne only and is not used in CHE. Efficacy in acne is related to inhibition of sebum secretion and this agent is known to cause/exacerbate rather than improve eczema. It is our understanding that adalapene is a topical formulation of isotretinoin only used in acne and that tretinoin is no longer available in the UK. Topical immunomodulators are licenced for moderate or severe atopic eczema only. TIMS were viewed as a useful topical option to delay or avoid the use of systemic therapy but useage has declined due to limited efficacy, inconvenience (interference with emollient therapy, need for overnight hand occlusion) and the potential for skin malignancy, particularly in patients who have received UV therapy. Oral corticosteroids may occasionally be used short term to gain control of particularly inflammatory presentations of CHE, but are not used in the most prevalent form of CHE which is predominantly hyperkeratotic.	appropriate comparators. Pimecrolimus is not recommended for this indication. Tacrolimus is not standard practice for this indication in the NHS.
Comparators	British Association of	Yes. This technology would probably be used ahead of other systemic agents such as azathioprine or cyclosporin therefore best alternatives might be topical	Comment noted. It was agreed at the scoping

	Dermatologists	tacrolimus or pimecrolimus or phototherapy	workshop that PUVA and immunosuppressive therapies (azathioprine and ciclosporin) were the most appropriate comparators. Pimecrolimus is not recommended for this indication. Tacrolimus is not standard practice for this indication in the NHS.
Comparators	Royal College of Nursing	Not sure how often and widely ultra violet light therapy is used in hand eczema or how effective it is. Should it be should be included as a comparator?	Comment noted. It was agreed at the scoping workshop that PUVA and immunosuppressive therapies (azathioprine and ciclosporin) were the most appropriate comparators. Pimecrolimus is

			not recommended for this indication. Tacrolimus is not standard practice for this indication in the NHS.

Comparators	Centre of Evidence-Based Dermatology	I would be very surprised if topical immunomodulatory therapy such as tacrolimus and pimecrolimus work when potent or super potent topical corticosteroids fail. At best they are supportive treatment for topical corticosteroids which may reduce the quantity or duration of topical corticosteroids and help to maintain remission. I see you have included other retinoid therapies. I must confess I have never used things like isotretinoin or acitretin or adapalene - all are powerful irritants which will dry hand eczema and make it much worse, but if you do have many groups who use such counter-intuitive treatment, then it needs to remain there. I would suggest that of all the comparators, oral ciclosporin is going to be the most frequently used for severe hand eczema that is unresponsive to topical corticosteroids. Topical PUVA treatment should be added. Also topical corticosteroids should be included because 'topical steroid resistant' patients may still have a transient response to these. Oral corticosteroids should be removed from the list because they are not appropriate treatment for chronic hand eczema, in which long-term treatment is anticipated.	Comment noted. It was agreed at the scoping workshop that PUVA and immunosuppressive therapies (azathioprine and ciclosporin) were the most appropriate comparators. Pimecrolimus is not recommended for this indication. Tacrolimus is not standard practice for this indication in the NHS.
Outcomes	Basilea Pharmaceuticals Ltd	The outcome measure of disease free period or maintenance of remission would be highly relevant to compare the effectiveness of interventions in CHE which is a relapsing remitting disease.	Comment noted. The outcomes included in the scope have been amended.
Outcomes	British Association of Dermatologists	Yes. Could also consider time lost from work	The NICE reference case specifies that costs and

			benefits will be considered from an NHS and Personal Social Services perspective.
Outcomes	Centre of Evidence-Based Dermatology	These are nice and simple. The only thing I would recommend that you consider is the timeframe. Hand eczema is typically a chronic relapsing remitting condition, and a time window of one year would be appropriate. As a consequence of the chronic nature of hand eczema, you should also look at time to relapse or prevention of relapses.	Comment noted. An appropriate time horizon will be used to take account of the condition. The outcomes in the scope have been amended accordingly.
Economic analysis	Basilea Pharmaceuticals Ltd	Time horizon would need to be up to 3 years to allow time spent in disease remission to be compared between the interventions	Comment noted. C&Cs agreed at the scoping workshop that that the general statement contained in the scope was adequate.
Economic analysis	Centre of Evidence-Based Dermatology	This seems appropriate. Including the personal perspective is extremely important as the indirect costs associated with hand eczema through time off work and inability to do housework, etc. are considerable.	The NICE reference case specifies that costs and

		Suggest time horizon of one year.	benefits will be considered from an NHS and Personal Social Services perspective.
Questions for consultation	Basilea Pharmaceuticals Ltd	Q1: Choice of appropriate comparator is complicated by the lack of reliable evidence base for any of the interventions currently used. On the basis of extent of useage, ciclosporin is suggested as the most appropriate comparator listed and for the same reason, PUVA is suggested as an additional comparator should a technology appraisal be undertaken. Q2: No Q3: No Q4: Single Technology Appraisal is the most appropriate of the options suggested because alitretinoin is the only technology to be licenced or otherwise supported by a substantial RCT evidence base in CHE patients. Much of the current variance in practice relates to a preferred sequence of intervention in steroid-refractory patients (based on familiarity/training) or the facilities locally available (eg. PUVA centre versus infrastructure for appropriate laboratory monitoring of systemic treatment) rather than an evidence based treatment algorithm. As such, it would be feasible to address the question of cost effectiveness of alitretinoin as a first line treatment option in patients unresponsive to topical corticosteroids in an STA. In contrast, the alternative MTA would require the appraisal to address multiple questions of relative positioning of unlicenced comparator agents in the absence of sufficient evidence to inform decision making. Basilea would suggest that a preferable option to improve clinical decision making would be a clinical guideline for the broader management of hand eczema, including crucially the questions of appropriate referral from primary	Comments noted. It was agreed at the scoping workshop that PUVA and immunosuppressive therapies (azathioprine and ciclosporin) were the most appropriate comparators. At the scoping workshop discussions around whether the appraisal should be a STA or MTA. Overall it was felt by the Consultees and Commentators that this appraisal would

		care and the role of patch testing. It is our understanding that a Cochrane review of existing treatments for CHE is ongoing and that the European Contact Dermatitis Research Group (EECDRG) is currently completing guidelines on the classification of CHE, both of which may greatly facilitate the work of producing a clinical guideline on CHE.	be suitable for the STA process.
Questions for consultation	Centre of Evidence-Based Dermatology	As stated above, I think oral ciclosporin is likely to be the most appropriate main comparator for oral alitretinoin. Care needs to be taken on the definition of 'refractory'. I am not sure about light therapy - hand and foot PUVA is certainly used quite commonly in dermatology departments for chronic hand eczema, so I suppose it should be in there. I doubt if there will be any comparative data for you however. In terms of subgroups of patients, I would have expected that the new technology could possibly be more effective in those forms of hand eczema which are not clearly atopic. The rationale is that retinoids dry the skin, and atopic eczema is typically associated with a generally dry skin. I would therefore expect adverse effects of alitretinoin to be worse in those with an atopic hand eczema.	Comments noted. It was agreed at the scoping workshop that PUVA and immunosuppressive therapies (azathioprine and ciclosporin) were the most appropriate comparators. It was also noted that the data on the comparators would very likely be of poor quality. At the scoping workshop it was agreed that no subgroups could be pre-defined.

The following consultees/commentators indicated that they had no comments on the draft remit and/or the draft scope

Glaxosmithkline

NHS QIS

Royal Pharmaceutical Society

Welsh Assembly Government