

Ciclesonide for the treatment of asthma

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Abstract: Ciclesonide is a nonhalogenated corticosteroid that is converted to its clinically active metabolite, desisobutyryl-ciclesonide, by esterases in the airways. Pharmacodynamic studies have shown that inhaled ciclesonide has potent antiinflammatory activity in patients with asthma, and does not appear to have clinically relevant systemic effects, even at high doses. It is highly protein-bound and rapidly metabolized by the liver, and thus has a low oral bioavailability. Ciclesonide is formulated as a solution for inhalation using a hydrofluoroalkane pressurized metered-dose inhaler. This formulation delivers a high fraction of respirable particles that yield high lung deposition with even distribution throughout the lungs and minimal oropharyngeal deposition. Results from numerous 12-week trials in patients (including children) with varying degrees of asthma show that morning or evening dosing with ciclesonide is more effective than placebo, and at least equivalent to other inhaled corticosteroids such as budesonide and fluticasone, with regard to improved spirometry, symptom scores, and less need for rescue medication. Results with once-daily ciclesonide are similar to those with twice-daily budesonide or fluticasone. At the dosages used in clinical trials, ciclesonide did not exert any untoward adverse effects and did not affect cortisol production. The favorable pharmacological properties of ciclesonide help explain the low incidence of adverse events, which are mostly mild to moderate in nature. Once-daily ciclesonide offers an efficacious treatment option for stepwise asthma management when inhaled corticosteroids are required.

Keywords: ciclesonide, asthma, inhaled corticosteroids, adults, children

Introduction

The number of persons worldwide with asthma has increased to around 300 million, and may reach 400 million by 2025 (GIA 2005). The reasons for this dramatic increase are under investigation and may relate to adoption of Western lifestyles and urbanization (GIA 2005). About 1% of all disability-adjusted life years are lost due to asthma, and asthma accounts for 1 in every 250 deaths worldwide (GIA 2005). Asthma is characterized by bronchospasm and inflammation, and airway remodeling may occur in some patients – all of which can result in moderate and severe persistent disease requiring long-term management (NAEPP 2002).

There is a problem with under-diagnosis of asthma (Hasselgren et al 2001) and, once diagnosed, with inadequate management of underlying inflammation, particularly in patients with intermittent disease. A study in adolescents with mild intermittent asthma found evidence of persistent airway inflammation, which suggests that these patients may benefit from early intervention with inhaled corticosteroids (ICS) (Spallarossa et al 2003). Such intervention in mild persistent asthma improves asthma control and reduces the risk of severe asthma exacerbations (Pauwels et al 2003).

Inhaled corticosteroids are the cornerstone of asthma therapy and are recommended for daily control of mild, moderate, and severe persistent asthma in adults and children (GIA 2004). While the established efficacy of ICS in asthma has led to their acceptance as first-line control of persistent asthma (GIA 2004), their use

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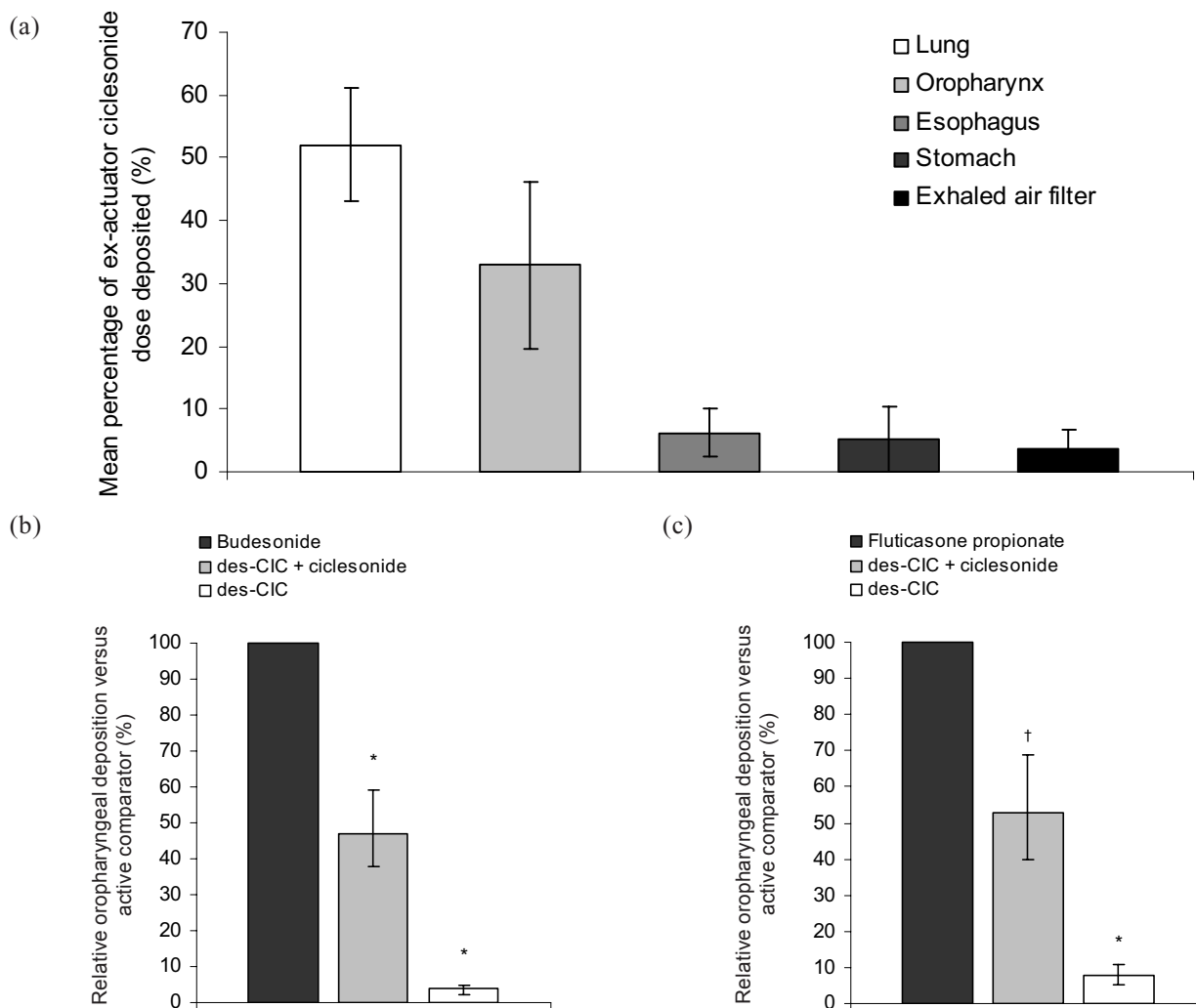


