

NATIONAL INSTITUTE FOR HEALTH AND CLINICAL EXCELLENCE

Final appraisal determination

Alitretinoin for the treatment of severe chronic hand eczema

This guidance was developed using the single technology appraisal (STA) process.

1 Guidance

- 1.1 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 physician's global assessment (PGA) **and**
 - a dermatology life quality index (DLQI) score of 15 or more.
- 1.2 Alitretinoin treatment should be stopped:
- as soon as an adequate response (hands clear or almost clear) has been achieved **or**
 - if the eczema remains severe (as defined by the PGA) at 12 weeks **or**
 - if an adequate response (hands clear or almost clear) has not been achieved by 24 weeks.
- 1.3 Only dermatologists, or physicians with experience in both managing severe chronic hand eczema and the use of systemic retinoids, should start and monitor treatment with alitretinoin.

- 1.4 When using the DLQI, healthcare professionals should take into account any physical, sensory or learning disabilities, or other communication difficulties that could affect the responses to the DLQI. In such cases, healthcare professionals should ensure that the DLQI continues to be a sufficiently accurate measure.

2 The technology

- 2.1 Oral alitretinoin (Toctino, Basilea Pharmaceuticals) is indicated for use in adults who have severe chronic hand eczema that is unresponsive to treatment with potent topical corticosteroids. Severe' chronic hand eczema (that is, marked signs of eczema, or oedema, fissures or functional impairment) is defined using the physician's global assessment (PGA; see section 3.2).
- 2.2 The recommended dosage is 30 mg once daily for 12–24 weeks. The dosage can be reduced to 10 mg once daily if there are unacceptable adverse effects. The summary of product characteristics (SPC) specifies that if a person still has severe disease after the first 12 weeks, stopping treatment should be considered. In the event of relapse, further treatment courses may be of benefit.
- 2.3 Alitretinoin is a derivative of retinoic acid (9-cis-retinoic acid) that binds to and activates intracellular retinoid receptors. These receptors regulate cellular differentiation and proliferation.
- 2.4 The most frequent adverse effects seen with alitretinoin include headache, dry mouth, anaemia, flushing and erythema. Increases in cholesterol and triglyceride levels (hyperlipidaemia) have also been observed. Adverse effects are generally dose related and reversible. Alitretinoin is teratogenic and therefore contraindicated in women of childbearing potential unless all of the conditions of the

Pregnancy Prevention Programme (as outlined in the SPC) are met. 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. For full details of side effects and contraindications, see the SPC.

- 2.5 Alitretinoin costs £411.43 for a pack of 30 × 30-mg capsules (excluding VAT; 'British national formulary' [BNF] edition 57). Costs may vary in different settings because of negotiated procurement discounts.

3 The manufacturer's submission

The Appraisal Committee (appendix A) considered evidence submitted by the manufacturer of alitretinoin and a review of this submission by the Evidence Review Group (ERG; appendix B).

- 3.1 The manufacturer approached the decision problem by comparing alitretinoin with ciclosporin, oral and topical PUVA (psoralen and long-wave ultraviolet radiation), and azathioprine. The population considered was adults with severe chronic hand eczema that is unresponsive to potent topical corticosteroids. The primary outcome measures outlined in the decision problem were overall severity of chronic hand eczema (as defined by the PGA), modified total lesion symptom score (mTLSS), patient's global assessment of improvement, time to response, time to relapse and a disease-specific quality of life measure, namely the dermatology life quality index (DLQI).
- 3.2 The primary outcome measure used in the clinical trials was severity of chronic hand eczema as defined by the PGA. This combined the grading of disease severity against a photographic

guide with an indication of symptoms (pruritus and/or pain) and degree of functional impairment. The PGA describes five severity states for chronic hand eczema (clear, almost clear, mild, moderate and severe), and a combined 'clear or almost clear' category was used to define response to treatment in the trials.

3.3 The manufacturer's submission presented evidence on the clinical effectiveness of alitretinoin from two multinational randomised controlled trials (RCTs): BAP0003, a 12-week phase II trial (n = 319) comparing three doses of alitretinoin (10 mg, 20 mg and 40 mg daily) with placebo; and BAP00089, a 24-week phase III trial (n = 1032) evaluating daily 10 mg and 30 mg doses of alitretinoin versus placebo. It also presented evidence from BAP00091, an extension of the BAP00089 RCT in which non-responding and responding–relapsing people were followed up for 24 weeks. In BAP00091, all people (n = 360) in BAP00089 whose eczema had not responded or who had disease relapse within 24 weeks of treatment received a further 12-week or 24-week course of either 10 mg or 30 mg of alitretinoin or placebo (people from BAP00089 who had received placebo were assigned to receive placebo again; people who had received alitretinoin were given a further course of treatment with the same dose of alitretinoin or assigned to receive placebo). All trials included people whose eczema had not responded to potent topical corticosteroids. The BAP00089 RCT included people with 'severe' eczema as defined by PGA score. The BAP0003 trial included people with either 'moderate' or 'severe' eczema as defined by PGA score.

