NATIONAL INSTITUTE FOR HEALTH AND CLINICAL EXCELLENCE

Alitretinoin for the treatment of severe chronic hand eczema

Response to consultee, commentator and public comments on the Appraisal Consultation Document (ACD)

Comments from consultee organisations and nominated experts

Consultee	Comment	Response
Skin Care Campaign/ National Eczema Society	**Do you consider that all of the relevant evidence has been taken into account?** The Skin Care Campaign (SCC) and National Eczema Society (NES) would like the committee to further consider the following information re: **RELEVENT and TIMELY ACCESS TO TREATMENT and COST EFFECTIVENESS** 1.3, 4.1, 4.4 and 4.15 "Only dermatologists with specialist experience in managing severe hand eczema should start and monitor treatment with alitretinoin." Patients are treated by a multi-disciplinary team, inc: specialist nurses, pharmacists and GPwSIs not just dermatologists. The SCC and NES suggest the recommendation should be: "1.3 Only clinicians with specialist experience in managing eczema should start and monitor treatment with alitretinoin." This will ensure that Patients will get better and faster treatment if all members of the specialist dermatology team – inc. specialist nurses, GPwSIs, PwSIs can prescribe and monitor this treatment.	The FAD has been amended accordingly. See also FAD section 4.17

Consultee	Comment	Response
Skin Care Campaign/ National Eczema Society	**PATIENT SAFETY** 2.4 “Alitretinoin should not be prescribed if the person’s eczema can be adequately controlled by standard measures, including skin protection, avoiding allergens and irritants, and treatment with potent topical corticosteroids.” Topical corticosteroids have several side effects and should be considered alongside Alitretinoin as a second line treatment. The SCC and NES suggest the recommendation should be: “Alitretinoin should not be prescribed if the person’s eczema can be adequately controlled by standard measures, including skin protection, avoiding allergens and irritants, and treatment with topical emollients.” This will ensure patients get the safest possible treatments.	NICE can only issue guidance within the marketing authorisation. The SPC for alitretinoin says “Toctino is indicated for use in adults who have severe chronic hand eczema that is unresponsive to treatment with potent topical corticosteroids”.

Consultee	Comment	Response
Skin Care Campaign/ National Eczema Society	**Do you consider that the summaries of clinical and cost effectiveness are reasonable interpretations of the evidence, and that the preliminary views on the resource impact and implications for the NHS are appropriate?** The Skin Care Campaign (SCC) and National Eczema Society (NES) would like the committee to further consider the following information re: **PATIENT SATISFACTION and HOLISTIC COST EFFECTIVENESS** 4.1, 4.2 and 4.12 “The Committee also agreed that the benefits of moving from the health state of severe chronic hand eczema to hands clear or almost clear would be considerable.” Almost clear is not good enough and still results in significant disability. The SCC and NES suggest the recommendation should be: “The Committee also agreed that the benefits of moving from the health state of severe chronic hand eczema to hands clear would be considerable.” This would highlight that any form of chronic hand eczema is debilitating and problematic for a person with it. (Continued..)	The definition of hands clear/ almost clear was used in the registration trials for alitretinoin and was therefore the basis of the effectiveness results.

Consultee	Comment	Response
Skin Care Campaign/ National Eczema Society	Recent research (Health Talk 2009) has shown that patients with chronic hand eczema clearly benefit from total clearance and nothing less: This survey showed that 88% had difficultly in doing everyday things such as cutting up vegetables, gardening, washing up and doing up buttons. The same survey showed that 96% found their hand eczema embarrassing. When asked “what was the worst thing about having hand eczema?” comments included: “Not being able to touch the people I love, leaving blood stains on clothes/door handles, constant infection risk” “Lost earnings.” “When it affected my relationship with my baby son because picking him up was so painful” “The mad itching, cracking skin, blisters that weep stinging” “The redness of my hands they look like an old woman's and I am in my 40's.” “The constant pain of split and broken weeping and bleeding skin, hurts all the time. It is embarrassing”.	See above response

Consultee	Comment	Response
Skin Care Campaign/ National Eczema Society	**Do you consider that the provisional recommendations of the Appraisal Committee are sound and constitute a suitable basis for the preparation of guidance to the NHS?** The Skin Care Campaign (SCC) and National Eczema Society (NES) would like the committee to further consider the following information re: **PATIENT SAFETY** 1.1 and 4.14 “the disease has not responded to a second-line treatment such as ciclosporin, azathioprine or PUVA (psoralen and long-wave ultraviolet radiation), or the person is intolerant of or has a contraindication to these treatments.” All of these second line treatments have very serious side-effects and have comparatively little evidence to prove their success e.g.: 4.3 “ciclosporin is associated with an increased risk of lymphoma and skin cancer, and PUVA is known to be carcinogenic.” It also seems negligent to prefer unlicensed treatments to licensed ones.The SCC and NES suggest the recommendation should be: “Alitretinoin should be included as a second-line treatment as an alternative to ciclosporin, azathioprine and PUVA (psoralen and long-wave ultraviolet radiation)." This will ensure patients will have a far safer treatment available to them. This would also be in line with and not contradict recommendation 6.1 for comparative phase III trials.	The FAD has been amended accordingly. See also FAD section 4.15

Consultee	Comment	Response
Skin Care Campaign/ National Eczema Society	**PATIENT SAFETY, DISCRIMINATION and COST EFFECTIVENESS** 1.2, 4.1 and 4.15 “Alitretinoin treatment should be stopped: • if the eczema does not show an adequate response (defined as hands clear or almost clear) within 12 weeks or • as soon as an adequate response (hands clear or almost clear) has been achieved.” This does not allow for a long enough period to properly achieve clear hands and will lead to some patients not properly benefiting from this treatment and money being wasted on not allowing enough treatment time to properly assess success. ‘almost’ is too subjective and would cause discrimination for some patients. The SCC and NES suggest the recommendation should be: “1.2 Alitretinoin treatment should be stopped: • if the eczema does not show an adequate response (defined as hands clear) within 24 weeks or • as soon as a successful response (hands clear) has been achieved.” This will allow enough time to see any benefits and leave no level of doubt / discrimination about ‘almost clear’.	The cost effectiveness analysis was based on stopping treatment after 12 weeks, if the symptoms were still classed as severe. The Committee did not have any evidence for the cost effectiveness if treatment would continue to 24 weeks in this situation. See FAD section 4.16

