

PRODUCT MONOGRAPH

 **ALVESCO®**

ciclesonide inhalation aerosol

100 mcg and 200 mcg/ actuation (ex-valve)

Corticosteroid for oral inhalation

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ciclesonide inhalation aerosol

PART I: HEALTH PROFESSIONAL INFORMATION

SUMMARY PRODUCT INFORMATION

Route of Administration	Dosage Form / Strength	All Non-medicinal Ingredients
Oral Inhalation	Metered Dose Inhaler 100 micrograms 200 micrograms per actuation (ex-valve)	propellant HFA-134a (norflurane) and ethanol

Note: All doses given in this monograph are ex-valve unless specified otherwise.

INDICATIONS AND CLINICAL USE

ALVESCO (ciclesonide) is indicated for:

- prophylactic management of steroid-responsive bronchial asthma in adults, adolescents and children 6 years of age and older.

Pediatrics:

At present, there is limited data regarding the use of ALVESCO in patients <6 years of age and therefore ALVESCO is not recommended for patients younger than 6 years.

Geriatrics (>65 years of age):

Based on the pharmacokinetic characteristics obtained in patients older than 65 years of age, dose adjustment is not necessary in elderly patients.

CONTRAINDICATIONS

- ALVESCO (ciclesonide) is contraindicated in patients with known hypersensitivity to any of the ingredients. For a complete listing, see Dosage Forms, Composition and Packaging section of the PM.

- ALVESCO is contraindicated in patients with untreated fungal, bacterial or tuberculosis infections of the respiratory tract
- ALVESCO is not to be used in the primary treatment of status asthmaticus or other acute episodes of asthma, or in patients with moderate to severe bronchiectasis.

WARNINGS AND PRECAUTIONS

General

It is essential that patients be instructed that ALVESCO (ciclesonide) is a preventative agent which must be taken daily at the intervals recommended by their doctors and is not to be used as acute treatment for an asthmatic attack. Patients should be advised to inform subsequent physicians of the prior use of corticosteroids. Treatment with ALVESCO should not be stopped abruptly, but tapered off gradually.

Monitoring 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 indicate 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 should be sought. In this situation, patients should be reassessed and consideration given to the need for increased anti-inflammatory treatment therapy (either higher doses of ALVESCO or a course of oral corticosteroids). Severe asthma exacerbations should be managed according to standard medical practice.

Carcinogenesis and Mutagenesis

See TOXICOLOGY.

Endocrine and Metabolism

Hypothyroidism: There is an enhanced effect of corticosteroids on patients with hypothyroidism.

Hematologic

Eosinophilic Conditions: In rare cases, patients on inhaled corticosteroid therapy may present with systemic eosinophilic conditions, with some patients presenting with clinical features of vasculitis consistent with Churg-Strauss syndrome, a condition that is often treated with systemic corticosteroid therapy. These events usually, but not always, have been associated with the reduction and/or withdrawal of oral corticosteroid therapy following the introduction of inhaled corticosteroids, and cases of serious eosinophilic conditions have been reported in this clinical setting.

Physicians should be alert to eosinophilia, vasculitic rash, worsening pulmonary symptoms, cardiac complications, and/or neuropathy presenting in their patients. A causal relationship between ciclesonide and these underlying conditions has not been established.

Hypoprothrombinemia: Acetylsalicylic acid should be used cautiously in conjunction with corticosteroids in hypoprothrombinemia.

Hepatic/Biliary/Pancreatic

Cirrhosis: There is an enhanced effect of corticosteroids on patients with cirrhosis.

Hepatic Insufficiency: Based on the pharmacokinetic characteristics obtained in patients with hepatic insufficiency, dose adjustment is not necessary in this population. There is limited 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.

