Drugs of the Future 2001, 26(11): 1033-1039

CCC: 0377-8282/2001

Ciclesonide

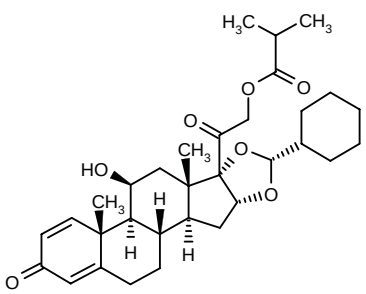
Rec INN

Treatment of Allergic Rhinitis
Antiallergy/Antiasthmatic

BY-9010
B-9207-015

16α,17α-[(*R*)-Cyclohexylmethylenedioxy]-11β-hydroxy-21-(isobutyryloxy)pregna-1,4-dien-3-one

(*R*)-11β,16α,17,21-Tetrahydroxypregna-1,4-diene-3,20-dione cyclic 16,17-acetal with cyclohexanecarboxaldehyde 21-isobutyrate



$C_{32}H_{44}O_7$ Mol wt: 540.6926

CAS: 126544-47-6

EN: 162123

Synthesis

Acylation of (11β,16α)-11,16,17,21-tetrahydroxypregna-1,4-diene-3,20-dione (I) with isobutyric anhydride in pyridine gives the 16,17,21-triester (II), which is treated with cyclohexanecarbaldehyde (IV) and hydrochloric acid in dioxane to yield the cyclic ketal (V) as a diastereomeric mixture (1). Finally, this mixture is resolved by HPLC chromatography and fractional crystallization (1, 2). Scheme 1.

Introduction

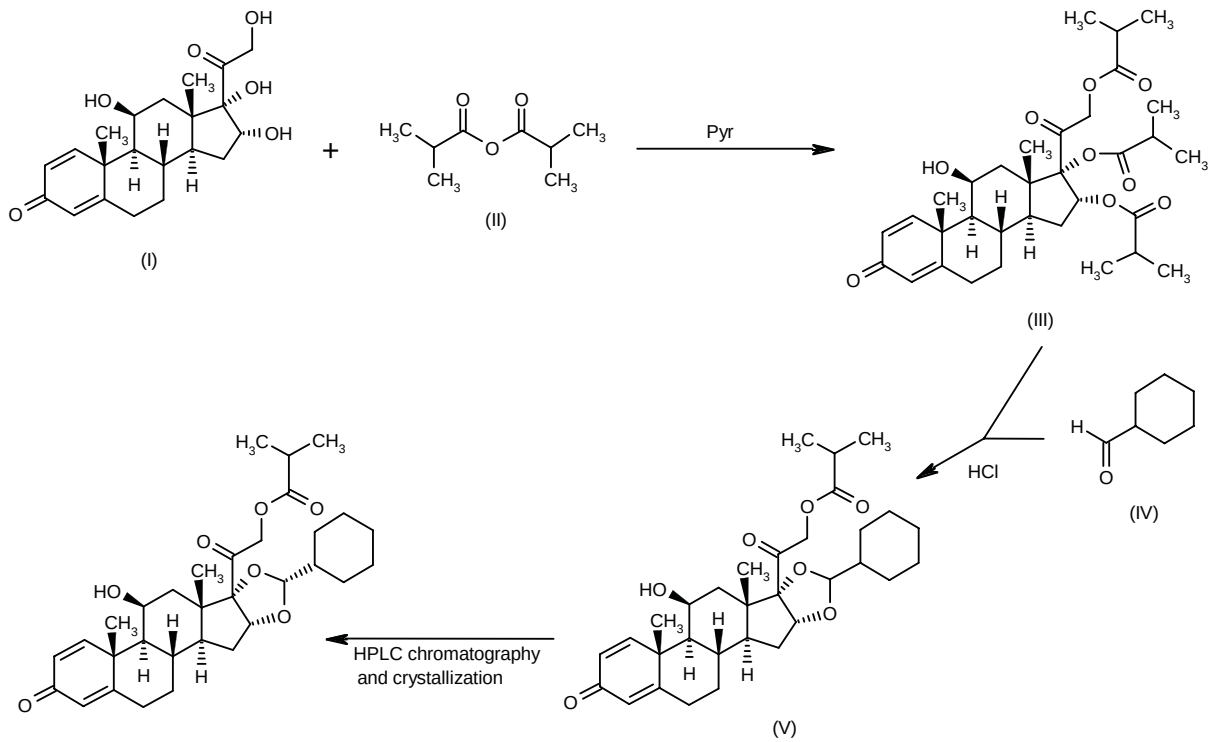
Asthma is among the most common chronic conditions in the world, with an estimated prevalence, according to epidemiology studies, of 6-12% in adults and children in industrialized countries. More than 50 million people worldwide, including an estimated 17 million in the United States alone, suffer from asthma. Furthermore, evidence indicates that asthma is increasing in both prevalence and severity. According to the National Heart, Lung, and Blood Institute (NHLBI), the prevalence of asthma has been increasing steadily over the past two decades in all ages, genders and racial groups, particularly among children under 4 years of age, and over 80 million individuals are projected to have asthma by the next century (3). Although the reason for this increase is not clear, both increased exposure to sensitizing allergens and reduced stimulation of the immune system during critical developmental periods – the result of living in more hygienic, sterile environments – have been proposed as culprits (4).