Consultee	Comment	Response
Royal College Physicians	Do you consider that the provisional recommendations of the Appraisal Committee are sound and constitute a suitable basis for the preparation of guidance to the NHS? **Alitretinoin is recommended, within its licensed indication, as a treatment option for adults with severe chronic hand eczema that has not responded to potent topical corticosteroids if:** **• the person has severe disease, as defined by the physicians global assessment (PGA) and a dermatology life quality index (DLQI) score of 15 or more, *and*** It is appropriate to use alitretinoin in patients with Chronic Hand Eczema (CHE) with severe disability. However given the restrictions below it will only be prescribed in secondary care by dermatologists. Given the current barriers to patients being referred to secondary care then, by definition, only patients with severe disability will be considered. Taking this into account the DLQI score of 15 is arguably a little high. It also appears that this has been arbitrarily selected. Might the committee need to show how this particular figure was arrived at? Existing NICE guidance for the use of anti TNFs in psoriasis is a DLQI of 10. Using this figure would demonstrate a consistent approach by NICE to the impact of differing dermatological diseases and might be perceived as "fairer" by external observers such as our patient groups.	The Committee considered that psoriasis and severe chronic hand eczema could have different effects on HRQoL See FAD section 4.13.

Consultee	Comment	Response
Royal College Physicians	**• the disease has not responded to a second-line treatment such as ciclosporin, azathioprine or PUVA (psoralen and long-wave ultraviolet radiation), or the person is intolerant of or has a contraindication to these treatments.** Most units will try patients with CHE on a trial of PUVA therapy: there is at least some evidence in favour of it's efficacy. If the NICE guidelines are to be evidence based then we would question both the committee's positioning of and recommendation of ciclosporin and azathioprine for CHE. While these treatments are indeed used in CHE (mainly because of the lack of useful alternative), efficacy is low and the evidence base is poor. In the hierarchy of evidence, should evidence-based guidance not place alitretinoin treatment after topical steroid therapy (as per the results of randomised controlled studies) and before PUVA (uncontrolled or poor quality trials) and then ciclosporine/azathioprine (expert opinion only and unlicensed for CHE). In the long term interests of patients' health it should also be pointed out that the recommendation as it stands is that long term systemic immunosuppressive treatment takes precedence over anti epidermal proliferation/differentiation treatment. In other words there is more potential for significant harm to patients through infection and neoplasia with cyclosporine/azathioprine therapy than there is with alitretinoin.	The FAD has been amended accordingly. See also FAD section 4.15

Consultee	Comment	Response
Royal College Physicians	**1.2 Alitretinoin treatment should be stopped:** **• if the eczema does not show an adequate response (defined as hands clear or almost clear) within 12 weeks or** **• as soon as an adequate response (hands clear or almost clear) has been achieved.** Should there be a comment on restarting Alitretinoin? Or is the implication that a second course can be introduced once the clinical picture deteriorates to the NICE thresholds above Again with the DLQI should re-treatment not be introduced at a lower threshold rather than allowing patients to deteriorate to pre treatment levels before further therapy? We appreciate that this might be outside the remit of the existing studies and guidance.	The Committee agreed that this level of detail would be outside the remit for a technology appraisal See FAD section 4.16.
	1.3 Only dermatologists with specialist experience in managing severe hand eczema should start and monitor treatment with alitretinoin. **1.4 When using the DLQI, healthcare professionals should take into account any disabilities (such as physical impairments) or linguistic or other communication difficulties that the person may have.** In such cases, healthcare professionals should ensure that their use of the DLQI continues to be a sufficiently accurate measure.	Noted.

Consultee	Comment	Response
Basilea	The preliminary recommendations set out in the appraisal consultation document, taking into account the available and relevant evidence, are perverse. Specifically; The proposal to use alitretinoin in severe chronic hand eczema after unlicensed second line treatments such as ciclosporin, azathioprine or PUVA is not justified by the clinical and health economic evidence Robust clinical data demonstrates that alitretinoin is effective and well tolerated when used within its marketing authorisation in patients unresponsive to potent topical corticosteroids The ERG, appraisal committee and expert clinical opinion have indicated that there is no reliable evidence base for the efficacy of the comparators in chronic hand eczema	Comment noted. The FAD has been amended accordingly. See also FAD section 4.15
Basilea	As described in section 4.3 of the ACD, the adverse effects of comparator treatments are of concern, whereas alitretinoin is recognised to offer greater safety, without the risk of adverse effects such as cancer associated with comparator therapies	See above response
Basilea	Utility values based upon relevant change in disease state should be used in the health economic model and these are provided by the BAP0003 study. These data and the ERG modifications of the model deliver an ICER of £15,084 per QALY gained	The Committee extensively discussed the various utility estimates, for example the Committee agreed that the utility estimate for PGA-defined severe chronic hand eczema in the Augustin study may have underestimated the impact of the condition. See also FAD section's 4.10 to 4.14

Consultee	Comment	Response
Basilea	*The addition of DLQI in the determination of eligibility of alitretinoin treatment is unnecessary:* The alitretinoin marketing authorisation specifies use only in patients who have severe chronic hand eczema that is unresponsive to treatment with potent topical corticosteroids The preliminary guidance already notes that patients should be classified as severe according to the Physicians Global Assessment (PGA), which was the validated assessment used in the clinical trials	The Committee agreed that the uncertainty about the relationship between DLQI score and PGA state was too great to base recommendations on PGA state alone, and that it would be appropriate to include guidance on DLQI eligibility criteria for treatment. See also FAD section 4.12 and 4.13
Basilea	Suggested stopping rules in section 1.2 should be clarified such that they are consistent with section 4.15 of the ACD and the licensed recommendations for alitretinoin	Comment noted. The FAD has been amended. See also FAD section 4.16
Basilea	Recommendations regarding who should initiate and monitor treatment with alitretinoin should be consistent with MHRA guidance and the wording of the alitretinoin SPC which are based on considerations of safety and practicality	Comment noted. The FAD has been amended. See also FAD section 4.17
Basilea	**Do you consider that all of the relevant evidence has been taken into account** Evidence critical to both the cost effectiveness calculations and the positioning of alitretinoin within the treatment pathway has been considered but inappropriately weighted, resulting in preliminary guidance that is perverse. In particular: NICE has given disproportionate weight to limited qualitative evidence from clinical specialists in support of comparator therapies that does not meet the criteria used by the ERG to question the reliability of quantitative efficacy estimates provided by Basilea	Comment noted. See also FAD section 4.15

