Alitretinoin for the treatment of severe chronic hand eczema

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Abstract

This paper presents a summary of the evidence review group (ERG) report into the clinical effectiveness and cost-effectiveness of alitretinoin for the treatment of adults with severe chronic hand eczema refractory to topical steroid treatment in accordance with the licensed indication, based upon the evidence submission from Basilea Pharmaceuticals Ltd to the National Institute for Health and Clinical Excellence (NICE) as part of the single technology appraisal process. The clinical evidence came from a single placebo-controlled randomised controlled trial of daily treatment with alitretinoin for 12–24 weeks, with follow-up for a further 24 weeks, in patients with severe chronic hand eczema (CHE) unresponsive to topical steroids. A statistically significantly greater proportion of patients using alitretinoin achieved the primary end point of clear or almost clear hands by week 24 than did those with placebo. Dose-dependent headache was the most commonly reported adverse event in patients treated with alitretinoin. Serious adverse events were rare, but alitretinoin was associated with increases in both total cholesterol and triglycerides, which has implications for risks of future cardiovascular events. The manufacturer submitted a de novo decision analytic model to estimate, over a time horizon of 3 years, the cost-effectiveness of alitretinoin versus the other relevant comparators identified by NICE. In response to the points of clarification put to it by the ERG regarding the initial submission, the manufacturer provided additional evidence and a revised decision analytic model with a 'placebo' arm. In the manufacturer's original

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Discussion of ERG reports is invited. Visit the HTA website correspondence forum (www.hta.ac.uk/correspond).

submission to NICE, the base-case incremental cost-effectiveness ratios (ICERs) reported for alitretinoin were £8614 per quality-adjusted life-year (QALY) versus ciclosporin, –£469 per QALY versus psoralen + UVA (with alitretinoin dominant) and £10,612 per QALY versus azathioprine. These ICERs decreased as the time horizon was extended in sensitivity analyses. In patients with hyperkeratotic CHE and in women of child-bearing potential, the ICER remained below £20,000. When the health-related quality of life (HRQoL) values used in the model were replaced with those derived from an alternative study, these ICERs increased significantly (to £22,312 per QALY for alitretinoin versus azathioprine). In the revised model, alitretinoin was reported to have an ICER of £12,931 per QALY gained versus supportive care (placebo). However, the model underestimates the costs of treatment associated with alitretinoin. The manufacturer assumed that patients receiving alitretinoin visited the dermatologist every 4 weeks and ceased treatment as soon as they responded to it. If, in practice, patients would receive treatment for longer than this, then the manufacturer's model will have significantly underestimated the costs to the NHS. Additional analyses undertaken by the ERG produced ICERs close to £30,000 per QALY gained for alitretinoin versus supportive care. This was largely due to uncertainty surrounding the impact of alitretinoin on HRQoL. The placebo-controlled trials conducted to date have established that alitretinoin can be efficacious for the treatment of severe CHE refractory to topical steroids, but longer term follow-up of trials or the implementation of registries is required to better establish the longer term efficacy or safety of alitretinoin. NICE recommended the use of alitretinoin for patients with severe CHE and a Dermatology Life Quality Index (DLQI) score of at least 15. Treatment was recommended to be stopped as soon as an adequate response was observed, or if CHE remained severe at 12 weeks, or if response was inadequate at 24 weeks.

Introduction

The National Institute for Health and Clinical Excellence (NICE) is an independent organisation within the NHS that is responsible for providing national guidance on the treatment and care of people using the NHS in England and Wales. One of the responsibilities of NICE is to provide guidance to the NHS on the use of selected new and established health technologies, based on an appraisal of those technologies.

NICE's single technology appraisal (STA) process is specifically designed for the appraisal of a single product, device or other technology, with a single indication, where most of the relevant evidence lies with one manufacturer or sponsor.[1] Typically, it is used for new pharmaceutical products close to launch. The principal evidence for an STA is derived from a submission by the manufacturer/sponsor of the technology. In addition, a report reviewing the evidence submission is submitted by the evidence review group (ERG); an external organisation independent of NICE. This paper presents a summary of the ERG report for the STA entitled 'Alitretinoin for the treatment of severe chronic hand eczema'.[2]