3.4 Both RCTs found that alitretinoin treatment resulted in a greater proportion of people with hands clear or almost clear at 12 and 24 weeks compared with placebo, as assessed by PGA score and patient's global assessment of improvement. The differences were

statistically significant (although in the BAP0003 trial, only the 40 mg dose of alitretinoin gave statistically significant results compared with placebo). In the BAP00089 trial, 47.7% of people were reported as having clear or almost clear skin by week 24 of treatment with 30 mg of alitretinoin, compared with 16.6% for placebo ($p < 0.001$). The BAP00089 trial also measured rates of remission and found that among people whose eczema had responded to alitretinoin treatment, 30% treated with 30 mg and 37% treated with 10 mg relapsed during the 24-week follow-up period. The manufacturer reported that in the BAP0003 study, 26% of people whose eczema had responded to treatment with alitretinoin relapsed (mTLSS score of 75% of the baseline value) within 12 weeks of the end of the treatment.

- 3.5 In the extension study (BAP00091), participants were divided into two cohorts. Cohort A consisted of 117 people whose eczema had relapsed within 24 weeks of treatment, and a double-blind design was used. People were assigned to receive the same dose of alitretinoin as in BAP00089 or placebo; those who had received placebo in BAP00089 were again assigned to the placebo group. In this trial, 21 people were given 10 mg of alitretinoin, 49 people were given 30 mg of alitretinoin and 47 people were given placebo, for a period of 12 or 24 weeks. A statistically significantly greater proportion of people treated again with 30 mg of alitretinoin had a PGA state of hands clear or almost clear than those treated with placebo (79.6% and 8.3% respectively, $p < 0.001$). Cohort B consisted of 243 people whose eczema had not responded to treatment in the original RCT. All were given 30 mg of alitretinoin and an open-label design was used. Nearly 50% of people whose eczema had not initially responded to treatment after 24 weeks

responded to a further 12-week or 24-week course of 30 mg of alitretinoin once daily.

- 3.6 The manufacturer also provided details of subgroup analyses from the BAP00089 trial. The 30 mg dose of alitretinoin resulted in a higher proportion of people with hands clear or almost clear than placebo in people with hyperkeratotic disease (54% versus 12%), pompholyx disease (33% versus 30%), and hyperkeratotic and pompholyx disease together (33% versus 12%). It was not stated whether these differences were statistically significant.
- 3.7 The manufacturer reported that information on health-related quality of life (HRQoL) was collected only during the phase II BAP0003 study and that 51.4% of people in both treatment groups (alitretinoin and placebo) completed DLQI questionnaires. The median change in HRQoL from baseline was greater with alitretinoin than with placebo (–3 [for doses of 20 and 40 mg of alitretinoin] and –2, respectively). The findings were not statistically significant, but the manufacturer pointed out that this may have been because of the lack of statistical power of the study. The manufacturer did not include the DLQI or any other measure of HRQoL in any subsequent trials or analyses.
- 3.8 The primary source of data on adverse events in the manufacturer’s submission was the phase III RCT (BAP00089). Treatment-related serious adverse events with alitretinoin were rare (an incidence of 1% at a dose of 30 mg). The most common adverse event was headache (20% at 30 mg; 11% at 10 mg), and a small proportion of people had elevated blood triglycerides (3% at 30 mg; 1% at 10 mg) and high total cholesterol (14% at 30 mg; 3% at 10 mg). The number of people who withdrew from the trial because of adverse events was 39 (9.5%) for 30 mg of alitretinoin

and 24 (5.7%) for 10 mg of alitretinoin. The number of people who refused to continue treatment for other reasons was 16 (3.9%) for 30 mg of alitretinoin and 24 (5.7%) for 10 mg of alitretinoin.

- 3.9 The manufacturer pointed out that there were no trials that compared alitretinoin directly with any of the comparators specified in the scope for the appraisal. It explained that subsequent searches were carried out to identify trials that assessed the efficacy of PUVA, ciclosporin and azathioprine for the treatment of chronic hand eczema. This search identified 13 trials of PUVA for the treatment of chronic hand eczema, of which eight met the criteria for inclusion in the review. One trial of ciclosporin and no trials of azathioprine were identified. The manufacturer explained that a mixed-treatment comparison could not be carried out because none of the RCTs using PUVA or ciclosporin had a placebo control arm, and therefore no common link could be established between the trials of alitretinoin, PUVA and ciclosporin.
- 3.10 The manufacturer submitted a cost-effectiveness analysis from a de novo Markov-based patient-level model using a hypothetical cohort of people with severe chronic hand eczema. The demographic characteristics of the model population reflected those of the participants in the BAP00089 trial, and 15% of the women were assumed to be of childbearing potential. The model had five health states that were defined according to PGA score: severe, moderate and mild chronic hand eczema, remission (people whose chronic hand eczema was rated as 'clear' or 'almost clear' by 24 weeks), and refractory disease (people whose chronic hand eczema was rated 'moderate', 'mild' or had returned to a PGA state of 'severe' at 24 weeks). The model was designed to compare oral alitretinoin with PUVA, ciclosporin, azathioprine and best supportive care. The model had a 3-year time horizon, and a