Figure 1 Deposition characteristics of ciclesonide: (a) Mean (\pm SD) percentage of a single dose of ^{99m}Tc -ciclesonide 320 μg deposited in the lung, oropharynx, esophagus, stomach, or exhaled air filter, in 12 adult patients with asthma (measured by 2D gamma-scintigraphy) (Newman et al 2004); (b) Relative oropharyngeal deposition of ciclesonide 800 μg inhaled via HFA MDI and desisobutyryl-ciclesonide (des-CIC) compared with budesonide 800 μg inhaled via CFC MDI in the first hour following administration, as measured in oropharyngeal wash samples from 18 healthy volunteers (values were calculated using molar dose-adjusted area under the curve data) (Nave R, Zech K, Bethke TD. 2005b. Lower oropharyngeal deposition of inhaled ciclesonide via hydrofluoroalkane metered-dose inhaler compared with budesonide via chlorofluorocarbon metered-dose inhaler in healthy subjects. *Eur J Clin Pharmacol*. 61:203-8. Copyright © 2005. Reproduced with permission from European Journal of Clinical Pharmacology); (c) Relative oropharyngeal deposition of ciclesonide 800 μg inhaled via HFA MDI and des-CIC compared with fluticasone propionate 1000 μg inhaled via HFA MDI in the first hour following administration in 18 patients with asthma. (Richter et al 2005).

* $p < 0.0001$ versus active comparator.

† $p < 0.001$ versus active comparator.

Abbreviations: CIC, ciclesonide; CFC, chlorofluorocarbon; HFA, hydrofluoroalkane; MDI, marked-dose inhaler; SD, standard deviation.

may be limited by local adverse effects such as oral candidiasis, and there is some concern about potential long-term systemic effects, including cortisol suppression, growth retardation in children, and risk of osteoporosis and fractures (Ellepola and Samaranyake 2001; Salvatoni et al 2003; Hubbard and Tattersfield 2004). Ciclesonide is a new once-daily ICS with similar efficacy to other ICS in asthma, and it possesses potential advantages in terms of reduced local and systemic adverse effects. It is available as 80 μg and 160 μg inhalers. Each actuation delivers either 80 μg or 160 μg of ciclesonide from the mouthpiece (ex-actuator). In the following review, some studies reported the

ciclesonide dose released from the valve, ie, ciclesonide 100 μg or 200 μg ex-valve, which are equivalent to ciclesonide 80 or 160 μg ex-actuator, respectively.

Pharmacology

Pharmacokinetics

Ciclesonide is a nonhalogenated ICS that is formulated as a solution for inhalation in a hydrofluoroalkane (HFA) pressurized metered-dose inhaler (MDI). This device delivers ciclesonide in fine particle spray (average particle size 1.1–2.1 μm) that yields a high fraction of respirable

particles (Rohatagi, Derandorf, et al 2003; Newman et al 2004; Rohatagi et al 2004). In adult patients with asthma, inhalation of a single dose of ^{99m}Tc -labeled ciclesonide 320 μg resulted in a mean of 52% of the ex-actuator dose reaching the lungs (Newman et al 2004). Deposition of ciclesonide within the lung was highest (approximately 55%) in the outermost regions, ie, small airways and alveoli. Oropharyngeal deposition of ciclesonide 800 μg (via HFA MDI) was half that of budesonide 800 μg (via chlorofluorocarbon [CFC] MDI), and conversion of ciclesonide to its active metabolite in the upper oropharynx was very low in a randomized, open-label, sequential treatment study in 18 healthy subjects (Nave, Zech, et al 2005). Oropharyngeal deposition of ciclesonide was also significantly lower than fluticasone in a study of 18 patients with asthma (Figure 1) (Richter et al 2005).

Animal (Nave, Meyer, et al 2005) and *in vitro* (Nave et al 2003) studies showed that ciclesonide is converted by esterases in lung tissue to the pharmacologically active metabolite, desisobutyl-ciclesonide (des-CIC), which has a 100-fold greater glucocorticoid receptor binding affinity than ciclesonide (Stoeck et al 2004). An *in vitro* study in human lung tissue slices showed a high proportion of des-CIC conjugation with fatty acids (Nave et al 2003). These lipid conjugates of des-CIC may explain the prolonged local antiinflammatory action of ciclesonide in the lung and its clinical efficacy with once-daily dosing.

The pharmacokinetics of ciclesonide and des-CIC were equivalent in 12 healthy volunteers and 12 patients with asthma after inhalation of a single dose of ciclesonide 1240 μg (ex-actuator MDI) (Bethke et al 2003). Pooled pharmacokinetic data from 151 healthy subjects and patients with asthma who participated in phase I studies show des-CIC has a clearance of 396 L/hr and a volume of distribution of 1190 L (Rohatagi, Arya, et al 2003).

Ciclesonide and des-CIC are highly protein-bound (~99%), which is an advantage over other ICS because it results in a low proportion of free, unbound drug in the systemic circulation (Rohatagi et al 2005) (Figure 2). *In vitro* studies show that ciclesonide is metabolized by hepatocytes to des-CIC within the first hour of exposure (Gu et al 2004). Des-CIC is, in turn, extensively metabolized to inactive metabolites (Nave et al 2003; Gu et al 2004). Elimination of des-CIC and other metabolites is predominantly through the feces (Nave, Bethke, et al 2004). Because of extensive first-pass metabolism, the systemic bioavailability of des-CIC after oral ingestion is < 1% (Nave, Bethke, et al 2004). Thus, any ciclesonide swallowed after

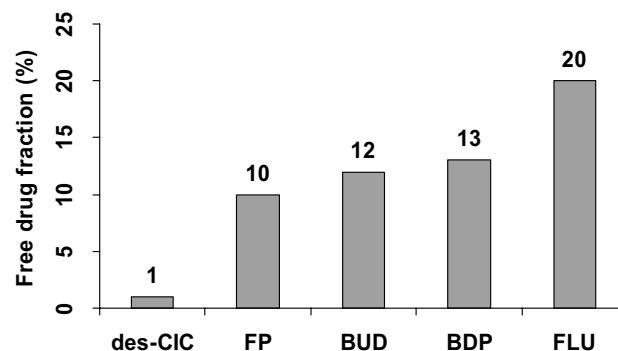


Figure 2 Fraction of free, unbound drug in plasma for des-CIC (Rohatagi et al 2005), fluticasone propionate (FP) (Rohatagi et al 1996), budesonide (BUD) (Ryrfeldt et al 1982), beclomethasone dipropionate (BDP) (Martin et al 1975), and flunisolide (FLU) (Mollmann et al 1997).

oral inhalation does not contribute to the systemic availability of the drug or its active metabolite. In addition, low systemic exposure to unbound des-CIC suggests a low potential for systemic adverse events after oral inhalation.

