

NATIONAL INSTITUTE FOR HEALTH AND CLINICAL EXCELLENCE

Alitretinoin for the treatment of severe chronic hand eczema

Premeeting briefing

This briefing presents major issues arising from the manufacturer's submission, Evidence Review Group (ERG) report and statements made by consultees and their nominated clinical specialists and patient experts. Please note that although condensed summary information is included for ease of reference, this briefing should be read in conjunction with the full supporting documents.

The manufacturer was asked to provide the following information:

- **further details of the trials identified in the systematic review, including the inclusion and exclusion criteria for each study**
- **clarification of the efficacy and safety results for the psoralen and UVA treatment (PUVA) trials identified**
- **clarification of which trials in the review collected quality-of-life data**
- **clarification of monthly response and relapse rates for the placebo arms of all the randomised controlled clinical trials (RCTs) identified**
- **clarification of the results for the subgroup (hyperkeratotic and pompholyx) populations and further details of the additional safety assessment undertaken**
- **further details of the methodology employed in the mixed treatment comparison**
- **the inclusion of a supportive care arm in the economic model**
- **further details of the methodology used to obtain the utility estimates in the economic model**
- **clarification of the definition of relapse used in the model and how time to relapse was operationalised**
- **analysis of relapse using a 50% (rather than 75%) of baseline modified total lesion symptom score (mTLSS)**

- **clarification of the assumptions used in the model and whether the model contained any additional hidden data.**

Licensed indication

Oral alitretinoin (Toctino, Basilea) 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 is defined by using the physician's global assessment (PGA) or marked signs of dermatitis, or oedema, fissures or functional impairment.

The recommended dose range is 10–30 mg once daily, and treatment may be given for 12–24 weeks, depending on response. Discontinuation of therapy should be considered for patients who still have severe disease after the initial 12 weeks of treatment. In the event of relapse, patients may benefit from further treatment courses. Alitretinoin should not be prescribed if the patient's eczema can be adequately controlled by standard measures, including skin protection, avoidance of allergens and irritants, and treatment with potent topical corticosteroids. Alitretinoin is teratogenic and therefore contraindicated in women of childbearing potential unless all of the conditions of the Pregnancy Prevention Programme are met.

Key issues for consideration

Clinical effectiveness

- What is the Committee's view on the plausibility of the efficacy estimates for alitretinoin from the RCTs, particularly in view of the observed rates of withdrawal?
- Does the Committee believe the definition of relapse used in the RCTs is appropriate and does it view the need to repeat treatment reflects current clinical practice in England and Wales?

- Considering that the RCTs were of up to 48 weeks duration, what is the Committee's view on the likely long-term efficacy of alitretinoin as a potentially life-long intermittent therapy?
- Does the Committee view the subgroup data as being robust enough to support guidance for people with different types of severe chronic hand eczema?

Cost effectiveness

- What is the Committee's view on the plausibility of the efficacy estimates for the comparator interventions used in the economic evaluation?
- What is the Committee's view on the appropriate utility estimates to be used in the cost effectiveness analysis?
- What is the Committee's view on the implementation of the decision analytic model used to carry out the cost effectiveness analysis?
- What is the Committee's view on the validity of the assumptions in the model? For example, in the model, treatment is discontinued if there has been no response to treatment at 4 and 8 weeks, whereas the summary of product characteristics (SPC) states that discontinuation of therapy should be considered after 12 weeks of treatment.
- Does the Committee believe that for people receiving best supportive care the cost of ongoing treatment with topical corticosteroids should be included in the model?
- What is the Committee's view on how often people would be reviewed by a dermatologist when receiving either treatment with alitretinoin or best supportive care in current clinical practice in England and Wales?
- What is the Committee's view on the plausibility of the cost-effectiveness estimates in the manufacturer's revised model given that adverse events have been omitted for the alitretinoin arm?
- Taking into account the exploratory analyses and corrections of the ERG, is the Committee satisfied that the estimates of the incremental cost-effectiveness of alitretinoin compared with best supportive care are robust?