Consultee	Comment	Response
Basilea	Statements of “adequate” efficacy in “some” patients are used to justify second-line positioning of unlicensed therapies ahead of alitretinoin There is no reliable evidence base for the use of unlicensed therapies for severe CHE but the safety risks are of concern to all stakeholders, whereas alitretinoin has excellent efficacy and safety data from large, double-blind, randomised, controlled trials	See above response.
Basilea	The use of the less appropriate source of DLQI data (Augustin data) substantially increases the ICER from approximately £15K per QALY to around £30K. This appears to be the economic basis for the proposed positioning of alitretinoin and the additional restrictions on patient eligibility which are unsound	The Committee agreed that the uncertainty about the relationship between DLQI score and PGA state was too great to base recommendations on PGA state alone, and that it would be appropriate to include guidance on DLQI eligibility criteria for treatment. See also FAD section 4.12 and 4.13
Basilea	NICE acknowledged the paucity of evidence for comparators at the Scope and Decision Problem meetings, however the scope remained comparative in nature. Subsequent rejection of the comparator model on the grounds that it was not reliable removed the possibility of comparator budget impact analysis	Comment noted. See FAD section 4.9

Consultee	Comment	Response
Basilea	The additional revised model requested of Basilea versus placebo was complex to programme and submit to NICE in the time requested. In the interests of time, adverse events were omitted because their inclusion would have had only a minor effect on the ICER generated We acknowledge and thank the ERG for correcting the minor error in VBA coding and for the helpful modifications they were able to make. However, neither the correction nor any modified assumptions in the ERG model make a qualitative difference to the ICERs, which remain within a cost effective range of approximately £15K per QALY when the most scientifically justifiable utility values from the BAP0003 study are used	Comment noted
Basilea	**Do you consider that the summaries of clinical and cost effectiveness are reasonable interpretations of the evidence, and that the preliminary views on the resource impact and implications for the NHS are appropriate?** The summary of cost effectiveness does not provide a reasonable interpretation of the data or clinical opinion regarding the efficacy of comparators, DLQI data and cost savings.	Comment noted

Consultee	Comment	Response
Basilea	There is no evidence base to demonstrate that the unlicensed comparator therapies show efficacy and safety in severe CHE such that they should be positioned prior to alitretinoin in the treatment pathway. While we appreciate and respect all of the clinical expert input into the NICE process, it seems inconsistent to accept and give weight to interpretations of verbal opinion from two clinical experts on the efficacy of unlicensed comparator therapies, while the personal opinion and input of seven experts into the comparator model was dismissed The suggestion that comparator therapies may produce an “adequate” response in “some” people with severe CHE is a perverse basis for the positioning of ciclosporin, azathioprine or PUVA ahead of alitretinoin which high quality trials demonstrate can clear/almost clear hands in nearly 50% of patients.	Comment noted.
Basilea	The BAP0003 data for DLQI is more relevant for use in health economic modeling than the Augustin cross sectional data and yields an ICER of around £15K or less. In the Augustin data, cross sectional QoL reports by patients will, in addition to the effect of PGA disease state, tend to be confounded by effects such as the impact of any comorbidity and personal factors that cannot be completely controlled for Additionally, cross sectional measurement does not capture the effects of changing from one disease state to another but instead infers this change upon those living in different disease states. This is a substantial limitation when considering and valuing the effects of a new treatment which is overcome by the use of prospective data from the BAP0003 study	The Committee acknowledged that both studies were subject to a high degree of uncertainty. See FAD section 4.10 to 4.14.

Consultee	Comment	Response
Basilea	A number of statements in section 4.12 suggest that the appraisal committee believed the Augustin study underestimated the impact of severe chronic hand eczema on quality of life. Also, as noted in 4.10, the Augustin finding of "higher utility for mild disease than for the state of hands clear or almost clear…" was regarded as counterintuitive by the committee. Taking into account the points above, it is more appropriate to use utility data derived from the BAP0003 study	Comment noted.
Basilea	In addition, there are inaccuracies regarding the DLQI data in section 4.10 as follows: An apparent distinction is made between the sources of DLQI data on the basis of whether they were directly obtained. Both datasets were directly obtained. The key difference was that the BAP0003 analysis used a longitudinal approach in the same group of patients over time (and thus would have reflected changes in disease severity) whereas the Augustin study was cross sectional in patients who had different PGA severities	Comment noted. The Committee acknowledged that both studies were subject to a high degree of uncertainty, as both estimated utilities indirectly. See also FAD section 4.10
Basilea	We believe that "utility" rather than "DLQI" was intended in the following sentence in section 4.10 " The Committee noted that the manufacturer did not use the DLQI scores from groups of people defined according to their PGA state directly, although this would have been possible	Comment noted. The FAD has been amended. See FAD section 4.10
Basilea	While precise cost minimisation calculations are uncertain, given that the cost of PUVA provision is higher than the acquisition cost of alitretinoin, even at the most simplistic level it would be reasonable to assume that savings would be realised following replacement of PUVA by alitretinoin. This is more certain than an assumption of greater efficacy or lower cost of PUVA that would be required to justify the placement of PUVA ahead of alitretinoin in the treatment pathway	Comment noted. See FAD section 4.9.
Basilea	When considering strictly the treatment pathway and the fact that there is no evidence to suggest better efficacy of comparators compared to alitretinoin, it is not clear why the relative cost of alitretinoin could not be considered (section 4.14)	The FAD has been amended accordingly. See FAD section 4.15.