Pharmacodynamics

Up to one third of des-CIC may be converted to lipophilic fatty acid esters that reside in lung tissue (Nave, Schmidt, et al 2004). Binding affinity of des-CIC to glucocorticoid receptors is comparable with budesonide (Stoeck et al 2004) and fluticasone (Belvisi et al 2005), and potent dose-dependent antiinflammatory activity in human bronchial epithelial cells have been described (Serpero et al 2004). Studies in rats showed that ciclesonide prevented and reversed allergic airways inflammation and remodeling (Leung et al 2005).

Inhaled ciclesonide (800 μg dry powder via Cyclohaler[®] twice daily for one week) reduced early- and late-phase reactions, compared with placebo, after allergen challenge in patients with asthma (Larsen et al 2003), and a minimally effective dose of 80 μg once daily was identified (Gauvreau et al 2005). Ciclesonide also reduced airway responsiveness to adenosine-5'-monophosphate (AMP) in a dose-dependent manner (100–1600 μg dry powder via Cyclohaler daily) in 29 patients with mild to moderate asthma (Taylor et al 1999). Ciclesonide (400 μg ex-valve HFA MDI in the morning) reduced airway responsiveness and inflammation similar to budesonide (400 μg via Turbuhaler[®]) in 15 patients with mild asthma (Kanniess et al 2001). Reduced methacholine or AMP hyperresponsiveness was observed with dosages of ciclesonide (400–1600 μg ex-valve HFA MDI) and fluticasone (500–2000 μg ex-valve CFC MDI) in two studies of patients with asthma (Lee et al 2004; Derom et al 2005).

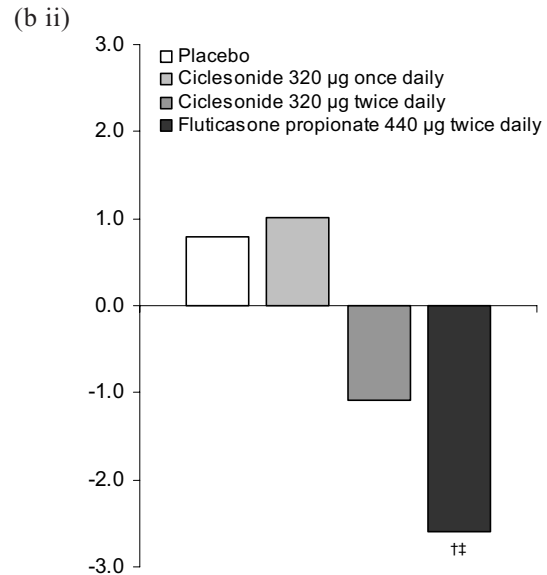
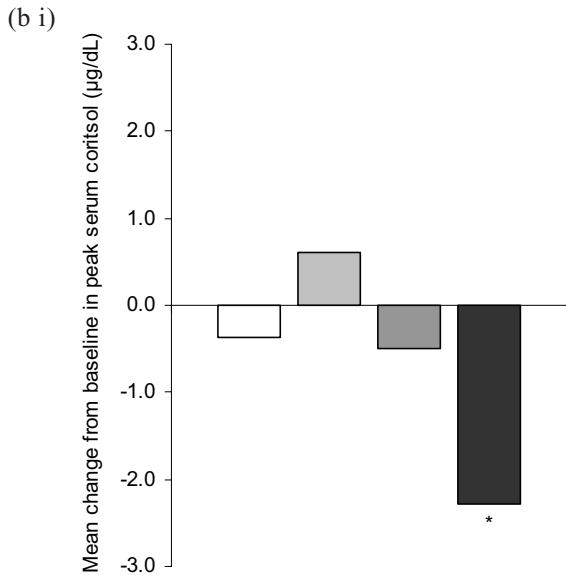
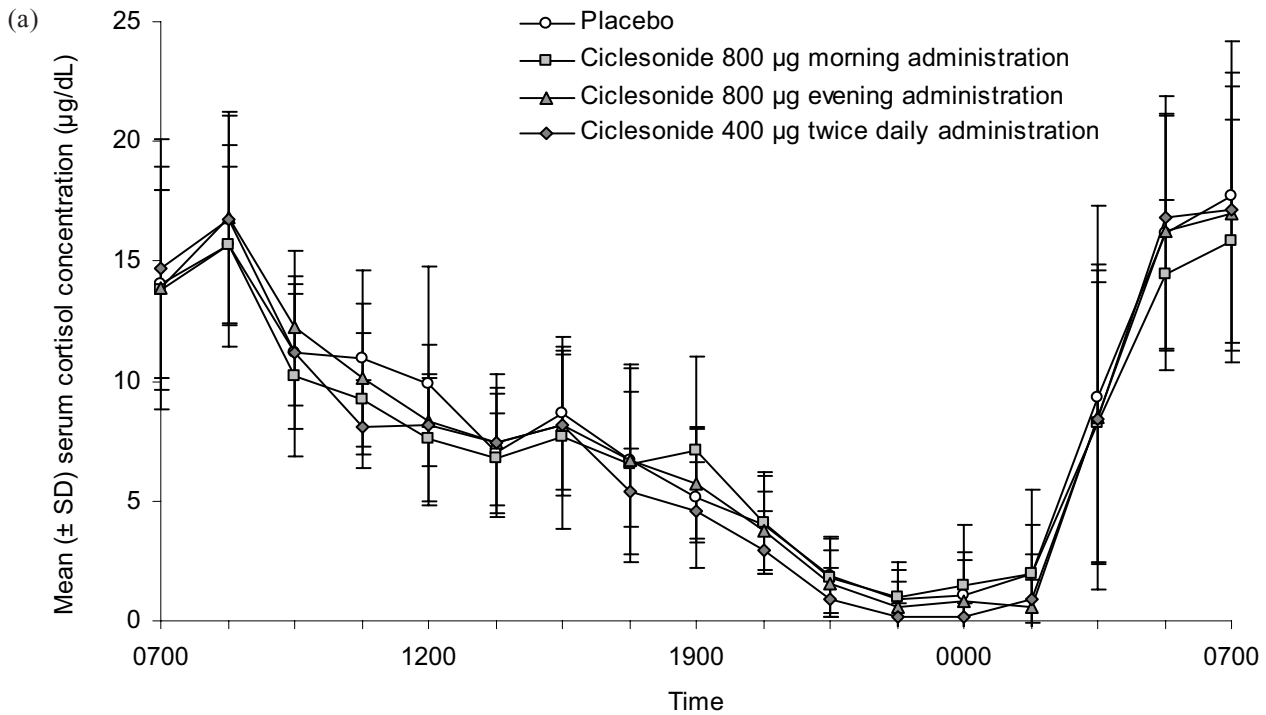


