Scottish Medicines Consortium

ciclesonide 80, 160 µg inhaler (Alvesco®) No. (184/05)

Altana Pharma Limited

10 June 2005 *(Amended March 2006)*

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:

Ciclesonide (Alvesco®) is accepted for restricted use within NHS Scotland for the prophylactic treatment of persistent asthma in adults (18 years and older).

Ciclesonide is restricted to asthma patients who require once a day administration and whose treatment is at step 2 or step 3 of the British Guideline on the Management of Asthma. Alternative inhaled steroids are available at lower costs.

Overleaf is the detailed advice on this product.

Chairman,
Scottish Medicines Consortium

Ciclesonide 80 µg and 160 µg inhaler (Alvesco®)

Licensed indication under review Prophylactic treatment of persistent asthma in adults (18 years and older)

Dosing information under review Starting dose: 160 µg once daily (administered in the evening, although morning administration has been shown to be effective). A dose reduction to 80 µg once daily may be an effective maintenance dose for some patients. The maximum dose is usually 160 µg daily.

UK launch date January 2005

Comparator medications

Beclometasone dipropionate, mometasone furoate, fluticasone propionate and budesonide are inhaled corticosteroids licensed for the prophylactic treatment of asthma in adults and are listed in the *British Guideline on the Management of Asthma* written by the British Thoracic Society and Scottish Intercollegiate Guidelines Network (revised edition; April 2004).

Cost per treatment period and relevant comparators

Drug	Dose	Cost per day (£)	Cost per year (£)
Ciclesonide non-CFC 160 µg/dose	**160 µg once daily**	**0.28**	**102**
Mometasone furoate (Asmanax twisthaler) Dry powder 400 µg/dose	400µg once daily	0.61	224
Budesonide (Pulmicort turbohaler) Dry powder 200 µg/dose	200 µg twice daily	0.37	135
Budesonide (Pulmicort, aerosol) CFC200 µg/dose	200 µg twice daily	0.21	76
Beclometasone dipropionate (Becotide) CFC 200 µg/dose	200 µg twice daily	0.06	20.09
Fluticasone propionate (Flixotide evohaler) non-CFC 50 µg/dose	100µg twice daily	0.18	66
Beclometasone dipropionate (Qvar) non-CFC 100 µg/dose	100 µg twice daily	0.17	63
Beclometasone dipropionate (generic) CFC 100 µg/dose	200 µg twice daily	0.16	60

Doses of inhaled steroids except ciclesonide taken from *The British Guideline on the Management of Asthma*. Prices taken from eVadis drug dictionary, NHS National Services Scotland (31/03/05) and based on the most comparable inhaler strength and size available.

Summary of evidence on comparative efficacy

Inhaled ciclesonide is converted in the lung to the active metabolite desisobutyryl-ciclesonide, a corticosteroid with anti-inflammatory activity. Doses of ciclesonide quoted are doses ex-actuator. Ciclesonide 160 µg ex-actuator is equivalent to a 200 µg metered dose (i.e. prior to deposition in the aerosol valve and mouthpiece). Metered doses are quoted for all other inhaled steroids.

Four phase III comparative studies have been conducted using varying doses of ciclesonide up to 320 µg per day. Primary and secondary endpoint results for two studies are displayed in the table. The remaining two comparative studies were considered by SMC based on confidential data supplied by the manufacturer.

In the first study 554 patients with mild to moderate asthma; forced expiratory volume in one second (FEV_1) 50–90% of predicted if pre-treated with short-acting bronchodilators only or FEV_1 80-100% predicted if pre-treated with low dose inhaled corticosteroid (dose = 500 µg beclometasone dipropionate /day or equivalent), or FEV_1 50-100% predicted if pre-treated with either theophylline, cromones, leukotriene antagonists or lipoxygenase inhibitors were recruited. Following a 1-4 week baseline where only rescue medication was permitted patients were treated with double blind ciclesonide 80 µg/day or 320 µg/day or open label budesonide 200 µg twice daily for 12 weeks.