Consultee	Comment	Response
Basilea	The cost minimisation analysis performed by Basilea provides evidence to suggest that over the longer term the costs of alitretinoin therapy will be offset by a reduction in the use of services that are more expensive for the NHS to provide. This is consistent with the opinion of the British Association of Dermatology reflected in their written submission	Comment noted
Basilea	It was acknowledged at the public appraisal committee that some of the wider societal aspects, such as improved ability for patients to return to work and reduced absenteeism for PUVA attendance, lie outside of the restricted NICE scope to consider. We however believe that the potential for direct NHS savings should be taken into account as well as the potential for better health benefits if PUVA resources were to be redirected to the care of more responsive conditions such as psoriasis	Comment noted
Basilea	**Do you consider that the provisional recommendations of the Appraisal Committee are sound and constitute a suitable basis for the preparation of guidance to the NHS?** The preliminary recommendations set out in the appraisal consultation document, taking into account the available and relevant evidence, are perverse for the reasons stated below.	Comment noted
Basilea	Robust clinical data demonstrates that alitretinoin is effective, well tolerated when used according to its licensed indication in patients unresponsive to potent topical corticosteroids	Comment noted
Basilea	The ERG, appraisal committee and expert clinical opinion have indicated that there is no reliable evidence base for the efficacy of the comparators in chronic hand eczema	Comment noted
Basilea	As described in section 4.3 of the ACD, the adverse effects of comparator treatments are of concern, whereas alitretinoin is recognised to offer greater safety, without the risk of cancer associated with comparator therapies	Comment noted

Consultee	Comment	Response
Basilea	The recommendation of treatments in a pathway for the NHS should be based on adequate weighting of their potential to do harm with value placed on the availability of risk:benefit evidence with which to obtain patient consent which is truly informed	Comment noted. See also FAD section 4.15
Basilea	The SPC safety information for alitretinoin is based on data from 1456 patients exposed during the clinical development trials in chronic hand eczema and is amended in agreement with regulatory authorities to ensure that the SPC remains an up to date summary of risk:benefit.	Comment noted
Basilea	No equivalent information is available to inform the use of comparators in CHE. These treatments are known to have serious short and long term toxicity that may be unpredictable as in the case of nephrotoxicity produced by ciclosporin, marrow suppression produced by azathioprine and the activation of latent infection and pre-existing cancers by both agents. Both oral immunosuppression and PUVA will increase the incidence of de novo malignancy over the longer term	The Committee was aware of the adverse events related to the comparator treatments. See also FAD sections 4.3 and 4.9
Basilea	If the appropriate BAP0003 DLQI data is used to generate utility estimates for alitretinoin, ICERs remain well within the conventional cost effective range at £15K per QALY or under even after inclusion of all the ERG suggested modifications	The Committee extensively discussed the various utility estimates, for example the Committee agreed that the utility estimate for PGA-defined severe chronic hand eczema in the Augustin study may have underestimated the impact of the condition. See also FAD section's 4.10 to 4.14

Consultee	Comment	Response
Basilea	The addition of DLQI in the determination of eligibility for alitretinoin treatment is unnecessary based on current evidence The preliminary guidance already notes that patients should be classified as severe according to the Physicians Global Assessment (PGA), which was the validated assessment used in the clinical trials Data from the BAP0003 study clearly shows patients with a PGA of "severe" were associated with a significantly reduced quality of life	The Committee agreed that the uncertainty about the relationship between DLQI score and PGA state was too great to base recommendations on PGA state alone, and that it would be appropriate to include guidance on DLQI eligibility criteria for treatment.See also FAD section 4.12 and 4.13
Basilea	Suggested stopping rules in section 1.2 should be clarified such that they are consistent with section 4.15 of the ACD and the licensed recommendations for alitretinoin. The wording of the alitretinoin marketing authorisation states that "Discontinuation of therapy should be considered for patients who still have severe disease after the initial 12 weeks of treatment" This is correctly interpreted in section 4.15 that states "treatment with alitretinoin should be stopped as soon as an adequate response (hands clear or almost clear) is achieved, or after 12 weeks if the symptoms are still classed as severe" which also reflects health economic model assumptions accepted in section 4.9 of the ACD. In contrast, the current wording used in section 1.2 of the ACD reflects neither the marketing authorisation nor sections 4.9 or 4.15	Comment noted. The FAD has been amended. See also FAD section 4.16

Consultee	Comment	Response
Basilea	Recommendations regarding who should initiate and monitor treatment with alitretinoin should be consistent with MHRA guidance and the wording of the alitretinoin SPC, which are based on considerations of safety and practicality Based on current evidence and consistent with the clinical experience of retinoids stated by all experts involved in the appraisal, there is no basis for additional restrictions on the qualifications or experience of those providing alitretinoin therapy or the setting in which it is delivered beyond those stated in the alitretinoin marketing authorisation. ACD wording in sections 1.3, 4.4 and 4.15 should be consistent with the wording of the alitretinoin SPC as follows, unless clear justification for alternative recommendations is available: "Toctino should only be prescribed by dermatologists, or physicians with experience in the use of systemic retinoids who have full understanding of the risks of systemic retinoid therapy and monitoring requirements"	Comment noted. The FAD has been amended. See also FAD section 4.17
Basilea	The basis for MHRA restrictions on the initiation of retinoids are their teratogenic potential and the requirement for reliable pregnancy prevention measures. These considerations are no different between alitretinoin and isotretinoin Patient management in the NHS is necessarily multidisciplinary, especially in the supportive relationship between specialist care and general practice. NICE advice to the NHS should reflect the sharing of some aspects of care in a chronic condition such as CHE with a broader range of healthcare professionals. This might be limited to sharing of the minimum required monitoring tasks (eg. lipid checks) or could extend to the provision of advice during therapy including when to stop treatment, which would reduce reliance on secondary or tertiary care services and bring care as close as possible to the patient	Comment noted. See FAD section 4.17
Basilea	**Are there any equality related issues that need special consideration that are not covered in the ACD?** No	Comment noted

