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Alvesco[®] significantly reduces small airway resistance and eosinophilic inflammation compared to fluticasone propionate DPI

Comparison of Effectiveness in Ciclesonide and Fluticasone Propionate on Small Airway Function in Mild Asthma

Hoshino M. *Allergology International* 2010;59:59-66.

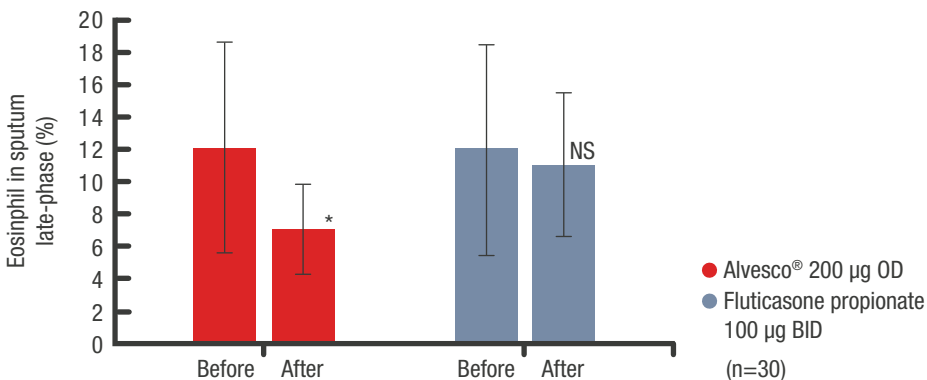
Abstract

Background: Inhaled corticosteroids (ICS) are the mainstay of asthma treatment, but conventional ICS may have limited effectiveness in inflammation and patency of small airways. Ciclesonide is delivered and deposited in the peripheral region of the lung as a small particle corticosteroid. The aim of the study is to compare the effects of ciclesonide with fluticasone propionate on small airway function in asthma.

Methods: Thirty mild persistent asthma patients treated with 200 µg of fluticasone propionate were randomized to receive either ciclesonide 200 µg once daily or fluticasone propionate 100 µg twice daily for 8 weeks. Small airway function was assessed by impulse oscillometry (IOS) and percentage of eosinophil induced sputum.

Results: We observed that ciclesonide significantly improved IOS measured resistance of small airways (R5-R20; $p < 0.05$), distal reactance (X5; $p < 0.01$), reactance area (AX; $p < 0.01$), and decreased late-phase sputum eosinophil level ($p < 0.01$) compared with fluticasone propionate. There were no significant changes in spirometry indices in either group during the study.

Conclusions: These findings suggest that ciclesonide improves small airway function and inflammation compared with fluticasone propionate in mild asthma. This study provides evidence that IOS and late-phase induced sputum allows detection of changes in the small airways that cannot be detected by spirometry.



* $p < 0.01$ vs. baseline



Alvesco[®] reduces small airway hyperresponsiveness

Particle size matters: Diagnostics and treatment of small airways involvement in asthma
Cohen J, Postma DS, Douma WR, et al. European Respiratory Journal July 2010. Epub ahead of print.

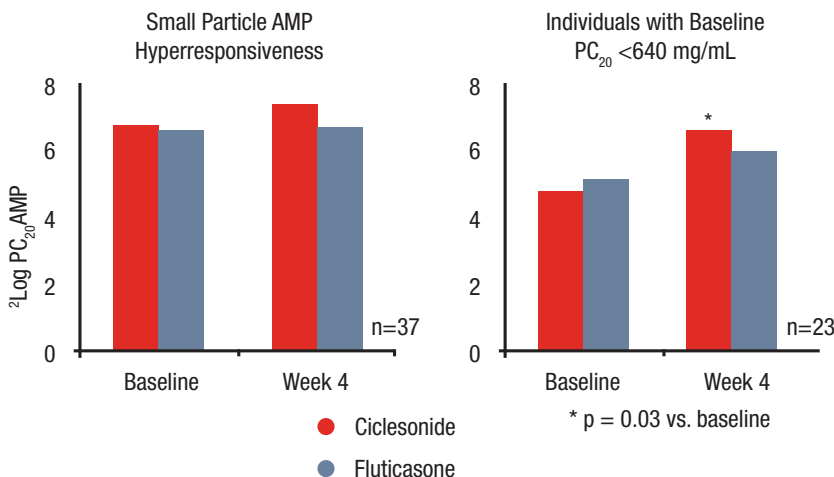
Abstract

Aim: Small airways are an important site of inflammation and obstruction in asthma, which contributes to the severity of airway hyperresponsiveness (AHR) that is usually measured by nebulisation of large-particle stimuli. We investigated whether small and large particle sizes of aerosolized adenosine-5'-monophosphate (AMP) provide similar severity of AHR. Additionally, effects of small-particle ICS ciclesonide and large-particle ICS fluticasone on AHR to large- and small-particle size AMP were assessed.

Methods: After a 4-week run-in period using open-label fluticasone 100 µg b.i.d., 37 mild-to-moderate asthmatics underwent provocations with standard size (3.7 µm), large-particle (9.9 µm) and small-particle (1.06 µm) AMP. Subjects received 4-week ciclesonide 160 µg s.i.d. or fluticasone 100 µg b.i.d. (double-blind, double-dummy) followed by large- and small-particle AMP provocation.

Results: Small-particle AMP induced a 20% fall in FEV₁ (PC₂₀) at a significantly higher dose than large-particle AMP. Ciclesonide and fluticasone had comparable effects on AMP provocations. Not all subjects reached a PC₂₀ at the highest AMP dose. In those who did, ciclesonide improved small-particle PC₂₀ AMP by 1.74 doubling doses (DD) ($p = 0.03$), whereas fluticasone did not. Conversely, fluticasone improved large-particle PC₂₀ AMP significantly (1.32 DD, $p = 0.03$), whereas ciclesonide did not.

Conclusions: Small-particle AMP provocation appears a promising tool to assess changes in small airways inflammation. Future adjustments are necessary taking into account the very small-particle size used, with large exhaled fractions. In asthmatics reaching a PC₂₀ with small- and large-particle AMP provocations, ciclesonide improves hyperresponsiveness with small-particle size AMP, and fluticasone with large-particle size. This warrants further research to target provocations and treatment to specific airway sizes.





Better access to small airways improves small airway function

Ciclesonide improves measures of small airway involvement in asthma

Cohen J, Douma WR, ten Hacken NHT, et al. *European Respiratory Journal* 2008;31:1213-1220.

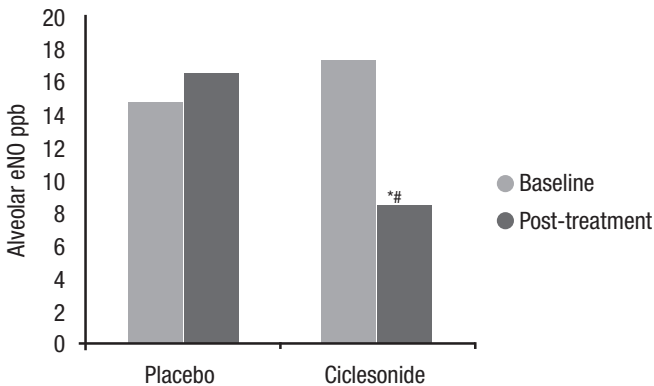
Abstract

Ciclesonide is delivered as a small-particle inhaled corticosteroid and improves lung function and airway hyperresponsiveness. The objective of the present study was to assess whether ciclesonide can specifically improve small airway function in asthma.

A total of 16 mild-to-moderate asthma patients (seven males; median (range) age 39 (19–56) yrs and forced expiratory volume in one second (FEV₁) 89 (62–120)% predicted) were randomised to 5 weeks' treatment with placebo or 320 µg ciclesonide once daily. The following small airway parameters were assessed: mean forced expiratory flow between 25 and 75% of forced vital capacity (FVC), percentage fall in FVC at provocative dose of adenosine-59-monophosphate and of methacholine (MCh) causing a 20% fall in FEV₁, expiratory lung volume on computed tomography (CT) scan after MCh challenge, single-breath nitrogen closing volume and alveolar exhaled nitric oxide (eNO).

Seven subjects received placebo and nine received ciclesonide. Both alveolar eNO and CT measurements of expiratory lung volume after MCh challenge decreased significantly with ciclesonide (median (range) decrease 4.4 (54.8–1.4) ppb and 59 (1,569– -117) mL, respectively), and compared with placebo (-0.4 (7.3– -3.4) ppb and -121 (20– -236) mL, respectively). Ciclesonide did not significantly improve other small airways parameters.