Immune

Patients who are on drugs that suppress the immune system are more susceptible to infections than healthy individuals. Chickenpox and measles, for example, can have a more serious or even fatal course in susceptible children or adults on corticosteroids. In such children or adults who have not had these diseases, particular care should be taken to avoid exposure. How the dose, route, and duration of corticosteroid administration affect the risk of developing a disseminated infection is not known. The contribution of the underlying disease and/or prior corticosteroid treatment to the risk is also not known. If exposed to chickenpox, prophylaxis with varicella zoster immune globulin (VZIG) may be indicated. If exposed to measles, prophylaxis with intramuscular pooled immunoglobulin (IG) may be indicated. If chickenpox develops, treatment with antiviral agents may be considered.

Corticosteroids may mask some signs of infections and new infections may appear. A decreased resistance to localised infections has been observed during corticosteroid therapy. This may require treatment with appropriate therapy or stopping the administration of ciclesonide until the infection is eradicated.

Infection

Candidiasis and Oral Hygiene: Therapeutic dosages of inhaled corticosteroids may cause the appearance of *Candida albicans* (thrush) in the mouth and throat. The rate reported of candidiasis in clinical trials with ALVESCO was low (0.6%, see ADVERSE REACTIONS). The development of pharyngeal and laryngeal candidiasis is a cause for concern because the extent of its penetration into the respiratory tract is unknown. Adequate oral hygiene is of primary importance in minimizing overgrowth of micro-organisms such as *Candida albicans*. Patients may find it helpful to rinse and gargle with water after using ALVESCO. Symptomatic candidiasis can be treated with topical anti-fungal therapy while still continuing to use ALVESCO.

Renal

Renal Insufficiency: Due to the lack of renal excretion of the active metabolite, dose adjustment should not be necessary in renally impaired patients, however, specific studies in this patient group have not been performed.

Respiratory

Paradoxical Bronchospasm: As with other inhalation therapy, paradoxical bronchospasm may occur which is characterized by an immediate increase in wheezing after dosing. This should be treated immediately with a fast-acting inhaled bronchodilator to relieve acute asthmatic symptoms. ALVESCO should be discontinued immediately, the patient assessed, and if necessary, alternative therapy instituted.

Systemic Steroid Replacement by Inhaled Steroid

Particular care is needed in asthmatic patients who are transferred from systemically active corticosteroids to inhaled corticosteroids because deaths due to adrenal insufficiency have occurred during and after transfer. For the transfer of patients being treated with oral corticosteroids, ALVESCO inhalation aerosol should first be added to the existing oral steroid therapy, which is then gradually withdrawn. Patients with adrenocortical suppression should be monitored regularly and the oral steroid reduced cautiously. Some patients transferred from other inhaled steroids or oral steroids remain at risk of impaired adrenal reserve for a considerable time after transferring to inhaled ciclesonide.

After withdrawal from systemic corticosteroids, a number of months are required for recovery of hypothalamic-pituitary-adrenal (HPA) function. During this period of HPA suppression, patients may exhibit signs and symptoms of adrenal insufficiency when exposed to trauma, surgery or infections, particularly gastroenteritis. Although ALVESCO inhalation aerosol may provide control of asthmatic symptoms during these episodes, it does not provide the systemic steroid which is necessary for coping with these emergencies. The physician may consider supplying oral steroids for use in times of stress (e.g. worsening asthma attacks, chest infections, surgery). During periods of stress or a severe asthmatic attack, patients who have been withdrawn from systemic corticosteroids should be instructed to resume systemic steroids immediately and to contact their physician for further instruction. These patients should also be instructed to carry a warning card indicating that they may need supplementary systemic steroids during periods of stress or a severe asthma attack. To assess the risk of adrenal insufficiency in emergency situations, routine tests of adrenal cortical function, including measurement of early morning and evening cortisol levels, should be performed periodically in all patients. An early morning resting cortisol level may be accepted as normal only if it falls at or near the normal mean level.

Transfer of patients from systemic steroid therapy to ALVESCO inhalation aerosol may unmask allergic conditions outside the pulmonary tract that were previously suppressed by the systemic steroid therapy, e.g., rhinitis, conjunctivitis, and eczema. These allergies should be symptomatically treated with anti-histamine and/or topical preparations, including topical steroids.