Consultee	Comment	Response
Basilea	**Other points** With reference to section 6 of the ACD, Basilea is a small biopharmaceutical company that has completed an extensive clinical development programme for alitretinoin in chronic hand eczema recruiting 1500 patients into randomised controlled trials. This figure exceeds the combined recruitment to all trials of alternative interventions in CHE that could be identified by the European Dermato-Epidemiology Network (EDEN) combined with any studies published since EDEN reported in 2004	Comment noted
Basilea	Additional phase IV studies are planned which will include an estimated 450 patients. These clinical studies aim to define the optimal use of different alitretinoin doses and dosing schedules in CHE, address the potential role of alternative treatments in augmenting or prolonging the response to alitretinoin and examine the potential for long term disease modification if skin barrier repair can be promoted by prolonged remission.	Comment noted.
Royal College of Nursing	Nurses working in this area of health have reviewed the Appraisal Consultation Document and consider it comprehensive. There are no additional comments to make on this document. The RCN will welcome national guidance to the NHS on the use of this health technology.	Comment noted
British Association of Dermatologists	Do you consider that all of the relevant evidence has been taken into account? We do consider that all of the relevant evidence has been taken into account.	Comment noted

Consultee	Comment	Response
British Association of Dermatologists	**Do you consider that the provisional recommendations of the Appraisal Committee are sound and constitute a suitable basis for the preparation of guidance to the NHS?** 1) We feel that too much emphasis is being placed on the DLQI as a severity assessment tool in this condition. This condition, being limited to a specific body site is very different to a generalised disease like psoriasis although the impact on quality of life is often large, given that it affects the hands. If DLQI is to be used then what is the evidence for a score of 15 as opposed to 10 for the biologics? This high score could exclude a significant number of deserving patients and it would make more sense to use the same DLQI as for the biologics, bearing in mind also that Alitretinoin is significantly less expensive than the biologics. This would demonstrate a consistent approach by NICE to the impact of differing dermatological diseases and might be perceived as "fairer" by external observers such as our patient groups.	Comment noted. See FAD section 4.13
British Association of Dermatologists	2) We also have concerns regarding the ranking of Alitretinoin relative to its conparators. Alitretinoin is licensed for this indication and the comparators of PUVA, Azathioprine and Ciclosporin are not. Although it is not always better to use a licensed product, by placing Alitretinoin after these comparators, it appears that NICE is actively advising unlicensed in preference to licensed treatment. In addition, there is more evidence to support the use of Alitretinoin however, without the comparative studies that have not yet been performed, there is no evidence that Alitretinoin is clinically superior to the other treatments. Given that the risks associated with the use of immunosuppressant drugs (especially infection and malignancies) are higher than with a retinoid, we would suggest that Alitretinoin would be better placed after PUVA and before Azathioprine and Ciclosporin or after the patient has failed on any one of the comparators.	Comment noted. The FAD has been amended. See also FAD section 4.15

Consultee	Comment	Response
British Association of Dermatologists	3) The ACD states that treatment should be discontinued as soon as an adequate response has been achieved. Should there be guidance about when to restart Alitretinoin and whether the same thresholds apply? There would be an argument for reintroducing at a lower level of disease severity to avoid patients relapsing to pre-treatment levels.	Comment noted. See FAD section 4.16
British Association of Dermatologists	4) See executable model proforma for comments on the economic case. The financial calculations here are very dependent on whether patients are attending to see a dermatologist every 4, 6 or 12 weeks for either support or monitoring of treatment. The reality in the NHS is that there is no spare capacity for additional follow up patients. It is therefore hypothetical to make these comparisons. The appraisal should consider the capacity that would have to be put in place in order for any option to be considered. This is likely to be dermatology nurse monitoring clinics which have different costs to dermatologist clinics and thus will alter the calculation.	The Committee accepted the ERGs view that patients would be followed up at dermatology clinic every 6 weeks. See also See also FAD section 4.9

Comments from commentator organisations

Commentator	Comment	Response
Department of Health	I wish to confirm that the Department of Health has no substantive comments to make, regarding this consultation.	Comment noted
Centre for Evidence Based Dermatology	Do you consider that all of the relevant evidence has been taken into account? Yes	Comment noted

Commentator	Comment	Response
Centre for Evidence Based Dermatology	Do you consider that the summaries of clinical and cost effectiveness are reasonable interpretations of the evidence, and that the preliminary views on the resource impact and implications for the NHS are appropriate? Yes – see the recent commentary that Dr John Ingram and myself recently did of one of the pivotal studies of Alitretinoin for chronic hand eczema.	Comment noted
Centre for Evidence Based Dermatology	**Do you consider that the provisional recommendations of the Appraisal Committee are sound and constitute a suitable basis for the preparation of guidance to the NHS?** Yes – I thought they were very reasonable and balanced for a preliminary recommendation for use in the NHS (Continued)	Comment noted
Centre for Evidence Based Dermatology	Just two little points for further reflection : a) Under 1.1 bullet point 2, you sensibly state that the disease has not responded to a second line treatment such as ciclosporin, azathioprine or PUVA. Both ciclosporin and PUVA are only short term, ie. 2-4 months, treatments to try and induce a remission, whereas I was under the impression that alitretinoin was more of a longer term treatment for maintaining remission. So somewhere early on, it needs to be stated what alitretinoin is meant to be doing – is it intended to induce a remission in severe hand eczema that is unresponsive to other treatment, or is it meant to induce remission and maintain that remission for 3-6 months? In which case, direct comparison with ciclosporin or PUVA may not be totally appropriate. In reality of course, some patients with severe hand eczema are given ciclosporin for longer than 3 or 4 months, and those that do respond may then be subsequently controlled with topical treatments that might have failed previously.	Comment noted. The FAD has been amended. See also FAD section 4.15

Commentator	Comment	Response
Centre for Evidence Based Dermatology	(b) I realise that the recommended dosage of 30mgs once daily is for 12-24 weeks, but some clearer guidance on what happens after 24 weeks should be given. Do you intend that patients who have found this treatment wonderful at 24 weeks should stop at that point and wait for a subsequent relapse for further treatment courses? If so, this should be more clearly stated as I will suspect slippage will occur beyond 24 weeks unless you make it really clear.	The Committee discussed the suggestion by consultees to provide specific advice about what treatments to give after 24 weeks. It agreed that this level of detail would be outside the remit for a technology appraisal. See also FAD section 4.16
Centre for Evidence Based Dermatology	Overall, I found the advice very sensible and balanced.	Comment noted
Centre for Evidence Based Dermatology	**Are there any equality related issues that need special consideration that are not covered in the ACD?** I cannot think of any equality issues here and you have rightly pointed out the limitations of DLQI for people with physical impairments or linguisitic difficulties.	Comment noted