Figure 3 Effects of ciclesonide treatment on serum cortisol levels: (a) Mean (\pm SD) 24-hour serum cortisol levels in 12 healthy male subjects on day 7 of treatment with either placebo or ciclesonide in a randomized, double-blind, cross-over study (Weinbrenner A, Huneke D, Zschiesche M, et al. 2002. Circadian rhythm of serum cortisol after repeated inhalation of the new topical steroid ciclesonide. *J Clin Endocrinol Metab.* 87:2160–3. Copyright © 2002. Reproduced with permission from the Endocrine Society); (b) Mean change from baseline in serum cortisol levels after 12 weeks of treatment in adult patients with mild to moderate persistent asthma randomized to receive placebo (n = 41), ciclesonide 320 µg once daily (n = 40), ciclesonide 320 µg twice daily (n = 42), or fluticasone propionate 440 µg twice daily (n = 41) (Lipworth BJ, Kaliner MA, LaForce CF, et al. 2005. Effect of ciclesonide and fluticasone on hypothalamic-pituitary-adrenal axis function in adults with mild-to-moderate persistent asthma. *Ann Allergy Asthma Immunol.* 94:465–72. Copyright © 2005. Reproduced with permission from the American College of Allergy, Asthma, & Immunology). Serum cortisol levels were measured following sequential stimulation with (i) low-dose (1 µg) and (ii) high-dose (250 µg) cosyntropin. Changes observed with ciclesonide treatment were not statistically different from placebo.

* p < 0.0001 versus active comparator.

† p < 0.001 versus active comparator.

Attenuation of exercise-induced bronchoconstriction by ciclesonide (40–320 µg ex-actuator MDI daily) was found in a study of 26 affected adults (Subbarao et al 2005).

Treatment with ciclesonide does not appear to have a clinically relevant effect on serum cortisol (Figure 3). There was no difference in serum cortisol concentrations when inhaled ciclesonide (800 µg ex-valve MDI daily for 7 days) was compared with placebo in 12 healthy volunteers (Weinbrenner et al 2002). Placebo-controlled studies in patients with asthma showed similar results at dosages up to 1280 µg (ex-actuator HFA MDI) daily for as long as 12 weeks (Chapman et al 2002; Ukena et al 2003; Kerwin et al 2004; Derom et al 2005; Lipworth et al 2005). In studies of up to 12 weeks' duration, ciclesonide (320–1280 µg ex-actuator HFA MDI daily) had significantly less effect on cortisol production than fluticasone propionate (880–1760 µg daily, ex-actuator HFA MDI or CFC MDI) (Derom et al 2005; Lee et al 2005; Lipworth et al 2005). An analysis of 17 trials in adults and children with asthma showed that inhaled ciclesonide (up to 1280 µg daily) had a negligible effect on endogenous cortisol concentrations (Pfister et al 2004). Switching to ciclesonide (800–1600 µg ex-valve MDI daily for up to 52 weeks) following high-dose therapy with another ICS was found to improve serum cortisol and markers of bone formation (O'Connor, Kilfeather, et al 2002; O'Connor, Sips, et al 2002). Short-term lower-leg growth rate was not affected by inhaled ciclesonide (40–160 µg HFA MDI daily for 2 weeks) in a study of 24 children with asthma (Agertoft and Pedersen 2005).

Clinical studies

Efficacy

Ciclesonide has been studied in numerous 12-week trials with comparison against baseline, placebo, and other ICS (Table 1). A placebo-controlled study of ciclesonide (80 or 320 µg ex-actuator HFA MDI each morning over 12 weeks) given to 360 patients with bronchial asthma (previously treated with constant beclomethasone dipropionate) showed that both dosages significantly improved peak expiratory flow (PEF) and forced expiratory volume in 1 second (FEV₁) compared with placebo (Langdon et al 2005). These results were corroborated in a similar 12-week trial of 329 patients with persistent asthma (Chapman et al 2005). Compared with placebo, ciclesonide 160 or 640 µg (ex-actuator HFA MDI) once daily in the morning were equally effective at maintaining morning PEF ($p < 0.0001$ for both doses), FEV₁ ($p < 0.05$) and forced vital capacity (FVC) ($p < 0.05$) (Chapman et al 2005). An open extension of this trial showed

that ciclesonide was effective over a period of 52 weeks (Chapman et al 2002). A collation of 2 identical placebo-controlled trials in 1015 patients with mild to moderate asthma showed that ciclesonide (80, 160, or 320 µg ex-actuator HFA MDI daily for 12 weeks) significantly improved FEV₁ ($p = 0.0007$, $p = 0.0004$, $p < 0.0001$, respectively) and reduced symptoms ($p < 0.0001$ for all dosages), daily albuterol use ($p < 0.0001$), and discontinuations ($p < 0.0001$) compared with placebo (Pearlman et al 2005). These results confirmed findings from a 12-week trial of ciclesonide 400 versus 800 µg (ex-valve MDI) twice daily in 365 patients with asthma pretreated with high-dose ICS, where improved PEF and a decrease in symptoms and rescue medications were found after 12 weeks of therapy (both doses produced equivalent results) (O'Connor, Sips, et al 2002). FEV₁ improvements were maintained over a 40-week open extension of this study (O'Connor, Kilfeather, et al 2002).

A study in 209 patients with bronchial asthma showed that ciclesonide 200 µg (ex-valve HFA MDI) for 8 weeks may be given in the morning or evening to produce significant improvements in symptoms (at least $p < 0.001$ compared with baseline), spirometry ($p < 0.05$), and rescue medication usage ($p < 0.05$), with evening dosing significantly improving morning PEF ($p < 0.05$ compared with morning dosing) (Postma et al 2001).