treatment course of alitretinoin was assumed to be given for between 12 and 24 weeks at an initial dosage of 30 mg once daily.

3.11 The efficacy estimates for alitretinoin in the model were taken from the phase III clinical trial (BAP00089) for the first treatment cycle, and from cohort A of the phase III extension trial (BAP00091) for subsequent treatment cycles. Estimates of efficacy of the comparators were obtained from a panel of seven dermatologists. Data on the number of adverse events and the probabilities of dose reduction or withdrawal from treatment were informed by BAP00089 or by the manufacturer's assumptions. Time to relapse following remission was informed by the BAP00089 trial for alitretinoin and by expert clinical opinion for the comparators. For alitretinoin, the estimates of the proportion of people who move to each PGA state after initial treatment were obtained from the BAP00089 trial, and retreatment estimates were obtained from the BAP00091 trial. The corresponding estimates for the comparator interventions were obtained from expert opinion.

3.12 The utility values for all health states were derived using data collected from the BAP0003 trial to predict DLQI scores that correspond to each PGA state. A published algorithm of the relationship between DLQI scores and EQ-5D scores in people with psoriasis was then used to predict EQ5D-based utility values from DLQI scores. The model applied the utility scores associated with the 'severe' PGA state to people whose disease was rated as severe and who were still receiving treatment, and to people whose disease was deemed to be refractory. The 'moderate' and 'mild' utility scores were applied to people receiving treatment whose disease was rated moderate and mild, respectively, on the PGA scale. The utility scores for the states of 'clear' and 'almost clear' were averaged to provide a single utility score that was applied to

people whose disease was in remission. The manufacturer also provided a set of alternative utility estimates from an unpublished study by Augustin. These EQ-5D scores were predicted from the observed average DLQI scores of the people within each PGA state. Adverse events were assumed to have no impact on HRQoL.

- 3.13 It was assumed that if an adverse event occurred (either headache or hyperlipidaemia), 20% of people with headache and 40% of people with hyperlipidaemia would switch to a lower dose (10 mg of alitretinoin, once daily); treatment would continue unchanged at 30 mg of alitretinoin for the remainder of people with headache or hyperlipidaemia. It was then assumed that those people who switched to the lower dose and who experienced a subsequent adverse event had a 20% probability of withdrawal owing to headache and a 40% probability of withdrawal owing to hyperlipidaemia. The people who withdrew would enter the refractory state, and the remaining people in this group would continue treatment with 10 mg of alitretinoin. The costs associated with treatment, monitoring and adverse events were included in the model.
- 3.14 The manufacturer's original base case resulted in an incremental cost-effectiveness ratio (ICER) of £8614 per quality-adjusted life year (QALY) gained for alitretinoin compared with ciclosporin. Alitretinoin dominated PUVA. A comparison of alitretinoin with azathioprine resulted in an ICER of £10,612 per QALY gained.
- 3.15 The manufacturer carried out two subgroup analyses. The first subgroup was people with hyperkeratotic disease. For this subgroup, the manufacturer adjusted the efficacy data for alitretinoin to reflect the improved efficacy that had been observed in the BAP00089 trial predominantly in people with hyperkeratotic

disease. The second subgroup analysis was in women of childbearing potential. The efficacy was assumed to be the same in these women as in the base case, but the care of these women was assumed to incur additional costs associated with conception counselling and pregnancy testing. The consequences of the Pregnancy Prevention Programme not working were not considered.

- 3.16 The manufacturer's subgroup analyses for people with hyperkeratotic disease resulted in an ICER of £11,177 per QALY gained for alitretinoin compared with ciclosporin. Alitretinoin dominated PUVA. The comparison of alitretinoin with azathioprine resulted in an ICER of £13,174 per QALY gained. The manufacturer's subgroup analyses for women of childbearing age resulted in ICERs for alitretinoin of £9109, £11,038 and £54 per QALY gained, compared with ciclosporin, azathioprine and PUVA, respectively.
- 3.17 In response to a request for clarification from the ERG, the manufacturer submitted a revised model comparing alitretinoin with best supportive care. The manufacturer's revised base case resulted in an ICER of £12,931 per QALY gained. The ICER was £15,018 per QALY gained for people with hyperkeratotic disease and £26,013 per QALY gained for people with hyperkeratotic and pompholyx disease.
- 3.18 The manufacturer undertook a one-way sensitivity analysis of the time horizon of the revised model. Using just a 1-year (rather than a 3-year) time horizon resulted in an ICER of £21,562 per QALY gained.