Inflammation and patency of small airways, reflected by alveolar exhaled nitric oxide and air trapping on computed tomography scan, both improve with ciclesonide even in this small number of patients. This indicates that ciclesonide exerts anti-inflammatory effects on small airways.



p = 0.05 compared with placebo;

* p = 0.05 compared with baseline



Low dose Alvesco[®] once-daily results in comparable increase in FEV₁ as fluticasone twice-daily

A 24-week comparison of low-dose ciclesonide and fluticasone propionate in mild to moderate asthma

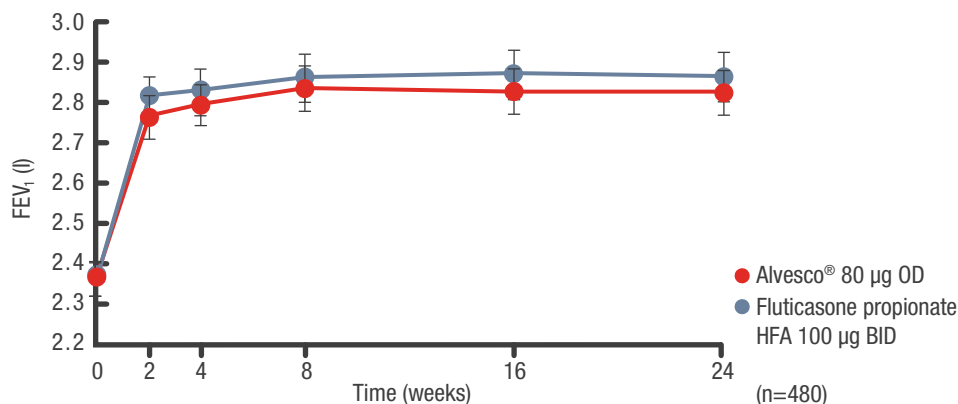
Dahl R, Engelsl tter R, Trebas-Pietras E, et al. *Respiratory Medicine* 2010;104:1121-1130.

Abstract

Objective: To compare the efficacy of ciclesonide (80 µg/day) with fluticasone propionate (200 µg/day) in mild to moderate persistent asthma.

Methods: Patients aged 12–75 years and previously treated with low doses of inhaled corticosteroid (fluticasone propionate 250 µg/day or equivalent) entered a 2–4 week run-in period during which only rescue medication was permitted. For inclusion into the double-blind, 24-week treatment period, patients had to show a forced expiratory volume in 1s (FEV₁) of 61–90% predicted and a decrease in FEV₁ during run-in of ≥10%. Patients (n = 480) were randomized to ciclesonide 80 µg (ex-actuator) once daily in the evening or fluticasone propionate 100 µg (ex-valve) twice daily. The primary efficacy variable was the change from baseline in FEV₁. Secondary efficacy variables included asthma control and asthma-specific quality of life.

Results: Both treatments significantly increased FEV₁ and other lung function variables from baseline (p<0.0001, both groups, all variables). The least squares mean increases in FEV₁ were 0.46 L (ciclesonide) and 0.52 L (fluticasone propionate); non-inferiority of ciclesonide to fluticasone propionate was demonstrated (p = 0.0002, per-protocol analysis). Five patients in each group experienced asthma exacerbations. Improvements in the percent of days with asthma control (days with no asthma symptoms and no use of rescue medication) and asthma-specific quality of life were comparable between treatments.





Alvesco[®] provides highly effective treatment with once-daily dosing

A randomized study comparing ciclesonide and fluticasone propionate in patients with moderate persistent asthma

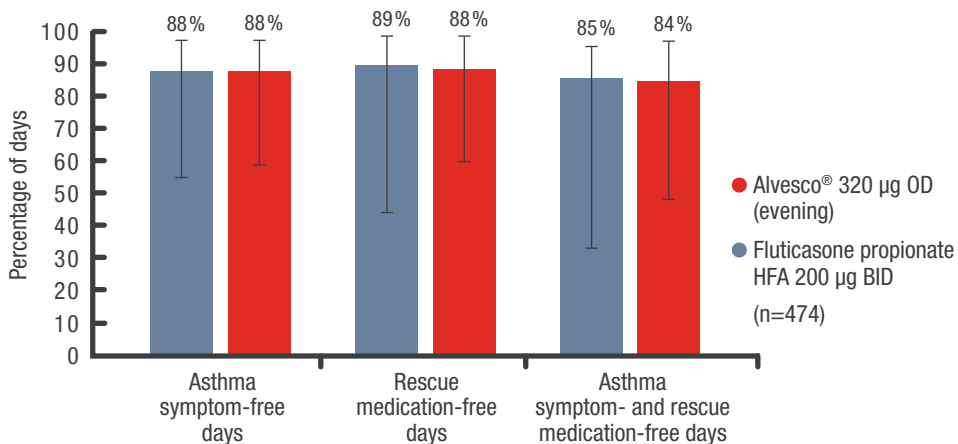
Boulet LP, Bateman ED, Voves R, et al. Respiratory Medicine 2007;101:1677-1686.

Abstract

Objective: To compare the effects of once-daily ciclesonide and twice-daily fluticasone propionate in patients with moderate persistent asthma.

Methods: Patients aged 12–75 years with moderate bronchial asthma entered a 1–4 week run-in period. For inclusion into the 12-week, randomized, open-label treatment period, patients had to have a forced expiratory volume in 1s (FEV₁) of either 60–80% of predicted or ≥80% of predicted and a defined use of rescue medication and asthma symptoms, depending on previous treatment. Patients received ciclesonide 320 µg once daily (exactuator) or fluticasone propionate 200 µg twice daily. Primary efficacy endpoint was change from baseline in FEV₁.

Results: In total, 474 patients were randomized. FEV₁ increased significantly from baseline with ciclesonide and fluticasone propionate in the intention-to-treat (ITT) and per-protocol (PP) analyses (all $p < 0.0001$). Treatment difference was -31 mL (95% confidence interval [CI]: -121, 59) in the PP analysis, demonstrating non-inferiority of ciclesonide. Similar findings were seen for other measures of lung function. In the ITT population, asthma symptom scores and rescue medication use decreased with both treatments (all $p < 0.0001$). Improvement in health-related quality of life (HRQoL) from baseline was significantly greater with ciclesonide than fluticasone ($p = 0.005$; one-sided). There were no cases of oral candidiasis in patients receiving ciclesonide and nine cases (3.8%) in those receiving fluticasone propionate ($p = 0.002$; one-sided).





Alvesco[®] shows significant improvement of morning PEF on second day of treatment

Ciclesonide is more effective than budesonide in the treatment of persistent asthma
Ukena D, Biberger C, Steinijans V, et al. Pulmonary Pharmacology & Therapeutics 2007;20:562-570.

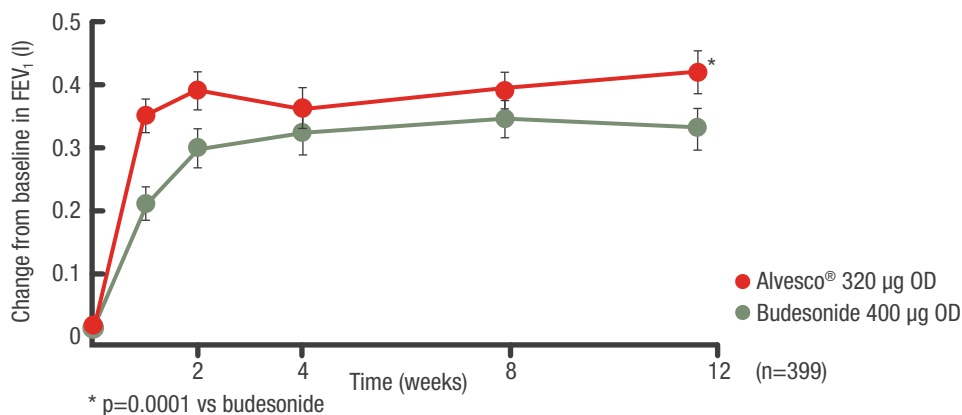
Abstract

Background: Ciclesonide is a lung-activated inhaled corticosteroid that provides effective control of persistent asthma. The objective of this study was to compare the efficacy and safety of once-daily ciclesonide versus once-daily budesonide in patients with asthma.

Methods: A total of 399 patients with asthma were randomised to receive once-daily ciclesonide 320 µg ex-actuator (equivalent to 400 µg ex-valve) or once-daily budesonide 400 µg for 12 weeks. The primary endpoint was forced expiratory volume in 1s (FEV₁). Additional efficacy variables included forced vital capacity (FVC), peak expiratory flow (PEF), asthma symptoms, use of rescue medication and time to onset of effect. Adverse events were monitored throughout the study.

Results: Both ciclesonide and budesonide significantly increased FEV₁ from baseline (416 and 321 mL, respectively; $p < 0.0001$). The increase in FEV₁ was significantly greater in ciclesonide-treated patients (95% confidence interval: 0.016–0.174; $p = 0.019$ versus budesonide). Similarly, ciclesonide and budesonide significantly improved FVC and PEF from baseline ($p < 0.0001$), and significantly greater increases occurred with ciclesonide ($p = 0.034$ and 0.019 versus budesonide, respectively). Analysis of morning PEF revealed an earlier onset of action for ciclesonide versus budesonide; a significant improvement was seen by day 2 ($p = 0.039$ versus baseline) with ciclesonide compared with day 7 for budesonide ($p = 0.047$ versus baseline). Adverse events occurred with a similar incidence in both treatment groups. Neither treatment caused significant changes in urinary cortisol levels.

Conclusion: Once-daily ciclesonide was more effective than once-daily budesonide in improving FEV₁, FVC and PEF. Ciclesonide also had an earlier onset of action than budesonide in patients with persistent asthma. Both ciclesonide and budesonide had good safety and tolerability profiles.