Description of the underlying health problem

It is estimated that between 0.5% and 0.7% of the general population suffer from severe chronic hand eczema (CHE).[3] Management of hand eczema includes avoidance of allergens and irritants, skin protection measures and use of topical corticosteroids where necessary. Patients with chronic disease may require treatment with the most potent steroid preparations available because drug penetration is impaired by significant hyperkeratosis of the hands. Approximately 50% of affected patients will be refractory to treatment with topical corticosteroids.[3] These patients suffer from painful cracks and blisters susceptible to secondary infections, itching and bleeding, which can limit manual dexterity and prevent employment. The visibility of disease, need for frequent visits to the doctor and regular application of greasy topical agents, all add to the burden of the disease. Severe CHE carries a debilitating social stigma which is associated with an impaired quality of life, comparable to that seen in patients with generalised eczema and psoriasis.[4] In addition, hand eczema has been shown to be a major cause of prolonged sick leave and has been reported to lead to job loss.[5] Patients with CHE have a poor prognosis; it is a self-perpetuating condition with a long-lasting and chronically relapsing course.[6] No licensed treatment options are available for these patients. The unlicensed options used in clinical practice include immunosuppressants, such as ciclosporin and azathioprine, and phototherapy.

Scope of the evidence review group report

Oral alitretinoin (9-*cis*-retinoic acid, Toctino®), an endogenous retinoid, is indicated for use in

adults who have severe chronic hand eczema that is unresponsive to treatment with potent topical corticosteroids. The recommended dose range for alitretinoin is 10–30 mg once daily. A treatment course of alitretinoin should be started at the higher dose of 30 mg and 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.

The ERG report presents an assessment of the manufacturer's (Basilea Pharmaceuticals Ltd) submission to NICE on the use of alitretinoin (within the context of the licensed indication) in adults with severe chronic hand eczema refractory to topical steroid treatment and attempted to compare it with the stated comparators: psoralen + UVA (PUVA), ciclosporin and azathioprine.

Evidence for the efficacy of alitretinoin came primarily from a phase III randomised placebo-controlled double-blinded trial and an extension study.[7,8] The primary report outcome was 'clear' or 'almost clear' hands as assessed by the physician's global assessment (PGA). Other outcomes reported included signs and symptoms of the disease, as measured by the modified Total Lesion Symptom Score (mTLSS), the patient global assessment (PaGA) of disease severity, and adverse events.

The manufacturer developed a de novo decision analytic model to estimate, over a time horizon of 3 years, the cost-effectiveness of alitretinoin versus the other relevant comparators identified by NICE. In response to the points of clarification put to them by the ERG regarding the initial submission, the manufacturer provided additional evidence and a revised decision analytic model. The model estimated costs and quality-adjusted life-years (QALYs) from the perspective of the NHS and Personal Social Services (PSS), which is consistent with NICE guidelines.

Methods

The ERG report comprised a critical review of the evidence for the clinical evidence and cost-effectiveness of the technology based upon the manufacturer's/sponsor's submission to NICE as part of the STA process.

As well as a detailed critical appraisal of the manufacturer's submission, the ERG completed searches of its own to take into account some of the issues raised in its review of the manufacturer's search strategies and also modified the manufacturer's decision analytic model to examine the impact of altering some of the key assumptions.

Results

Summary of submitted clinical evidence

The main clinical effectiveness data were derived from a single placebo-controlled randomised controlled trial (RCT) of daily treatment with alitretinoin for 12–24 weeks (BAP00089), with follow-up for a further 24 weeks, in patients with severe CHE unresponsive to topical steroids. In this study, a statistically significantly greater proportion of patients using alitretinoin achieved the primary end point of clear or almost clear hands (as assessed by the PGA) by week 24 than did those with placebo: 48% with alitretinoin 30 mg ($p < 0.001$); 28% with alitretinoin 10 mg ($p < 0.005$); 16.6% with placebo. The severity of disease was also reduced when assessed by patients using the PaGA. The majority of patients who responded to alitretinoin treatment remained in remission during the 24-week follow-up period. A high PGA response rate to retreatment with alitretinoin was observed, although a similarly high response to placebo was observed among first-line 'placebo responders', and PGA results were not consistent with the PaGA evaluations. The main effectiveness data from all reported trials are presented in *Table 1*.

Dose-dependent headache was the most commonly reported adverse event in patients treated with alitretinoin, with rates of 20% in the alitretinoin 30-mg group and 11% in the 10-mg group. Serious adverse events were rare, but alitretinoin was associated with increases in both total cholesterol and triglycerides, which has implications for risks of future cardiovascular events.