1 Decision problem

1.1 *Decision problem approach in the manufacturer's submission*

Population	Adults with severe chronic hand eczema that is unresponsive to topical corticosteroids.
Intervention	Alitretinoin within its licensed indication.
Comparators	Ciclosporin Oral and topical PUVA Azathioprine
Outcomes	The primary efficacy measure for therapeutic response – Physician's global assessment (PGA) of overall chronic hand eczema severity Modified total lesion symptom score (mTLSS) Patient's global assessment of improvement (PaGA) Time to response Time to relapse Disease-specific quality of life measure (dermatology life quality index – DLQI) Safety and tolerability
Economic evaluation	The cost effectiveness of treatment is assessed in terms of incremental cost per quality-adjusted life year (QALY) with quality adjustments made using a mapping function relating changes in the DLQI and the EQ-5D. The model considers the use of standard therapies over 3 years with sensitivity analysis run over 1, 6, 10 and 20 years. Costs are considered from an NHS perspective in the base-case economic model analysis.
Subgroups to be considered	People with different forms of chronic hand eczema, such as hyperkeratotic hand eczema, and women of child-bearing potential.

1.2 *Evidence Review Group comments*

1.2.1 Population

The ERG judged that the population specified matched that in the appraisal scope and the licensed indication. However the ERG pointed out that in clinical practice people with either 'moderate' or 'severe' CHE as defined by the PGA measure may often be offered treatment with alitretinoin (for further

details, see page 12 of the ERG report) because some people with a moderate PGA score would still be diagnosed with severe disease and may qualify for treatment with alitretinoin as per licence (marked signs of dermatitis, or oedema, fissures, or functional impairment). In other words, the diagnosis of severe CHE is not reliant on the patient being rated as PGA 'severe'.

1.2.2 Intervention

The ERG concluded that the description of the intervention in the decision problem reflected the scope and the SPC.

1.2.3 Comparators

The ERG judged that the inclusion of ciclosporin, azathioprine and oral and topical PUVA was in accordance with the NICE scope and reflects clinical practice in England and Wales. The ERG explained that it had requested that best supportive care be included in the economic model. The ERG identified that in the manufacturer's revised model, alitretinoin was compared with placebo, with both groups receiving supportive treatments in the form of emollients and dermatologist visits, but not topical corticosteroids. The ERG considered on the basis of the opinion of its clinical adviser that the exclusion of the use of topical corticosteroids may not reflect current clinical practice.

1.2.4 Outcomes

The ERG judged that all outcomes in the manufacturer's submission (except the definition of relapse) matched that in the appraisal scope and the licensed indication, and were appropriate for the NHS. The definition of relapse used in the manufacturer's submission was an mTLSS score of 75% of the baseline value. The ERG pointed out that people with mTLSS scores just less than 75% are also likely to have severe chronic hand eczema. Results of the analysis indicated that the outcome of time to relapse was sensitive to changes in this threshold.

1.2.5 Economic evaluation

The ERG concluded that the manufacturer's approach to economic modelling in the decision problem was reasonable, although errors were identified in the way the model was executed.

1.2.6 Subgroups

The ERG did not make any comments on the appropriateness of the defined subgroups in the scope. However, the ERG did note that that the main trial BAP00089 was not powered to consider sub-groups and, in particular, the 'pompholyx only' group is very small, and that no definitive conclusions about the effects of alitretinoin on subgroups should be drawn from this trial.

2 Clinical-effectiveness evidence

2.1 *Clinical effectiveness in the manufacturer's submission*

The manufacturer identified two RCTs and an extension of one of the RCTs that met the criteria for inclusion in the review. These were a phase II trial comparing three doses of alitretinoin (10 mg, 20 mg and 40 mg) with placebo (BAP0003), a phase III trial evaluating 10 mg and 30 mg daily doses of alitretinoin versus placebo (BAP00089), and an extension of trial BAP00089 in which people with non-responding and responding–relapsing eczema were followed up (BAP00091). All people whose eczema did not respond during BAP00089 were allocated to receive 30 mg of alitretinoin daily. All trials involved people whose eczema was unresponsive to topical corticosteroids.

The BAP00089 RCT included people with a 'severe' PGA score and the BAP0003 trial included people with either a 'moderate' or 'severe' PGA score. Both RCTs were multinational studies conducted in a number of EU countries and Canada.

Both RCTs found that more people had clear or almost clear hands at 12 and 24 weeks when taking alitretinoin compared with placebo, as assessed by both the physician’s (PGA) and patient’s (PaGA) global assessments. The difference was statistically significant (table 1).