Alvesco[®] provides effective asthma control and good tolerability in asthma control compared to beclomethasone

Efficacy and safety of inhaled ciclesonide compared with chlorofluorocarbon beclomethasone dipropionate in adults with moderate to severe persistent asthma

Adachi M, Ishihara K, Inoue H, et al. Respirology 2007;12:573-580.

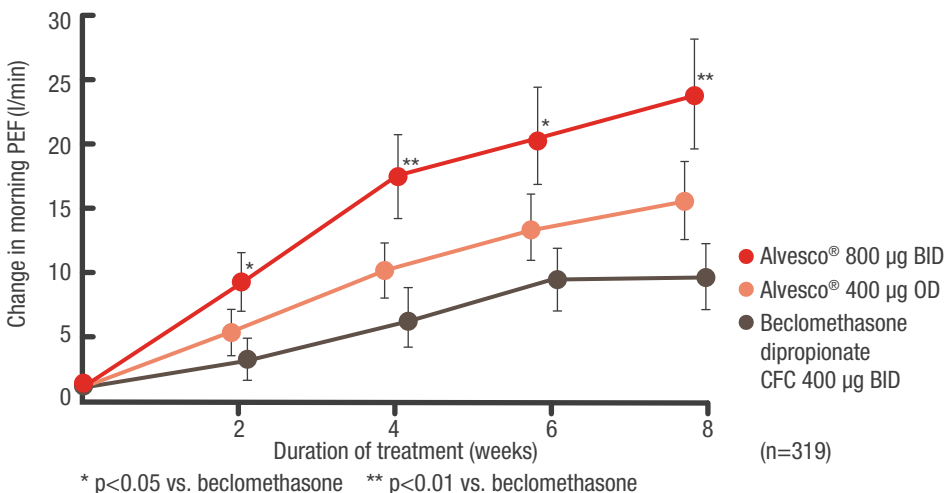
Abstract

Background and Objective: Inhaled corticosteroids are recognized as first-line therapy in the management of asthma; however, their use may be limited by systemic and local side-effects. Ciclesonide, a novel pro-drug inhaled corticosteroid, is activated in the lungs and is expected to have less systemic and local side-effects. This study evaluated the efficacy and safety of ciclesonide in hydrofluoroalkane (HFA) compared with beclomethasone dipropionate (BDP) in a chlorofluorocarbon (CFC) formulation in adult patients with moderate to severe asthma.

Methods: This was a multicentre, randomized, open-label, parallel-group comparative study. The patients were given 800 µg/day of CFC-BDP in the four-week baseline period. After the baseline period, 319 patients were randomly allocated into three groups which, respectively, received HFA-ciclesonide 400 µg/day (without a spacer), HFA-ciclesonide 800 µg/day (without spacer) and CFC-BDP 800 µg/day (with spacer) for the eight-week treatment period. The primary efficacy variable was morning PEF.

Results: The morning PEF increased by 16.02 L min⁻¹ in the 400 µg HFA-ciclesonide group, 23.98 L min⁻¹ in the 800 µg HFA-ciclesonide group and 5.91 L min⁻¹ in the 800 µg CFC-BDP group. Better outcomes were achieved by the use of 800 µg/day of HFA-ciclesonide compared with 800 µg/day of CFC-BDP ($p = 0.001$). There was no difference in adverse events between the groups.

Conclusion: In adult patients with moderate to severe asthma, 800 µg/day of HFA-ciclesonide was significantly more effective than 800 µg/day of CFC-BDP. Ciclesonide at doses of 400 µg/day and 800 µg/day was safe and well tolerated.





Alvesco[®] at high doses allows early and sustained reduction of oral steroid dose

Ciclesonide reduces the need for oral steroid use in adult patients with severe, persistent asthma

Bateman ED, Karpel J, Casale T, et al. Chest 2006;129:1176-1187.

Abstract

Study Objectives: Oral corticosteroids (OCS) may be associated with systemic adverse events (AEs), which can be reduced by replacing OCS with inhaled corticosteroids (ICS). The potential of ciclesonide, a novel ICS, to reduce OCS use in patients with severe, persistent asthma was evaluated in this study.

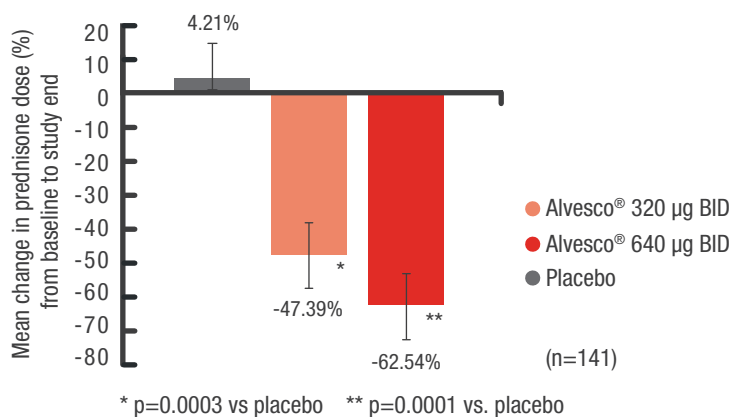
Design: A phase III, 12-week, international, multicenter, double-blind, placebo-controlled, parallel-group study.

Patients: Adult and adolescent patients (≥ 12 years old; $n = 141$) with severe, persistent, oral steroid (prednisone)-dependent asthma.

Interventions: Patients were randomized to receive ciclesonide (640 $\mu\text{g/day}$ or 1,280 $\mu\text{g/day}$ [ex-actuator]) b.i.d. or placebo for 12 weeks. Weekly evaluations determined eligibility for prednisone dose reduction based on predetermined criteria.

Measurements and Results: The prednisone dose was significantly reduced by 47% and 63% in the groups receiving ciclesonide, 640 $\mu\text{g/d}$, and ciclesonide, 1,280 $\mu\text{g/d}$, respectively, vs an increase of 4% in the placebo group (both $p \leq 0.0003$) at week 12. By week 12, prednisone was discontinued by approximately 30% of patients in the ciclesonide-treated groups, vs 11% of patients in the placebo group (both $p \leq 0.04$). FEV₁ improved significantly at week 12 in the ciclesonide treatment groups vs placebo ($p < 0.03$). The occurrence of local and systemic AEs was comparable between all treatment groups.

Conclusion: Study results suggest that ciclesonide significantly reduces the need for OCS in patients with severe, persistent asthma, while maintaining asthma control.





A switch to Alvesco[®] can optimize treatment of moderate-to-severe persistent asthma

Comparison of twice-daily inhaled ciclesonide and fluticasone propionate in patients with moderate-to-severe persistent asthma

Bateman ED, Linnhof AE, Homik L, et al. *Pulmonary Pharmacology & Therapeutics* 2008;21:264-275.

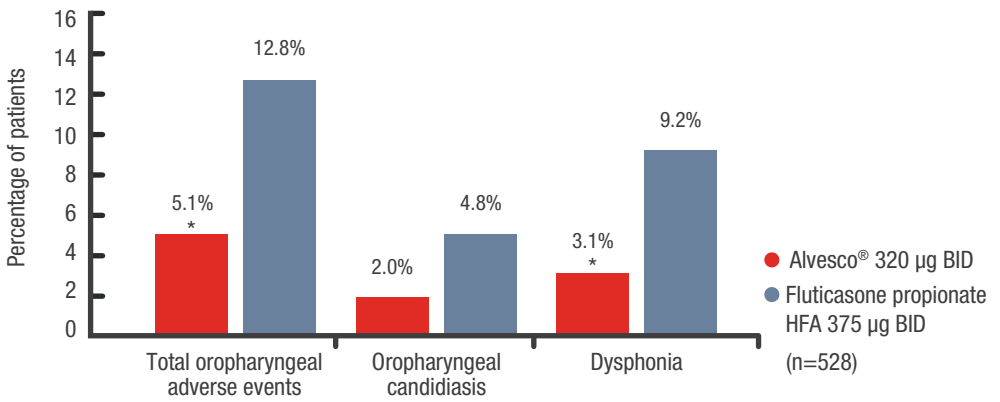
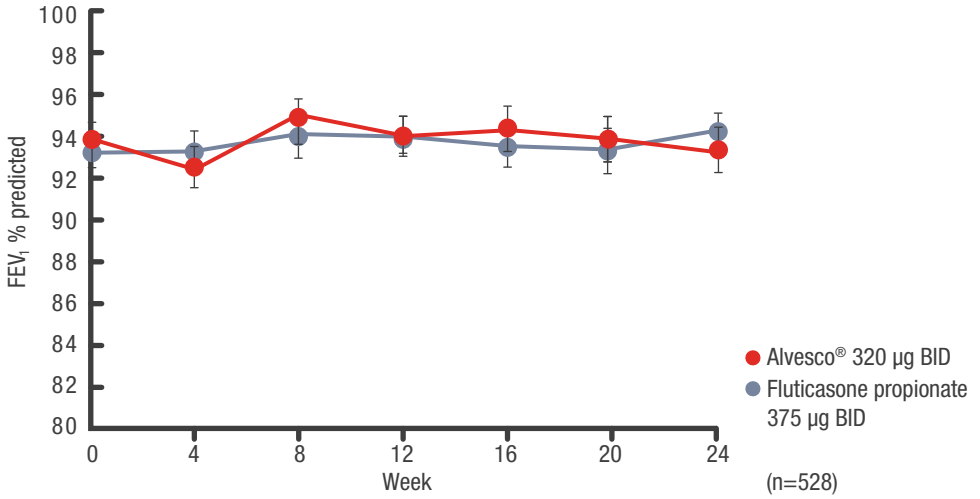
Abstract

Objective: To investigate the relative efficacy of ciclesonide and fluticasone propionate (FP) administered at comparable microgram doses in maintaining asthma control in patients with moderate-to-severe persistent asthma.

