

Basilea Comments to Appraisal Consultation Document (ACD)

Summary

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
- 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
- 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 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

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

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

1) 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
- 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
- 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
- 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
- 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

2) 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.

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.

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
- 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

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
- 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”

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

- 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 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
- 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

3) 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.

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 or cost effectiveness evidence.

- Robust clinical data demonstrates that alitretinoin is effective, well tolerated when used according to its licensed indication 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
- 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
- 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
- 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.
- 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
- 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 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

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

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”

- 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

4) Are there any equality related issues that need special consideration that are not covered in the ACD?

No.

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
- 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.