Scottish Medicines Consortium

alitretinoin 10mg, 30mg capsules (Toctino®) No. (538/09)
Basilea Pharmaceuticals Ltd

06 February 2009

The Scottish Medicines Consortium (SMC) has completed its assessment of the above product and advises NHS Boards and Area Drug and Therapeutic Committees (ADTCs) on its use in NHS Scotland. The advice is summarised as follows:

ADVICE: following a full submission

alitretinoin (Toctino®) is accepted for use within NHS Scotland in adults who have severe chronic hand eczema that is unresponsive to treatment with potent topical corticosteroids.

Evidence is limited to a randomised placebo-controlled study where alitretinoin was superior to placebo in terms of the primary endpoint, Physician Global Assessment of response.

It is recommended that alitretinoin is dispensed by a hospital-based pharmacy.

Overleaf is the detailed advice on this product.

Chairman
Scottish Medicines Consortium

Indication

Indicated for use in adults who have severe chronic hand eczema that is unresponsive to treatment with potent topical corticosteroids.

Patients in whom the eczema has predominantly hyperkeratotic features are more likely to respond to treatment than in those in whom the eczema predominantly presents as pompholyx.

Dosing information

Alitretinoin 30mg once daily for 12 to 24 weeks. A reduction to 10mg once daily may be considered in patients with unacceptable adverse reactions to the higher dose.

Alitretinoin should only be prescribed by dermatologists, or physicians with experience in the use of systemic retinoids who have full understanding of the risks of systemic retinoid therapy and monitoring requirements.

Product availability date

8 September 2008

Summary of evidence on comparative efficacy

Retinoids are derivatives of vitamin A that display key regulatory functions in epidermal growth and differentiation. Alitretinoin (9-cis-retinoic acid) is an endogenous retinoid and its mechanism of action in the treatment of chronic hand eczema (CHE) is unknown. Severe CHE has an approximate prevalence of 0.5% to 0.7% in the general population. It has multi-factorial causes and follows a chronically remitting and relapsing course.

One phase III randomised controlled study has compared the efficacy of alitretinoin to placebo in patients aged 18 to 75 years with severe CHE for at least 6 months after initial diagnosis. The CHE was required to be refractory to topical corticosteroid therapy (no response, transient response to ongoing therapy, or lack of tolerability) after at least 8 weeks of treatment within the previous 6 months, 4 weeks of which was on the most potent corticosteroid class. Female patients were required to be post-menopausal, hysterectomised, or willing to use two methods of contraception. Patients were randomised in blocks of five without stratification to receive alitretinoin 30mg, alitretinoin 10mg, or placebo (2:2:1) once daily for up to 24 weeks. Patients who responded with a Physician Global Assessment (PGA) of clear or almost clear after 12 weeks stopped treatment at this time, while all others continued therapy until week 24.

The primary endpoint was the percentage of PGA responders at end of therapy (week 12 or 24), with response defined as clear or almost clear hands. The PGA comprises five classifications (clear, almost clear, mild, moderate, severe) related to the features of CHE (erythema, scaling, lichenification/hyperkeratosis, vesiculation, oedema, fissures, and pruritus/pain) and was performed at screening and every 4 weeks during treatment, or at the last evaluation in case of premature withdrawal. Secondary endpoints included time to response; time to relapse; partial response (defined as a PGA of clear, almost clear or mild); modified Total Lesion Symptom Score (mTLSS); and Patient Global Assessment (PaGA). The mTLSS was calculated as the sum of scores (0 = absent, 1 = mild, 2 = moderate, 3 = severe) assigned by the physician for the CHE features described previously. The PaGA of improvement was assigned by the patient as ‘clear or almost clear’ (at least 90% clearing of

disease signs and symptoms compared to baseline), 'marked improvement' (at least 75% clearing), 'moderate improvement' (at least 50% clearing), 'mild improvement' (at least 25% clearing), 'no change', or 'worsening'. All efficacy evaluations were based on the intention-to-treat population that included all randomised patients and were analysed according to their randomisation with the last observation carried forward (LOCF) in cases of missing data.

All responding patients were followed up for a further 24 weeks after treatment completion to assess relapse. No medication likely to be active against CHE was allowed during this time. Relapse was defined as an mTLSS score of at least 75% of the baseline score.

Alitretinoin 30mg and 10mg groups were significantly superior to placebo in terms of the primary endpoint. Clear or almost clear skin was achieved in 48% (195/409) and 28% (115/418) of patients treated with alitretinoin 30mg or 10mg respectively, compared to 17% (34/205) of patients in the placebo group. The time to response was significantly shorter in the alitretinoin 30mg group compared with the alitretinoin 10mg group. Secondary endpoints are included in the table below.