Systemic Effects

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 increased intraocular pressure, with or without glaucoma. Therefore, it is important that the dose of inhaled corticosteroid is titrated to the lowest dose at which effective control of asthma is maintained.

Long Term Effects: The long-term effects of ciclesonide in human subjects are still unknown. In particular, the local effects of the drug on developmental or immunologic processes in the mouth, pharynx, trachea, and lungs are unknown. There is also no information about the possible long-term systemic effects of the agent (see Monitoring and Laboratory Tests).

Special Populations

Pregnant Women: There are no adequate and well controlled studies in pregnant women. However, serum concentrations of ciclesonide are generally very low following inhaled administration; thus, fetal exposure is expected to be negligible and the potential for reproductive toxicity low. As with other inhaled corticosteroids, ciclesonide should only be used during pregnancy when the potential benefit to the mother justifies the potential risk to the mother, fetus or infant. Infants born to mothers who received corticosteroids during pregnancy should be observed carefully for hypoadrenalism.

The extent of exposure in pregnancy during clinical trials: Very Limited: individual cases only.

Nursing Women: It is unknown if ciclesonide and/or its active metabolite is excreted in human milk. In rats, however, very low levels of ciclesonide and/or its metabolites (<0.05% of dose) were found to be excreted into the milk following intravenous or oral administration. As with other inhaled corticosteroids, ALVESCO should only be used in nursing women when the potential benefit to the mother justifies the potential risk to the mother and/or infant.

Pediatrics (< 6 years of age): At present, there is limited data regarding the use of ALVESCO in patients <6 years of age and therefore ALVESCO is not recommended for patients younger than 6 years.

Geriatrics (> 65 years of age): Based on the pharmacokinetic characteristics obtained in patients older than 65 years of age, dose adjustment is not necessary in this population.

Monitoring and Laboratory Tests

As with all inhaled corticosteroids, during long-term therapy, HPA axis function (e.g. blood cortisol levels) and effects on the eye (examination for cataracts, increased intraocular pressure and glaucoma) should be assessed periodically by a specialist. See Systemic Effects.

ADVERSE REACTIONS

Adverse Drug Reaction Overview

Inhaled corticosteroid therapy may be associated with dose dependent increases in incidence of ocular complications, reduced bone density, suppression of HPA axis responsiveness to stress, and inhibition of growth velocity in children. Although such events have been associated with inhaled corticosteroid therapy, no significant difference was detected between inhaled ALVESCO (ciclesonide) and placebo on HPA function and serum cortisol levels. See DETAILED PHARMACOLOGY.

Glaucoma may be exacerbated by inhaled corticosteroid treatment for asthma or rhinitis. In patients with established glaucoma who require long-term inhaled corticosteroid treatment, it is prudent to measure intraocular pressure before commencing the inhaled corticosteroid and to monitor it subsequently. In patients without established glaucoma, but with a potential for developing intraocular hypertension, intraocular pressure should be monitored at appropriate intervals. In all patients who are receiving long-term inhaled corticosteroid therapy, intraocular pressure should be monitored at appropriate intervals (see Monitoring and Laboratory Tests).

In elderly patients treated with inhaled corticosteroids, the prevalence of posterior subcapsular and nuclear cataracts is probably low but increases in relation to the daily and cumulative lifetime dose. Cofactors such as smoking, ultraviolet B exposure, or diabetes may increase the risk.

A reduction of growth velocity in children or teenagers may occur as a result of inadequate control of chronic diseases such as asthma or from use of corticosteroids for treatment. Physicians should closely follow growth of all children taking corticosteroids by any route and weigh the benefits of corticosteroid therapy and asthma control against the possibility of growth suppression if any child's or adolescent's growth appears slowed. In a one-year study, ALVESCO was shown to have no effect on growth rates compared to placebo when administered to pediatric patients at doses of up to 200 micrograms per day (see CLINICAL TRIALS).

Osteoporosis and bone fracture are complications of long term asthma treatment with parenteral or oral steroids. Inhaled corticosteroid therapy has also been associated with dose dependent bone loss, although the risk is much less with inhaled therapy than with oral and parenteral therapy.