No direct comparisons of alitretinoin with any of the relevant treatment comparators (PUVA, ciclosporin or azathioprine) were available. Nor were any trial data on these comparators available to permit formal indirect comparisons of alitretinoin with its comparators.

Summary of submitted cost-effectiveness evidence

The manufacturer submitted a de novo decision analytic model to estimate, over a time horizon of 3 years, the cost-effectiveness of alitretinoin versus

TABLE 1 *Primary and secondary study end points from controlled trials included in manufacturer's submission*

Trial	Treatment	Response: PGA[a] (95% CI)	Response: PaGA[a]	Symptom change: mTLSS[b] (95% CI)	Health-related quality of life: DLQI[c]	Relapse rate[d]
BAP00089	Placebo	16.6% (11.8 to 22.4)	15%	–39% (–47 to –27)		
	10 mg	27.5% (23.3 to 32.1), $p < 0.005$[e]	24%, $p < 0.02$[e]	–56% (–63 to –50), $p < 0.001$[e]		29.6% (at 6 months)
	30 mg	47.7% (42.7 to 52.6), $p < 0.001$[e]	40%, $p < 0.001$[e]	–75% (–79 to –69), $p < 0.001$[e]		37.4% (at 6 months)
BAP00091 (Cohort A)	Placebo (previously placebo)	69.2%	23.1%	–40.3%		
	Placebo (previously 10 mg)	10%				
	Placebo (previously 30 mg)	8.3%				
	10 mg	47.6%	75.5%	–78.8%, $p = 0.02$[f]		
	30 mg	79.6%	38.1%	–67.4%, $p < 0.001$[f]		
BAP00091 (Cohort B)	30 mg	46.2%	42.4%	–49.7%		
BAP00003	Placebo	27%	12%	–25% (–42 to –14)	–2	26%
	10 mg	39%, $p =$ ns[e]	29%, $p = 0.014$[e]	–59% (–73 to –42), $p = 0.03$[e]	–2	25%
	20 mg	41%, $p =$ ns[e]	34%, $p = 0.002$[e]	–52% (–73 to –42), $p = 0.002$[e]	–3	26%
	40 mg	53%, $p < 0.001$[e]	43%, $p < 0.001$[e]	–59% (–80 to –44), $p < 0.001$[e]	–3	32.5%
BAP00200	10 mg	12.5% (1.6, to 38.3)				
	30 mg	62.5% (35.4 to 84.8)				

CI, confidence interval; DLQI, Dermatology Life Quality Index; mTLSS, modified Total Lesion Symptom Score; ns, not stated; PaGA, patient global assessment; PGA, physician's global assessment.
a Percentage with clear/almost clear hands.
b Median change in mTLSS score from baseline.
c Median within-patient change from baseline to week 12.
d Percentage with mTLSS score 75% of baseline value.
e Compared with placebo.
f Compared with placebo (previously 30 mg).

the other relevant comparators identified by NICE. In response to the points of clarification put to it by the ERG regarding the initial submission, the manufacturer provided additional evidence and a revised decision analytic model.

In the manufacturer's original submission to NICE, the base-case incremental cost-effectiveness ratios (ICERs) reported for alitretinoin were £8614 per QALY versus ciclosporin, –£469 per QALY versus PUVA (with alitretinoin dominant) and £10,612 per QALY versus azathioprine. These ICERs decreased as the time horizon was extended in sensitivity analyses. In patients with hyperkeratotic CHE and in women of child-bearing potential, the ICER remained below £20,000. When the health-related quality of life (HRQoL) values used in the model were replaced with those derived from an alternative study, these ICERs increased significantly (to £22,312 per QALY for alitretinoin versus azathioprine). In the revised model, which compared alitretinoin only to placebo, the ICER was reported to be £12,931.

Commentary on the robustness of submitted evidence

Strengths

The manufacturer's submission incorporated a full systematic review of the literature of the effects of alitretinoin in severe CHE refractory to topical steroid treatment. The main findings are derived from a single generally well-conducted placebo-controlled RCT and an associated follow-up trial of retreatment.

The submission also included a review of the literature of the cost-effectiveness of alitretinoin in severe CHE. As no existing economic evaluations were identified, the manufacturer undertook a de novo economic evaluation in order to compare alitretinoin with comparators identified by NICE, consisting of ciclosporin, PUVA and azathioprine. The model estimated costs and QALYs from the perspective of the NHS and PSS, which is consistent with NICE guidelines.