Comments received from members of the public

NHS professional 1	Manufacturer's submission	There is unfortunately limited trial data on therapies in hand eczema	Comment noted

NHS professional 1	Consideration of the evidence	I have a particular clinical interest in occupational contact dermatitis, which is often chronic hand eczema. In certain occupations, hand eczema can result in significant time off work. One of the benefits of this treatment is that patients may potentially return to work more rapidly.	Comment noted
NHS professional 1	Consideration of the evidence	Also, PUVA therapy involves two visits to hospital or clinic each week. Whilst some patients may choose this therapy ahead of other systemic treatments, some would prefer not to have the inconvenience of these multiple visits.	Comment noted
NHS professional 1	Consideration of the evidence	Finally, the side effect profile of ciclosporin and azathiprine is greater than with alitretinoin, so I would have thought that these might have been considered as potential therapies alongside each other, rather than ciclosporin and azathioprine first.	The Committee was aware of the adverse events related to the comparator treatments. See also FAD sections 4.3 and 4.9
NHS professional 1	Implementation	Local audit is essential and we are already looking at implementing this locally.	Comment noted
NHS professional 1	Proposed recommendations for further research	I would agree that these trials would be very useful.	Comment noted

NHS professional 2	Appraisal Committee's preliminary recommendations	I do not feel that the DLQI is necessarily applicable to isolated hand eczema and am not aware that it has been a validated tool to measure disease severity for hand eczema.	The Committee agreed that the uncertainty about the relationship between DLQI score and PGA state was too great to base recommendations on PGA state alone, and that it would be appropriate to include guidance on DLQI eligibility criteria for treatment. See also FAD section 4.12 and 4.13
NHS professional 2	Appraisal Committee's preliminary recommendations	I do not think that alitretinoin should only be available to patients who have not responded to other second line treatments. Many of these other second line agents have a significantly higher side effect profile than alitretinoin particularly significant immunosuppression with all the attendant risks. Furthermore, these other agents do not have a formal license for this indication. I think the physician should be given the opportunity to pick a second line agent on an individual basis, based on each case, with no restriction in the order in which the agents are chosen.	The FAD has been amended. See FAD section 4.15.
NHS professional 3	Appraisal Committee's preliminary recommendations	I believe a DLQI of 15 is too, especially bearing in mind a DLQI of only 10 is recommended by NICE for pts with psoriasis to receive biologic therapies which are potentially much more risky to patients and expensive. The DLQI is not especially weighted towards occupataional problems which is where pts with chronic hand eczema really suffer and this will deny many pts who need a safe effective therapy for their disease. I would prefer a lack of response to other drugs as indicator. Anyone who is not troubled by their hand eczema is not going to take ciclosporin or azathiaprine because of the risks involved	The Committee considered that psoriasis and severe chronic hand eczema could have different effects on HRQoL See FAD section 4.13.

NHS professional 4	Appraisal Committee's preliminary recommendations	I am surprised that non response to a drug like ciclosporin is required prior to considering alitretinoin as a treatment option. The toxicity of cilclosporin is far greater si I would have considered alitretnoin to be within the same cohort of second line treatments.	Comment noted. The FAD has been amended See also FAD section 4.15
NHS professional 5	Appraisal Committee's preliminary recommendations	I have done a Medline search on azathiaprine and chronic hand eczema and could not find any literature regarding its use so am surprised that it is regarded as a prerequisite for use prior to consideration of alitretinoin. Â PUVA also requires multiple hospital visits (usually twice weekly) for 10-15 weeks which is an option many working patients with hand eczema cannot persue. I am not aware that any of the suggested first line systemic therapies (aza, ciclo, PUVA) have hand eczema as a licensed indication which may have medicolegal implications when a licenced agent is now available	Comment noted. The FAD has been amended See also FAD section 4.15

NHS professional 6	Appraisal Committee's preliminary recommendations	1 Â I accept that only patients with severe impairment should receive alitretinoin, but I have two comments: A Â I am not sure how a DLQI of 15 was chosen nor what the impact of using this level would be it seems high (certainly when compared to the level required for the use of biologics in severe psoriasis) I suspect that many deserving patients who might benefit greatly from the drug would be denied it. B Â Although I accept that this is not the remit of this appraisal to judge the use of DLQI and other such measures, I have concerns that new interventions for any skin disorder will be required to meet more exacting standards than existing approaches (licensed or not) it seems incongruous, and will gradually give rise to significant anomalies.	The Committee considered that psoriasis and severe chronic hand eczema could have different effects on HRQoL See FAD section 4.13.
NHS professional 6	Appraisal Committee's preliminary recommendations	2 Â I have concerns that drugs that are not licensed for this indication, but with a significant toxicity profile, MUST be used before alitretinoin. If patients eventually move on to alitretinoin they will either have developed some complication or suffered some (potentially avoidable) adverse event, or would have failed on treatment and have experienced a longer period of distress and discomfort than might have been necessary.	The Committee was aware of the adverse events related to the comparator treatments. See also FAD sections 4.3 and 4.9

NHS professional 6	The technology	I have never been convinced that the retinoids should be singled out for the "pregnancy prevention protocol". Many drugs used in dermatology are teratogenic, but are not subject to the same level of attention doctors simply advised their patients on the risks. Furthermore, the process does not prevent pregnancy - only the patient can do that the process may detect pregnancies earlier than would otherwise be the case, but that is NOT the same and to suggest it is by using the word "prevention" is disingenuous. The manufacturers will no doubt disagree, but I think this whole charade should be dropped	Comment noted
NHS professional 6	Proposed recommendations for further research	This looks like a good idea at first sight, but none of the other agents has yet been shown to work de facto by double-blind trial. Surely, comparator studies should follow proof that something actually works?	Comment noted
NHS professional 6	Related NICE guidance	These pieces of work are useful in clinical practice I think the restrictions on the calcineurin inhibitors were understandable, but I see no reason why either should not be used first-line as an option against topical steroids in some children, nor why there is a restriction on initiation in primary care.	Comment noted
NHS professional 7	Appraisal Committee's preliminary recommendations	The DLQI required for the prescribing of alitretinoin is in excess of that required to prescribe biologicals for patients with severe psoriasis (DLQI >10). This is unreasonable and puts these patients at a disadvantage to receive efficacious treatment.	The Committee considered that psoriasis and severe chronic hand eczema could have different effects on HRQoL See FAD section 4.13.

