

NEW DRUG EVALUATION

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CICLESONIDE

Ciclesonide (Alvesco®) is a once-daily inhaled corticosteroid licensed for the prophylaxis of persistent asthma in adults. In one published clinical trial, ciclesonide showed a smaller reduction in morning peak expiratory flow (PEF) from baseline (patients usual ICS), compared with placebo. There are no clinical trials directly comparing ciclesonide with beclometasone, which remains the first-line inhaled corticosteroid in the BTS/SIGN Asthma Guidelines. Currently, evidence that ciclesonide does not impair adrenal cortisol production is very limited. Until further comparative evidence is available, ciclesonide should not be prescribed in preference to other inhaled corticosteroids.

What is it?

Ciclesonide (Alvesco®, Altana Pharma AG) is a once-daily inhaled corticosteroid delivered via a hydrofluoroalkane metered-dose inhaler (MDI).¹ It is licensed for the prophylaxis of persistent asthma in adults (Step 2 BTS/SIGN Asthma Guideline).²

The manufacturer recommends starting treatment at 160 mcg once daily (OD; maximum dose), which can then be reduced to 80 mcg/day in some patients.¹ Ciclesonide is not licensed in patients under 18 years of age.¹

Ciclesonide is a pro-drug, which is converted to the active metabolite (des-ciclesonide) by esterases in lung tissue. As with other hydrofluoroalkane MDIs, a high level of lung deposition occurs (approximately 52% of inhaled dose)^{1,3}. The combination of these factors with a low oral bioavailability and high protein binding have been reported to minimise ciclesonide's systemic and oropharyngeal side-effects.^{1,4}

How effective is it?

A 12-week randomised, double-blind, parallel group study (n=329) comparing ciclesonide 160 mcg/day (n=107) and 640 mcg/day (n=112) with placebo, has been published.⁴ Patients included had mild to moderate asthma and were previously stabilised on a regular dose of inhaled corticosteroid (ICS) equivalent to 400-800 mcg/day beclometasone or 200-500 mcg/day fluticasone. This was continued throughout the two-week run-in period, after which the subjects were randomised to treatment with ciclesonide or placebo.

Change in morning peak expiratory flow (PEF) from baseline and lack of efficacy (LOE) were the efficacy end-points. A small reduction in PEF was seen with ciclesonide 160mcg and 640 mcg/day (-4 L/min and -1 L/min, respectively), whereas a large reduction in PEF was seen with placebo (-28 L/min;

$p < 0.0001$). This study had a high overall drop out rate (44%) mainly due to LOE (ciclesonide 30%, placebo 63%).

High-dose ciclesonide has been investigated in three (12 week) unpublished trials.⁵⁻⁷ Patients were pre-treated with inhaled beclometasone (400-1,600 mcg/day) during the run-in phase. Ciclesonide treatment was associated with a 5 % increase in morning PEF ($p < 0.001$)⁵ and a 20-28L/min difference when compared with placebo ($p < 0.001$).^{6,7}

The only studies to include treatment with ciclesonide at its licensed dose (80-160mcg/day) have not been fully published and are available as abstracts only. The studies included unlicensed high dose ciclesonide (320mcg/day)⁸, budesonide (200mcg BD)^{8,9} and fluticasone (88mcgBD)¹⁰ as comparators. Ciclesonide produced improvements in FEV₁ similar to budesonide^{8,9} and fluticasone.¹⁰ However a full evaluation of these trials could not be done due to lack of published data.

How safe is it?

Paradoxical bronchospasm occurs in 1% of patients treated with ciclesonide.¹ Other side effects include hoarseness (0.9%), sore throat (0.6%)¹ and a low incidence of oral candidiasis (0-2.4%).^{3,11}

Only one fully published trial evaluates the effect of ciclesonide on cortisol production, compared with placebo (primary end-point). 12 healthy volunteers were given ciclesonide (800mcg/day) or placebo for 7 days.¹² No significant suppression of cortisol production could be detected, however the short duration of the study may have an impact on the results. Two further trials have compared unlicensed, high-dose ciclesonide with fluticasone (880mcg/day, n=164¹¹ or 2,000mcg, n=14¹³). When compared with fluticasone, significantly less suppression of cortisol production was shown with ciclesonide at 10hours ($p < 0.05$)¹³ and both serum and urinary cortisol levels at 12

weeks ($p < 0.01$ and $p < 0.001$ respectively).¹¹
 Other unpublished trials support these findings.