Table: Some secondary endpoints from the phase III

	Alitretinoin		**Placebo (n=205)**
	30mg (n=409)	**10mg (n=418)**	
Partial response, N (%)	254 (62%)***	207 (50%)**	74 (36%)
Median % reduction in modified TLSS	75%***	56%***	39%
PaGA, N (%) (clear or almost clear)	163 (40%)***	101 (24%)*	31 (15%)
Median time to relapse (months)	5.5	6.2	5.4
*p<0.02 compared with placebo, **p<0.01 compared with placebo, ***p<0.001 compared with placebo			

TLSS= Total Lesion Symptom Score: PaGA=Patient Global Assessment.

Follow-up of responders for 6 months revealed that 64% (125/195) of patients who had received alitretinoin 30mg and 72% (83/115) who had received alitretinoin 10mg did not meet the criteria for relapse.

A re-treatment extension study to assess the efficacy and safety of a second 12 to 24 week course of alitretinoin (10mg or 30mg) included patients who had previously responded to treatment but relapsed within 24 weeks. Patients who had previously received alitretinoin were randomised to their previous treatment or placebo (2:1) for 12 to 24 weeks and patients who had previously received placebo were all assigned to placebo. The numbers of patients receiving alitretinoin 30mg, 10mg, and placebo were 49, 21, and 34 respectively. In the alitretinoin 30mg re-treatment group almost 80% of patients achieved a response compared to 48% in the alitretinoin 10mg re-treatment group and approximately 10% in the placebo groups.

Summary of evidence on comparative safety

In the pivotal study the adverse event rates were 60% (244/410), 52% (216/418), and 50% (101/203) in the alitretinoin 30mg, alitretinoin 10mg and placebo groups respectively.

Adverse effects appeared to be dose dependent and were typical retinoid effects. Headache was the most frequent adverse event, reported in 20%, 11%, and 6% patients in the alitretinoin 30mg, alitretinoin 10mg, and placebo groups. Headache led to treatment withdrawal in 4.2% (17/409), 1.4% (6/418), and <1% (1/205) patients respectively. Severe headache was reported in 5% of patients in the alitretinoin 30mg group. Other adverse events more common in the alitretinoin 30mg arm versus alitretinoin 10mg or placebo included erythema (7% versus 2% in both other groups), dry lips (4% versus 2%), nausea (3% versus 2%), and flushing (4% versus 1%).

Decreased thyroid stimulating hormone and raised cholesterol and triglycerides outside the protocol-defined ranges were observed in the alitretinoin arms. The Summary of Product Characteristics (SPC) for alitretinoin notes that that serum cholesterol and triglycerides (fasting values) should be monitored. Alitretinoin should be discontinued if hypertriglyceridaemia cannot be controlled at an acceptable level or if symptoms of pancreatitis occur.

Summary of clinical effectiveness issues

There are no studies comparing alitretinoin with phototherapy or systemic treatments in patients with CHE unresponsive to topical steroids therefore the relative efficacy of alitretinoin versus comparators is not known.

There are a number of weaknesses relating to the pivotal study. The study design allowed LOCF to be used for missing data and this may introduce some bias. In addition, no quality of life data were collected in the study. Clinical signs and symptoms of CHE cause substantial occupational, social and psychological disability; however, the impact of alitretinoin on these in a controlled trial setting is unknown. The median time to relapse was similar in all groups.

In the extension study, where responders were followed up for 6 months after treatment was completed, relapse was seen in 36% of responders who had been in the alitretinoin 30mg group and 28% who had been in the alitretinoin 10mg group.

In the pivotal study no dose reductions were allowed, although the licensed dose allows a reduction to alitretinoin 10mg once daily in patients with unacceptable adverse reactions to the higher dose. The adverse event frequency may therefore be higher in the study than in clinical practice.

Patients entered into the study required a patch-test to have been carried out during the 6 months before randomisation. Experts consulted by SMC agreed that this is likely to be carried out in Scottish practice, particularly in cases of non-responsive hand dermatitis.

Alitretinoin is teratogenic and women of childbearing potential must meet the conditions of the Pregnancy Prevention Programme. This includes regular pregnancy testing and the use of, preferably, two complementary forms of contraception including a barrier method. Prescriptions for alitretinoin in women of childbearing potential should be limited to 30 days

of treatment and continuation of treatment requires a new prescription. There should be a maximum of 7 days between prescribing and dispensing the prescription.

There are no other medicines specifically licensed for the treatment of chronic hand eczema. Treatments currently used for this condition are used outwith their licensed indications and consequently evidence of efficacy is limited.

