

NICE STA

Alitretinoin for the treatment of chronic eczema of the hand, refractory to steroids

Comments on the ACD from the British Association of Dermatologists

i) We do consider that all of the relevant evidence has been taken into account.

iv) We do not feel that there are any equality related issues that need special consideration that are not covered in the ACD.

ii) and iii) See comments below:

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.

2) We also have concerns regarding the ranking of Alitretinoin relative to its comparators. 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.

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.

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.

**National Institute for Health and Clinical Excellence
Centre for Health Technology Evaluation**

Pro-forma Response

Executable Model

**Alitretinoin for the treatment of chronic eczema of the hand,
refractory to steroids**

The economic model enclosed and its contents are confidential and are protected by intellectual property rights, which are owned by **Basilea Medical**. It has been sent to you for information only. It cannot be used for any other purpose than to inform your understanding of the appraisal. Accordingly, neither the model nor its contents should be divulged to anyone other than those individuals within your organisation who need to see to them to enable you to prepare your response. Those to whom you do show the documents must be advised they are bound by the terms of the Confidentiality Acknowledgement and Undertaking Form that has already been signed and returned to the Institute by your organisation.

You may not make copies of the file and you must delete the file from your records when the appraisal process, and any possible appeal, are complete. You must confirm to us in writing that you have done so. You may not publish it in whole or part, or use it to inform the development of other economic models.

The model must not be re-run for purposes other than the testing of its reliability.

Please set out your comments on reliability in writing providing separate justification, with supporting information, for each specific comment made. Where you have made an alteration to the model details of how this alteration was implemented in the model (e.g. in terms of programme code) must be given in sufficient detail to enable your changes to be replicated from the information provided. Please use the attached pro-forma to present your response.

Please prepare your response carefully. Responses which contain errors or are internally inconsistent (for example where we are unable to replicate the results claimed by implementing the changes said to have been made to the model) will be rejected without further consideration.

Results from amended versions of the model will only be accepted if their purpose is to test robustness and reliability of the economic model. Results calculated purely for the purpose of using alternative inputs will not be accepted.

No electronic versions of the economic model will be accepted with your response.

Responses should be provided in tabular format as suggested below (please add further tables if necessary).

April 2009

Issue 1 Unlicensed therapies lacking in evidence must be used before licensed therapy

Description of problem	Description of proposed amendment	Result of amended model or expected impact on the result (if applicable)
<p>According to GMC, use of unlicensed medicines should be considered where the clinician takes responsibility for an assessment that there is not a licensed more effective therapy. (Good practice in prescribing medicines 2008). This was raised by the clinical experts but not recorded in the ACD. According to GMC, the clinician prescribing off label must be satisfied that an "alternative licensed medicine would not meet the patients needs." "Be satisfied that it would better serve the patients needs than an appropriate licensed alternative"</p> <p>And "Be satisfied that there is a sufficient evidence base and experience of using the medicine to demonstrate its safety and efficacy and document the reasons for choosing the therapy in the patients' notes" and must discuss this with the patient.</p> <p>In a guideline development process alitretinoin would be more highly recommended than the comparators</p>	<p>We suggest that the clinician be given latitude to choose the most appropriate therapy for the patient based on his knowledge of the alternative therapies and considering that the alternatives are much cheaper than alitretinoin.</p> <p>A compromise might be to require that a single second line therapy (azathioprine, ciclosporin or PUVA) has been ineffective or contraindicated.</p>	<p>Insert ICER resulting from amended model. If the model has not been re-run, if appropriate, describe your expectations of how the problem might have an impact on the result</p>

<p>because the level of evidence for its use is exceeded. Put another way, the positioning alitretinoin after failure of azathioprine, ciclosporin and PUVA does not have an evidence base.</p>		
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Issue 2 Related to 1 clinical and economic case for positioning of alitretinoin

Description of problem	Description of proposed amendment	Result of amended model or expected impact on the result (if applicable)
<p>That the appraisal will make this treatment available to patients with high need disabling hand dermatitis who have failed other therapies is welcomed. Clinical experts recognised the need to restrict the use of this treatment which would have a large budget impact. However, a typical patient will have to fail a line of therapy including potent topical steroids, azathioprine, ciclosporin and PUVA which could mean a long road with much resource use before alitretinoin is used and this was not the model used in the economic assessment. Patients would typically require 12 months of ineffective therapy with loss of earnings before gaining access to alitretinoin.</p>	<p>The cost benefit of about 18-20 months of repeated therapeutic failures attended with side effects followed finally by alitretinoin could be compared to that of intermittent alitretinoin as first line therapy. There are uncertainties around the benefit of current therapies that make such assessment challenging but with sensitivity analysis based on uncertainty of the manufacturers model an estimate of saving by earlier introduction of alitretinoin in the algorithm could be decisive.</p>	<p>Insert ICER resulting from amended model. If the model has not been re-run, if appropriate, describe your expectations of how the problem might have an impact on the result</p>

<p>Receiving an effective treatment early in the algorithm of therapy will have cost, quality of life and societal benefits. Insisting on failure of all of these treatments will inevitably lead to greater use of the first line therapies which are not currently favoured because of their toxicity.</p>		
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Issue 3 Choice DLQI threshold

Description of problem	Description of proposed amendment	Result of amended model or expected impact on the result (if applicable)
<p>In earlier appraisals for anti-TNF therapy in psoriasis a DLQI >10 was accepted as evidenced by Prof A Finlay as indicative of severe QOL impairment for psoriasis requiring admission or secondary drug therapies. We have no doubt that patients with severe hand dermatitis would have DLQIs of this order but question the evidence supporting the choice of this threshold which could deny therapy to a patient with DLQI for example of 13 which would represent quite disabling disease.</p>	<p>Give details of any amendments/corrections made in sufficient detail to allow these to be reproduced</p>	<p>Insert ICER resulting from amended model. If the model has not been re-run, if appropriate, describe your expectations of how the problem might have an impact on the result</p>

(please cut and paste further tables as necessary)