Clinical Trial Adverse Drug Reactions

Because clinical trials are conducted under very specific conditions the adverse drug reaction rates observed in the clinical trials may not reflect the rates observed in practice and should not be compared to the rates in the clinical trials of another drug. Adverse drug reaction information from clinical trials is useful for identifying drug-related adverse events and for approximating rates.

Use in adolescents and adults:

The clinical trial safety database for ALVESCO consists of a total of 9162 patients (740 adolescents and 8422 adults) treated with ALVESCO, 100 to 1600 micrograms per day, in clinical studies ranging in duration from 2 weeks to 1 year. The majority of short-term trials had a randomized, blinded design. Three long-term studies were of open-label design.

Approximately 6.6% of patients in placebo-controlled clinical trials experienced adverse events assessed as possibly related to treatment with ALVESCO by the investigator and/or sponsor (vs. 6.5% of patients treated with placebo). In the majority of cases (56.4%), these were mild and did not require discontinuation of treatment with ALVESCO. Approximately 6.2% of patients treated with ALVESCO discontinued clinical trial participation due to an adverse event vs. 16.4% of patients in the placebo group. The primary adverse event leading to discontinuation was asthma in both treatment groups (ALVESCO, 4.4% vs. placebo, 13.8%).

The following adverse reactions were reported during placebo-controlled clinical trials in $\geq 1\%$ of patients:

Table 1 Common Adverse Reactions¹ ($\geq 1 - <10\%$) in Placebo-Controlled Clinical Trials

	ALVESCO n=1850 (%)	Placebo n= 934 (%)
Respiratory		
Paradoxical bronchospasm ²	1.8	1.9

¹Assessed as possibly related to the treatment by investigator and/or sponsor.

²Paradoxical bronchospasm refers to a known adverse drug reaction of all inhaled drugs, which may be related to the active drug substance, excipients, or in the case of metered dose inhalers, to the cooling caused by the propellant or evaporation. Suspected paradoxical bronchospasm includes the preferred terms: chest discomfort, chest pain, asthma, bronchospasm, cough, dyspnea, obstructive airways disorder, wheezing.

Dose Response Information: The incidence of possibly treatment-related adverse events was generally comparable among the ALVESCO dose groups, with the exception of respiratory, thoracic and mediastinal disorders which showed a trend towards dose dependency. This could be due to the fact that the higher dose groups tended to include patients with more severe asthma.

Special Populations: No safety signals specific for gender or for age were found in clinical trials.

The following adverse reactions (assessed as possibly related to treatment by the investigator and/or sponsor) were reported in clinical trials with ALVESCO (placebo-controlled, active-controlled and open label studies):

Common Clinical Trial Adverse Drug Reactions (≥1% - <10%)

Respiratory: Paradoxical bronchospasm (1.6%), Dysphonia (1.0%).

Uncommon Clinical Trial Adverse Drug Reactions (≥0.1% to <1%)

Cardiovascular: Palpitations (0.1%).

Eye: Cataract subcapsular (0.1%).

Gastrointestinal: Nausea (0.2%), Dry mouth (0.1%), Dyspepsia (0.1%).

Infections: Oral candidiasis (0.6%), Candidiasis (0.1%), Oral fungal infection (0.1%), Pharyngitis (0.1%).

Injury: Contusion (0.1%).

Investigations: ALT increased (0.1%), Gamma-glutamyltransferase increased (0.1%), Weight increased (0.1%).

Nervous System: Headache (0.4%), Dysgeusia (0.3%), Dizziness (0.1%).

Respiratory, thoracic and mediastinal disorders: Pharyngolaryngeal pain (0.4 %), Throat irritation (0.3%), Dry throat (0.1%).

Skin: Rash (0.1%).

The incidence of local oropharyngeal adverse reactions in ALVESCO-treated patients was low and comparable to placebo, see Table 2.