The treatment of asthma has a dual focus: the short-term treatment of acute symptoms with bronchodilators, together with the prevention or eventual reversal of chronic inflammation using antiinflammatory drugs (5). Inhaled corticosteroids are the gold standard of asthma maintenance therapy and systemic corticosteroids are used to treat severe exacerbations in the hospital setting. Corticosteroids decrease bronchial hyperreactivity and improve lung function, symptomatology and quality of life. Inhaled corticosteroids are considered to be safe and are generally well tolerated, although they can produce side effects. The benefits are considered to outweigh the risks, however. Nonetheless, corticosteroids are not curative and their therapeutic benefits disappear when thay are discontinued (6-8). Given their importance in the treatment of asthma, several companies are pursuing the development of new corticosteroids and new formulations of marketed corticosteroids.

Allergic rhinitis is the inflammation of the mucus membrane of the nose that occurs in response to an airborne antigen, or allergen. Allergic rhinitis is the sixth most

N.E. Mealy, M. Bayès, J. Castañer. Prous Science, P.O. Box 540, 08080 Barcelona, Spain.

Scheme 1: Synthesis of Ciclesonide



prevalent chronic disease, affecting 10-20% of the general population. Anywhere from 20-40 million Americans are believed to suffer from allergic rhinitis, including 10-30% of adults and up to 40% of children. The incidence of allergies, and allergic asthma, is on the rise. As for asthma, theories to explain this increase tend to point to the healthier, as well as wealthier, conditions of industrialized countries and associated lifestyle changes.

Allergic rhinitis is a significant risk factor for sinusitis and asthma; according to the American Academy of Allergy, Asthma & Immunology (AAAAI), 40-50% of adults and 95-98% of children with asthma also have allergic rhinitis. Untreated allergies can also predispose an individual to dermatological disorders such as atopic dermatitis, eczema or urticaria.

Intranasal steroids are gaining in popularity as first-line therapies for allergic rhinitis, particularly in patients with moderate or severe symptoms or in those with perennial allergic rhinitis with predominantly nasal symptoms. Intranasal corticosteroids address the process of allergic inflammation that contributes to the late-stage symptom of nasal congestion. When used prophylactically, they can also prevent the early-phase response to allergens. Overall, inhaled corticosteroids effectively relieve sneezing, itching, rhinorrhea and congestion, and a meta-analysis of clinical studies concluded that they are more effective than antihistamines for controlling rhinitis, with the added benefit of relieving congestion (9). Their use in children must be closely controlled, however, as steroids have been suggested to have an adverse effect on growth.

Systemic side effects limit the dose at which inhaled corticosteroids can be administered for long-term therapy (10). Potential adverse effects of treatment with corticosteroids include abnormalities in glucose metabolism (11), impairment of growth (12-17), adrenal suppression (18-24) and cataracts (25). Research efforts are currently focused on the design of novel steroids with high potency and reduced systemic side effects. Researchers at Byk Gulden adopted the on-site activation approach and synthesized a series of acetals and esters of 16-α-hydroxyprednisolone and fluocinolone, and selected ciclesonide as a very promising steroid for the treatment of asthma and allergic rhinitis.

Pharmacological Actions

Ciclesonide is a new-generation inhaled nonhalogenated glucocorticoid with high local antiinflammatory properties. It is an ester prodrug, essentially devoid of oral bioavailability, which is activated upon cleavage by endogenous esterases. Advantages of on-site activation include targeted activation in the lung, minimal systemic adverse effects and minimal orpharyngeal side effects (10).