Table 1 Main results of the two included RCTs comparing alitretinoin with placebo (Intention to treat population)

Study	N	Population	Treatment duration/ dose	PGA % (p value) Hands clear or almost clear ALI vs PLA	PaGA % Hands clear or almost clear ALI vs PLA	Median % change in score from baseline (p value) ALI vs PLA
BAP00089 (phase III)	1032	Severe CHE refractory to topical steroids	24 weeks/ 30 mg	47.7 vs 16.6 (< 0.001)	40.0 vs 15.0 (< 0.001)	75 vs 39.0 (<0.001)
			24 weeks/ 10 mg	27.5 vs 16.6 (< 0.001)	24 vs 15 (< 0.02)	56 vs 39 (< 0.001)
BAP0003 (phase II)	319	Moderate to severe CHE refractory to topical steroids	12 weeks/ 40 mg	53 vs 27 (< 0.001)	43 vs 12 (< 0.001)	70.5 vs 25.0 (<0.001)
			12 weeks/ 10 mg	39 vs 27 (ns)	29 vs 12 (0.014)	59 vs 25 (0.03)
ALI, alitretinoin; CHE, chronic hand eczema; PaGA, patient’s global assessment; PGA, physician’s global assessment; PLA, placebo.						

The BAP00089 trial also measured rates of remission and found that among people who had responded to alitretinoin treatment, 35% for 30 mg and 28% for 10 mg remained in remission during the 24-week follow-up period.

The manufacturer also provided details of the BAP00089 trial subgroup analysis. Alitretinoin 30 mg had a greater rate of PGA-measured response than placebo in people with hyperkeratotic disease (54% vs 12%), both

hyperkeratotic and pompholyx disease (33% vs 12%) and pompholyx disease (33% vs 30%) (for further details, see page 47 of the manufacturer's submission).

The manufacturer explained that in the BAP0003 study, 26% of responders to treatment with alitretinoin had disease relapse (mTLSS score of 75% of the baseline value) within 12 weeks after the end of the treatment.

In the extension study (BAP00091), patients were split into two cohorts. Cohort A consisted of 117 people who had disease relapse within 24 weeks of treatment, and a double-blind design was used. A statistically significantly greater number of people retreated with 30 mg alitretinoin had a PGA of hands clear or almost clear than those given placebo (79.6% vs 8.3%, $p < 0.001$). Cohort B consisted of 243 people whose disease did not respond to treatment in the original RCT, and an open-label design was used. Nearly 50% of people whose disease had not initially responded to treatment after 24 weeks were responsive to a further 12–24-week course of once-daily 30 mg alitretinoin.

The manufacturer concluded that extended treatment courses beyond 24 weeks may be beneficial for some people.

2.1.1 Health-related quality of life

The manufacturer explained that information on health-related quality of life (HRQoL) was collected during the phase II study (BAP0003) and that 51.4% of people in both treatment groups completed DLQI questionnaires. The median within-patient change in HRQoL from baseline was greater with alitretinoin than with placebo (-3 vs -2). The manufacturer explained the findings were not statistically significant, but pointed out that this may be due to the lack of statistical power of the study. The manufacturer did not include the DLQI or any other measure of health related quality of life in any subsequent trials or analyses (for further details, see page 28 of the ERG report).

2.1.2 Adverse events

The primary source of data on adverse events in the manufacturer's submission came from the phase III RCT (BAP00089), which compared 10 mg and 30 mg doses of alitretinoin for treatment duration of 24 weeks. Treatment-related serious adverse events were rare (1% at the 30 mg dose). The most common adverse effect was headache (20%, 30 mg and 11%, 10 mg), and a small proportion of people had elevated blood triglycerides (3%, 30 mg and 1%, 10 mg) and high cholesterol (14% 30mg, 3% 10mg and 3% placebo) (for further details, see pages 67–8 in the manufacturer's submission).

2.1.3 Mixed-treatment comparison

The manufacturer pointed out that there were no trials that included all the treatment options. The manufacturer 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. The manufacturer explained that 13 trials of PUVA in chronic hand eczema were identified, of which 8 met the criteria for inclusion in the review. One trial of ciclosporin and no trials of azathioprine were identified. (For further details of the characteristics of these studies, see pages 55–7 of the manufacturer's submission). However, 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 link could be established between the trials of alitretinoin, PUVA and ciclosporin.