Weaknesses

At present, there is a relatively limited quantity of evidence available on the clinical effects of alitretinoin. Although the RCTs presented were adequately designed and conducted, the ERG noted high numbers of withdrawals from the main efficacy trial, a lack of clear evidence for the reported subgroup effects and unexplained inconsistencies between PGA and PaGA scores in the retreatment trial.

Limitations in the submitted evidence primarily impacted on the generalisability of the manufacturer's conclusions to clinical practice. The main observed effects of alitretinoin were relative to placebo with additional emollients where required. Therefore it remains unknown to what extent alitretinoin is effective relative to emollients and topical corticosteroids combined (the current first-line treatment choice).

For inclusion in the main RCT (BAP00089), diagnosis as 'severe' on the PGA outcome measure was a pre-requisite. In clinical practice, it seems likely that a proportion of patients considered for treatment with alitretinoin would fall into the less severe PGA 'moderate' state. There is some evidence from the phase II trial BAP00003 that a 'PGA moderate' CHE population would respond to alitretinoin treatment, but there is no evidence for the effects of the 30 mg dose in this population.

The cost-effectiveness section of the submission had major shortcomings. The efficacy estimates for treatments other than alitretinoin were based on expert clinical opinion only. While the use of expert opinion may be justified where trial data do not exist to inform the relevant parameters, it should be elicited in a methodologically rigorous manner. The ERG remains unconvinced that this elicitation process generated reliable estimates of the efficacy of each of the comparator treatments. The estimates of HRQoL were derived in a two-stage prediction model that incorporated an algorithm developed for patients with psoriasis. Direct evidence of the impact of alitretinoin on HRQoL was only available from the phase II trial, which did not include the recommended 30 mg starting dose of alitretinoin and showed no difference between alitretinoin (10 mg, 20 mg and 40 mg) and placebo.

Serious issues remain around the implementation of the model in EXCEL. Inspection of the VBA (Visual Basic for Applications) code indicated that a number of the assumptions given in the written submission were not implemented correctly. In particular, the first 4 weeks of every subsequent treatment cycle were omitted. The definition of relapse used in the model did not correspond to that used in the relevant clinical trials. As a consequence the estimated costs and health outcomes presented by the manufacturer may be regarded as unreliable. The ERG attempted to amend the model to provide more appropriate estimates of the ICERs, but in some cases this was not feasible.

Furthermore, the model originally submitted to NICE did not include a 'supportive care' (or 'placebo') arm and the treatment effects for alitretinoin were not placebo adjusted; as such, the model did not address whether alitretinoin was a cost-effective alternative to supportive care. Consequently, the ERG does not regard the ICERs generated by the manufacturer's original model as providing a reliable indication of the cost-effectiveness of alitretinoin compared with each of the comparators considered.

Areas of uncertainty

Crucially, there is no evidence on the efficacy and safety of alitretinoin beyond around 48 weeks. Given the chronic recurring nature of CHE, longer term follow-up is required to detect potentially rare adverse events and possibly to characterise the cardiovascular risks posed by the observed increase in cholesterol levels associated with alitretinoin treatment.

There was also no direct or indirect evidence presented for the clinical effects of alitretinoin relative to the comparators specified in the scope

for the treatment of CHE (PUVA, ciclosporin and azathioprine). No additional evidence was identified by the ERG.

A change in threshold for the definition of 'relapse' from 75% to 50% of baseline mTLSS substantially reduced the time to relapse observed in the 30-mg alitretinoin group. If clinicians were to consider retreatment for less severe 'relapses', this would have clinical and cost implications in terms of the reduced time between treatment periods.

As the relief of symptoms and consequent improvement in HRQoL are the aims of treatment for chronic hand eczema, the ERG believes that the economic evaluation of alitretinoin should be based on good evidence of the improvement in HRQoL offered by alitretinoin. However, the estimates used in the submission are subject to a great deal of uncertainty due to the two-stage prediction employed and the paucity of direct observations in the population of interest.

The ERG modified the manufacturer's model to examine the impact of altering some of the key assumptions. However, as the manufacturer did not undertake a probabilistic sensitivity analysis, the combined impact of uncertainty in the inputs to the economic model on the overall decision uncertainty could not be evaluated.