- 3.19 The ERG highlighted a number of concerns with the clinical and cost effectiveness information in the manufacturer's submission, including:
- the validity of the efficacy estimates for the comparators
 - the possibility that the population and some assumptions in the model may not reflect clinical practice in England and Wales
 - the high degree of uncertainty because derived utility values were used rather than directly observed HRQoL values
 - errors in the model's visual basic for applications (VBA) code.
- 3.20 The ERG regarded the comparisons of alitretinoin with azathioprine, ciclosporin and PUVA in the original manufacturer's submission to be of limited value. This was because the efficacy data for the comparators were based on expert clinical opinion only. Although the ERG accepted that there was no appropriate clinical trial evidence, it did not think the elicitation process used was sufficiently rigorous. It therefore questioned the validity of the efficacy estimates for the comparators used in the model, and noted the absence of any quantification of the uncertainty around these estimates. The ERG therefore viewed the comparison of alitretinoin with placebo in the revised model to be of greater relevance, and focused its evaluation on this aspect of the model.
- 3.21 The ERG questioned whether the model population (people with severe chronic hand eczema as defined by PGA score) reflected the population of people with corticosteroid-refractory chronic hand eczema for whom clinicians would aim to provide treatment.
- 3.22 The ERG was unsure of the validity of some of the model assumptions. These included the assumptions that people would stop treatment as soon as their disease responded, even if this was after only 4 or 8 weeks of treatment; that all people who relapse

return to the PGA severe state, even though the time to relapse was informed by trial data that used a definition of relapse based on return to 75% baseline mTLSS; and that people receiving alitretinoin would visit a dermatologist every 4 weeks.

- 3.23 The ERG viewed the derived utility values used in the model as a major source of uncertainty for the cost-effectiveness analysis. It also considered that the utility estimates obtained using the directly observed relationship between PGA state and DLQI score from the Augustin study may be a more appropriate basis for modelling than the analysis of change in DLQI score calculated based on PGA state from the BAP0003 trial.
- 3.24 The ERG stated that there were errors in the model's VBA code. This meant that the first 4 weeks of every treatment cycle except the first cycle were omitted from the model. It also pointed out that adverse events associated with alitretinoin had been removed from the revised model that compared alitretinoin with best supportive care.
- 3.25 The ERG carried out an additional exploratory cost-effectiveness analysis using the manufacturer's original model. It explained that the results given by the manufacturer were not fully incremental, consisting of pairwise comparisons between alitretinoin and the comparators. The ERG explained that integrating the supportive care arm from the revised model into a fully incremental analysis was possible because the manufacturer removed adverse events from the revised model and did not report on the adverse-event profile associated with supportive care. The ERG's incremental analysis found that alitretinoin extendedly dominated ciclosporin, alitretinoin dominated PUVA, best supportive care dominated

azathioprine, and the comparison of alitretinoin with best supportive care resulted in an ICER of £12,931 per QALY gained.

3.26 The ERG also conducted exploratory sensitivity analyses using the manufacturer's revised model (which compared alitretinoin with best supportive care). Using the utility estimates from the Augustin study and the assumption that people (except women of childbearing potential) see a dermatologist once every 6 weeks if they are taking alitretinoin and once every 12 weeks if they are receiving best supportive care (rather than once every 4 weeks) resulted in an ICER of £27,997 per QALY gained for alitretinoin compared with best supportive care.

3.27 Using the ERG-modified VBA code so that people with relapsing disease moved to the appropriate PGA state (30.6% of people whose disease relapsed moved to the moderate state and the remainder to the severe state) resulted in an ICER of £29,864 per QALY gained for alitretinoin compared with best supportive care. Reinstating adverse events for alitretinoin resulted in an ICER of £29,200 per QALY gained for alitretinoin compared with best supportive care.

3.28 Using all modifications described in sections 3.26 and 3.27, but keeping the utility data from the original model (taken from BAP0003), resulted in an ICER of £15,084 per QALY gained for alitretinoin compared with best supportive care. Using all modifications described in 3.26 and 3.27, including the alternative utility data from the Augustin study, resulted in an ICER of £30,918 per QALY gained for alitretinoin compared with best supportive care.

