## Ciclesonide for Asthma

**Generic (Trade Name):** Ciclesonide (Alvesco®)

**Manufacturer:** Altana AG

**Indication:** Ciclesonide is being investigated for the treatment of asthma in adults and children four years of age and older. Regulatory approval of ciclesonide for the treatment of asthma is being sought. It is also being evaluated for the treatment of allergic rhinitis.

**Current Regulatory Status:** On June 6, 2002, Altana AG announced that it had submitted ciclesonide for regulatory approval in Great Britain, Australia, Canada and Switzerland.¹ In the US, a new drug application was submitted to the Food and Drug Administration (FDA) on December 30, 2003.² In the US, ciclesonide is being developed jointly by Altana AG and Aventis Pharma. There is a cooperation agreement between Altana AG and Teijin Ltd. for ciclesonide’s development and marketing in Japan, Taiwan and Korea.

**Description:** Ciclesonide, which is a new once daily inhaled corticosteroid, is an ester prodrug that requires hydrolyzation by endogenous esterases in the lung to form its active metabolite (B-9207-021).³ The activated ciclesonide has an approximately 100-fold greater affinity for glucocorticoid receptors compared with the parent compound and produces high local anti-inflammatory activity.³

**Current Treatment:** There are many classes of medications used for the management of asthma,⁴ including inhaled corticosteroids (i.e., budesonide, beclomethasone, fluticasone), inhaled short- and long-acting bronchodilators (i.e., salbutamol, terbutaline, fenoterol, ipratropium, salmeterol, formoterol), inhaled and oral anti-allergy medications (i.e., cromoglycate, nedocromil), oral bronchodilators (i.e., salbutamol, orciprenaline), oral leukotriene receptor antagonists (i.e., zafirlukast, montelukast), oral xanthine products (i.e., theophylline, aminophylline, oxtriphylline) and oral systemic corticosteroids (used for acute exacerbations only). The choice of agents depends on the severity of the asthma. The mildest cases are typically treated with inhaled short-acting bronchodilators as needed. If symptoms persist, a regular inhaled corticosteroid is added. The inhaled steroid dose is typically low. It is increased gradually if symptoms worsen. In mild cases of asthma, alternatives to low-dose inhaled corticosteroids include low-dose theophylline, leukotriene receptor antagonists and inhaled anti-allergy medications. A long-acting bronchodilator may be added to the regimen if symptoms become moderate to severe.

**Cost:** Since ciclesonide is not marketed anywhere, no cost is available.

**Evidence:** Published clinical data on ciclesonide are lacking. A few small trials have been published, but only in abstract form.
Ciclesonide versus placebo
Two trials compared ciclesonide to placebo. One trial randomized 360 adult patients to receive 100 µg ciclesonide, 400 µg ciclesonide or placebo. Peak expiratory flow (PEF) was significantly greater in both treatment groups compared with placebo (p=0.0012 for 100 µg and p=0.0006 for 400 µg). Forced expiratory volume in one second (FEV1) was also significantly greater in both treatment groups compared with placebo (p=0.0044 for 100 µg and p=0.0001 for 400 µg). The other trial randomized 329 adult patients to 200 µg ciclesonide, 800 µg ciclesonide or placebo. PEF and FEV1 remained stable in the treatment groups, but declined in the placebo group. The differences in morning PEF were significant (p<0.0001 for 200 µg and p<0.0001 for 800 µg) and the differences in FEV1 were significant (p=0.007 for 200 µg and p=0.0108 for 800 µg) compared with placebo.

Ciclesonide versus budesonide
One trial randomized 554 patients to either ciclesonide 80 µg or 320 µg once daily or budesonide 200 µg twice daily for 12 weeks. FEV1 and forced vital capacity (FVC) increased in all three groups. Asthma symptoms and the use of bronchodilator rescue medications were decreased in all three groups. No significant differences were reported. There were no changes in 24-hour urinary cortisol excretion at 12 weeks compared to baseline in patients receiving ciclesonide. There was, however, a statistically significant suppression in cortisol in patients receiving budesonide.

In another trial, patients pre-treated with beclomethasone dipropionate 400 µg to 800 µg or equivalent, received 1,600 µg budesonide for two to four weeks. Those patients who had an increase in FEV1 (>7%) and an FEV1 between 65% to 90% were then randomized to receive ciclesonide 320 µg or budesonide 400 µg once daily for 12 weeks. There were no significant differences in FEV1. FVC decreased by 124 mL in the ciclesonide group compared with 221 mL in the budesonide group (p<0.01). There were significantly more symptom-free days in the ciclesonide group (43% versus 34%, p=0.0288), but the changes in symptoms and number of rescue-medication-free days were similar between the groups.

One trial randomized 399 patients to receive 320 µg ciclesonide or 400 µg budesonide once daily for 12 weeks. There was a significant increase in FEV1 (416 mL versus 321 mL, p<0.0185 ) and FVC (455 mL versus 352 mL, p=0.0335) in the ciclesonide group compared with budesonide-treated patients. The improvement in asthma symptoms and the use of rescue medication were similar in both groups. There were no significant changes from baseline in urine cortisol in both groups.

A press release from an Altana AG web site discusses larger phase III comparative clinical trials with ciclesonide versus budesonide (COMPASS study) and versus fluticasone (ASSET study). Results from the COMPASS study have been presented in this
report,\textsuperscript{9,10} but information on the ASSET study is minimal. One presentation by the manufacturer reports a lower incidence of adverse events in ciclesonide-treated patients compared with those treated with fluticasone [35/335 (10%) versus 59/345 (17%)]. It is not reported whether the difference was statistically significant.\textsuperscript{12}

Other trials have also been conducted. One trial compared the efficacy of ciclesonide taken in the morning versus the evening.\textsuperscript{13} Others evaluated ciclesonide's effect on airway responsiveness to stimuli used to induce a bronchoconstriction [i.e., adenosine-5-monophosphate (AMP), allergen challenge].\textsuperscript{14-16} Another study was conducted in patients with allergic rhinitis.\textsuperscript{17}

**Adverse Effects:** Adverse event data on ciclesonide are limited (likely because there is a lack of clinical trials that are published in full). The incidence of adverse events was not reported in any of the studies.\textsuperscript{5-9} Studies show that ciclesonide has a minimal propensity to suppress cortisol,\textsuperscript{7,9,10,13,16,18} but data on cortisol suppression with longer treatment periods are lacking.

**Commentary:** Ciclesonide is an inhaled corticosteroid for the management of asthma in adults and children four years of age or older. There are no studies describing its effect on clinical outcomes such as exacerbations, hospitalizations, quality of life and long-term adverse events. Initial data demonstrating a lack of cortisol suppression with two weeks of therapy appear promising, but longer term data are necessary as long-term administration is required for continued control of asthma and allergic rhinitis.

**References:**