A series of *in vitro* studies compared ciclesonide, its metabolite, budesonide, fluticasone propionate and beclomethasone dipropionate. The binding affinity for the human glucocorticoid receptor was similar for the metabolite (K_i = 0.31 nM), budesonide (K_i = 0.44 nM) and fluticasone (K_i = 0.24 nM), while ciclesonide displayed about 10 times lower affinity (K_i = 37 nM). The metabolite and budesonide were again more effective against concanavalin A-induced proliferation of human peripheral blood mononuclear cells (PBMCs; IC_{50} = 1.34 and 1.65 nM, respectively) than ciclesonide (IC_{50} = 10.82 nM). Several TNF-α release assays demonstrated similar efficacy for the active metabolite of ciclesonide and budesonide and fluticasone, whereas ciclesonide was either much less or not effective. The *S*-epimer of ciclesonide showed little or no activity in any of these assays. These findings further support the prodrug status of ciclesonide and suggest comparable antiinflammatory efficacy of its active metabolite to available corticosteroids (26).

In vivo studies were performed in rats comparing ciclesonide and budesonide for antiinflammatory activity. Ciclesonide was at least if not more potent than budesonide in inhibiting antigen-induced airways eosinophilia in Brown-Norway rats (IC_{50} = 0.5 and 1 g/kg intratracheally, respectively), and granuloma formation in the cotton pellet model (ID_{50} = 2 and 3 μg/pellet, respectively). On the other hand, it was associated with less thymus involution in this model (ID_{50} = 303 and 154 μg/pellet), as well as less thymus involution (ID_{50} = 2226 and 339 μg/kg), adrenal involution (ID_{25} = 1746 and 214 μg/kg) and decrease in body weight (ID_{25} = 2166 and 261 μg/kg) following oral administration for 28 days (27, 28).

In Brown-Norway rats with eosinophilic inflammation induced by Sephadex or allergen challenge, ciclesonide was up to 7.5-fold less potent than fluticasone in inhibiting eosinophilia following intratracheal administration, but it was also 22-fold less active than fluticasone in inducing femoral growth plate hypoplasia, suggesting a superior therapeutic index (29).

Metabolism

The hepatic metabolism of ciclesonide and its major active metabolite, B-9207-021, were studied in human liver microsomes using [^{14}C]-labeled compounds. Labeled ciclesonide was shown to be metabolized initially to B-9207-021, which was then hydroxylated to at least two metabolites. The formation of the major metabolite was found to be catalzyed by an esterase, while cytochrome P-450 enzymes, especially CYP3A4, were involved in the further metabolism of the main metabolite of ciclesonide (30).

Clinical Studies

The safety and efficacy results from clinical studies with ciclesonide in healthy subjects and patients with asthma are summarized in Tables I and II.

In a double-blind trial in 12 healthy subjects, no significant differences were seen between ciclesonide, given in three different dose regimens, and placebo as regards suppression of cortisol incretion (31).

Results from a double-blind, randomized, placebo-controlled, crossover study in 25 patients with asthma comparing ciclesonide (400 or 800 μg once daily or 800 μg b.i.d.) and fluticasone propionate (500 or 1000 μg b.i.d.) demonstrated a decrease in hyperresponsiveness to adenosine in all patients. Unlike fluticasone, ciclesonide did not significantly suppress cortisol secretion (32).

Ciclesonide (100 or 400 μg once daily) was compared to placebo in a multicenter, double-blind, randomized, placebo-controlled study over 12 weeks in 360 patients with bronchial asthma. Both doses of ciclesonide significantly increased morning peak expiratory flow (PEF), in contrast to placebo. No clinically relevant adverse events related to drug were reported (33).

The effects of ciclesonide (400 μg) were also compared to those of budesonide (400 μg), both administered as a single morning dose for 2 weeks, in a crossover trial in 15 evaluable steroid-naive patients with asthma. Although only budesonide significantly increaed FEV_1, the other effects of the drugs, *i.e.*, reductions in airways responsiveness to inhaled AMP, sputum eosinophilia and exhaled nitric oxide, were very similar (34).

Another study addressed the impact of time of administration on the efficacy of ciclesonide. A total of 209 asthmatic patients entered this double-blind, randomized, parallel study to receive inhaled ciclesonide at a dose of 200 mcg in the morning or the evening for 8 weeks. Asthma control was similarly improved with both morning and evening administration, although evening administration appeared to be associated with a greater improvement in morning PEF. No significant differences in safety were observed and cortisol secretion was not significantly affected on either regimen (35).