NHS professional 7	Appraisal Committee's preliminary recommendations	The necessity to have already prescribed cyclosporin and azathioprine puts these patients at unneccesary risks. Firstly these drugs are not licenced for hand eczema and there is little evidence base supporting their use. Secondly these drugs increase the risk of skin cancers and possibly systemic malignancies. Synthetic retinoids do not have this risk and if anything protect against skin cancer and therefore there would be a logic to use alitretinoin before ciclosporin and azathioprine.	The FAD has been amended. See also FAD section 4.15
NHS professional 8	Appraisal Committee's preliminary recommendations	I think the use of the DLQI is reasonable. However I am concerned by the suggestion that azathioprine or ciclosporin should be used before the prescription of alitretinoin. These are toxic drugs which are not licensed for severe chronic hand eczema and I feel this is unethical. Patient safety must be our prime consideration.	The FAD has been amended. See also FAD section 4.15
NHS professional 9	Appraisal Committee's preliminary recommendations	DLQI of 10 is considered severe for Psoriasis, why has committee recommended DLQI of 15?	The Committee considered that psoriasis and severe chronic hand eczema could have different effects on HRQoL See FAD section 4.13.
NHS professional 9	Proposed recommendations for further research	I use a cheaper alternative retinoid Acitretin for hyperkeratotic variant of hand eczema and I am sure other dermatologists do as well. Â Acitretin is approved for use in Psoriasis and other conditions. Â Phase III trial should compare alitretinoin with Acitretin for subgroup of patients with hyperkeratotic eczema where alitretinoin is found to be Â most useful. I seldom use Ciclosporin or Azathioprine, while I do use PUVA often. I find it difficult to even consider Ciclosporin or Azathioprine for eczema limited to hands only.	Comment noted

NHS professional 10	Appraisal Committee's preliminary recommendations	The advantage of Alitretinoin is that it provides long lasting remission and lacks side effects associated with immunosuppressants such as Ciclosporin or Azathioprine. It therefore does not make any sense to me to make this treatment a third line agent after these other toxic treatments, especially given that the Alitretinoin will be stopped if there is not improvement within 12 weeks.	The FAD has been amended. See FAD section 4.15.

NHS professional 11	Appraisal Committee's preliminary recommendations	I have concerns about the requirement to use the other drugs first. Ciclosporin is significantly more toxic than alitretinoin and its use is constrained, in particular, by nephrotoxicity. Both azathioprine and ciclosporin are immunosuppressant, and PUVA is carcinogenic. Alitretinoin has none of these disadvantages. Evidence for efficacy of the other drugs in chronic hand eczema is not satisfactory. In current practice, ciclosporin is very rarely used in this indication, and azathioprine rarely. PUVA is used more often but provides only a short term benefit. Prednisolone can be highly effective but is really only suitable for very short term use and its use is usually followed by prompt relapse. Methotrexate and acitretin are also very occasionally used but on insubstantial anecdotal evidence (retinoid molecules are not interchangeable, and exhibit different efficacy/toxicity profiles). There is, therefore, no established satisfactory treatment for severe hand eczema, unless it responds to topical corticosteroids. Existing systemic treatments are probably not very effective and are certainly hazardous.	The FAD has been amended accordingly. See FAD section 4.15.
NHS professional 12	Appraisal Committee's preliminary recommendations	I do not feel it is appropriate to have a higher DLQI score (15)to start allitretinoin than for biologic use in psoriasis (10).	The Committee considered that psoriasis and severe chronic hand eczema could have different effects on HRQoL See FAD section 4.13.

NHS professional 12	Appraisal Committee's preliminary recommendations	I also feel it is v inappropriate to suggest we use cyclosporin and azathioprne pre-allitretinoin which I dont think even have licenses for use in treating hand eczema. Both these oral agents have significant side effects such that I v rarely would ever use ciclosporin for eczema or prsoriasis. I do not have an issue with use of PUVA pre allitretinoin	The FAD has been amended. See also FAD section 4.15
NHS professional 12	Consideration of the evidence	re 4.5, do ciclosporin and azathiprine have a license to treat hand eczema- if not how could the manufactureres of allitretinoin do a legitimate trial gainst these agents?	Comment noted
NHS professional 13	Appraisal Committee's preliminary recommendations	1. The DLQI value of 15 required for consideration for this treatment exceeds that recommended by NICE by patients with psoriasis (namely 10) for use of a biologic drug (a group of drugs with more serious side-effects than alitrtinoin). This is inconsistent and unfair to patients with hand dermatitis. I suggest you should alter the DLQI requirement in this context to 10.	The Committee considered that psoriasis and severe chronic hand eczema could have different effects on HRQoL See FAD section 4.13.
NHS professional 13	Appraisal Committee's preliminary recommendations	2. The second line treatment drugs suggested for use before alitretinoin can be considered have more serious potential side effects than alitretinoin. These must be familiar to you- hypertension/kidney disease with ciclosporin, liver disease/blood dyscrasias with azathioprine. As regards topical PUVA- it rarely has any effect at all in severe hand dermatitis and is a poor comparator	The FAD has been amended. See also FAD section 4.15

NHS professional 14	Appraisal Committee's preliminary recommendations	Confimation on whether alitretinoin is suitable for prescribing in primary care in England Â would be useful in light of the SMCs recommendation that alitretinoin is dispensed by a hospital-based pharmacy in Scotland. Cost pressures can stimulate requests from acute trusts for high cost drugs to be prescribed under shared care where suitable.	Comment noted
NHS professional 15	Appraisal Committee's preliminary recommendations	Unclear as to the justification of recommendation 1.1. A DLQI of 10 - as required for biologics for psoriasis would be more appropriate	The Committee considered that psoriasis and severe chronic hand eczema could have different effects on HRQoL See FAD section 4.13.
NHS professional 15	Appraisal Committee's preliminary recommendations	Other systemic treatments such as cyclosporin are as expensive and perhaps more toxic than alitretinoin. This should therefore be offered as a second line treatment, along with the other treatments mentioned.	The FAD has been amended. See also FAD section 4.15