The second randomised study had a double-blind double dummy parallel group study design and recruited 529 patients. Patients were eligible if they had a FEV_1 80-100% predicted at baseline and were pre-treated with a constant dose of inhaled steroids (dose = 500 µg /day of beclometasone dipropionate or equivalent) during the four weeks prior to baseline and went on to receive treatment if the FEV_1 was 50–90% of predicted and there was a decrease in FEV_1 =10% of initial after withdrawal of the inhaled steroid. Patients were treated with ciclesonide 160 µg once daily or fluticasone propionate 100 µg twice daily for 12 weeks.

Table: Comparative studies; results for primary and secondary endpoints

Study	Primary endpoints	Secondary endpoints
Study 1	**Change in FEV_1** Ciclesonide 80 µg once daily 9% Ciclesonide 320 µg once daily 8% Budesonide 200 µg twice daily 10% For all treatments, all endpoints increased significantly ($p<0.0001$). There were no significant differences between treatments.	PEF am and pm improved in all arms Asthma symptoms and use of rescue medication decreased significantly in all arms Urine cortisol significantly suppressed in budesonide arm, but not in ciclesonide arms
Study 2	**Change in FEV_1** Ciclesonide 160 µg once daily +506ml Fluticasone propionate 100 µg twice daily +536ml **Change in FVC** Ciclesonide 160 µg once daily +531ml Fluticasone propionate 100 µg twice daily +523ml **PEF am** Ciclesonide 160 µg once daily +29L/min Fluticasone propionate 100 µg twice daily+36L/min	Comparable for reducing asthma symptoms and use of rescue medication $p<0.0001$ from baseline for all variables

FEV_1: forced expiratory volume in one second, FVC: forced vital capacity, PEF: peak expiratory flow.

Summary of evidence on comparative safety

A pooled analysis of short (up to 12 weeks) and long (up to 1 year) trials was conducted to assess safety, and included 4759, 934 and 2039 patients treated with ciclesonide, active control and placebo respectively. The authors concluded that systemic and local adverse events possibility related to treatment with ciclesonide were similar in all dose groups.

A randomised placebo controlled trial was conducted to evaluate the effect of ciclesonide (320 µg od, 640 µg once daily and 640 µg twice daily) on 24 hour plasma and urinary cortisol levels, in comparison with fluticasone propionate (500 µg twice daily, 1000 µg twice daily), in steroid naïve asthma patients. The study was blinded for placebo and ciclesonide only. The mean 24 hour plasma concentration of cortisol was decreased with fluticasone propionate and there was no decrease with ciclesonide treated patients. The 24 hour urinary cortisol excretion was significantly reduced for fluticasone propionate only.

Summary of clinical effectiveness issues

The British Guideline on the Management of Asthma states that in adults there is little evidence that the use of inhaled steroids at doses of beclometasone dipropionate (or equivalent) up to 800 µg per day will have any detrimental effects apart from oral candidiasis and dysphonia. A recent systematic review reported no effect on bone density at daily doses up to 1000 µg. However, it is recommended that the dose of inhaled steroid used is the lowest that maintains asthma control.

The Medicines Partnership report; A Question of Choice: Compliance in Medicine Taking, was published in June 2003 and a supplementary chapter; Compliance with Medicines in Asthma was published in October 2003. The supplementary chapter concludes with a statement that interventions which teach strategies for prevention and relief of acute attacks, are effective in improving illness management. These include a simple regimen as well as better patient understanding of their illness and treatment through individualised verbal and written information, reinforced by the patient's clinician and pharmacist. The report contains equivocal evidence of superior compliance with a once daily regimen over a twice daily regimen.

Summary of comparative health economic evidence

Ciclesonide 160µg is clinically equivalent to budesonide 400 µg and fluticasone propionate 200 µg. A cost-minimisation analysis was presented which compared annual drug costs only although these varied substantially depending on the device used and the pack size. Other NHS costs such as GP visits were not included because they were assumed to be equal across all drugs. Ciclesonide is comparable in price with other drug in this class and has a once daily dosing regimen and thus offers a suitable alternative for some asthma patients.

Budget impact

The manufacturer estimated a net budget impact of £145,000 in year 1 rising to £563,000 in year 3 and £997,000 in year 5.