The results from a double-blind, randomized, placebo-controlled, crossover trial in 29 evaluable patients with mild to moderate asthma treated with ciclesonide at doses of 100, 400 and 1600 μg daily provided further support for the idea that AMP responsiveness may be a more sensitive marker of the dose-response relationhips of inhaled corticosteroids than inflammatory parameters in sputum. Although a significant decrease in sputum eosinophilia was seen on the two higher doses, this effect was not dose-dependent. In contrast, the decreases in airways responsiveness to AMP were dose-dependent (36-38).

Short-term treatment with inhaled ciclesonide (800 μg b.i.d. for 1 week) in a study in 11 patients resulted in significant inhibition of both the early- and late-phase asthmatic responses to allergen compared to placebo, with no significant effect on 24-h urinary cortisol levels (39).

The efficacy and safety of ciclesonide in the treatment of allergic rhinitis have also been investigated in a

Table I: Randomized, double-blind clinical trials of inhaled ciclesonide in patients with asthma (Prous Science Integrity database).

Study drug	n	Results FEV_1 (l)	FVC (l)	AMP PC_{20} (mg/ml)	(DC)	Eosinophils in sputum (%)	ECP (µg/l)	PEF (l/min)	Lack of efficacy	Conclusions	Ref.
Ciclesonide	37									Dose-dependent reduction in airway responsiveness to AMP. Good tolerability	31-36
50 µg bid x 2w		+0.13		+7.0	1.6	–1.9	+0.6				
Ciclesonide											
200 µg bid x 2w		+0.30[p]		+24.6[p]	2.0[p]	–6.0[b]	–10.8[b]				
Ciclesonide											
800 µg bid x 2w		+0.14		+48.6[p]	3.4[p]	–2.7[bb]	–10.3				
Placebo											
Ciclesonide	209							morning/evening*		Efficacy in lung function measurements, symptoms, use of rescue medication and number of asthma exacerbations either administered in the morning or in the evening. Good tolerability	33
200 µg od morning x 8w		0.31[b]	0.10[b]					3/7	4.5%		
Ciclesonide											
200 µg od evening x 8w		0.31[b]	0.22[b]					30[m,bb]/16[b]	5.0%		
Ciclesonide	16									Ciclesonide as effective as budesonide in improvement in airway responsiveness and reduction of exhaled nitric oxide	32
400 µg od morning x 2w		+0.09		+16.1[bb]	2.35	–4.5[bb]	–0.31[b]				
Budesonide											
400 µg od morning x 2w		+0.26[bb]		+27.9[bb]	2.82	–1.7	–0.09				
Ciclesonide	360									Dose-dependent improvement in efficacy. Good tolerability	31
100 µg od x 12w								+2[p]	38%		
Ciclesonide											
400 µg od x 12w								+3[pp]	23%		
Placebo								–18	55%		
		Early/late test (%)**									
Ciclesonide	11									Efficacy in inhibiting the asthmatic reaction to allergen	37
800 µg bid x 7d		–12.6[p]/–10.1[p]									
Placebo		–26.9/–21.4									
Ciclesonide	25									All active treatments decrease airway responsiveness to AMP	30
400 µg od x 7d					2.03						
Ciclesonide											
800 µg od x 7d					2.09						
Ciclesonide											
800 µg bid x 7d					2.58						
Fluticasone											
500 µg bid x 7d					2.54						
Fluticasone											
1000 µg bid x 7d					2.69						

FEV_1: forced expiratory volume; FVC: forced vital capacity; AMP PC_{20}: airway responsiveness measured by the provocative concentrations of AMP which caused a 20% fall in FEV_1; ECP: concentrations of eosinophilic cationic protein; PEF: peak expiratory flow; DC: double concentrations; [p]p <0.05 *vs.* placebo; [pp]p <0.001 *vs.* placebo; [b]p <0.05 *vs.* baseline; [bb]p <0.01 *vs.* baseline; [m]p <0.05 *vs.* morning administration; *measurements performed in the morning and in the evening; **allergen-induced asthma.

Table II: Randomized, double-blind clinical trials of systemic effect of inhaled ciclesonide (Prous Science Integrity database).