Methods: This randomized, open-label, parallel-group study enrolled patients aged 12–75 years with a ≥6-month history of bronchial asthma. To enter a 2-week run-in period, patients had to have received FP 500–1000 µg/day or equivalent at a stable dose for ≥4 weeks and have a forced expiratory volume in 1s (FEV₁) ≥80% of predicted. To enter the treatment period, patients had to have the following during run-in: FEV₁ ≥80% of predicted; reversibility of ΔFEV₁ ≥12% after 200–400 µg salbutamol; and ≥1 day without asthma symptoms during the last 7 days. Patients were randomized to twice-daily ciclesonide 320 µg (ex-actuator) or twice-daily FP 330 µg (ex-actuator) for 6 months. Efficacy was assessed by lung function, asthma exacerbations, asthma symptoms and rescue medication use. Patients completed the standardized version of the Asthma Quality of Life Questionnaire (AQLQ[S]). Adverse events (AEs), including local oropharyngeal AEs, were recorded.

Results: 528 patients were randomized (ciclesonide, $n = 255$; FP, $n = 273$). In both groups, FEV₁ was maintained from baseline to study end (mean increase: ciclesonide 11 mL, FP 24 mL; intention-to-treat [ITT] analysis). The least squares mean±standard error of the mean for the treatment difference was -13 ± 29 (95% confidence interval [CI]: -70, 44) in the ITT analysis and -27 ± 34 (95% CI: -93, 40) in the per-protocol (PP) analysis, demonstrating non-inferiority of ciclesonide to FP. Morning, evening and site-measured PEF improved significantly with both treatments (ITT and PP analyses: $p < 0.05$). Six patients receiving ciclesonide and seven receiving FP (ITT analysis) experienced an asthma exacerbation requiring treatment with oral corticosteroids. Both treatments significantly decreased asthma symptom score sum (ITT and PP analyses: $p \leq 0.0001$) and rescue medication use (ITT and PP analyses: $p < 0.05$), with no significant difference between treatments. Both treatments significantly improved overall AQLQ(S) score (ITT and PP analyses: $p < 0.05$). Significantly more patients experienced candidiasis and dysphonia with FP compared with ciclesonide ($p = 0.0023$).

Conclusion: Ciclesonide 320 µg and FP 330 µg administered twice daily over 6 months provided similar efficacy in patients with moderate or severe persistent asthma previously well-controlled by high doses of ICS at baseline. Ciclesonide was associated with fewer local AEs than FP.



* p<0.01 vs.fluticasone



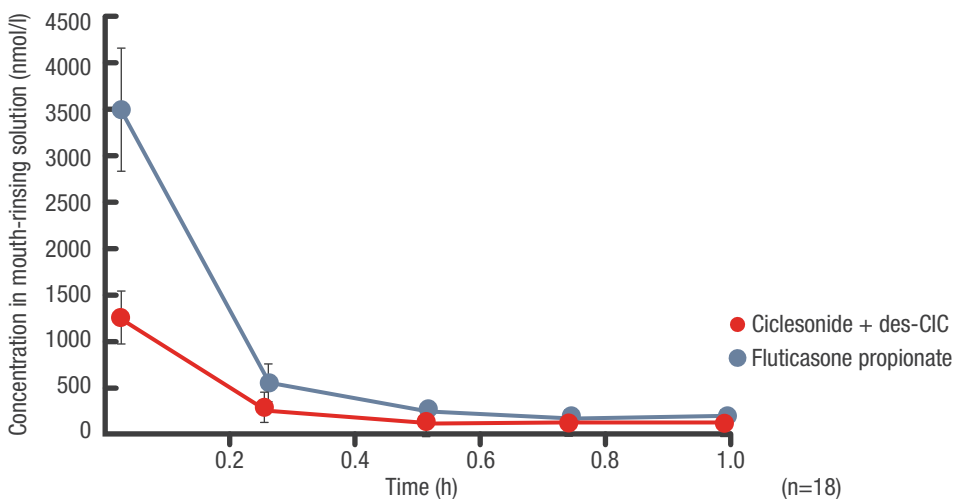
Alvesco[®] shows less oropharyngeal deposition than fluticasone propionate

Comparison of the oral deposition of inhaled ciclesonide and fluticasone propionate in patients with asthma

Richter K, Kannies F, Biberger C, et al. *Journal of Clinical Pharmacology* 2005;45:146-152.

Abstract

Ciclesonide is a novel inhaled corticosteroid that is converted in the lungs to its active metabolite, desisobutyryl-ciclesonide (des-CIC). The aim of this study was to compare the deposition of ciclesonide, as well as its conversion to des-CIC, in the oropharyngeal cavity with fluticasone propionate (FP) following inhalation via hydrofluoroalkane-propelled metered-dose inhalers (HFA-MDIs). Eighteen asthmatics inhaled ciclesonide 800 µg followed by FP 1000 µg or vice versa in an open, randomized, 2-treatment, 2-sequence study design. The oropharynx was washed out immediately and at 15, 30, 45, and 60 minutes after inhalation. Samples were analyzed for ciclesonide, des-CIC, and FP using liquid chromatography with tandem mass-spectrometric detection. Concentration-time curves and area under the concentration-time curve (AUC) were calculated for each drug. Ciclesonide and FP were recovered in almost all samples. Within 60 minutes after inhalation, the amounts of both ciclesonide and FP decreased sharply, and low residual levels were detected after 30 minutes. des-CIC was detected in relatively low concentrations, with maximum concentration 30 minutes following inhalation. The $AUC_{0-60min}$ for ciclesonide (250.4 nmol x h/L) and des-CIC (37.8 nmol x h/L) were found to be significantly lower compared with FP (636.2 nmol.h/L, $P < .001$). Approximately 50% less ciclesonide and 90% less metabolite were present in the oropharynx compared with FP. Less than 20% of the residual ciclesonide in the oropharynx was metabolized to des-CIC. These findings indicate that oropharyngeal deposition of ciclesonide is only half that of FP following inhalation from an HFA-MDI. Furthermore, there is little activation of ciclesonide to its active metabolite in the oropharynx, suggesting a decreased likelihood of inhaled ciclesonide-associated oropharyngeal side effects.





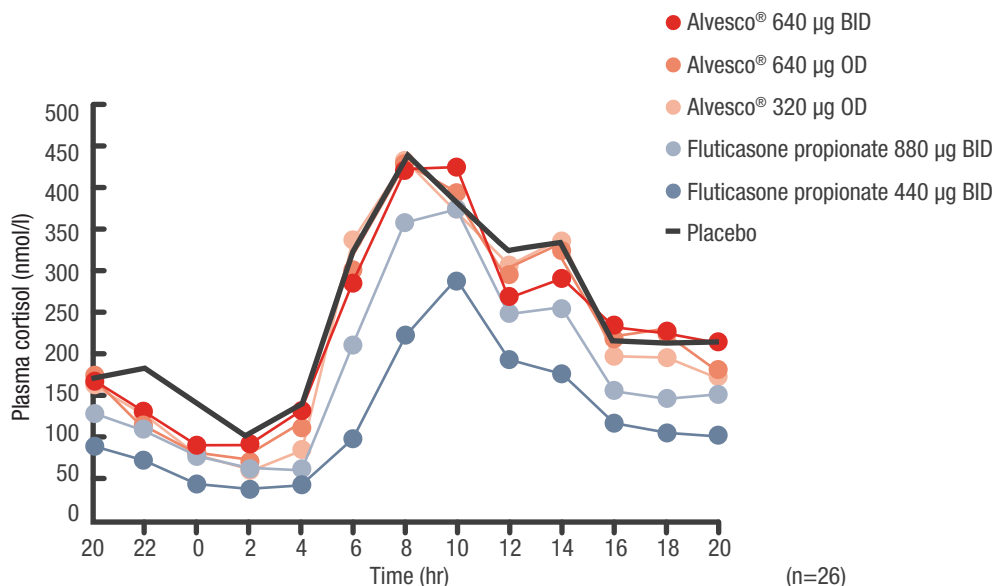
Alvesco® does not significantly suppress plasma corticosteroid levels

Effects of inhaled ciclesonide and fluticasone propionate on cortisol secretion and airway responsiveness to adenosine 50monophosphate in asthmatic patients

Derom E, Van de Velde V, Marissens S, et al. Pulmonary Pharmacology & Therapeutics 2005;18:328-336.