3.29 Full details of all the evidence are in the manufacturer's submission and the ERG report, which are available from www.nice.org.uk/TAxxx

4 Consideration of the evidence

4.1 The Appraisal Committee reviewed the data available on the clinical and cost effectiveness of alitretinoin, having considered evidence on the nature of severe chronic hand eczema and the value placed on the benefits of alitretinoin by people with the condition, those who represent them, and clinical specialists. It also took into account the effective use of NHS resources.

Clinical effectiveness

4.2 The Committee heard from the clinical specialists and patient expert that there is a need for new treatments for people with severe chronic hand eczema that is refractory to topical corticosteroids. This is because treatment options are limited and there are no licensed treatments available. The Committee also heard that severe chronic hand eczema is a very debilitating condition. This is because it can be disfiguring, can result in severe functional limitation and may be associated with depression, anxiety and social stigma.

4.3 The Committee discussed the treatment options currently available in the UK for people with severe chronic hand eczema that is refractory to topical corticosteroids. These are the immunosuppressants ciclosporin and azathioprine, and PUVA. It heard the clinical specialists' concerns about using treatments that work by suppressing the immune system because of potential adverse effects over the longer term, such as re-activation of tuberculosis. For this reason, the clinical specialists stated that they would be cautious in their use of immunosuppressants and that such treatments would be reserved for people with the most severe symptoms. The Committee also heard from the clinical specialists about concerns over the adverse effects of comparator treatments:

for example, ciclosporin is associated with an increased risk of lymphoma and skin cancer, and PUVA is known to be carcinogenic. The Committee heard from the patient expert that alitretinoin would be well tolerated by most people, with limited short-term or long-term adverse effects that would be no worse than those of the current treatments. The clinical specialists confirmed that there was an increase in blood levels of triglycerides and cholesterol in some people using alitretinoin, but that these effects would be carefully monitored and medically managed in practice.

4.4 The Committee noted the subgroup analyses provided by the manufacturer for people with hyperkeratotic and/or pompholyx disease. However, it heard from the clinical specialists that it would be impractical to differentiate these subgroups in practice. The clinical specialists also stated that they would expect treatment with alitretinoin for severe chronic hand eczema to be started and monitored by specialist dermatologists with appropriate expertise in managing hand eczema.

4.5 The Committee discussed the clinical effectiveness of alitretinoin in treating severe chronic hand eczema and considered all of the available evidence. It agreed that an RCT comparing alitretinoin with the current treatments for severe chronic hand eczema would have been ideal. The Committee was aware that the alternative treatments for this disease generally lack a robust evidence base, and so the manufacturer was unable to conduct an indirect comparison of alitretinoin with the standard treatments. The Committee noted the trial comparing 10 mg and 30 mg doses of alitretinoin with best supportive care, which demonstrated that alitretinoin was more clinically effective than best supportive care.

The Committee therefore concluded that alitretinoin is a clinically

effective treatment for severe chronic hand eczema compared with best supportive care.

Cost effectiveness

- 4.6 The Committee discussed the plausibility of the efficacy estimates for the comparators in the manufacturer's model. The Committee heard from the ERG that using a panel of dermatologists to determine the efficacy estimates for the comparators for the model was appropriate. However, the manufacturer did not provide details of the range of opinions obtained, whether the opinions had been weighted or whether the estimates had been adjusted to exclude the effect of placebo. The Committee therefore agreed that the estimates of efficacy for the comparators in the model should be considered with caution. The Committee also heard from the clinical specialists that the efficacy estimates for the comparators in the manufacturer's model did not reflect experience in clinical practice – in particular, azathioprine is considered to be more clinically effective than best supportive care. The specialists stated that in their experience some people's eczema would respond adequately to one of the available comparator treatments. The Committee noted comments from consultees on the side effects of treatment and the weak evidence base for azathioprine, ciclosporin and PUVA. Overall, the Committee concluded that the evidence base for the potential comparators azathioprine, ciclosporin and PUVA was weak and highly contentious. It agreed that an analysis of the cost effectiveness of alitretinoin compared with azathioprine, ciclosporin and PUVA could not be reliably considered further, given the present state of knowledge. It would therefore only consider the revised economic model comparing alitretinoin with best supportive care.

- 4.7 The Committee noted that the manufacturer's base case for 30 mg of alitretinoin compared with best supportive care and the corresponding ERG analysis both gave ICER estimates of approximately £13,000 per QALY gained. The Committee noted that this analysis included discontinuing treatment as soon as an adequate response (defined as hands clear or almost clear) was achieved, or after 12 weeks if the symptoms were still classed as severe, or after 24 weeks if an adequate response (hands clear or almost clear) was not achieved.
- 4.8 The Committee noted that the ERG had explored the following modifications to the manufacturer's model:
- People (except women of childbearing potential) would see a dermatologist once every 6 weeks with alitretinoin and once every 12 weeks with best supportive care.
 - The VBA code was modified so that people with disease moved to an appropriate PGA state (30.6% of people with relapsing disease moved to the moderate state and the remainder to the severe state).
 - Adverse events associated with alitretinoin treatment were reinstated from the original model.
- 4.9 The Committee discussed the ERG's assumptions and modifications. Firstly, it considered the assumption in the manufacturer's model that people would stop treatment before 12 weeks if an adequate response was achieved. The Committee heard from the clinical specialists that this assumption did reflect clinical practice in the UK and that people receiving alitretinoin would be seen by a dermatologist every 6 weeks. The Committee therefore accepted this assumption. The Committee then discussed whether people would be treated again only when the condition had relapsed to a severe state. The Committee heard from the clinical