Table 2 Local Adverse Reactions¹ in Placebo-Controlled Clinical Studies

	ALVESCO n=1850 (%)	Placebo n= 934 (%)
Gastrointestinal		
Dry Mouth	0.2	0.1
Local Infections		
Oral candidiasis	0.5	0.4
Oral fungal infection NOS	0.1	0.0
Nervous System		
Dysgeusia	0.4	0.1
Respiratory		
Dysphonia/hoarseness	0.9	0.4

Table 2 Local Adverse Reactions¹ in Placebo-Controlled Clinical Studies

	ALVESCO n=1850 (%)	Placebo n= 934 (%)
Dry Throat	0.2	0.0
Pharyngitis	0.1	0.0
Throat irritation	0.1	0.0

¹Adverse events considered to be possibly related to treatment by investigator and/or sponsor

Use in Children

The clinical trial safety database for ALVESCO in pediatric patients consists of a total of 3754 children 4-11 years of age treated with ALVESCO, 50 to 200 micrograms per day, in clinical studies ranging in duration from 2 weeks to 1 year. The incidence of possibly treatment related adverse events was similar in frequency and nature to that seen in adults and adolescents. The most commonly reported adverse drug reaction was headache (0.5%).

Abnormal Hematologic and Clinical Chemistry Findings

Examination of the percentage of patients with normal values at baseline and values above or below the normal range at the end of treatment did not demonstrate any trends with respect to changes in hematology and biochemistry values. See Uncommon Clinical Trial Adverse Drug Reactions above.

Post-Market Adverse Drug Reactions

Spontaneous adverse events reported during postmarketing use of ciclesonide are described below. As the events were reported spontaneously, no exact incidences can be provided. The following events were reported in postmarketing use, and causal relation to ciclesonide treatment could not be ruled out:

There have been rare reports of immediate or delayed hypersensitivity reactions such as angioedema with swelling of lips, tongue and pharynx as well as increased intraocular pressure in susceptible patients.

Post-Market Clinical Trial Adverse Drug Reactions

There have been uncommon reports of vomiting, bad taste; cough after inhalation, and eczema, and rare reports of abdominal pain and hypertension in the ongoing clinical trial database.

DRUG INTERACTIONS

Overview

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

The serum levels of ciclesonide and its active metabolite M1, are low. However, co-administration with a potent inhibitor of the cytochrome P 450 3A4 system (e.g. itraconazole, ritonavir or nelfinavir) should be considered with caution because there might be an increase in ciclesonide/active metabolite serum levels, as was observed when orally inhaled ciclesonide was concomitantly administered with ketoconazole (see Drug-Drug Interactions below). The risk of clinical adverse effect (e.g. cushingoid syndrome) cannot be excluded.

Drug-Drug Interactions

The drugs listed in the following table are based on drug-drug interaction clinical studies:

Table 3 **Summary of Drug-Drug Interaction Clinical Trials conducted with ciclesonide**

Ciclesonide	Effect	Clinical comment
Ketoconazole	The exposure of the ciclesonide active metabolite (M1) increased approximately 3.5 fold.	Co-administration should be considered with caution. The risk of clinical adverse effect cannot be excluded.
Erythromycin	No pharmacokinetic interaction was observed in this study.	No special precautions are necessary.

Ciclesonide is not expected to influence the metabolism of other drugs.

Drug-Food Interactions

Interactions with food have not been established. Drug-food interactions are unlikely for inhaled corticosteroids.

Drug-Herb Interactions

Interactions with herbal products have not been established.

Drug-Laboratory Interactions

Interactions with laboratory tests have not been established. Drug-laboratory interactions are unlikely for inhaled corticosteroids.

DOSAGE AND ADMINISTRATION

Recommended Dose and Dosage Adjustment

Adults and adolescents 12 years of age and older

- The recommended starting dose of ALVESCO (ciclesonide) therapy for most patients, whether previously maintained on either bronchodilators alone or inhaled corticosteroids, is 400 micrograms once daily.
- The recommended dose range is 100 to 800 micrograms per day.
- ALVESCO can be administered as 1 or 2 puffs once daily either in the morning or evening.
- Some patients with more severe asthma may be more adequately controlled on 800 micrograms daily (administered as 400 micrograms twice daily).
- As with all inhaled corticosteroids, the dose of ALVESCO should be adjusted according to individual response.