Abstract

The efficacy and systemic effects of ciclesonide, a novel glucocorticosteroid, inhaled via pressurized metered-dose inhaler (pMDI) were compared with fluticasone propionate pMDI in 26 patients with asthma, using a randomized, double blind, placebo-controlled, double dummy, 6-period crossover study design. Treatments were placebo, ciclesonide 320 µg (ex-actuator dose) once daily (o.d.), ciclesonide 640 µg o.d., ciclesonide 640 µg twice daily (b.i.d.), fluticasone propionate 440 µg (ex-actuator dose) b.i.d., and fluticasone propionate 880 µg b.i.d. The primary variable was area under the plasma cortisol concentration-time curve over 24 h (plasma cortisol AUC₀₋₂₄ relative to placebo) derived from samples taken every 2 h, on the 9th day of treatment. Secondary variables were 24-h urinary cortisol excretion and PC₂₀ for adenosine 5'-monophosphate (AMP) (relative to placebo and expressed in doubling concentrations). Ciclesonide did not affect 24-h cortisol secretion. Fluticasone propionate suppressed cortisol secretion as demonstrated by a decrease in plasma cortisol AUC₀₋₂₄ relative to placebo, by 29% (95% CI 15–41) and 59% (95% CI 51–66) with 440 and 880 µg b.i.d., respectively. PC₂₀ more than doubled with each active treatment, but no statistically significant dose-response effect could be established. It was concluded that moderate to high doses of fluticasone propionate suppressed cortisol secretion, that ciclesonide did not suppress cortisol secretion, and that all active treatments decreased hyperresponsiveness to AMP.



Cortisol suppression is a surrogate marker for HPA-axis function



Alvesco[®] does not affect growth

Assessment of the long-term safety of inhaled ciclesonide on growth in children with asthma.

Skoner DP, Maspero J, Banerji, et al. *Pediatrics* 2008;121:e1-14.

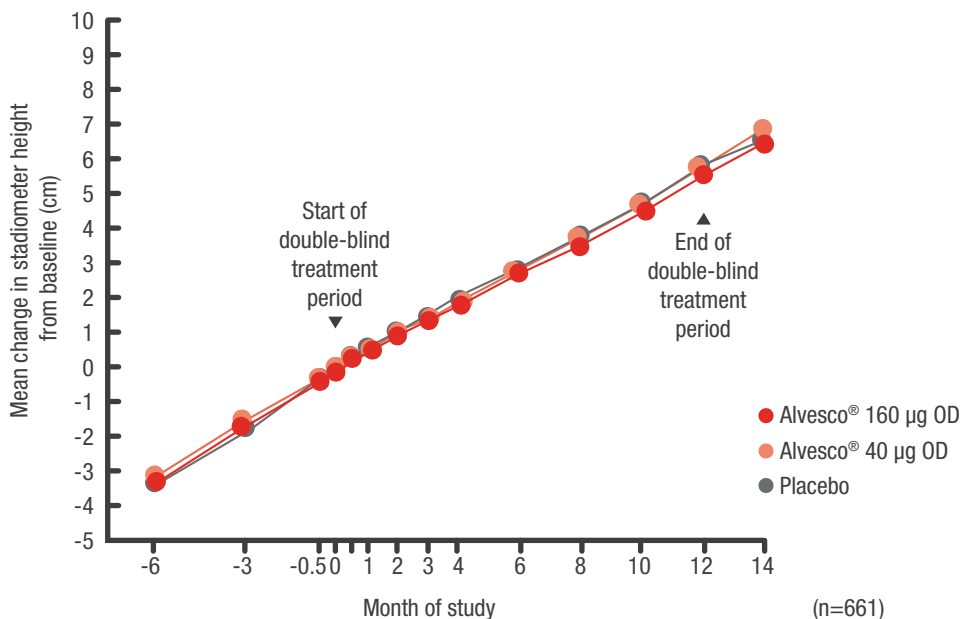
Abstract

Objective: To assess the effects of the new inhaled corticosteroid ciclesonide on growth in children with asthma.

Methods: We performed a multicenter, randomized, double-blind, placebo-controlled study to assess the effects of inhaled ciclesonide on growth in children with mild, persistent asthma. After a 6-month run-in period, 661 prepubertal children who were aged 5.0 to 8.5 years were randomly assigned to once-daily morning treatment for 1 year with ciclesonide 40 or 160 microg (ex-actuator) or placebo, followed by a 2-month follow-up period. The primary end point was the linear growth velocity (linear regression estimate) over the double-blind treatment period. Growth was recorded as the median of 4 stadiometer measurements. Adverse events and 10-hour overnight and 24-hour urinary free cortisol levels were also assessed.

Results: Mean linear growth velocity during run-in was comparable between groups: 160 microg, 6.20 cm/year; 40 microg, 6.59 cm/year; placebo, 6.49 cm/year. Mean differences from placebo (5.75 cm/year) in growth velocity over the double-blind treatment period were -0.02 cm/year for ciclesonide 40 microg and -0.15 cm/year for ciclesonide 160 microg. Both ciclesonide treatments were noninferior to placebo with respect to growth velocity. The overall incidence of adverse events was comparable between groups, and no significant changes in 10-hour overnight or 24-hour urinary free cortisol levels were noted between groups during the double-blind treatment period.

Conclusions: Ciclesonide demonstrated no detectable effect on childhood growth velocity, even at the highest dosage, which may ease concerns about systemic adverse events.





Summary of Product Characteristics

1. NAME OF THE MEDICINAL PRODUCT

Alvesco 80 micrograms pressurised inhalation, solution

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

1 actuation (delivered dose from the mouthpiece) contains 80 micrograms of ciclesonide.

For a full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Pressurised inhalation, solution

Clear and colourless

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Treatment to control persistent asthma in adults and adolescents (12 years and older).

4.2 Posology and method of administration

The medicinal product is for inhalation use only.

Dosing recommendation for adults and adolescents:

The recommended dose of Alvesco is 160 micrograms once daily, which leads to asthma control in the majority of patients. However in severe asthmatics, a 12 week study has shown that a dose of 640 micrograms/day (given 320 micrograms twice daily) has demonstrated a reduction in the frequency of exacerbations but without an improvement in lung function (see section 5.1). Dose reduction to 80 micrograms once daily may be an effective maintenance dose for some patients.

Alvesco should preferably be administered in the evening although morning dosing of Alvesco has also been shown to be effective. The final decision on evening or morning dosing should be left to the discretion of the physician.

Symptoms start to improve with Alvesco within 24 hours of treatment. Once control is achieved, the dose of Alvesco should be individualised and titrated to the minimum dose needed to maintain good asthma control.

Patients with severe asthma are at risk of acute attacks and should have regular assessments of their asthma control including pulmonary function tests. Increasing use of short-acting bronchodilators to relieve asthma symptoms indicates deterioration of asthma control. If patients find that short-acting relief bronchodilator treatment becomes less effective, or they need more inhalations than usual, medical attention must be sought. In this situation, patients should be reassessed and consideration given to the need for increased anti-inflammatory treatment therapy (e.g. a higher dose of Alvesco for a short period [see section 5.1] or a course of oral corticosteroids). Severe asthma exacerbations should be managed the usual way.

To address specific patient needs, such as finding it difficult to press the inhaler and breathe in at the same time, Alvesco can be used with the AeroChamber Plus spacer device.



Specific patient groups:

There is no need to adjust the dose in elderly patients or those with hepatic or renal impairment.

To date, there are insufficient data available in the treatment of children under 12 years of age with ciclesonide.

Instructions for use / handling:

The patient needs to be instructed how to use the inhaler correctly.

If the inhaler is new or has not been used for one week or more, three puffs should be released into the air. No shaking is necessary as this is a solution aerosol.

During inhalation, the patient should preferably sit or stand, and the inhaler should be held upright with the thumb on the base, below the mouthpiece.

Instruct the patient to remove the mouthpiece cover, place the inhaler into their mouth, close their lips around the mouthpiece, and breathe in slowly and deeply. While breathing in through the mouth, the top of the inhaler should be pressed down. Then, patients should remove the inhaler from their mouth, and hold their breath for about 10 seconds, or as long as is comfortable. The patient is not to breathe out into the inhaler. Finally, patients should breathe out slowly and replace the mouthpiece cover.

The mouthpiece should be cleaned with a dry tissue or cloth weekly. The inhaler should not be washed or put in water.

For detailed instructions see Patient Information Leaflet.

4.3 Contraindications

Hypersensitivity to ciclesonide or any of the excipients.

4.4 Special warnings and precautions for use


As with all inhaled corticosteroids, Alvesco should be administered with caution in patients with active or quiescent pulmonary tuberculosis, fungal, viral or bacterial infections, and only if these patients are adequately treated.

As with all inhaled corticosteroids, Alvesco is not indicated in the treatment of status asthmaticus or other acute episodes of asthma where intensive measures are required.

As with all inhaled corticosteroids, Alvesco is not designed to relieve acute asthma symptoms for which an inhaled short-acting bronchodilator is required. Patients should be advised to have such rescue medication available.

Systemic effects of inhaled corticosteroids may occur, particularly at high doses prescribed for prolonged periods. These effects are much less likely to occur than with oral corticosteroids. Possible systemic effects include adrenal suppression, growth retardation in children and adolescents, decrease in bone mineral density, cataract and glaucoma. It is therefore important that the dose of inhaled corticosteroid is titrated to the lowest dose at which effective control of asthma is maintained.

It is recommended that the height of children and adolescents receiving prolonged treatment with inhaled corticosteroids is regularly monitored. If growth is slowed, therapy should be reviewed with the aim of reducing the dose of inhaled corticosteroid, if possible to the lowest dose at which effective control of asthma is maintained. In addition, consideration should be given to referring the patient to a paediatric respiratory specialist.