specialists that they may find it difficult not to begin treatment again before a person's hands had returned to the severe state. The Committee therefore accepted the ERG's assumption of earlier retreatment in a proportion of people. Finally, the Committee accepted that the adverse events associated with alitretinoin treatment needed to be reinstated in the revised model. The Committee noted that the modelling of the adverse events did not capture all monitoring and treatment related to cardiovascular risk or outcomes related to long-term effects that may result from increased blood lipid levels. However, the Committee acknowledged that, because modelling was plausible only to compare alitretinoin with best supportive care, long-term adverse effects of currently used treatments (such as an increased risk of cancer) were also not included in the modelling. For the same reason, the high cost of PUVA was not included in the economic evaluation.

- 4.10 The Committee discussed the relative merits and disadvantages of the methods used to estimate utility values in the BAP0003 trial and the Augustin study. The Committee acknowledged that both studies were subject to a high degree of uncertainty, as both estimated utilities indirectly. 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. Instead, the manufacturer used a two-stage process to obtain utility estimates via DLQI scores for PGA states. In comparison, the Augustin study measured DLQI scores directly in groups of people defined according to their PGA state. However, the Augustin study identified a higher utility value for mild disease than for the state of hands clear or almost clear, which the Committee noted was counterintuitive.

- 4.11 The Committee noted the sensitivity analyses provided by the ERG, and that using some of the ERG's plausible assumptions would lead to small increases in the ICERs. However, it also noted that the major driver of the model was the choice of the utility values, with a much bigger utility gain from moving from the severe PGA state to the hands clear or almost clear state in the BAP0003 study (0.33) than in the Augustin study (0.14). The Committee noted that including all modifications suggested by the ERG and using the original utility values (derived from the BAP0003 trial) increased the ICER for alitretinoin compared with best supportive care to £15,000 per QALY gained. Including all modifications suggested by the ERG and using the utility values from the Augustin study increased the ICER to £31,000 per QALY gained.
- 4.12 The Committee then noted the concerns expressed by the patient expert and clinical specialists that the likely impact of chronic hand eczema on quality of life for people whose eczema is classified as severe may have been underestimated in the Augustin study (that is, the DLQI score estimated for the PGA severe state may not accurately reflect the impact of eczema in people who would be considered as candidates for alitretinoin in practice). In the absence of more robust data, 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. The Committee also agreed that the benefits of moving from the state of severe chronic hand eczema to the state of hands clear or almost clear would be considerable.
- 4.13 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. The Committee discussed what DLQI score was appropriate to define eligibility for treatment with alitretinoin. The Committee considered concerns raised by consultees that a DLQI score of 15 was too high, but thought that this score reflected the deterioration in quality of life produced by a condition affecting the hands that is severe as defined by the PGA. The Committee noted comments from consultees advocating a DLQI score of 10, in line with the current eligibility criteria for biological treatments for psoriasis. However, the Committee considered that psoriasis and severe chronic hand eczema could have different effects on HRQoL. It also agreed, on the basis of the testimony of the patient expert, that severe chronic hand eczema is likely to be associated with a particularly high DLQI score.

4.14 The Committee discussed the implications for the cost effectiveness of alitretinoin of using different DLQI thresholds. It noted that the benefit of alitretinoin had been established in a population with severe disease for whom the manufacturer had calculated a DLQI score of 15. It concluded that the economic case had therefore been made for this population. The Committee therefore concluded that treatment with alitretinoin for people whose eczema is sufficiently severe to result in a DLQI score of 15 or more would represent a cost-effective use of NHS resources.

4.15 The Committee discussed the place of alitretinoin in the pathway of care. It heard that the different comparator treatments could be effective in achieving an adequate response in some people with severe chronic hand eczema. However, the Committee agreed that it was not appropriate to make recommendations about the place of alitretinoin in the pathway of care because robust cost-effectiveness estimates were not available for alitretinoin compared with any active comparator treatments. It also noted that

azothiaprine and ciclosporin, although licensed for related conditions, do not have a marketing authorisation for severe chronic hand eczema. In addition, the Committee noted the concerns of consultees about the adverse effects associated with comparator treatments and the lack of RCT evidence of their effectiveness in treating severe chronic hand eczema.