Children 6-11 years of age

- The recommended starting dose of ALVESCO therapy for most patients, whether previously maintained on either bronchodilators alone or inhaled corticosteroids, is 100 to 200 micrograms once daily.
- The recommended dose range is 100 to 200 micrograms per day, administered as 1 or 2 puffs once daily either in the morning or evening.
- As with all inhaled corticosteroids, the dose of ALVESCO should be adjusted according to individual response.

At present there is limited efficacy data regarding the use of ALVESCO in patients <6 years of age and therefore ALVESCO is not recommended for patients younger than 6 years.

Symptoms can start to improve with ALVESCO within 24 hours of treatment. Clinically, ALVESCO has been shown to improve lung function as measured by FEV₁, peak expiratory flow, improved asthma symptom control, reduced exacerbations, and decreased need for inhaled beta₂-agonists.

It is important to gain control of asthma symptoms and optimize pulmonary function as soon as possible. If there has been no improvement within one to two weeks, the patient should consult with their physician. Due to its prophylactic nature, ALVESCO should be taken regularly even when patients are asymptomatic. The patient should be aware that the benefit

of ALVESCO depends on regular use even when they are experiencing no symptoms. When patient symptoms remain under satisfactory control, the dose of ALVESCO should be titrated to the lowest dose at which effective control of asthma is maintained. Patients should be instructed to seek medical attention if their asthma symptoms worsen, or if their need for rescue medication increases.

Dose adjustments are not necessary in elderly patients, patients with liver impairment and patients with renal impairment.

Missed Dose

It is very important that ciclesonide is used regularly. If a dose is missed, the next dose should be taken when it is due.

Administration

ALVESCO is for oral inhalation use only. To ensure the proper dosage and administration of the drug, the patient must be instructed by a physician or other health professional in the use of the inhalation aerosol (see CONSUMER INFORMATION). Inhaler technique of patients should be checked regularly to make sure that correct method is used and inhaler actuation is synchronized with inhalation to ensure optimum delivery to the lungs.

In patients who find co-ordination of a pressurized metered dose inhaler difficult, a spacer device (AeroChamber Plus[®]) may be used with ALVESCO.

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 ALVESCO is a solution aerosol. The mouthpiece should be cleaned with a dry tissue or cloth weekly. No part of the inhaler should be washed or put into water.

Patients should be instructed to use the following technique to administer their medication:

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

Transferring a patient from an oral steroid to ALVESCO

The patient should be in a relatively stable phase. A high dose of ALVESCO should be given in combination with the oral steroid for about 10 days. Then the oral steroid should be gradually reduced to the lowest possible level. The gradual withdrawal of the systemic steroid is started by reducing the daily dose by 1.0 mg of prednisone (or equivalent of another corticosteroid) at seven day intervals if the patient is under close observation. If close observation is not feasible, the withdrawal of the systemic steroid should be more gradual at approximately 1.0 mg of the daily dose of prednisone (or equivalent) every ten days. If withdrawal symptoms appear, the previous dose of the systemic drug should be resumed for a week before any further decrease is attempted.

OVERDOSAGE

Single doses of up to 3200 micrograms inhaled ALVESCO (ciclesonide) were administered to healthy volunteers and were well tolerated.

The potential for acute toxic effects following overdose of inhaled ciclesonide is low. The only effect that follows inhalation of large amounts of the drug over a short period of time may be temporary suppression of adrenal function, symptoms of which may include: weakness, nausea, and hypotension. In such cases, treatment with ALVESCO should be continued at a dose sufficient to control asthma. Recovery of adrenal function can be verified by measuring plasma cortisol.

If higher than recommended doses are administered continuously over prolonged periods, some degree of adrenal suppression may occur, therefore monitoring of adrenal reserve should be considered. Gradual reduction of the inhaled dose may be required. Treatment with ALVESCO should be continued at a dose sufficient to control asthma.

For management of a suspected drug overdose, contact your regional Poison Control Centre.