Compared with other ICS

Ciclesonide has been compared with budesonide and fluticasone in several studies (Table 1). In 554 patients with asthma, ciclesonide 80 or 320 µg (ex-actuator HFA MDI) each morning was equal in efficacy to budesonide 200 µg via (Turbuhaler) twice daily for 12 weeks with regard to significant improvements in FEV₁, FVC, PEF, asthma symptoms, and use of rescue medication (Hansel et al 2004). Similar 12-week efficacy to budesonide (200 µg ex-valve MDI twice daily) was found with ciclesonide (160 µg ex-actuator MDI, morning or evening) in a study of 404 patients pretreated with ICS (Gadgil et al 2005). FEV₁ was maintained, and level of symptoms and use of rescue medications were decreased or remained stable with all regimens. Evening doses of ciclesonide (320 µg ex-actuator HFA MDI) and budesonide (400 µg via Turbuhaler) have been compared over 12 weeks in 399 patients with asthma (Ukena et al 2003). Ciclesonide produced significantly better FEV₁ ($p < 0.0185$) and FVC ($p < 0.0335$) results than budesonide and produced an earlier onset of morning PEF improvement (day 3 vs week 2). Once-daily morning

Table 1 Efficacy and tolerability of ciclesonide in patients with asthma in clinical studies of 12 weeks' duration

Study	Study design (n)	Inclusion criteria	Dosages (μg)	Main results	Overall efficacy	Tolerability and quality of life
Langdon et al 2005	mc, r, pg, db, P n = 360	Low-moderate-dose ICS; FEV ₁ 60%–90% predicted; demonstrated reversibility	C 80 od am C 320 od am	PEFam: C80 > P ($p = 0.0012$); C320 > P ($p = 0.0006$) PEFpm: C80 > P ($p = 0.0121$); C320 > P ($p = 0.0048$) FEV ₁ : C80 > P ($p = 0.0044$); C320 > P ($p = 0.0001$) FVC: C80 > P ($p = 0.0203$); C320 > P ($p = 0.0197$) SR: C > P ($p < 0.0001$ change from BL) Resc: C < P ($p < 0.01$ change from BL) LOE: C80 > P ($p \leq 0.0052$); C320 > P ($p < 0.0001$); C320 > C80 ($p = 0.0087$)	C > P	Safe and well tolerated Serum and urinary cortisol levels: C80 \equiv C320 \equiv P
Chapman et al 2005	mc, r, pg, db, P n = 329	Moderate-dose ICS; FEV ₁ 60%–90% predicted; demonstrated reversibility	C 160 od am C 640 od am	PEFam: C160 \equiv C640 > P ($p < 0.0001$ AD) FEV ₁ : C160 \equiv C640 > P ($p < 0.05$ AD) FVC: C160 \equiv C640 > P ($p < 0.05$ AD) SR: C > P ($p \leq 0.0006$ change from BL) Resc: C < P ($p < 0.0001$ change from BL) LOE: P > C160 \equiv C640 ($p < 0.0001$ AD)	C160 \equiv C640 > P	Cortisol levels: C160 \equiv C640 \equiv P
Berger et al 2004; Nayak et al 2005; Pearlman et al 2005	mc, r, pg, db, P n = 1015	Mild to moderate asthma; FEV ₁ 60%–85% predicted; ≥ 12 years old	C 80 od C 160 od C 320 od	FEV ₁ : C80 > P ($p = 0.0007$); C160 > P ($p = 0.0004$); C320 > P ($p < 0.0001$) SR: C > P ($p < 0.0001$ AD) Resc: C < P ($p < 0.0001$ AD) LOE: C < P ($p < 0.0001$ AD)	C > P	Oral candidiasis: C \equiv PHPA function: C had no effect Overall AQLQ: C80, C160, C320 > P ($p < 0.0001$ AD)
O'Connor, Sips, et al 2002	r, pg, db n = 365	High-dose ICS; PEF am $\leq 80\%$ predicted; demonstrated reversibility; symptom scores ≥ 4 last week; resc ≥ 14 puffs last week	C 400 bid C 800 bid (C ex-valve)	PEFam: C800 > BL ($p = 0.0002$); C1600 > BL ($p = 0.001$) SR: C > BL ($p < 0.0001$ AD) Resc: C800 < BL ($p = 0.0045$); C1600 \equiv BL ($p = 0.0758$)	C400 bid \equiv C800 bid > BL	Safe and well tolerated Serum and urinary cortisol levels: C > BL ($p < 0.05$ AD) Serum osteocalcin levels: C > BL ($p < 0.05$ AD)
Postma et al 2001	r, pg, db ^a n = 209	Mild to moderate asthma; FEV ₁ 50%–90% predicted; demonstrated reversibility; resc meds only during past 4 weeks	C 200 od am C 200 od pm (C ex-valve)	PEFam: Cpm > Cam ($p < 0.05$) \equiv BL PEFpm: Cpm > BL ($p < 0.05$) \equiv Cam FEV ₁ : Cam \equiv Cpm > BL ($p < 0.05$) FVC: Cam \equiv Cpm > BL ($p < 0.05$) SR: Cam \equiv Cpm > BL ($p < 0.001$) Resc: Cam \equiv Cpm < BL ($p < 0.05$)	Cam \equiv Cpm > BL	Safe and well tolerated Urinary cortisol excretion: Cam \equiv Cpm \equiv BL