2.2 Evidence Review Group comments

The ERG noted that the manufacturer provided a detailed description of their search strategy. The ERG carried out an independent search, which did not identify any additional RCTs that should have been included in the reviews, for alitretinoin or any of the comparator interventions. The ERG viewed the

manufacturer's approach to validity assessment of the RCTs included in the review as generally adequate (for further details, see pages 17–18 of the ERG report).

The ERG viewed the BAP00089 trial on which the manufacturer based its primary evaluation of the clinical effectiveness of alitretinoin as a generally well-conducted placebo-controlled trial. However, the ERG noted there were high numbers of withdrawals, a lack of clear evidence for the reported subgroup effects and unexplained inconsistencies between PGA and PaGA scores (for further details, see page 24 of the ERG report). The ERG explained that people with PGA-defined moderate disease might be treated with alitretinoin in clinical practice, but the phase II trial that was carried out in this population (BAP0003) did not include the licensed dose of 30 mg.

The ERG pointed out that there does not appear to be direct clinical evidence on the effectiveness and safety of alitretinoin beyond 48 weeks. The ERG explained that given the very high rate of withdrawals (25.5% in BAP00089) and the fact that people responding at 12 weeks were observed for a maximum of 36 weeks, the average time over which people were actually observed is likely to be considerably shorter than 48 weeks.

The ERG explained that response–remission was primarily defined in terms of PGA state, but relapse was defined as an mTLSS score in which a four-point scale was used to grade seven different signs and symptoms of chronic hand eczema and a score of 75% of the baseline value was used. The manufacturer states that this figure was considered by dermatologists to reflect the usual definition of relapse - requires re-treatment with systemic agents or phototherapy. However, clinical advice to the ERG indicated that the choice of 75% of baseline mTLSS score as a threshold was arbitrary and might be considered a high threshold in the context of re-treatment decisions. The ERG asked the manufacturer to assess the sensitivity of the results to other thresholds for retreatment, such as 50% of baseline mTLSS.

With regard to the evidence for the comparator technologies specified in the decision problem, the ERG noted that direct evidence for their effectiveness was very limited in quantity, of poor quality and limited relevance. A multiple treatment comparison based on empirical evidence was therefore impossible.

2.3 *Statements from professional/patient groups and nominated experts*

The statements from clinical specialists note that chronic hand eczema is usually treated in primary care and that topical corticosteroids are used to treat the inflammatory aspects of chronic hand eczema. The clinical specialists also stated that people with chronic hand eczema that is refractory to topical corticosteroids would be referred to secondary care and be given topical PUVA (which would require twice-weekly visits to hospital over a 2–3-month period) or systemic therapy (immunosuppressants or retinoid therapy), all of which have their own advantages and disadvantages. The clinical specialists stated that there is little evidence to support these therapies, but there is clinical consensus that some people will have a good response to these therapies but in an unpredictable way.

The statements note that dermatologists are trained and competent with treating people using oral retinoids, but have very little experience of using alitretinoin. The clinical experts were concerned about the issue of teratogenesis and judged that care could be shared with a specialist dermatology nurse to supervise a pregnancy prevention plan. Clinical specialists also emphasised that correct diagnosis is important because other conditions are similar to hand eczema, such as psoriasis and some fungal infections.

The clinical specialists viewed alitretinoin as potentially very beneficial for hyperkeratotic eczema because it is usually treated with retinoid-based therapies in clinical practice. Alitretinoin was also believed to be particularly beneficial for people with occupationally induced chronic hand eczema who

are unable to leave their job (for example, for socioeconomic reasons) and for people from ethnic groups that have a higher incidence of hypertension or renal disease because alitretinoin would not be contraindicated, unlike some other available therapies. The statements noted that if significant numbers of people were treated with alitretinoin, additional dermatology clinic staff would be needed.

The statements noted that the main disadvantages with alitretinoin compared with currently available treatments for people with chronic hand eczema refractory to topical corticosteroids were:

- the risk of hyperlipidaemia and hypertriglyceridaemia and the subsequent need to monitor fasting lipids;
- the teratogenicity of alitretinoin and the subsequent need for a pregnancy prevention plan; and
- the increased risk of thyroid dysfunction and the subsequent need for monitoring.

It is believed that alitretinoin would be tolerated by the majority of people, but that people would need regular advice and support due to its side-effect profile.