ACTION AND CLINICAL PHARMACOLOGY

Mechanism of Action

Ciclesonide exhibits low binding affinity to the glucocorticoid receptor and is pharmacologically inactive. Once inhaled, ciclesonide is converted by esterases in the lungs to its active metabolite, 21 des-methylpropionyl-ciclesonide (M1), which is a potent glucocorticoid that binds to glucocorticoid receptors in the lung resulting in local pronounced anti-inflammatory activity.

Pharmacodynamics

The active metabolite of ciclesonide (M1) exhibits high receptor affinity. Ciclesonide possesses a unique combination of properties that limits systemic exposure to the active drug

including: the conversion to the active metabolite predominantly in the lung, high lung deposition, reversible formation of fatty acid conjugates of M1 in lung tissue slices, high clearance, low oral bioavailability, high protein binding, and low receptor affinity of metabolites other than M1. The clinical effects of ciclesonide on the HPA function and serum cortisol levels were investigated and, at therapeutic doses, no significant difference was detected between inhaled ciclesonide and placebo. See DETAILED PHARMACOLOGY.

Pharmacokinetics

Ciclesonide is presented in HFA-134a propellant and ethanol as a solution aerosol, delivering 50 mcg, 100 mcg or 200 mcg ciclesonide ex-valve. The doses are proportionally formulated with respect to dose and puff strength and exhibit bioequivalent systemic exposure when the same dose is inhaled by the three different formulation strengths. Across the recommended dose range, ciclesonide demonstrates linear pharmacokinetics with increases in systemic exposure proportional to dose. When a single dose of 3200 mcg of ciclesonide was administered, a greater than proportional increase in systemic exposure was observed.

The pharmacokinetic characterization of ciclesonide focused on the active metabolite (M1) of ciclesonide, as it is the active moiety. While systemic drug levels of M1 are relevant for the systemic effect profile, a close relationship between systemic exposure and efficacy response is not assumed for asthma treatment with inhaled corticosteroids due to their topical mode of action. Since ciclesonide is poorly absorbed via the gastrointestinal tract and shows an extensive first pass metabolism, systemic exposure will depend on the drug fraction that is absorbed via the lung. The following table describes the pharmacokinetic characteristics of the active metabolite M1 in healthy patients between 22 and 43 years of age following single and repeated inhalation of 400 mcg ciclesonide once daily. Pharmacokinetic data of healthy subjects and asthma patients were also shown to be similar. See DETAILED PHARMACOLOGY for further information.

Table 4 Summary of the Pharmacokinetic Parameters of ciclesonide active metabolite (M1) in healthy subjects following inhalation of 400 mcg ciclesonide (n=18), mean values (standard deviation)

	Active Metabolite (M1)			
	C _{max} (µg/l)	AUC* (µg*h/l)	t _{max} (h)	t _½ (h)
Single Dose	0.30 (0.13)	1.72 (0.73)	1.08 (0.62)	5.23 (1.28)
Steady State	0.37 (0.06)	2.18 (0.42)	0.94 (0.44)	6.72 (1.04)

*Single Dose = AUC_(0,inf); Steady State = AUC_(0,24h)

Absorption: Studies with oral and intravenous dosing of radiolabelled drug have shown low oral absorption (24.5%). When inhaled the oral bioavailability of both ciclesonide and the active metabolite is negligible (<0.5% for ciclesonide, <1% for the active metabolite). Based on a γ -scintigraphy experiment, lung deposition in healthy subjects is 52%. The systemic bioavailability for the active metabolite is >50% when using the ciclesonide metered-dose

inhaler. As the oral bioavailability for the active metabolite is <1%, the swallowed portion of the inhaled drug effectively does not contribute to the systemic absorption. Ciclesonide undergoes extensive first pass metabolism. See Table 4 for information regarding the pharmacokinetic characteristics (AUC, T_{max} and C_{max}) of ciclesonide following single and repeated dose administration.