Conclusions

In response to a request from the ERG, the manufacturer provided a revised model with a 'placebo' arm, and the comparison of alitretinoin with placebo made in this revised model is of greater merit given the more reliable efficacy data in the comparator arm. In this analysis, alitretinoin was reported to have an ICER of £12,931 per QALY gained versus supportive care (placebo). However, the omission of adverse events from this revised model, in combination with a number of other factors, means that the model underestimates the costs of treatment associated with alitretinoin.

TABLE 2 *Results of additional analyses comparing the impact of two alternative health-related quality of life estimates provided by the manufacturer*

	BAP0003 utility data			Augustin utility data		
Treatment	**Cost**	**QALYs**	**ICER (per QALY)**	**Cost**	**QALYs**	**ICER (per QALY)**
Analysis 1: Base-case reanalysis						
Supportive care	£481.40	1.79		£481.40	2.05	
Alitretinoin (30 mg)	£3369.21	2.01	£13,431.67	£3369.21	2.16	£27,996.89
Analysis 2: Patients relapse into PGA moderate and severe						
Supportive care	£481.60	1.78		£481.60	2.05	
Alitretinoin (30 mg)	£3509.33	1.99	£14,525.65	£3509.33	2.15	£29,864.39
Analysis 3a: Potentially child-bearing women only						
Supportive care	£481.40	1.79		£481.40	2.05	
Alitretinoin (30 mg)	£3548.95	2.01	£14,267.64	£3548.95	2.16	£29,739.38
Analysis 3b: Men only						
Supportive care	£481.40	1.79		£481.40	2.05	
Alitretinoin (30 mg)	£3337.49	2.01	£13,284.14	£3337.49	2.16	£27,689.38
Analysis 4: Reinstate adverse events for alitretinoin only						
Supportive care	£481.40	1.79		£481.40	2.05	
Alitretinoin (30 mg)	£3370.37	2.00	£14,072.21	£3370.37	2.15	£29,199.56

ICER, incremental cost-effectiveness ratio; PGA, physician's global assessment; QALYs, quality-adjusted life-years.

The manufacturer assumed that patients receiving alitretinoin visited the dermatologist every 4 weeks and ceased treatment as soon as they responded to it, even if this was after only 4 or 8 weeks of treatment. If, in practice, patients would receive treatment for longer than this, then the manufacturer's model will have significantly underestimated the costs to the NHS.

Additional analyses undertaken by the ERG produced ICERs close to £30,000 per QALY gained for alitretinoin versus supportive care. This was largely due to uncertainty surrounding the impact of alitretinoin on HRQoL. Utilising the alternative HRQoL estimates identified by the manufacturer resulted in a two-fold increase in the ICER (see *Table 2* for a comparison of the different estimates). There remains considerable uncertainty as to the true ICER of alitretinoin versus the relevant treatment comparators.

Implications for research

Given the limited duration of the available evidence, longer term follow-up of trials or the implementation of registries may be required to better establish the longer term efficacy and safety of alitretinoin. The placebo-controlled trials conducted to date have established that alitretinoin can be efficacious for the treatment of severe CHE refractory to topical steroids. However, future studies should include a relevant HRQoL measure (such as the Dermatology Life Quality Index and the European Quality of Life – 5 Dimensions) alongside measures of therapeutic response and may want to establish the efficacy of alitretinoin relative to current first-line treatment (emollients plus topical steroids) and other treatments that are used in this indication (PUVA, azathioprine, ciclosporin).

Summary of NICE guidance issued as a result of the STA

The guidance issued by NICE states that:

NICE recommended Alitretinoin as a possible treatment for people with severe chronic hand eczema if:

- their eczema has not improved with treatments called potent topical corticosteroids **and**
- standard assessments (PGA and DLQI) show that their eczema is severe and is affecting their quality of life.

Alitretinoin treatment should be stopped:

- as soon as the eczema has clearly improved **or**
- if the eczema remains severe after 12 weeks **or**
- if the eczema has not clearly improved after 24 weeks.

Treatment with alitretinoin should be started and monitored only by doctors who:

- are skin specialists (dermatologists) **or**
- have experience in both treating people with severe chronic hand eczema and using drugs like alitretinoin.

When assessing how a person's eczema affects their quality of life, healthcare professionals should take into account any disabilities or difficulties in communicating which might mean that the standard assessments do not provide accurate information.

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