There is no data available in patients with severe hepatic impairment. An increased exposure in patients with severe hepatic impairment is expected and these patients should therefore be monitored for potential systemic effects.

The benefits of inhaled ciclesonide should minimise the need for oral steroids. However, patients transferred from oral steroids remain at risk of impaired adrenal reserve for a considerable time after transferring to inhaled ciclesonide. The possibility of respective symptoms may persist for some time.

These patients may require specialised advice to determine the extent of adrenal impairment before elective procedures. The possibility of residual impaired adrenal response should always be considered in an emergency (medical or surgical) and elective situations likely to produce stress, and appropriate corticosteroid treatment considered.

For the transfer of patients being treated with oral corticosteroids:

The transfer of oral steroid-dependent patients to inhaled ciclesonide, and their subsequent management, needs special care as recovery from impaired adrenocortical function, caused by prolonged systemic steroid therapy, may take a considerable time.

Patients who have been treated with systemic steroids for long periods of time, or at a high dose, may have adrenocortical suppression. With these patients adrenocortical function should be monitored regularly and their dose of systemic steroid reduced cautiously.

After approximately a week, gradual withdrawal of the systemic steroid is started by reducing the dose by 1 mg prednisolone per week, or its equivalent. For maintenance doses of prednisolone in excess of 10 mg daily, it may be appropriate to cautiously use larger reductions in dose at weekly intervals.

Some patients feel unwell in a non-specific way during the withdrawal phase despite maintenance or even improvement of respiratory function. They should be encouraged to persevere with inhaled ciclesonide and to continue withdrawal of systemic steroid, unless there are objective signs of adrenal insufficiency.

Patients transferred from oral steroids whose adrenocortical function is still impaired should carry a steroid warning card indicating that they need supplementary systemic steroid during periods of stress, e.g. worsening asthma attacks, chest infections, major intercurrent illness, surgery, trauma, etc.

Replacement of systemic steroid treatment with inhaled therapy sometimes unmasks allergies such as allergic rhinitis or eczema previously controlled by systemic drug.

Paradoxical bronchospasm with an immediate increase of wheezing or other symptoms of bronchoconstriction after dosing should be treated with an inhaled short-acting bronchodilator, which usually results in quick relief. The patient should be assessed and therapy with Alvesco should only be continued, if after careful consideration the expected benefit is greater than the possible risk. Correlation between severity of asthma and general susceptibility for acute bronchial reactions should be kept in mind (see section 4.8).

Patients inhaler technique should be checked regularly to make sure that inhaler actuation is synchronised with inhaling to ensure optimum delivery to the lungs.

Concomitant treatment with ketoconazole or other potent CYP3A4 inhibitors should be avoided unless the benefit outweighs the increased risk of systemic side effects of corticosteroids (see section 4.5).



4.5 Interaction with other medicinal products and other forms of interaction

In vitro data indicate that CYP3A4 is the major enzyme involved in the metabolism of the active metabolite of ciclesonide M1 in man.

In a drug-drug interaction study at steady state with ciclesonide and ketoconazole as a potent CYP3A4 inhibitor, the exposure to the active metabolite M1 increased approximately 3.5-fold, whereas the exposure to ciclesonide was not affected. Therefore the concomitant administration of potent inhibitors of CYP 3A4 (e.g. ketoconazole, itraconazole and ritonavir or nelfinavir) should be avoided unless the benefit outweighs the increased risk of systemic side effects of corticosteroids.

4.6 Pregnancy and lactation

There are no adequate and well-controlled studies in pregnant women.

In animal studies glucocorticoids have been shown to induce malformations (see section 5.3). This is not likely to be relevant for humans given recommended inhalation doses.

As with other glucocorticoids, ciclesonide should only be used during pregnancy if the potential benefit to the mother justifies the potential risk to the fetus. The lowest effective dose of ciclesonide needed to maintain adequate asthma control should be used.

Infants born of mothers who received corticosteroids during pregnancy are to be observed carefully for hypoadrenalism.

It is unknown whether inhaled ciclesonide is excreted in human breast milk. Administration of ciclesonide to women who are breast-feeding should only be considered if the expected benefit to the mother is greater than any possible risk to the child.

4.7 Effects on ability to drive and use machines

Inhaled ciclesonide has no or negligible influence on the ability to drive and use machines.

4.8 Undesirable effects

Approximately 5% of patients experienced adverse reactions in clinical trials with Alvesco given in the dose range 40 to 1280 micrograms per day. In the majority of cases, these were mild and did not require discontinuation of treatment with Alvesco.

System Organ Class	Frequency (>1/1,000, <1/100)	Rare (1/10,000 – 1/1,000)
Cardiac Disorders		Palpitations**
Gastrointestinal Disorders	Nausea, vomiting* Bad taste	Abdominal pain* Dyspepsia*
General disorders and administration site conditions	Application site reactions Application site dryness	
Immune System Disorders		Angioedema Hypersensitivity
Infections and infestations	Oral fungal infections*	
Nervous System Disorders	Headache*	
Respiratory, thoracic and mediastinal disorders	Dysphonia Cough after inhalation* Paradoxical bronchospasm*	
Skin and subcutaneous tissue disorders	Eczema and rash	
Vascular disorders		Hypertension

* Similar or lower incidence when compared with placebo

** Palpitations were observed in clinical trials in cases mostly confounded with concomitant medication with known cardiac effects (e.g. theophylline or salbutamol).

Paradoxical bronchospasm may occur immediately after dosing and is an unspecific acute reaction to all inhaled medicinal products, which may be related to the active substance, the excipient, or evaporation cooling in the case of metered dose inhalers. In severe cases, withdrawal of Alvesco should be considered.

Systemic effects of inhaled corticosteroids may occur, particularly at high doses prescribed for prolonged periods. Possible systemic effects include Cushing's syndrome, Cushingoid features, adrenal suppression, growth retardation in children and adolescents, decrease in bone mineral density, cataract, glaucoma (see also section 4.4).

4.9 Overdose

Acute:

Inhalation by healthy volunteers of a single dose of 2880 micrograms of ciclesonide was well tolerated.

The potential for acute toxic effects following overdose of inhaled ciclesonide is low. After acute overdosage no specific treatment is necessary.

Chronic:

After prolonged administration of 1280 micrograms of ciclesonide, no clinical signs of adrenal suppression were observed. However, if higher than recommended dosage is continued over prolonged periods, some degree of adrenal suppression cannot be excluded. Monitoring of adrenal reserve may be necessary.



5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Other drugs for obstructive airway diseases, Inhalants, Glucocorticoids, ATC Code: R03B A08

Ciclesonide exhibits low binding affinity to the glucocorticoid-receptor. Once orally inhaled, ciclesonide is enzymatically converted in the lungs to the principal metabolite (C21-des-methylpropionyl-ciclesonide) which has a pronounced anti-inflammatory activity and is thus considered as the active metabolite.

In four clinical trials, ciclesonide has been shown to reduce airway hyperresponsiveness to adenosine monophosphate in hyperreactive patients with maximal effect observed at the dose of 640 micrograms. In another trial, pretreatment with ciclesonide for seven days significantly attenuated the early and late phase reactions following inhaled allergen challenge. Inhaled ciclesonide treatment was also shown to attenuate the increase in inflammatory cells (total eosinophils) and inflammatory mediators in induced sputum.

A controlled study compared 24-hour plasma cortisol AUC in 26 adult asthmatic patients following 7 days of treatment. Compared to placebo, treatment with ciclesonide 320, 640, and 1,280 micrograms/day did not statistically significantly lower the 24-hour time averages of plasma cortisol ($AUC_{(0-24)}/24$ hours) nor was a dose-dependent effect seen.

In a clinical trial involving 164 adult male and female asthmatic patients, ciclesonide was given at doses of 320 micrograms or 640 micrograms/day over 12 weeks. After stimulation with 1 and 250 micrograms cosyntropin, no significant changes in plasma cortisol levels were observed versus placebo.

Double-blind placebo-controlled trials of 12-weeks duration in adults and adolescents have shown that treatment with ciclesonide resulted in improved lung function as measured by FEV_1 and peak expiratory flow, improved asthma symptom control, and decreased need for inhaled beta-2 agonist.

In a 12-week study of 680 severe asthmatics, previously treated with 500-1,000 micrograms fluticasone propionate per day or equivalent, 87.3% and 93.3% of patients remained exacerbation-free during treatment with 160 or 640 micrograms of ciclesonide, respectively. At the end of the 12 week study period, the results showed a statistically significant difference between the doses of 160 micrograms and 640 micrograms/day ciclesonide with regard to the occurrence of an exacerbation after the first day of the study: 43 patients/339 (= 12.7%) in the 160 micrograms/day group and 23 patients/341 (6.7%) in the 640 micrograms/day group (Hazard ratio=0.526; $p=0.0134$). Both ciclesonide doses resulted in comparable FEV_1 values at 12 weeks. Treatment-related adverse events were seen in 3.8% and 5% of patients treated with 160 or 640 micrograms per day of ciclesonide respectively. No study was performed to compare 160 micrograms, 320 micrograms and 640 micrograms daily dose in patients with severe asthma.

5.2 Pharmacokinetic properties

Ciclesonide is presented in HFA-134a propellant and ethanol as a solution aerosol, which demonstrates a linear relationship between different doses, puff strengths and systemic exposure.