Table I continued

Study	Study design (n)	Inclusion criteria	Dosages (μ g)	Main results	Overall efficacy	Tolerability and quality of life
Hansel et al 2004	r,pg,db(C); open (Bu) n = 554	FEV ₁ 50%–90% predicted	C 80 od am C 320 od am Bu 200 bid (Turbuhaler [®])	PEFam: C80 \equiv C320 \equiv Bu > BL (p < 0.0001) PEFam: C80 \equiv C320 \equiv Bu > BL (p < 0.0001) FEV ₁ : C80 \equiv C320 \equiv Bu > BL (p < 0.0001) FVC: C80 \equiv C320 \equiv Bu > BL (p < 0.0001) SR: C80 \equiv C320 \equiv Bu > BL (p < 0.0001) Resc: C80 \equiv C320 \equiv Bu < BL (p < 0.0001)	C80 \equiv C320 \equiv Bu > BL	Urinary cortisol excretion: C80 \equiv C320 \equiv Bu < BL (p < 0.05)
Gadgil et al 2005	NR n = 404	Low-dose ICS; FEV ₁ \geq 70% predicted; 2-week run-in with Bu 200 μ g twice daily	C 160 od am C 160 od pm Bu 200 bid (pMDI)	FEV ₁ : Cam \equiv Cpm \equiv Bu \equiv BL SR: Cam \equiv Cpm \equiv Bu \equiv BL Resc: Cam \equiv Cpm \equiv Bu \equiv BL LOE: Cam \equiv Cpm \equiv Bu \equiv BL	Cam \equiv Cpm \equiv Bu	NR
Ukena et al 2003	mc, r, pg, db, dd n = 399	FEV ₁ 50%–90% predicted	C 320 od pm Bu 400 od pm (Turbuhaler [®])	FEV ₁ : C > Bu (p = 0.0185) > BL (p < 0.0001) FVC: C > Bu (p = 0.0335) > BL (p < 0.0001) PEFam: C > Bu (earlier onset) SR: C \equiv Bu > BL	C > Bu > BL	Urinary cortisol levels: C \equiv Bu \equiv BL
Boulet et al 2003	mc, r, pg, db n = 359	Moderate-dose ICS then Bu 1600 μ g od \times 2–4 weeks; FEV ₁ 65%–90% predicted on Bu	C 320 od am Bu 400 od am (Turbuhaler [®])	FEV ₁ : C \equiv Bu FVC: C > Bu (p < 0.01) SR: C > Bu (p = 0.0288) ^b Resc: C \equiv Bu	C \equiv Bu	NR
Buhl et al 2004	mc, r, db n = 529	FEV ₁ 80%–100% predicted, pretreated with low-dose ICS; FEV ₁ 50%–90% predicted after 1–4 weeks without ICS	C 160 od pm F 88 bid	PEFam: C \equiv F > BL (p < 0.0001) FEV ₁ : C \equiv F > BL (p < 0.0001) FVC: C \equiv F > BL (p < 0.0001) SR: C \equiv F > BL (p < 0.0001) Resc: C \equiv F < BL (p < 0.0001)	C \equiv F	NR
Magnussen et al 2005	mc, r, db n = 697	1–4 weeks without ICS; FEV ₁ 61%–90% predicted; 12–75 years old	C 80 od pm C 160 od pm F 88 bid	FEV ₁ : C80 \equiv C160 \equiv F > BL (p < 0.0051 AD) SR: C80 \equiv C160 \equiv F > BL (p < 0.0001 AD) Resc: C80 \equiv C160 \equiv F > BL (p < 0.0001 AD)	C80 \equiv C160 \equiv F	NR
Bernstein et al 2004; Bernstein et al 2005; Busse et al 2005	mc, r, pg, db, dd, P n = 531	Moderate to severe asthma; high-dose ICS; FEV ₁ 40%–65% predicted; \geq 12 years old	C 160 bid C 320 bid F 440 bid	FEV ₁ : C320 > P (p = 0.0374); C640 > P (p = 0.0008); F > P p = (0.0001) SR: C320, C640, F > P (p < 0.0001 AD) Resc: C320, C640, F > P (p < 0.0001 AD) LOE: C320, C640, F > P (p < 0.0001 AD)	C \equiv F	Oral candidiasis: P \equiv C320 \equiv C640 < F HPA function: C320 \equiv C640 \equiv F \equiv P \equiv BL AQLQ: C320, C640, F > P (p < 0.0001)

Table 1 continued

Study	Study design (n)	Inclusion criteria	Dosages (μg)	Main results	Overall efficacy	Tolerability and quality of life
Gelfand et al 2005; Miller et al 2005; Shapiro et al 2005	mc, r, pg, db, P n = 1031	Children with mild to severe persistent asthma/ FEV_1 60%–85% predicted; 4–11 years old	C 40 od C 80 od C 160 od	FEV_1 : C40 = P ($p = 0.26$), C80 > P ($p = 0.01$), C160 > P ($p = 0.008$) SR: C40 > P ($p = 0.0022$), C80 > P ($p < 0.0001$), C160 > P ($p < 0.0001$) Resc: C40, C80, C160 < P LOE: C40, C80, C160 < P ($p = 0.02$ AD)	C > P	Well tolerated in all groups Oral candidiasis: 3 cases (all C) in 1025 patients Serum and urinary cortisol levels: P \equiv C40, C80, C160 Pediatric AQLQ (in 793 children ≥ 7 years old): C40 > P ($p = 0.01$), C80 > P ($p = 0.004$), C160 > P ($p = 0.002$)
Pedersen, Garcia, et al 2004; Pedersen, Gyurkovits, et al 2004	mc, r, db n = 556	Children and adolescents with mild-to-severe asthma/2–4 weeks without ICS; FEV_1 50%–90% predicted /6 to 15 years old	C 80 bid F 88 bid	PEFam: C \equiv F > BL ($p < 0.0001$) PEFpm: C \equiv F > BL ($p < 0.0001$) FEV_1 : C \equiv F > BL ($p < 0.0001$) SR: C \equiv F > BL ($p < 0.0001$) Resc: C \equiv F < BL ($p < 0.0001$)	C \equiv F > BL	Adverse events: C \equiv F Urinary cortisol levels: C ^c > F ($p = 0.0062$)

^a 8-week study^b C produced more symptom-free days^c C increased levels from BL

Abbreviations: AD, all/both drug doses; am, morning; AQLQ, Juniper Asthma Quality of Life Questionnaire; bid, twice daily; BL, baseline; Bu, budesonide; C, ciclesonide ex-actuator dose via HFA-MDI unless otherwise stated; db, double-blind; dd, double-dummy; FEV_1 , forced expiratory flow in one second; F, fluticasone propionate ex-actuator dose via MDI; FVC, forced vital capacity; HPA, hypothalamic pituitary adrenal; ICS, inhaled corticosteroid; LOE, discontinuation due to lack of efficacy; mc, multicenter; n, number of patients; NR, not reported; od, once daily; P, placebo; PEF, peak expiratory flow; pg, parallel group; pm, evening; r, randomized; Resc, need for rescue medications; SR, symptom control (reduction of symptoms).

regimens of ciclesonide 320 μg (ex-actuator HFA MDI) and budesonide 400 μg (via Turbuhaler) were compared in a study of 359 patients with asthma who had been pretreated with high-dose ICS (Boulet et al 2003). Ciclesonide produced equivalent FEV_1 results to budesonide, but better FVC results ($p < 0.01$), and more symptom-free days ($p = 0.0288$), and there was no difference between the two drugs in the need for rescue medication.

Ciclesonide 160 μg once daily in the evening has been compared with fluticasone 88 μg twice daily (ex-actuator HFA MDI both drugs) in 529 patients with asthma (Buhl et al 2004). The results showed that ciclesonide produced significant improvements from baseline in FEV_1 , FVC, and morning PEF (all $p < 0.0001$ compared with baseline) that were equivalent to fluticasone. Equivalent symptom reduction and need for rescue medication were also observed with the two drugs. Similar results were observed in a study of 697 patients with persistent asthma (Magnussen et al 2005). In this study, equivalency to fluticasone (88 μg twice daily) was found with ciclesonide 80 and 160 μg once daily

(all drugs ex-actuator MDI). Ciclesonide has also been compared with fluticasone in 531 patients in severe persistent asthma (Busse et al 2005). Following 12 weeks' treatment, and compared with placebo, FEV_1 improved with fluticasone 440 μg (ex-actuator CFC MDI) twice daily ($p < 0.0001$) and dose-dependently with twice daily ciclesonide (ex-actuator HFA MDI) 160 μg ($p = 0.0374$) or 320 μg ($p = 0.0008$). All 3 regimens improved asthma symptoms and need for albuterol compared with placebo ($p < 0.0001$ for all comparisons).