NHS professional 16	Appraisal Committee's preliminary recommendations	It is not appropriate to consider alitretinoin oral therapy only after a patient has been treated with oral immunosuppresants and/or PUVA/UVB.These treatments have no firm evidence base for chronic hand eczema nor are they licensed.Alitretinoin is not immunosuppresant and should be considered as the first systemic therapeutic option once topical treatment has failed.Chronic hand eczema is a disabling condition, especially for manual workers, causing much time to be lost from work.It is therefore not in the patients best interest to have to proceed through unlicensed medications requiring further time off work for monitoring, before alitretionoin is prescribed.I have prescribed alitretinoin and found it to be highly effective,safe and well tolerated at 30mgs/day for 12 weeks.	The FAD has been amended accordingly. See also FAD section 4.15
NHS professional 16	The technology	From experience well tolerated at 30mgs/day for 12 weeks.	Comment noted
NHS professional 16	Manufacturer's submission	Confirms that there is no firm evidence of superiority of the comparator therapies in the treatment of CHE.	Comment noted
NHS professional 16	Section 4	Alitretinoin is clinically much more effective than current best supportive care.As a result fewer appointments in secondary care are likely to be needed and so alitretinoin is also more cost effective.	Comment noted
NHS professional 16	Proposed recommendations for further research	Do not support the proposal for comparison phase 111 trials using unlicensed immunosuppressants with poor evidence base.	Comment noted

NHS professional 17	Appraisal Committee's preliminary recommendations	I agree that alitretinoin should be used only in severe cases. I am concerned, however, about the DLQI of 15. Why is that when in other conditions, such as psoriasis, you accept a DLQI of 10?	The Committee considered that psoriasis and severe chronic hand eczema could have different effects on HRQoL See FAD section 4.13.
NHS professional 17	Appraisal Committee's preliminary recommendations	It also feels wrong to demand that we use unlicensed drugs before trying it. I agree that in many cases I may use some of those drugs first, but it should be a clinical decision, as all other treatments are unlicensed. I am sure if any of the suggested first line systemics submitted their case for a license or nice guidelines, they would not be approved, so how can we justify the decision in this guidelines?	The FAD has been amended. See FAD section 4.15.
NHS professional 17	Section 4	same comments as in Appraisal Committee's preliminary recommendations	Comment noted
NHS professional 17	Section 8	If the nice guidelines are going to put first non-licensed treatments, then the review date should be sooner, ie 2years	Comment noted
NHS professional 18	Appraisal Committee's preliminary recommendations	I am concerned that the recommendation is to use this drug as third line after immunosuppressive drugs considering that the alitretinoin side effect profile looks so innocuous.	The FAD has been amended .See also FAD section 4.15

NHS professional 18	Appraisal Committee's preliminary recommendations	Also Â I see no reason that dermatologists would have to be those with specialist expertise in CHE as the condition is easily diagnosed and has defined Â treatment options.	Comment noted. We can only issue guidance within marketing authorisation. The SPC for alitretinoin says "Toctino should only be prescribed by dermatologists, or physicians with experience in the use of systemic retinoids .".
NHS professional 19	Appraisal Committee's preliminary recommendations	A DLQI of 15 or more is unreasonable. A patient only needs a DLQI of 10 or more for treatment with the more expensive biologics for psoriasis, why should this be even higher for alitretinoin?	The Committee considered that psoriasis and severe chronic hand eczema could have different effects on HRQoL See FAD section 4.13.
NHS professional 19	Appraisal Committee's preliminary recommendations	I feel as a consultant dermatologist we should be able to make the decision when to start a systemic agent and in which order. Alitretinoin is a licensed treatment for hand eczema is is not an immunosupressant unlike the other options, I feel therefore that it should be a second line option not third. I would like to be able to use it prior to submitting the patient to unlicensed immunosupressive treatment options such as ciclosporin, if I felt it was appropriate to that patient.	The FAD has been amended. See FAD section 4.15.
NHS professional 19	Appraisal Committee's preliminary recommendations	There are only a limited number of patients that fall into the severe hand eczema category that require systemic agents, certainly nothing compared to the numbers requiring biologics for psoriasis	Comment noted

NHS professional 19	Appraisal Committee's preliminary recommendations	I agree that a period of 12 weeks to show response is adequate is sufficient.	Comment noted
Other 1	Appraisal Committee's preliminary recommendations	Severe hand eczema in my experience of 30 years never responds to Azothiaprine. There is no published evidence of hand eczema responding to this when it has not responded to potent topical steroids. 30% may respond to PUVA but relapse is common. PUVA with attendances 3 times a week, usually for 1 to 2 hours to allow application of topical psoralens is usually not compatible with gainful employment and takes at least 12 weeks for any response to be obtained.Unfortunately PUVA treatment is rarely available outside normal working hours. Ciclosporin works in about 20% of severe cases, with relapse common on discontinuation and side effects often limit its long term use. There really is a need for specialist centres to be able to prescribe Alitretinoin for those who cannot work because of their dermatitis in preference to the current second line treatments, as efficacy and safety appears to be superior.There is also a need for patients to be thoroughly investigated to exclude any missed allergens,and therefore patients with severe hand dermatitis should be referred on to regional centres for further investigation. Returning people back to work needs to be a priority.	The FAD has been amended accordingly. See FAD section 4.15.
NHS professional 20	Appraisal Committee's preliminary recommendations	DLQI is not well validated in CHE, and if included should be reduced DLQI >10 to be consistent with guidance for use of biologics in severe psoriasis Â	The Committee considered that psoriasis and severe chronic hand eczema could have different effects on HRQoL See FAD section 4.13.

NHS professional 20	Appraisal Committee's preliminary recommendations	Medicolegal concerns- why should unlicensed treatments be used ahead of licensed preparations	The FAD has been amended. See FAD section 4.15.
NHS professional 20	Appraisal Committee's preliminary recommendations	Clinicians should choose therapies based on needs of patients- the SMC guidance on this subject is far more practical and allows for better quality of patient care	Comment noted