Professional organisations explained that the advantages of alitretinoin compared with PUVA for people with chronic hand eczema refractory to topical corticosteroids were:

- the absence of long-term cancer risk (including skin cancer);
- the absence of a requirement for a specialist operator for therapy;
- longer treatment course; and
- less frequent visits to hospital.

Clinical specialists explained that the main advantages of alitretinoin compared with immunosuppressant therapy for people with chronic hand eczema refractory to topical corticosteroids were the absence of risk of

hypertension and nephrotoxicity (associated with cyclosporin) and reduced need for monitoring and visits to hospital.

No statements from patient organisations were received.

3 Cost effectiveness

3.1 Cost effectiveness in the manufacturer's submission

The manufacturer explained that a systematic search was undertaken, but no existing cost-effectiveness studies were identified.

The manufacturer submitted a de novo economic model. The model was a Markov-based patient-level model using a cohort of people with severe chronic hand eczema with demographic characteristics reflecting those of the BAP0089 trial (that is, the average characteristics were: age 48 years; weighing 81 kg; 57% male; and 15% of the women were assumed to be of child-bearing potential). The model had five health states that are defined according to the PGA score: severe, moderate and mild chronic hand eczema, remission and refractory disease.

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. People were assumed to stop alitretinoin treatment as soon as a response was achieved (including a response after 4–8 weeks), without finishing the 12-week course of treatment. The model was designed to compare oral alitretinoin with PUVA, ciclosporin, azathioprine and best supportive care. People who remained in the severe PGA state after 12 weeks were assumed to withdraw from treatment and enter the refractory state. People with chronic hand eczema rated PGA clear or almost clear by 24 weeks were deemed to be in remission, while those with a moderate or mild PGA score or those whose disease had returned to the PGA severe state at 24 weeks were assumed to be refractory. People in remission were assumed to relapse to a severe PGA state after a median time of 24 weeks. At this point the model assumed that a further treatment course

with alitretinoin was given under the same circumstances as the first course, although the transition probabilities between states were updated to reflect that it was retreatment.

Throughout the model, if either headache or hyperlipidaemia occurred, it was assumed that for some people the dosage would be reduced to 10 mg once daily but that for others the dosage would remain the same. If a further adverse event occurred while on the lower dosage, it was assumed that some people would withdraw from treatment and enter the refractory state, while the remaining people would continue treatment. It was assumed that only one adverse event could occur in each 4-week period. The model did not use a half-cycle correction (because of uncertainty surrounding transitions through the model) and had a 3-year time horizon. The treatment cycle was assumed to follow a similar pattern for the comparator treatments.

The efficacy estimates in the model for alitretinoin were taken from the phase III clinical trial (BAP00089) for the first treatment cycle and from the follow-up cohort A of the phase III trial (BAP00091) for subsequent treatment cycles. Estimates for the comparator interventions were derived from a panel meeting of seven dermatologists (for further details, see page 100 of the manufacturer's submission). Data on the number of adverse events and the probabilities of dose reduction or withdrawal from treatment were informed by either the clinical trial (BAP00089) or by the manufacturer's assumptions (for further details, see pages 90–2 of the manufacturer's submission). Time to relapse following remission was informed by the BAP00089 trial in the case of alitretinoin and by clinical opinion for the comparators. The estimates for the proportion of people in each disease state were based on expert opinion. Transition probabilities were based on data from the alitretinoin RCTs.

Table 2 contains details of the efficacy estimates used in the manufacturer's model, taken from the manufacturer's response to the request for clarification (for further details, see pages 104–5 of the clarification response).

Table 2 Efficacy estimates for the comparator interventions

Ciclosporin	Disease severity			
Week	Clear/almost clear	Mild	Moderate	Severe
4	10%	10%	10%	70%
8	30%	20%	20%	30%
12	50%	10%	10%	0%
16	50%	10%	10%	0%
PUVA				
Week	Clear/almost clear	Mild	Moderate	Severe
4	0%	0%	10%	90%
8	15%	5%	10%	70%
12	40%	5%	5%	50%
16	50%	10%	10%	30%
Azathioprine				
Week	Clear/almost clear	Mild	Moderate	Severe
4	0%	0%	0%	100%
8	0%	0%	5–10%	90–95%
12	0%	10%	40%	50%
16	5%	15%	30%	0%
20	5%	20%	25%	0%
24	10%	20%	20%	0%
48	10%	10%	10%	0%

Table 2 shows that it was estimated that of the people with severe chronic hand eczema whose disease was refractory to topical corticosteroids, after 16 weeks of treatment, 50% would have disease response (hands clear or almost clear) with ciclosporin, 50% with PUVA and 5% with azathioprine.