Absorption:

Studies with oral and intravenous dosing of radiolabeled ciclesonide have shown an incomplete extent of oral absorption (24.5%). The oral bioavailability of both ciclesonide and the active metabolite is negligible (<0.5% for ciclesonide, <1% for the metabolite). Based on a γ -scintigraphy experiment, lung deposition in healthy subjects is 52%. In line with this figure, the systemic bioavailability for the active metabolite is >50% by using the ciclesonide metered dose inhaler. As the oral bioavailability for the active metabolite is <1%, the swallowed portion of the inhaled ciclesonide does not contribute to systemic absorption.



Distribution:

Following intravenous administration to healthy subjects, the initial distribution phase for ciclesonide was rapid and consistent with its high lipophilicity. The volume of distribution averaged 2.9 l/kg. The total serum clearance of ciclesonide is high (average 2.0 l/h/kg) indicating a high hepatic extraction. The percentage of ciclesonide bound to human plasma proteins averaged 99%, and that of the active metabolite 98-99%, indicating an almost complete binding of circulating ciclesonide/active metabolite to plasma proteins.

Metabolism:

Ciclesonide is primarily hydrolysed to its biologically active metabolite by esterase enzymes in the lung. Investigation of the enzymology of further metabolism by human liver microsomes showed that this compound is mainly metabolized to hydroxylated inactive metabolites by CYP3A4 catalysis. Furthermore, reversible lipophilic fatty acid ester conjugates of the active metabolite were detected in the lung.

Excretion:

Ciclesonide is predominantly excreted via the faeces (67%), after oral and intravenous administration, indicating that excretion via the bile is the major route of elimination.

Pharmacokinetic characteristics in patients:

Asthmatic patients

Ciclesonide shows no pharmacokinetic changes in mild asthmatic patients compared to healthy subjects.

Renal or hepatic insufficiency, elderly

According to population pharmacokinetics, age has no impact on the systemic exposure of the active metabolite.

Reduced liver function may affect the elimination of corticosteroids. In a study including patients with hepatic impairment suffering from liver cirrhosis, a higher systemic exposure to the active metabolite was observed.

Due to the lack of renal excretion of the active metabolite, studies on renal impaired patients have not been performed.

5.3 Preclinical safety data

Preclinical data with ciclesonide reveal no special hazard for humans based on conventional studies of safety pharmacology, repeated dose toxicity, genotoxicity, or carcinogenic potential.

In animal studies on reproductive toxicity, glucocorticosteroids have been shown to induce malformations (cleft palate, skeletal malformations). However, these animal results do not seem to be relevant for humans given recommended doses.

A treatment-related effect on the ovaries (namely atrophy) was observed at the top dose in two 12-month studies in dogs. This effect occurred at systemic exposures 5.27-8.34 times those noted at the 160 µg daily dose. The relevance of this finding to humans is unknown.

Animal studies with other glucocorticoids indicate that administration of pharmacological doses of glucocorticoids during pregnancy may increase the risk for intrauterine growth retardation, adult cardiovascular and/or metabolic disease and/or permanent changes in glucocorticoid receptor density, neurotransmitter turnover and behaviour. The relevance of these data to humans administered ciclesonide by inhalation is unknown.



6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Norflurane (HFA-134a)

Ethanol, anhydrous

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

60 and 120 metered actuations – 3 years

6.4 Special precautions for storage

This medicinal product does not require any special storage conditions.

The container contains a pressurised liquid. Do not expose to temperatures higher than 50°C.

The container should not be punctured, broken or burnt even when apparently empty.

6.5 Nature and contents of container

The inhaler comprises a pressurised container made from aluminium and is sealed with a metering valve, mouthpiece, and cap.

60 metered actuations

120 metered actuations

Not all pack sizes may be marketed.

6.6 Instructions for use and handling

Patients should be carefully instructed in the proper use of their inhaler (see Patient Information Leaflet).

As with most inhaled medicinal products in pressurised containers, the therapeutic effect of this medicinal product may decrease when the container is cold. However, Alvesco delivers a consistent dose from –10°C to 40°C.

7. MARKETING AUTHORISATION HOLDER

Nycomed GmbH, Byk-Gulden-Str. 2, D-78467 Konstanz, Germany

8. MARKETING AUTHORISATION NUMBER(S)

[To be completed nationally]

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

[To be completed nationally]

10. DATE OF REVISION OF THE TEXT

27 September 2009



1. NAME OF THE MEDICINAL PRODUCT

Alvesco 160 micrograms pressurised inhalation, solution.

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

1 actuation (delivered dose from the mouthpiece) contains 160 micrograms of ciclesonide.

For a full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Pressurised inhalation, solution

Clear and colourless

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Treatment to control persistent asthma in adults and adolescents (12 years and older).

4.2 Posology and method of administration

The medicinal product is for inhalation use only.

Dosing recommendation for adults and adolescents:

The recommended dose of Alvesco is 160 micrograms once daily, which leads to asthma control in the majority of patients. However in severe asthmatics, a 12 week study has shown that a dose of 640 micrograms/day (given 320 micrograms twice daily) has demonstrated a reduction in the frequency of exacerbations but without an improvement in lung function (see section 5.1). Dose reduction to 80 micrograms once daily may be an effective maintenance dose for some patients.

Alvesco should preferably be administered in the evening although morning dosing of Alvesco has also been shown to be effective. The final decision on evening or morning dosing should be left to the discretion of the physician.

Symptoms start to improve with Alvesco within 24 hours of treatment. Once control is achieved, the dose of Alvesco should be individualised and titrated to the minimum dose needed to maintain good asthma control.

Patients with severe asthma are at risk of acute attacks and should have regular assessments of their asthma control including pulmonary function tests. Increasing use of short-acting bronchodilators to relieve asthma symptoms indicates deterioration of asthma control. If patients find that short-acting relief bronchodilator treatment becomes less effective, or they need more inhalations than usual, medical attention must be sought. In this situation, patients should be reassessed and consideration given to the need for increased anti-inflammatory treatment therapy (e.g. a higher dose of Alvesco for a short period [see section 5.1] or a course of oral corticosteroids). Severe asthma exacerbations should be managed the usual way.

To address specific patient needs, such as finding it difficult to press the inhaler and breathe in at the same time, Alvesco can be used with the AeroChamber Plus spacer device.

Specific patient groups:

There is no need to adjust the dose in elderly patients or those with hepatic or renal impairment.

To date, there are insufficient data available in the treatment of children under 12 years of age with ciclesonide.



Instructions for use / handling:

The patient needs to be instructed how to use the inhaler correctly.

If the inhaler is new or has not been used for one week or more, three puffs should be released into the air. No shaking is necessary as this is a solution aerosol.

During inhalation, the patient should preferably sit or stand, and the inhaler should be held upright with the thumb on the base, below the mouthpiece.

Instruct the patient to remove the mouthpiece cover, place the inhaler into their mouth, close their lips around the mouthpiece, and breathe in slowly and deeply. While breathing in through the mouth, the top of the inhaler should be pressed down. Then, patients should remove the inhaler from their mouth, and hold their breath for about 10 seconds, or as long as is comfortable. The patient is not to breathe out into the inhaler. Finally, patients should breathe out slowly and replace the mouthpiece cover.

The mouthpiece should be cleaned with a dry tissue or cloth weekly. The inhaler should not be washed or put in water.

For detailed instructions see Patient Information Leaflet.

4.3 Contraindications

Hypersensitivity to ciclesonide or any of the excipients.

4.4 Special warnings and precautions for use

As with all inhaled corticosteroids, Alvesco should be administered with caution in patients with active or quiescent pulmonary tuberculosis, fungal, viral or bacterial infections, and only if these patients are adequately treated.

As with all inhaled corticosteroids, Alvesco is not indicated in the treatment of status asthmaticus or other acute episodes of asthma where intensive measures are required.


As with all inhaled corticosteroids, Alvesco is not designed to relieve acute asthma symptoms for which an inhaled short-acting bronchodilator is required. Patients should be advised to have such rescue medication available.

Systemic effects of inhaled corticosteroids may occur, particularly at high doses prescribed for prolonged periods. These effects are much less likely to occur than with oral corticosteroids. Possible systemic effects include adrenal suppression, growth retardation in children and adolescents, decrease in bone mineral density, cataract and glaucoma. It is therefore important that the dose of inhaled corticosteroid is titrated to the lowest dose at which effective control of asthma is maintained.

It is recommended that the height of children and adolescents receiving prolonged treatment with inhaled corticosteroids is regularly monitored. If growth is slowed, therapy should be reviewed with the aim of reducing the dose of inhaled corticosteroid, if possible to the lowest dose at which effective control of asthma is maintained. In addition, consideration should be given to referring the patient to a paediatric respiratory specialist.

There is no data available in patients with severe hepatic impairment. An increased exposure in patients with severe hepatic impairment is expected and these patients should therefore be monitored for potential systemic effects.

The benefits of inhaled ciclesonide should minimise the need for oral steroids. However, patients transferred from oral steroids remain at risk of impaired adrenal reserve for a considerable time after transferring to inhaled ciclesonide. The possibility of respective symptoms may persist for some time.