Study drug	n	Cortisol levels	Conclusions	Ref.
Studies in patients with asthma				
Ciclesonide 50 μg bid x 2w	37	+162 nmol/l	No significant changes in morning serum cortisol levels. Good tolerability	31-36
Ciclesonide 200 μg bid x 2w		+73 nmol/l		
Ciclesonide 800 μg bid x 2w		+18 nmol/l		
Placebo				
Ciclesonide 200 μg od morning x 8w	209	10.47 nmol/mmol creat	No differences in cortisol levels after administration in the morning or in the evening. Good tolerability	33
Ciclesonide 200 μg od evening x 8w		13.88 nmol/mmol creat		
Ciclesonide 400 μg od x 7d	25	–11%	Fluticasone, but not ciclesonide, suppresses cortisol secretion	30
Ciclesonide 800 μg od x 7d		–10%		
Ciclesonide 800 μg bid x 7d		–11%		
Fluticasone 500 μg bid x 7d		–29%[c]		
Fluticasone 1000 μg bid x 7d		–59%[c]		
Studies in healthy subjects				
Ciclesonide	12	$AUC_{0\text{-}24h}$	800 mg/day does not lead to suppression of cortisol levels independent of time of dosing	31
800 μg od morning x 7d		6.75 μg/dl		
Ciclesonide 800 μg od evening x 7d		7.08 μg/dl		
Ciclesonide 400 μg bid x 7d		6.75 μg/dl		
Placebo		7.22 μg/dl		

[p]*p* <0.05 *vs.* placebo; [c]*p* <0.05 *vs.* ciclesonide

double-blind, randomized, placebo-controlled, crossover trial in 24 subjects who were symptom-free at the time of the study. A dose of 200 μg/nostril was administered for 7 days and intranasal pollen allergen provocation was performed before starting treatment and on all treatment days. Subjective symptoms of obstruction, itching and rhinorrhea improved from day 2 of treatment, and rhinal airflow showed significant improvement from day 5. Excellent tolerance at both the local and systemic levels was seen (40, 41).

Manufacturers

Byk Gulden Lomberg Chemische Fabrik GmbH (DE); codeveloped with Aventis Pharmaceuticals, Inc. (US) in the U.S. and licensed to Teijin Ltd. (JP) for Japan, Korea and Taiwan.

References

1. Calatayud, J., Conde, J.R., Luna, M. (Byk Elmu SA). *Acetals and esters of 16α-hydroxyprednisolone and fluocinolone.* BE 1005876, CH 683343, DE 4129535, ES 2034893, FR 2666585, GB 2247680, JP 1992257599, US 5482934.

2. Amschler, H., Flockerzi, D., Gutterer, B. (Byk Gulden Lomberg Chemische Fabrik GmbH). *Process for R-epimer enrichment of 16,17-acetal derivs. of 21-acyloxy pregnan-1,4-dien-11β,16α, 17α-triol-3,20-dione derivs.* DE 19635498, WO 9809982.

3. Barbers, R. *Asthma in Y2K and beyond.* Curr Opin Pulm Med 2000, 6: 1.

4. Holgate, S.T. *The epidemic of allergy and asthma.* Nature 1999, 402(6760, Suppl.): B2-4.

5. Bousquet, J., Jeffery, P.K., Busse, W.W., Johnson, M., Vignola, A.M.. *Asthma: From bronchoconstriction to airways inflammation and remodeling.* Am J Respir Crit Care Med 2000, 161: 1720-45.

6. Blaiss, M.S., Heinly, T. *Pharmacologic agents for the long-term control of asthma.* P&T 1999, 24: 416.

7. Barnes, P.J. *Endogenous inhibitor mechanisms in asthma.* Am J Respir Crit Care Med 2000, 161: S176-81.

8. Szelenyi, I., Hochhaus, G., Heer, S., Küsters, S., Marx, D., Poppe, H., Engel, J. *Loteprednol etabonate: A soft steroid for the treatment of allergic diseases of the airways.* Drugs Today 2000, 36: 313-20.

9. Weiner, J.M., Abramson, M.J., Puy, R.M. *Intranasal corticosteroids versus oral H_1 receptor antagonists in allergic rhinitis:*

Systematic review of randomised controlled trials. BMJ - Br Med J 1998, 317: 1624-9.

10. Dietzel, K., Engelstätter, R., Keller, A. *Ciclesonide: An on-site-activated steroid.* Prog Respir Res 2001, 31: 91-3.