What other options are there?

All inhaled corticosteroids (BNF section 3.2) are licensed for prophylaxis of asthma symptoms in adults.¹⁴ Beclometasone is the most commonly prescribed inhaled corticosteroid with fluticasone and budesonide being used as alternatives.

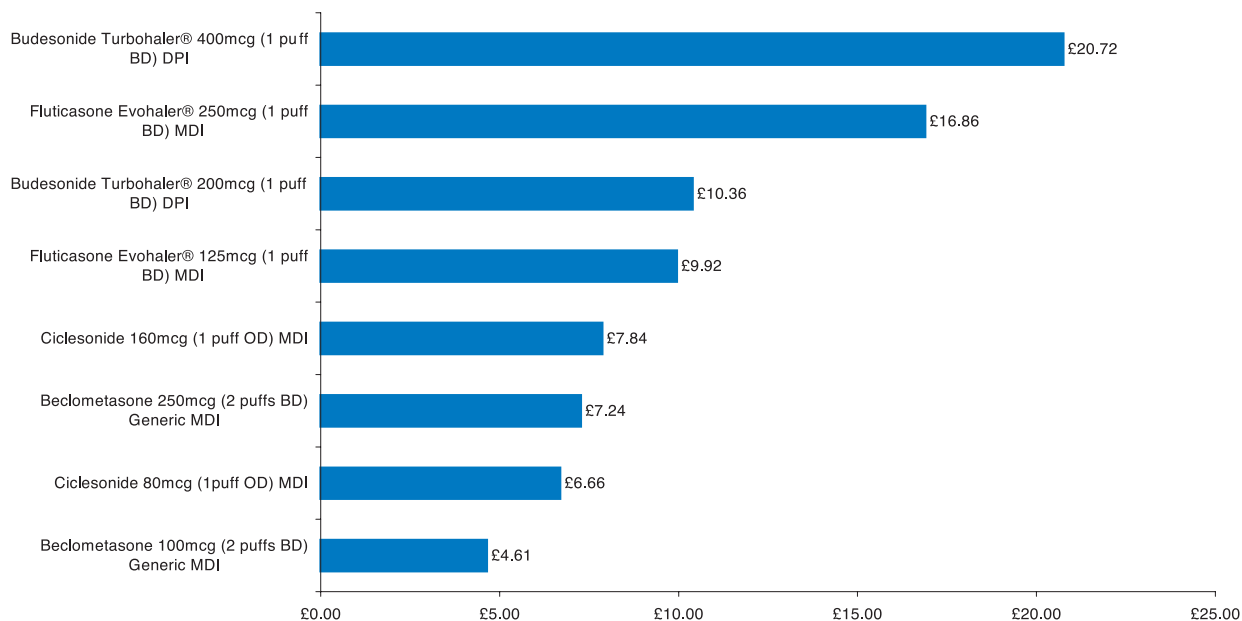
When should it be used?

Although there is evidence of benefit for ciclesonide compared with placebo, there is little evidence of improved efficacy or safety compared with other inhaled corticosteroids. Therefore a present a role for ciclesonide cannot be defined.

Until further research is under taken into the effects of ciclesonide on cortisol production (including direct comparisons with other ICS), use of this agent with the aim of avoiding systemic steroid effects is not recommended.

How much does it cost?

Cost for 28 days treatment (prices from eMIMS August 2005/Drug Tariff August 2005)



Key MDI = Metered dose inhaler DPI = Dry powder inhaler
 N.B. Doses shown are for general comparison only and do not imply therapeutic equivalence

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KEY RCT - randomised controlled trial, CT-controlled trial, G-guideline, Abs- abstract

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