4.16 The Committee discussed comments from consultees that treatment should not be stopped if the eczema remains severe (as defined by the PGA) at 12 weeks, because a longer time period would be needed to assess a response to treatment. However, it noted that the SPC for alitretinoin specifies that discontinuation of treatment should be considered if symptoms are still classed as severe at 12 weeks, and that such treatment discontinuation was included in the cost-effectiveness analysis. The Committee agreed with the suggestion from consultees to state in the guidance that treatment with alitretinoin should be stopped if an adequate response (hands clear or almost clear) has not been achieved by 24 weeks. The Committee also 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.

4.17 The Committee also discussed whether only dermatologists with specialist experience in managing severe hand eczema should start and monitor treatment with alitretinoin. The Committee noted consultee comments that other clinical staff should be included, as this would enable people to receive treatment more quickly. The Committee acknowledged that specialist nurses could have an important role in the management of severe chronic hand eczema, but agreed that guidance on who should start and monitor treatment with alitretinoin should reflect the marketing authorisation

for the drug. Therefore it is recommended that only dermatologists, or physicians with experience in both managing severe hand eczema the use of systemic retinoids, should start and monitor treatment with alitretinoin.

4.18 In considering the evidence and reaching its conclusions, the Committee was aware of NICE's duties under the equalities legislation, and considered whether those duties required it to alter or to add to its recommendations in any way. The Committee was aware that a number of the questions in the DLQI focus on aspects that depend on physical activity, such as shopping, working in the home or garden, or sport. The DLQI would therefore need to be used judiciously in people with a physical disability to take account of their lower baseline level of physical activity. Furthermore, sensory or learning disabilities, or other communication difficulties, could also affect the responses to the DLQI. The Committee agreed that in such cases, healthcare professionals should ensure that the DLQI continues to be a sufficiently accurate measure.

4.19 The Committee additionally heard from the clinical specialists that there may be people who, for cultural reasons, will be unable to comply with some aspects of treatment of severe chronic hand eczema (for example, wearing gloves or not carrying out certain household tasks that expose them to known irritants). However, the Committee noted that the SPC for alitretinoin states that it should not be prescribed if the patient's eczema can be adequately controlled by standard measures, including skin protection and avoidance of allergens and irritants. Therefore it was not possible for the Committee to consider this group separately.

5 Implementation

5.1 The Secretary of State and the Welsh Assembly Minister for Health and Social Services have issued directions to the NHS on implementing NICE technology appraisal guidance. When a NICE technology appraisal recommends use of a drug or treatment, or other technology, the NHS must provide funding and resources for it within 3 months of the guidance being published. If the Department of Health issues a variation to the 3-month funding direction, details will be available on the NICE website. The NHS is not required to fund treatments that are not recommended by NICE.

5.2 NICE has developed tools to help organisations put this guidance into practice (listed below). These are available on our website (www.nice.org.uk/TAXXX). [NICE to amend list as needed at time of publication]

- Slides highlighting key messages for local discussion.
- Costing report and costing template to estimate the savings and costs associated with implementation.
- Implementation advice on how to put the guidance into practice and national initiatives which support this locally.
- Audit support for monitoring local practice.

6 Recommendations for further research

- 6.1 The Committee recommends that phase III trials should be conducted that compare alitretinoin with ciclosporin, azathioprine and PUVA in people who have severe chronic hand eczema that is unresponsive to treatment with potent topical corticosteroids.
- 6.2 The Committee recommends that a study should be conducted that estimates utility values using directly observed health-related quality of life values (such as EQ-5D scores) in people with severe chronic hand eczema that is unresponsive to treatment with potent topical corticosteroids.

7 Related NICE guidance

- Tacrolimus and pimecrolimus for atopic eczema. NICE technology appraisal guidance 82 (2004). Available from www.nice.org.uk/TA82
- Frequency of application of topical corticosteroids for eczema. NICE technology appraisal guidance 81 (2004). Available from www.nice.org.uk/TA81

8 Review of guidance

- 8.1 The guidance on this technology will be considered for review in August 2012. The Guidance Executive will decide whether the technology should be reviewed based on information gathered by NICE, and in consultation with consultees and commentators.

Ken Stein

Vice Chair, Appraisal Committee

July 2009

Appendix A: Appraisal Committee members and NICE project team

A *Appraisal Committee members*

The Appraisal Committee is one of NICE's standing advisory committees. Its members are appointed for a 3-year term. A list of the Committee members who took part in the discussions for this appraisal appears below. The Appraisal Committee meets three times a month except in December, when there are no meetings. The Committee membership is split into three branches, each with a chair and vice chair. Each branch considers its own list of technologies, and ongoing topics are not moved between the branches.