3.1.1 Estimates of the proportion of people who would relapse (return to 75% baseline chronic hand eczema severity) with comparator therapies

For ciclosporin it was estimated that 30% of people would relapse 4 weeks after completing treatment, 50% would relapse after 8 weeks and 80% would relapse after 12 weeks.

For PUVA, it was estimated that 10% of people would relapse 4 weeks after completing treatment, 20% after 8 weeks, 40% after 12 weeks, 60% after 16 weeks, and 80% after 20 weeks.

For azathioprine, the manufacturer explained that the panel of dermatologists had estimated 2–3 months to relapse, but that this was difficult to estimate.

3.1.2 Subgroups

The manufacturer carried out two subgroup analyses. For the first subgroup (people with hyperkeratotic disease) the manufacturer adjusted the efficacy data for alitretinoin to reflect the improved efficacy (table 7.2.2 in the manufacturer's submission) that had been observed in trials predominantly of people with hyperkeratotic disease treated with alitretinoin (for further details, see page 85 of the manufacturer's submission and page 7 of the clarification response).

The second subgroup analysis was in women of child-bearing potential. The efficacy was assumed to be the same in these patients as in the base case, but these patients were assumed to incur additional costs associated with conception, pregnancy consultation and testing (for further details, see page 89 of the manufacturer's submission).

3.1.3 Health-related quality of life

The utilities for all states were derived using data collected from the BAP0003 trial and a previously published algorithm examining the relationship between DLQI and EQ-5D in people with psoriasis (for further details, see pages 102–3 of the manufacturer's submission). The model applied the utility scores associated with PGA state 'severe' to people whose disease was rated PGA severe and who were still receiving treatment and to those people whose disease was deemed to be refractory. The 'moderate' and 'mild' utility scores were applied to those people receiving treatment whose disease was rated moderate to mild on the PGA scale. The utility scores for 'clear' and 'almost clear' were averaged to provide a single utility score which was applied to people whose disease was in remission. Adverse events were assumed to have no impact on HRQoL.

3.1.4 Resources and costs

The costs associated with patient treatment, monitoring and adverse events were identified in the manufacturer's submission (for a summary of these, see pages 40–1 of the ERG report).

3.1.5 Results

The base-case results, as presented in the original model in the manufacturer's submission for the comparator treatments are summarised in table 3 below.

Table 3 Base-case results of the manufacturer's economic analysis from the original model (tables 7.3.1–3, pages 111–13 in the manufacturer's submission)

Comparison	Incremental QALY	Incremental cost	ICER
Alitretinoin vs ciclosporin	0.21	£1,808	£8,614
Alitretinoin vs PUVA	0.20	-£94	-£469 (alitretinoin dominant)
Alitretinoin vs azathioprine	0.24	£2,583	£10,612
ICER, incremental cost-effectiveness ratio; PUVA, psoralen and UVA treatment; QALY, quality-adjusted life year.			

3.1.6 Results of the manufacturer's one-way sensitivity analyses in the original modelling

The following changes to the model resulted in a more than twofold increase in the cost-effectiveness estimate for alitretinoin compared with:

- ciclosporin: decreasing the time horizon to 1 year (ICER = £15,936), using alternative utility estimates (ICER = £16,759), reduce efficacy estimate for alitretinoin by 30% (ICER = £19,833), increase efficacy of ciclosporin by 50% (ICER = £13,503)
- PUVA: increasing the time horizon (6 years ICER = £1614, 10 years ICER = £2171, 20 years = ICER=£2160), decreasing the PUVA cost

estimate to £49 per session (ICER = £3649), increase efficacy of PUVA by 50% (ICER = £8281).

The following changes to the model resulted in incremental cost-effectiveness ratios (ICERs) of more than £20,000 per QALY gained:

- Change the incremental utility to 0.12 for alitretinoin compared with azathioprine (ICER = £22,312).
- Reduce the efficacy of alitretinoin by 30% but the efficacy for azathioprine remains unchanged (ICER = £20,063).
- Increase the efficacy of azathioprine by 50% (ICER = £26,746).