Summary of comparative health economic evidence

The manufacturer presented a cost-utility analysis comparing alitretinoin with ciclosporin in patients with severe CHE that is unresponsive to treatment with potent topical corticosteroids. A Markov model was used to estimate the costs and benefits over a 12 year time horizon and used clinical data from the pivotal clinical studies for the alitretinoin group and a study from the literature for the ciclosporin arm. Utility values were derived from a study of patients with CHE who completed the Dermatology Life Quality Index and these scores were converted into utilities using a method from the literature. The utilities were comparable with values in the literature for similar health states and the method used to derive the utility values was similar to the method used by NICE in a previous Health Technology Appraisal (HTA) of psoriasis. The manufacturer estimated a cost per QALY of £11,803 based on an increased cost of £1,949 and a QALY gain of 0.165. A cost-minimisation analysis was also presented which compared alitretinoin with a number of other second-line agents including phototherapy.

There were a number of weaknesses with the analysis:

- LOCF was used to impute missing data from the study and this is likely to have introduced some bias into the analysis;
- An indirect comparison was necessary as no direct comparative data were available comparing alitretinoin with relevant comparators. There were a number of weaknesses with this including: the comparison was a naïve indirect comparison which involved simply comparing the results from the relevant individual study groups; the data used for the ciclosporin group was based on very few patients (n=12) and was a sub-group of the whole study population; no patient characteristics were available for this sub-group; and different outcome measures were used in the alitretinoin and ciclosporin trials.

However, on balance the economic case was considered demonstrated.

Summary of patient and public involvement

A Patient Interest Group Submission was not made.

Additional information: comparators

The immunosuppressive agents ciclosporin and azathioprine have been used for the treatment of CHE. In addition psoralens UVA (PUVA) is used (but not included in cost of relevant comparator below) and also tacrolimus ointment may be used for moderate to severe atopic dermatitis.

Cost of relevant comparators

Drug	Dose regimen	Cost per course (£)
Alitretinoin	**30mg daily orally for 12 to 24 weeks**	**1,152 to 2,304**
Ciclosporin (Neoral) *	2.5 to 5mg/kg daily (in two divided doses) orally for 8 weeks	249 to 479
Azathioprine**	1 to 3mg/kg/day orally for 24 weeks	47 to 54
Tacrolimus ointment 0.1% and 0.03% *	Apply 0.1% ointment twice daily until symptoms improve. Reduce to once daily or switch to 0.03% ointment if condition allows	0.62 to 0.68 per gram

Doses are for general comparison and do not imply therapeutic equivalence. Costs from eVadis on 26 November 2008. * licensed for severe atopic dermatitis **unlicensed indication

Treatment regimens based on; BNF edition 56 (September 2008) and company submission for azathioprine; SPCs for ciclosporin and alitretinoin and based on a body weight of 70kg (where applicable).

Additional information: budget impact

The manufacturer estimated there would be 1,257 treatments with alitretinoin in year 1, rising to 4,493 in year 5, based on a market share of 10% in year 1 rising to 45% in year 5. The gross drug cost was estimated to be £1.8m in year 1 rising to £6.2m in year 5. The net budget impact was estimated to be cost savings of £677k in year 1 rising to £3.7m in year 5. The manufacturer's figures included savings from displaced therapies including phototherapy and other second-line agents. These estimated savings are believed to be significantly overestimated as only marginal savings will be released from reduced phototherapy sessions. The gross costs estimated by the manufacturer are likely to be more indicative of the actual medicines budget impact.

Advice context:

No part of this advice may be used without the whole of the advice being quoted in full.

This advice represents the view of the Scottish Medicines Consortium and was arrived at after careful consideration and evaluation of the available evidence. It is provided to inform the considerations of Area Drug & Therapeutics Committees and NHS Boards in Scotland in determining medicines for local use or local formulary inclusion. This advice does not override the individual responsibility of health professionals to make decisions in the exercise of their clinical judgement in the circumstances of the individual patient, in consultation with the patient and/or guardian or carer.

This assessment is based on data submitted by the applicant company up to and including 19 January 2009.

Drug prices are those available at the time the papers were issued to SMC for consideration. These have been confirmed from the eVadis drug database.

The undernoted references were supplied with the submission.

Ruzicka T, Lynde C, Jemec G et al. Efficacy and safety of oral alitretinoin (9-cis retinoic acid) in patients with severe chronic hand eczema refractory to topical corticosteroids: results of a randomised, double-blind, placebo-controlled, multicentre trial. British Journal of Dermatology 2008;158:808–817

Ruzicka T, Gupta A, Jemec G et al., Efficacy and safety of oral alitretinoin (9-cis retinoic acid) in patients with severe chronic hand eczema refractory to topical treatment (BACH study) Poster EADV-275. The 16th European Academy of Dematology and Venereology Congress, April 2007

Ruzicka T, Lahfa M, Lynde C et al. Retreatment study of alitretinoin (9-cis retinoic acid) in severe chronic hand eczema refractory to topical treatment. Poster EADV-280 The 16th European Academy of Dematology and Venereology Congress, April 2007