Efficacy in children

Ciclesonide (40, 80, or 160 μg ex-actuator HFA MDI once daily) was compared with placebo in a 12-week study of 1031 children with persistent asthma (Shapiro and Bensch 2005). FEV_1 significantly improved compared with placebo in all doses. There were fewer discontinuations due to lack of efficacy with ciclesonide, as well as significantly less asthma symptoms, less need for albuterol, and a decrease in nocturnal awakenings, compared with placebo. Another

12-week study compared ciclesonide 80 µg twice daily with fluticasone 88 µg twice daily (both drugs ex-actuator HFA MDI) in 556 children and adolescents with mild to severe asthma (Pedersen, Garcia, et al 2004). Compared with baseline both drugs significantly improved FEV₁ and morning and evening PEF. Asthma symptoms and need for rescue medications were lowered with both drugs. The authors concluded that the drugs showed equivalent efficacy in this patient population.

Quality of Life

Quality of life (QoL) assessment in 2 of the studies in Table 1 showed that ciclesonide improved QoL significantly over placebo and was comparable with fluticasone in patients aged 12 years or older (Bernstein et al 2005; Nayak et al 2005). Ciclesonide also improved QoL in children aged 7 years or older in a placebo-controlled study in pediatric patients (Miller et al 2005).

Tolerability

A low propensity for typical ICS adverse events was presented in the pharmacodynamics section of this review. In addition, ciclesonide was well tolerated in all of the clinical trials reported in Table 1. For example, in the

placebo-controlled study of 329 patients with persistent asthma, adverse events with ciclesonide (160 or 640 µg ex-actuator HFA MDI once daily for 12 weeks) were mostly mild or moderate and were unrelated to study medication, and severe adverse events were reported in 7% or less of all patients (Chapman et al 2005). The most frequent adverse events included asthma (14% and 13% in ciclesonide 160 and 640 µg groups, respectively, compared with 29% in the placebo group), headache (16%, 13%, and 17%, respectively), upper respiratory tract infection (6%, 8%, and 13%), and rhinitis (15%, 9%, and 13%). Oral candidiasis did not occur, and cortisol levels were similar in all groups.

Table 1 shows the key tolerability results from published studies in adults and children. At the dosages used, ciclesonide did not exert any untoward adverse effects, and did not suppress cortisol production. A pooled analysis of studies shows that among 6846 patients with asthma who were treated with ciclesonide, another ICS, or placebo, the incidence of oral adverse events was similar for ciclesonide and placebo-treated patients, and that other ICS produced the most oral candidiasis and hoarseness (Figure 4) (Engelstatter et al 2004). Another pooled analysis among 7732 patients with asthma concluded that ciclesonide and placebo recipients experienced similar incidences of adverse events (Hafner et al 2004).

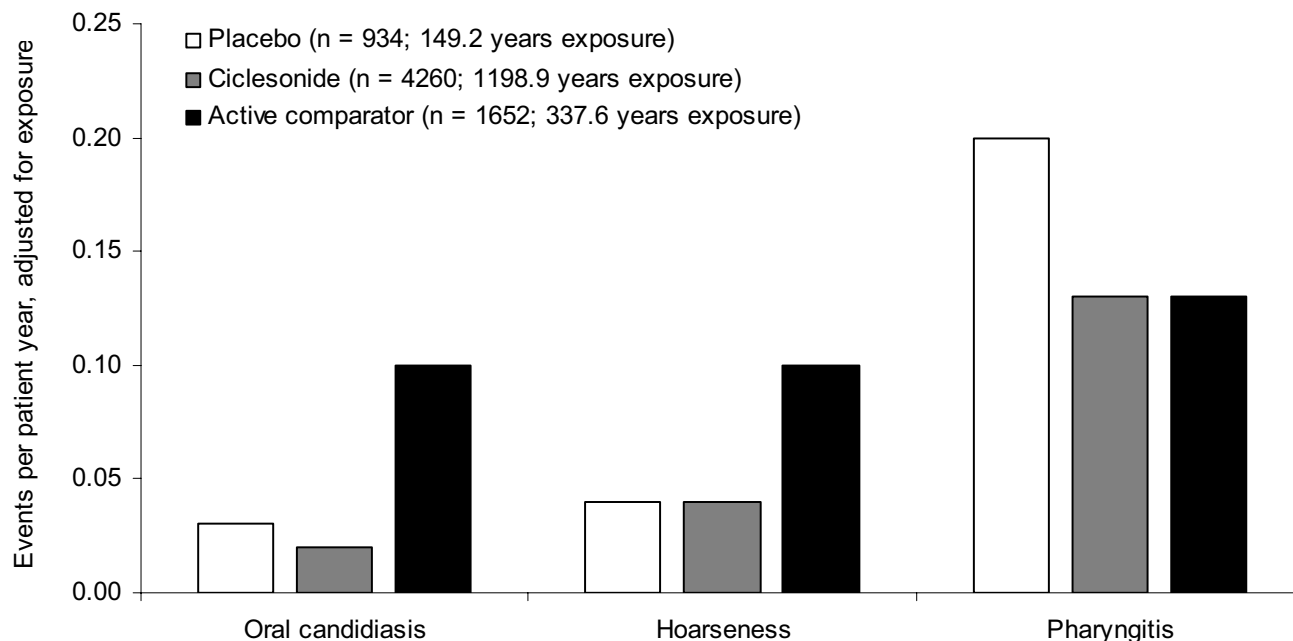


Figure 4 Occurrence of oropharyngeal adverse events with ciclesonide. Derived from a pooled analysis of the number of oral adverse events per patient year (adjusted for exposure time) in a total of 6846 patients with asthma who received placebo, ciclesonide, or active comparator (budesonide, beclomethasone dipropionate, or fluticasone propionate) in phase II and III studies (Engelstatter et al 2004). This subanalysis of 2755 patients who received placebo (n = 388), ciclesonide 80–640 µg/day (n = 1621), or fluticasone propionate 176 or 880 µg/day (n = 746) for 12 weeks showed that the incidence of oral adverse events associated with ciclesonide 640 µg/day (n = 465) was lower than with fluticasone 880 µg/day (n = 483) (Engelstatter R, Banerji D, Stenijans VV. 2004. Low incidence of oropharyngeal adverse events in asthma patients treated with ciclesonide: results from a pooled analysis [abstract]. *Am J Respir Crit Care Med.* 169:A92. Copyright © 2004. Reproduced with permission from AJRCCM).