The manufacturer did not submit a probabilistic sensitivity analysis because there was considerable uncertainty regarding the clinical efficacy data for comparators in this evaluation (for further details, see page 108 of the manufacturer’s submission).

3.1.7 The manufacturer’s revised model of alitretinoin compared with best supportive care

In response to clarification the manufacturer submitted a revised model, this differed from the original model in that it did not contain any adverse events and the one-way sensitivity analysis did not include changes to efficacy or utility estimates. See table 4 below for a summary of the results.

Table 4 Base-case results of the economic analysis from the revised manufacturer’s model

Comparison	Incremental QALY	Incremental cost	ICER
Alitretinoin vs BSC	0.22	£2,780	£12,931
Alitretinoin vs BSC (hyperkeratotic population)	0.19	£2,834	£15,018
Alitretinoin vs BSC (hyperkeratotic/pompholyx population)	0.08	£2,300	£26,013
BSC, best supportive care; ICER, incremental cost-effectiveness ratio; QALY, quality-adjusted life year.			

3.1.8 Results of the one-way sensitivity analysis of the revised model

The manufacturer undertook a one-way sensitivity analysis of the model time horizon. Only using a 1-year time horizon resulted in a cost-effectiveness estimate greater than £20,000 per QALY (ICER = £21,562).

3.2 *ERG comments*

The ERG said that the use of a de novo economic model was appropriate.

The ERG questioned whether the model population (people with severe chronic hand eczema measured by PGA score) reflected the population of people with corticosteroid-refractory chronic hand eczema for whom clinicians would aim to provide treatment.

The ERG regarded the comparisons of alitretinoin against azathioprine, ciclosporin and PUVA made in the original submission to be of limited value given that the efficacy data for those comparators were based on expert clinical opinion only, albeit in the absence of appropriate clinical trial evidence. The ERG did not, however, judge the elicitation process used to be sufficiently rigorous, and therefore were skeptical of the validity of the efficacy estimates for the comparator interventions used in the model, and noted the absence of any quantification of uncertainty in the elicited beliefs (for further details, see page 43 of the ERG report). The ERG therefore viewed the comparison of alitretinoin with placebo made in the revised model to be of greater relevance and therefore focused their evaluation on this aspect of the model.

.The ERG was unsure of the validity of the following model assumptions:

- people would stop treatment as soon as their disease responded, even if this was after only 4 or 8 weeks of treatment
- all people who relapse are assumed to return to the PGA severe state, even though the time to relapse is informed by trial data that used a definition of relapse based on return to 75% baseline mTLSS

- all ciclosporin patients move to the refractory state after 80 weeks, even though some are in remission at 76 weeks and people in remission after receiving alitretinoin would not be treated with topical corticosteroids (for further details, see pages 47–8 of the ERG report)
- that people receiving alitretinoin would visit the dermatologist every 4 weeks.

The ERG also considered that the utility estimates derived using the directly observed relationship between PGA states and DLQI from the [REDACTED] study (presented in the manufacturer's sensitivity analysis- for further details, see page 79 of the manufacturer's submission) could be viewed as a more appropriate basis for modelling than the analysis of change in DLQI based on PGA from the BAP0003 trial (see page 102 of the manufacturer's submission). The ERG noted that both studies suggested some correlation between increasing mean DLQI and increasing severity of PGA state (see tables 6.9.1 and 6.9.2 on pages 78-79 of the manufacturer's submission), but mean DLQI scores for the matching PGA states differed between the studies, and the trend was less pronounced in the [REDACTED] study than in BAP00003.

The ERG highlighted some differences between the [REDACTED] and BAP0003 trial which might have contributed to the disparity in mean DLQI scores studies (for further details, see page 28-9 of the ERG report):

- In BAP0003, 65% of the population had PGA-moderate CHE
- There were a different proportion of men and women in [REDACTED] et al ([REDACTED] men compared to 74% in BAP0003)
- There was a longer duration of disease (9.2 years compared to 4.1 in BAP0003)
- [REDACTED]
[REDACTED] study might be viewed as more appropriate than

basing that calculation on the predicted DLQI scores for the patients included in BAP00091 (where DLQI was predicted using the algorithm developed in the BAP0003 trial (for further details, see pages 58-9 of the ERG report).