11. Eigen, H., Rosenstein, B.J., FitzSimmons, S., Schidlow, D.V. *Cystic Fibrosis Foundation Prednisone Trial Group. A multicenter study of alternate-day prednisone therapy in patients with cystic fibrosis.* J Pediatr 1995, 126: 515-23.

12. Allen, D.B. *Growth suppression by glucocorticoid therapy*. Endocr Metab Clin North Am 1996, 25: 699-717.

13. Allen, D.B. *Influence of inhaled corticosteroids on growth: A pediatric endocrinologist's perspective.* Acta Paediatr 1998, 87: 123-9.

14. Doull, D.M., Freezer, N.J., Holgate, S.T. *Growth of prepubertal children with mild asthma treated with inhaled beclomethasone dipropionate.* Am J Respir Crit Care Med 1995, 151: 1715-9.

15. Allen, D.B., Mullen, M., Mullen, B. *A meta-analysis of the effect of oral and inhaled corticosteroids on growth.* J Allergy Clin Immunol 1994, 93: 967-76.

16. Todd, G., Dunlop, K., McNaboe, J., Ryan, M.F., Carson, D., Shields, M.D. *Growth and adrenal suppression in asthmatic children treated with high-dose fluticasone propionate.* Lancet 1996, 348: 27-9.

17. Lai, H.-C., FitzSimmons, S.C., Allen, D.B., Kosorok, M.R., Rosenstein, B.J., Campbell, P.W., Farrell, P.M. *Risk of persistent growth impairment after alternate-day prednisone treatment in children with cystic fibrosis.* New Engl J Med 2000, 342: 851-9.

18. Clark, D.J., Grove, A., Cargill, R.I., Lipworth, B.J. *Comparative adrenal suppression with inhaled budesonide and fluticasone propionate in adult asthmatic patients.* Thorax 1996, 51: 262-6.

19. Grahnen, A., Eckernas, S.-A., Hermdin, R.M., Ling-Andersson, A. *An assessment of the systemic activity of single doses of inhaled fluticasone propionate in healthy volunteers.* Br J Clin Pharmacol 1994, 38: 521-5.

20. Grahnen, A., Jansson, B., Brundin, R.M., Ling-Andersson, A., Lonnebo, A., Johansson, M., Eckernas, S.A. *A dose-response study comparing suppression of plasma cortisol induced by fluticasone propionate from Diskhaler and budesonide from Turbuhaler.* Eur J Clin Pharmacol. 1997, 52: 261-7.

21. Grove, A., Allam, C., McFarlane, L.C., McPhate, G., Jackson, C.M., Lipworth, B.J. *A comparison of the systemic bioactivity of inhaled budesonide and fluticasone propionate in normal subjects.* Br J Clin Pharmacol 1994, 38: 527-32.

22. Lonnebo, A., Grahnen, A., Jansson, B., Brundin, R.M., Ling-Andersson, A., Eckernas, S.-A. *An assessment of the systemic effects of single and repeated doses of inhaled fluticasone propionate and inhaled budesonide in healthy volunteers.* Eur J Clin Pharmacol 1996, 49: 459-63.

23. Clark, D.J., Lipworth, B.J. *Dose-response of inhaled drugs in asthma. An update.* Clin Pharmacokinet 1997, 32: 58-74.

24. Thorsson, L., Dahlstrom, K., Edsbacker, S., Kallen, A., Paulson, J., Wiren, J.E. *Pharmacokinetics and systemic effects of inhaled fluticasone propionate in healthy subjects.* Br J Clin Pharmacol 1997, 43: 155-61.

25. Cumming, R.G., Mitchell, P., Leeder, S.R. *Use of inhaled corticosteroids and the risk of cataracts.* New Engl J Med 1997, 337: 8-14.

26. Stoeck, M., Hatzelmann, A., Belvisi, M.G., Foster, M.L., Bundschuh, D.S. *In vitro anti-inflammatory activity of the new glucocorticoid ciclesonide in human cells.* Eur Respir J 2001, 18(Suppl. 33): Abst P679.

27. Bundschuh, D.S., Marx, D., Hatzelmann, A., Beume, R., Haefner, D., Hochhaus, G., Montoro, F., Riedel, R., Stoeck, M. *Pre-clinical anti-inflammatory activity and safety profile of the new glucocorticoid ciclesonide.* Eur Respir J 2001, 18(Suppl. 33): Abst 1013.