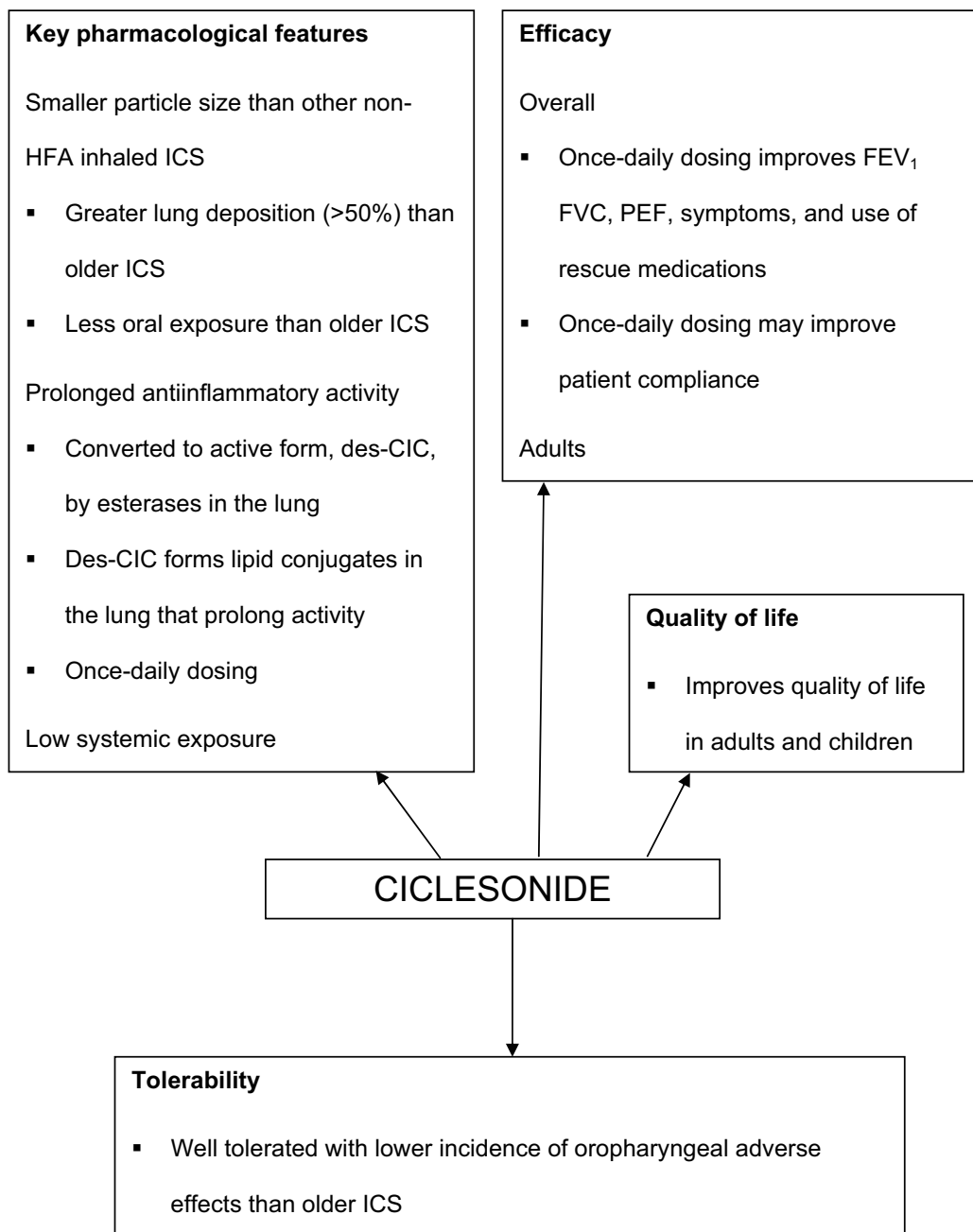


Figure 5 Clinical summary of ciclesonide in asthma. All features and comments are derived from referenced information in the text.
Abbreviations: des-CIC, desisobutryl-ciclesonide; ICS, inhaled corticosteroids; FEV₁, forced expiratory volume in 1 second; FVC, forced vital capacity; HFA, hydrofluoroalkane; PEF, peak expiratory flow.

The long-term safety profile of once-daily ciclesonide during a 52-week multicenter, open-label extension study in 226 patients was similar to that in the 12-week studies. Overall, 13 patients (5.75%) experienced at least 1 adverse event that was considered possibly related to ciclesonide treatment, including one case each of oral candidiasis and pharyngitis. There were no clinically relevant changes from baseline to study endpoint in HPA function as measured by 24-hour urinary free cortisol levels (corrected for creatinine)

and peak serum cortisol concentrations following cosyntropin 1 µg stimulation (Berger et al 2005).

Patient support/disease management programs

Current asthma treatment guidelines incorporate a stepwise approach to therapy, based on asthma severity (BTS & SIGN 2004; GIA 2004). Inhaled corticosteroids are recommended from the second step onwards, where regular controller

therapy is required. Poor adherence to ICS is common and is associated with negative outcomes in patients with asthma (Williams et al 2004). Complex treatment regimens are considered to be an important factor underlying patient noncompliance, and once-daily drug regimens have been suggested as a means of improving compliance with ICS, and hence the outcomes of treatment, for patients with asthma (Campbell 1999). The ciclesonide efficacy and safety results show that it can be recommended for stepwise asthma therapy when ICS are required. Once-daily administration (morning or evening) offers greater patient acceptability than other twice-daily ICS. The low systemic availability and high protein binding of ciclesonide (Rohatagi et al 2005) are features that may explain the low incidence of adverse events. Figure 5 provides a clinical summary of ciclesonide based on its pharmacological properties and clinical trial results.

Conclusion

Ciclesonide has good efficacy equivalent at least to that of the most widely used ICS medications for the treatment of asthma: budesonide and fluticasone. Ciclesonide has a favorable pharmacodynamic and pharmacokinetic profile, with potential for reduced local and systemic adverse effects compared with other ICS. In clinical trials, it had oropharyngeal effects that were similar to placebo, and did not suppress cortisol production. Initial results from long-term, open studies are promising, and future trials, including outcomes data, will enable the role of ciclesonide in asthma management to be further defined.

In clinical practice, the once-daily dosing regimen of ciclesonide should aid patient compliance, which could potentially improve outcomes and QoL for adults and children with asthma. Overall, ciclesonide offers an efficacious alternative to ICS for persistent asthma, with a convenient dosing regimen and the potential for reduced systemic adverse effects.

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