Guidelines and protocols

The British Guideline on the Management of Asthma, revised in April 2004, was produced by the British Thoracic Society and the Scottish Intercollegiate Guidelines Network (SIGN). Step 2 of the stepwise management of asthma recommends the use of a regular inhaled steroid when there has been an exacerbation of asthma in the last two years, or when the $ß_2$ agonist is used more than twice weekly or when the patient is symptomatic more than twice a week or waking one night a week. The steroids recommended are beclometasone dipropionate, budesonide, fluticasone propionate and cautiously, mometasone furoate. The guideline predates the availability of ciclesonide. Options at step 3 include adding a long-acting $ß_2$ receptor agonist and increasing the dose of inhaled steroid, at step 4 increasing the dose of inhaled steroid further, and at step 5 using an oral steroid.

Additional information

Following a full submission mometasone furoate was accepted for restricted use as a second line agent following treatment failure on first-line inhaled steroids by the Scottish Medicines Consortium in November 2003.

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 25 May 2005.

Drug prices are those available at the time the papers were issued to SMC for consideration.

The undernoted references were supplied with the submission. Those shaded grey are additional to those supplied with the submission.

1. *Hansel T, Biberger C, Engelstätter R. Ciclesonide 80 µg or 320 µg daily achieves lung function improvement comparable with budesonide 200 µg twice daily in patients with persistent asthma. Abstract presented at the British Thoracic Society Meeting, 2004*
2. *Altana Pharma Limited. Data on file.*
3. *Buhl R, Wolf S, Tiesler C et al. Once daily ciclesonide is as effective as twice daily fluticasone propionate in improving lung function in patients with asthma. Abstract presented at the British Thoracic Society Meeting, 2004.*
4. *Buhl R, Wolf S, Tesler C et al. In patients with mild and moderate asthma, once daily ciclesonide is as effective as twice daily fluticisone propionate in providing asthma control. Abstract presented at the British Thoracic Society Meeting, 2004.*
5. *Postma DS, Sevette C, Martinat Y et al. Treatment of asthma by the inhaled corticosteroid ciclesonide given either in the morning or evening. Eur Respir J 2001;17: 1083–1088.*
6. *Chapman KR, D'Urzo AD, Oedekoven C, Steinijans VW, Wurst W. Effects of ciclesonide versus placebo on lung function after 12 weeks of treatment in patients with asthma. Poster presented at American Thoracic Society Meeting, Atlanta, Georgia 2002.*
7. *Chapman KR, Patel P, Boulet LP et al. Efficacy and long-term safety of ciclesonide in asthmatic patients as demonstrated in a 52 week long study. Abstract presented at the European Society Meeting, Stockholm, Sweden 2002.*
8. *Altana Pharma Limited. Ciclesonide 160 µg (Alvesco®). Summary of Product Characteristics. 16 April 2004*
9. *Häfner D, Jimenez-Kocker AM, Bethke TD et al. The incidence of local adverse events is comparable in asthma patients receiving ciclesonide or placebo: results from a pooled analysis. Abstract presented at the British Thoracic Society Meeting, 2004.*
10. *Häfner D, Kassel W, Wurst W et al. The incidence of adverse events is comparable in asthma patients receiving ciclesonide or placebo: results from a pooled analysis. Abstract presented at the British Thoracic Society Meeting, 2004.*
11. *Pauwels RA, Derom E, van de Velde V, Marissens S, Vincken W. Effects of inhaled ciclesonide and fluticasone propionate on cortisol secretion and PC_{20} for adenosine in asthma patients. Poster presented at the American Thoracic Society Meeting, Atlanta, Georgia, 2002*
12. *Scottish Intercollegiate Guidelines Network and the British Thoracic Society. Guideline on the Management of Asthma. Revised April 2004.*

13. *Carter S, Taylor D. A question of choice – compliance in medicine taking. A preliminary Review. Medicines Partnership. June 2003. [Accessed on 21 March 2005] http://www.concordance.org/research-evidence/major-reviews/a-question-of-choice*
14. *Carter S, Taylor D. A question of choice – compliance in medicine taking. Supplementary chapter – compliance with medicines in asthma. Medicines Partnership. October 2003. [Accessed on 21 March 2005] http://www.concordance.org/research-evidence/major-reviews/a-question-of-choice*