Committee members are asked to declare any interests in the technology to be appraised. If it is considered there is a conflict of interest, the member is excluded from participating further in that appraisal.

The minutes of each Appraisal Committee meeting, which include the names of the members who attended and their declarations of interests, are posted on the NICE website.

Professor Keith Abrams

Professor of Medical Statistics, University of Leicester

Dr Ray Armstrong

Consultant Rheumatologist, Southampton General Hospital

Dr Jeff Aronson

Reader in Clinical Pharmacology, University Department of Primary Health Care, University of Oxford

Dr Darren Ashcroft

Reader in Medicines Usage and Safety, School of Pharmacy and Pharmaceutical Sciences, University of Manchester

Professor David Barnett (Chair)

Professor of Clinical Pharmacology, University of Leicester

Dr Peter Barry

Consultant in Paediatric Intensive Care, Leicester Royal Infirmary

Dr Mark Chakravarty

External Relations Director – Procter & Gamble Pharmaceuticals & Personal Health, Oral Care Europe

Dr Martin Duerden

Medical Director, Conwy Local Health Board

Mrs Eleanor Grey

Lay member

Mr Terence Lewis

Lay member, Mental Health Consultant, National Institute for Mental Health in England

Professor Gary McVeigh

Professor of Cardiovascular Medicine, Queen's University, Belfast

Dr Ruairidh Milne

Senior Lecturer in Public Health, National Coordinating Centre for Health Technology

Dr Neil Milner

General Practitioner, Tramways Medical Centre, Sheffield

Dr John Pounsford

Consultant Physician, Frenchay Hospital, Bristol

Dr Stephen Saltissi

Consultant Cardiologist, Royal Liverpool University Hospital

Dr Lindsay Smith

General Practitioner, East Somerset Research Consortium

Mr Roderick Smith

Finance Director, West Kent Primary Care Trust

Mr Cliff Snelling

Lay member

Professor Ken Stein (Vice Chair)

Professor of Public Health, Peninsula Technology Assessment Group (PenTAG), University of Exeter

Professor Andrew Stevens

Professor of Public Health, Department of Public Health and Epidemiology, University of Birmingham

Dr Rod Taylor

Associate Professor in Health Services Research, Peninsula Medical School, Universities of Exeter and Plymouth

Ms Nathalie Verin

Health Economics Manager, Boston Scientific UK and Ireland

Mr Colin Watts

Consultant Neurosurgeon, Addenbrooke's Hospital, Cambridge

Mr Tom Wilson

Director of Contracts and Information Management and Technology, Milton Keynes PCT

B NICE project team

Each technology appraisal is assigned to a team consisting of one or more health technology analysts (who act as technical leads for the appraisal), a technical adviser and a project manager.

Helen Tucker

Technical Lead

Joanna Richardson

Technical Adviser

Jeremy Powell

Project Manager

Appendix B: Sources of evidence considered by the Committee

A The Evidence Review Group (ERG) report for this appraisal was prepared by the Centre for Reviews and Dissemination (CRD), University of York:

- Paulden M, Rodgers M, Griffin S et al. Alitretinoin for the treatment of severe chronic hand eczema, March 2009

B The following organisations accepted the invitation to participate in this appraisal as consultees and commentators. They were invited to comment on the draft scope, the ERG report and the appraisal consultation document (ACD). Organisations listed in I were also invited to make written submissions. Organisations listed in II, III and IV had the opportunity to give their expert views. Organisations listed in I, II and III also have the opportunity to appeal against the final appraisal determination.

I. Manufacturer/sponsor:

- Basilea Pharmaceuticals

II. Professional/specialist and patient/carer groups:

- British Association of Dermatologists
- British Contact Dermatitis Society
- Royal College of Nursing
- Royal College of Physicians
- Skin Care Campaign

III. Other consultees:

- Department of Health
- Welsh Assembly Government

IV. Commentator organisations (did not provide written evidence and without the right of appeal):

- British National Formulary
- Cochrane Skin Group, Centre of Evidence-based Dermatology, University of Nottingham
- Department of Health, Social Services and Public Safety for Northern Ireland
- NHS Quality Improvement Scotland

C The following individuals were selected from clinical specialist and patient expert nominations from the non-manufacturer/sponsor consultees and commentators. They gave their expert personal view on alitretinoin by attending the initial Committee discussion and providing written evidence to the Committee. They were also invited to comment on the ACD.

- Dr Graham Johnston, Consultant Dermatologist, Leicester Royal Infirmary, nominated by the British Association of Dermatologists – clinical specialist
- Dr Anthony Ormerod, Reader in Dermatology, University of Aberdeen, nominated by the British Association of Dermatologists – clinical specialist
- Andrew Langford, Chief Executive, the Skin Care Campaign, nominated by the Skin Care Campaign – patient expert