28. Bundschuh, D.S., Riedel, R., Hatzelmann, A., Häfner, D., Hochhaus, G., Montoro, F., Beume, R., Stoeck, M. *Efficacy and safety profile of the novel on-site activated corticosteroid ciclesonide.* Am J Respir Crit Care Med 2001, 163(5, Suppl.): A588.

29. Belvisi, M.G., Bundschuh, D.S., Stoeck, M., Wicks, S., Underwood, S., Battram, C.H., Webber, S.E., Haddad, E.-B., Foster, M.L. *Pre-clinical in vivo assessment of ciclesonide, a novel corticosteroid for the treatment of asthma.* Eur Respir J 2001, 18(Suppl. 33): Abst P682.

30. Hall, M., Peet, C.F., Boddington, T.K.S., Enos, T., Nave, R., Zech, K. *Enzymology of the human hepatic metabolism of ciclesonide (B9207-015).* Xenobiotic Metab Dispos 2000, 15(Suppl.): Abst 11PE-12.

31. Drollmann, A., Weinbrenner, A., Hüneke, D., Ziesche, M., Engel, G., Bethke, T., Steinijans, V., Wurst, W., Siegmund, W. *Repeated inhalation of the new topical steroid ciclesonide does not lead to suppression of endogenous cortisol release in healthy subjects.* Eur Respir J 2001, 18(Suppl. 33): Abst P680.

32. Derom, E., Van De Velde, V., Marissens, S., Vincken, W., Pauwels, R.A. *Efficacy and systemic effects of ciclesonide and fluticasone in asthma patients.* Eur Respir J 2001, 18(Suppl. 33): Abst 1015.

33. Drollmann, A., Langdon, C., Engelstätter, R., Rathgeb, F., Steinijans, V.W., Wurst, W. *Ciclesonide is effective in the treatment of bronchial asthma.* Eur Respir J 2001, 18(Suppl. 33): Abst P681.

34. Kanniess, F., Richter, K., Böhme, S., Jörres, R.A., Magnussen, H. *Effect of inhaled ciclesonide on airway responsiveness to inhaled AMP, the composition of induced sputum and exhaled nitric oxide in patients with mild asthma.* Pulm Pharmacol Ther 2001, 14: 141-7.

35. Postma, D.S., Sevette, C., Martinat, Y., Schlösser, N., Aumann, J., Kafé, H. *Treatment of asthma by the inhaled corticosteroid ciclesonide given either in the morning or evening.* Eur Respir J 2001, 17: 1083-8.

36. Taylor, D.A., Jensen, M.W., Kanabar, V., Engelstätter, R., Steinijans, V.W., Barnes, P.J., O'Connor, B.J. *A dose-dependent effect of the novel inhaled corticosteroid ciclesonide on airway responsiveness to adenosine-5'-monophosphate in asthmatic patients.* Am J Respir Crit Care Care Med 1999, 160: 237-43.

37. Taylor, D.A., Jensen, M.W., Harris, J.G., Engelstatter, R., O'Connor, B.J. *Airway responsiveness to AMP: A sensitive method to evaluate the dose-response relationship of an inhaled steroid in asthma.* Annu Cong Eur Respir Soc (Sept 20-24, Berlin) 1997, Abst 1948.

38. Jensen, M.W. Taylor, D.A., Engelstatter, R., Kanabar, V., O'Connor, B.J. *A novel inhaled steroid, ciclesonide, reduces airway responsiveness to AMP in a dose-related manner.* Am J Respir Crit Care Med 1998, 157(3): A406.

39. Dahl, R., Nielsen, L.P., Christensen, M.B., Engelstatter, R. *Ciclesonide – an inhaled corticosteroid prodrug – inhibits allergen induced early and late phase reactions.* Eur Respir J 1998, 12(Suppl. 28): Abst P0475.

40. Schmidt, B.M.W., Timmer, W., Georgens, A.C., Hilt, M., Mattinger, C., Wurst, W., Hörmann, K., Wehling, M. *The new topical steroid ciclesonide is effective in the treatment of allergic rhinitis.* J Clin Pharmacol 1999, 39: 1062-9.

41. Schmidt, B.M.W., Timmer, W., Georgens, A. et al. *The new topical steroid ciclesonide is effective in the treatment of allergic rhinitis.* Naunyn-Schmied Arch Pharmacol 1999, 359(3, Suppl.): Abst 477.