- The use of derived utility values, whether from [REDACTED] or BAP0003 and BAP00091, is a major source of uncertainty for the cost-effectiveness analysis. The ERG highlighted that the most appropriate basis for assessing the effectiveness of alitretinoin would be directly observed health-related quality of life values (such as EQ-5D scores) in the relevant patient population.

The ERG also pointed out that the assumption in the manufacturer's submission that all patients will 're-enter the severe state' upon relapse (see page 96 of the manufacturer's submission) did not appear to be implemented correctly in the model's visual basic for applications (VBA) code (for further details, see page 49 of the ERG report). This was because the first 4 weeks of every treatment cycle, except the initial cycle, are omitted from the model. Also, the clinical trial data used to inform the response to second-line treatment are derived from a patient population with less severe disease than that modelled, and so may overestimate the response rates in patients who restart treatment once their chronic hand eczema is rated as PGA severe (for further details, see pages 44–5 and 49–50 of the ERG report).

The ERG pointed out that adverse events associated with alitretinoin had been removed from the model of alitretinoin compared with best supportive care (for further details, see pages 45–6 of the ERG report).

3.2.1 ERG's exploration of the manufacturer's original model

The ERG explained that the results given by the manufacturer were not fully incremental, consisting of pair-wise comparisons between alitretinoin and each of the other treatment comparators. The ERG carried out an incremental analysis, the results are presented in Table 5 below.

Table 5 Results of the ERG incremental analysis of the manufacturer’s original analysis combined with placebo (table 14, page 58 of the ERG report)

Treatment	Cost (£)	QALYs	ICER (£ per QALY)
Azathioprine	852.08	1.76	Dominated by BSC
BSC*	611.83	1.79	N/A
Ciclosporin	1,690.83	1.80	Extendedly Dominated by alitretinoin
PUVA	3,641.94	1.80	Dominated by alitretinoin
Alitretinoin* (30 mg)	3,391.98	2.01	12,931 (vs BSC)

BSC, best supportive care; ICER, incremental cost-effectiveness ratio; QALY, quality-adjusted life year.

*These results integrate the supportive care arm given in the revised model into a fully incremental analysis. The ERG explained this was straightforward because the manufacturer removed adverse events from the revised model and did not report on the adverse-event profile associated with best supportive care. Removing adverse events from the original model allowed a fully incremental analysis to be carried out with the inclusion of the supportive care arm from the revised model.

3.2.2 The results of the ERG scenario analyses using the revised model submitted by the manufacturer (see table 16, page 61 of the ERG report)

The use of the revised utility estimates based on the [REDACTED] study and the assumption that people (except women of child-bearing potential) see a dermatologist once every 6 weeks with alitretinoin and once every 12 weeks with supportive care (rather than once a month) resulted in an ICER of £27,997 for alitretinoin compared with best supportive care.

Using the ERG-modified VBA code so that patients with disease relapse moved to the appropriate PGA state (30.6% of patients with relapsing disease moved to the moderate state and the remainder to the severe state) resulted in an ICER of £29,864 for alitretinoin compared with best supportive care.

Reinstating adverse events for alitretinoin resulted in an ICER of £29,199 for alitretinoin compared with best supportive care.

Using all the above modifications, but keeping the utility data from the original model, resulted in an ICER of £15,084 for alitretinoin compared with best supportive care.

Use of all the above modifications and the alternative utility data based on the [REDACTED] study resulted in an ICER of £30,918 for alitretinoin compared with best supportive care.

3.2.3 The results of the ERG subgroup analysis

Using only a potentially child-bearing women population resulted in an ICER of £29,739 for alitretinoin compared with best supportive care.

Using a men-only population resulted in an ICER of £27,689 for alitretinoin compared with best supportive care.

3.3 Further considerations following premeeting briefing teleconference

At the premeeting briefing teleconference no additional issues were considered.

4 Authors

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Appendix A: Sources of evidence considered in the preparation of the premeeting briefing

- A The ERG (ERG) report for this appraisal was prepared by Centre for Reviews and Dissemination (CRD) University of York:
- Paulden M et al, Alitretinoin for the treatment of severe chronic hand eczema, March 2009.
- B Submissions or statements from the following organisations:
- I Manufacturer/sponsor
- Basilea Medical
- II Professional/specialist, patient/carer and other groups:
- British Association of Dermatologists
 - British Contact Dermatitis Society
 - Royal College of Physicians
- C Additional references used: None