These patients may require specialised advice to determine the extent of adrenal impairment before elective procedures. The possibility of residual impaired adrenal response should always be considered in an emergency (medical or surgical) and elective situations likely to produce stress, and appropriate corticosteroid treatment considered.

For the transfer of patients being treated with oral corticosteroids:

The transfer of oral steroid-dependent patients to inhaled ciclesonide, and their subsequent management, needs special care as recovery from impaired adrenocortical function, caused by prolonged systemic steroid therapy, may take a considerable time.

Patients who have been treated with systemic steroids for long periods of time, or at a high dose, may have adrenocortical suppression. With these patients adrenocortical function should be monitored regularly and their dose of systemic steroid reduced cautiously.

After approximately a week, gradual withdrawal of the systemic steroid is started by reducing the dose by 1 mg prednisolone per week, or its equivalent. For maintenance doses of prednisolone in excess of 10 mg daily, it may be appropriate to cautiously use larger reductions in dose at weekly intervals.

Some patients feel unwell in a non-specific way during the withdrawal phase despite maintenance or even improvement of respiratory function. They should be encouraged to persevere with inhaled ciclesonide and to continue withdrawal of systemic steroid, unless there are objective signs of adrenal insufficiency.

Patients transferred from oral steroids whose adrenocortical function is still impaired should carry a steroid warning card indicating that they need supplementary systemic steroid during periods of stress, e.g. worsening asthma attacks, chest infections, major intercurrent illness, surgery, trauma, etc.

Replacement of systemic steroid treatment with inhaled therapy sometimes unmasks allergies such as allergic rhinitis or eczema previously controlled by systemic drug.

Paradoxical bronchospasm with an immediate increase of wheezing or other symptoms of bronchoconstriction after dosing should be treated with an inhaled short-acting bronchodilator, which usually results in quick relief. The patient should be assessed and therapy with Alvesco should only be continued, if after careful consideration the expected benefit is greater than the possible risk. Correlation between severity of asthma and general susceptibility for acute bronchial reactions should be kept in mind (see section 4.8).

Patients inhaler technique should be checked regularly to make sure that inhaler actuation is synchronised with inhaling to ensure optimum delivery to the lungs.

Concomitant treatment with ketoconazole or other potent CYP3A4 inhibitors should be avoided unless the benefit outweighs the increased risk of systemic side effects of corticosteroids (see section 4.5).

4.5 Interaction with other medicinal products and other forms of interaction

In vitro data indicate that CYP3A4 is the major enzyme involved in the metabolism of the active metabolite of ciclesonide M1 in man.

In a drug-drug interaction study at steady state with ciclesonide and ketoconazole as a potent CYP3A4 inhibitor, the exposure to the active metabolite M1 increased approximately 3.5-fold, whereas the exposure to ciclesonide was not affected. Therefore the concomitant administration of potent inhibitors of CYP 3A4 (e.g. ketoconazole, itraconazole and ritonavir or nelfinavir) should be avoided unless the benefit outweighs the increased risk of systemic side effects of corticosteroids.

4.6 Pregnancy and lactation

There are no adequate and well-controlled studies in pregnant women.

In animal studies glucocorticoids have been shown to induce malformations (see section 5.3). This is not likely to be relevant for humans given recommended inhalation doses.

As with other glucocorticoids, ciclesonide should only be used during pregnancy if the potential benefit to the mother justifies the potential risk to the fetus. The lowest effective dose of ciclesonide needed to maintain adequate asthma control should be used.

Infants born of mothers who received corticosteroids during pregnancy are to be observed carefully for hypoadrenalism.

It is unknown whether inhaled ciclesonide is excreted in human breast milk. Administration of ciclesonide to women who are breast-feeding should only be considered if the expected benefit to the mother is greater than any possible risk to the child.

4.7 Effects on ability to drive and use machines

Inhaled ciclesonide has no or negligible influence on the ability to drive and use machines.


4.8 Undesirable effects

Approximately 5% of patients experienced adverse reactions in clinical trials with Alvesco given in the dose range 40 to 1280 micrograms per day. In the majority of cases, these were mild and did not require discontinuation of treatment with Alvesco.

System Organ Class	Frequency Uncommon (>1/1,000 – <1/100)	Rare (1/10,000 – 1/1,000)
Cardiac Disorders		Palpitations**
Gastrointestinal Disorders	Nausea, vomiting* Bad taste	Abdominal pain* Dyspepsia*
General disorders and administration site conditions	Application site reactions Application site dryness	
Immune System Disorders		Angioedema Hypersensitivity
Infections and infestations	Oral fungal infections*	
Nervous System Disorders	Headache*	
Respiratory, thoracic and mediastinal disorders	Dysphonia Cough after inhalation* Paradoxical bronchospasm*	
Skin and subcutaneous tissue disorders	Eczema and rash	
Vascular disorders		Hypertension

* Similar or lower incidence when compared with placebo

** Palpitations were observed in clinical trials in cases mostly confounded with concomitant medication with known cardiac effects (e.g. theophylline or salbutamol).



Paradoxical bronchospasm may occur immediately after dosing and is an unspecific acute reaction to all inhaled medicinal products, which may be related to the active substance, the excipient, or evaporation cooling in the case of metered dose inhalers. In severe cases, withdrawal of Alvesco should be considered.

Systemic effects of inhaled corticosteroids may occur, particularly at high doses prescribed for prolonged periods. Possible systemic effects include Cushing's syndrome, Cushingoid features, adrenal suppression, growth retardation in children and adolescents, decrease in bone mineral density, cataract, glaucoma (see also section 4.4).

4.9 Overdose

Acute:

Inhalation by healthy volunteers of a single dose of 2880 micrograms of ciclesonide was well tolerated.

The potential for acute toxic effects following overdose of inhaled ciclesonide is low. After acute overdose no specific treatment is necessary.

Chronic:

After prolonged administration of 1280 micrograms of ciclesonide, no clinical signs of adrenal suppression were observed. However, if higher than recommended dosage is continued over prolonged periods, some degree of adrenal suppression cannot be excluded. Monitoring of adrenal reserve may be necessary.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Other drugs for obstructive airway diseases, Inhalants, Glucocorticoids, ATC Code: R03B A08


Ciclesonide exhibits low binding affinity to the glucocorticoid-receptor. Once orally inhaled, ciclesonide is enzymatically converted in the lungs to the principal metabolite (C21-des-methylpropionyl-ciclesonide) which has a pronounced anti-inflammatory activity and is thus considered as the active metabolite.

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Distribution:

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Ciclesonide is predominantly excreted via the faeces (67%), after oral and intravenous administration, indicating that excretion via the bile is the major route of elimination.

Pharmacokinetic characteristics in patients:

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Ciclesonide shows no pharmacokinetic changes in mild asthmatic patients compared to healthy subjects.



Renal or hepatic insufficiency, elderly

According to population pharmacokinetics, age has no impact on the systemic exposure of the active metabolite.

Reduced liver function may affect the elimination of corticosteroids. In a study including patients with hepatic impairment suffering from liver cirrhosis, a higher systemic exposure to the active metabolite was observed.

Due to the lack of renal excretion of the active metabolite, studies on renal impaired patients have not been performed.

5.3 Preclinical safety data

Preclinical data with ciclesonide reveal no special hazard for humans based on conventional studies of safety pharmacology, repeated dose toxicity, genotoxicity, or carcinogenic potential.

In animal studies on reproductive toxicity, glucocorticosteroids have been shown to induce malformations (cleft palate, skeletal malformations). However, these animal results do not seem to be relevant for humans given recommended doses.

A treatment-related effect on the ovaries (namely atrophy) was observed at the top dose in two 12-month studies in dogs. This effect occurred at systemic exposures 5.27-8.34 times those noted at the 160 µg daily dose. The relevance of this finding to humans is unknown.

Animal studies with other glucocorticoids indicate that administration of pharmacological doses of glucocorticoids during pregnancy may increase the risk for intrauterine growth retardation, adult cardiovascular and/or metabolic disease and/or permanent changes in glucocorticoid receptor density, neurotransmitter turnover and behaviour. The relevance of these data to humans administered ciclesonide by inhalation is unknown.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Norflurane (HFA-134a)
Ethanol, anhydrous

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

60 and 120 metered actuations – 3 years

6.4 Special precautions for storage

This medicinal product does not require any special storage conditions.

The container contains a pressurised liquid. Do not expose to temperatures higher than 50°C.

The container should not be punctured, broken or burnt even when apparently empty.



6.5 Nature and contents of container

The inhaler comprises a pressurised container made from aluminium and is sealed with a metering valve, mouthpiece, and cap.

60 metered actuations
120 metered actuations

Hospital packs:
10 x 60 metered actuations
10 x 120 metered actuations

Not all pack sizes may be marketed.

6.6 Instructions for use and handling

Patients should be carefully instructed in the proper use of their inhaler (see Patient Information Leaflet).

As with most inhaled medicinal products in pressurised containers, the therapeutic effect of this medicinal product may decrease when the container is cold. However, Alvesco delivers a consistent dose from -10°C to 40°C.

7. MARKETING AUTHORISATION HOLDER

Nycomed GmbH, Byk-Gulden-Str. 2, D-78467 Konstanz, Germany

8. MARKETING AUTHORISATION NUMBER(S)

[To be completed nationally]

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

[To be completed nationally]

10. DATE OF REVISION OF THE TEXT

27 September 2009