Distribution: Following intravenous administration to healthy subjects, 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 is 99% and that of the active metabolite is greater than 98%. Only the unbound drug in the systemic circulation (approximately 1-2%) is available for further systemic pharmacodynamic effect. The active metabolite showed no accumulation in red blood cells, as could be concluded from high plasma/whole blood ratio of 1.5-1.6 at 0.5-6 hours post-dosing.

Metabolism: Ciclesonide is a prodrug and is hydrolysed to its pharmacologically active metabolite by esterase enzymes primarily in the lungs. 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. Lipophilic fatty acid ester conjugates of the active metabolite in the lung were detected using *in vitro* techniques.

Excretion: After oral and intravenous administration, ciclesonide is predominantly excreted via the faeces (78 and 68%, respectively), indicating that excretion via the bile is the major route of elimination. After intravenous administration, the clearance of ciclesonide was 152 ± 37 L/h and that of the active metabolite, M1 (assuming full conversion from ciclesonide) was 228 ± 65 L/h. The half-life estimated from the terminal elimination phase after inhaled administration of ciclesonide was approximately 6 h.

Special Populations and Conditions

Geriatrics: In a comparison between one study in elderly subjects and another study in young healthy subjects, there was an approximately 2-fold increase in the rate and extent of exposure to the active metabolite in elderly patients. However, in a population pharmacokinetic analysis of 9 studies, age did not impact the clearance or volume of distribution of the active metabolite.

Pediatrics: In two 12 week clinical studies investigating the safety and efficacy of ALVESCO (ciclesonide) in asthmatic patients between 4-11 years of age, serum samples were taken from 53 patients for pharmacokinetic analysis. The pharmacokinetics of the active metabolite M1 were found to be similar to adults.

Hepatic Insufficiency: 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 (1.8 to 2.8 times) to the active metabolite was observed. See DETAILED PHARMACOLOGY.

Renal Insufficiency: Due to the low rate of renal excretion of ciclesonide metabolites, studies on renally impaired patients have not been performed.

STORAGE AND STABILITY

The container contains a pressurized liquid and should not be pierced. It is recommended that ALVESCO (ciclesonide) be stored at room temperature between 15-25°C. Do not freeze.

DOSAGE FORMS, COMPOSITION AND PACKAGING

ALVESCO (ciclesonide) is a solution aerosol. Additional ingredients are propellant HFA-134a (Norflurane) and ethanol. The inhaler is comprised of an aluminum canister sealed with a metering valve, actuator and cap.

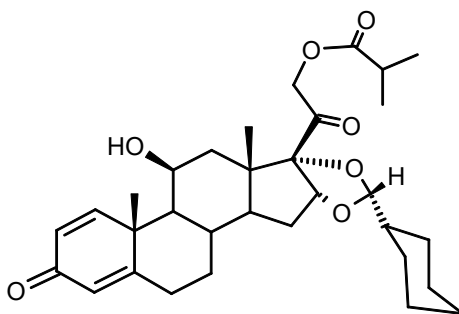
ALVESCO is available in two strengths: 100 mcg per actuation (ex-valve) and 200 mcg per actuation (ex-valve). ALVESCO is available in canisters containing 30, 60 or 120 actuations for the 100mcg, and in canisters containing 30 or 120 actuations for the 200mcg.

PART II: SCIENTIFIC INFORMATION

PHARMACEUTICAL INFORMATION

Drug Substance

Proper Name:	ciclesonide
Chemical Name:	[11 beta, 16 alpha (R)]-16, 17-[(Cyclohexylmethylene)-bis(oxy)]-11-hydroxy-21-(2-methyl-1-oxopropoxy)pregna-1,4-diene-3,20-dione
Molecular Formula:	C ₃₂ H ₄₄ O ₇
Molecular Weight:	540.7 g/mol
Structural Formula:	



Physical Form:	White to yellow white powder
Solubility:	<0.5 mg/L in water (room temperature); soluble in ethanol, acetone, methylenechloride, chloroform

CLINICAL TRIALS

Use in Adolescents and Adults

Study demographics and trial design

Approximately 4600 patients were treated with ALVESCO (ciclesonide) in 21 short-term studies of up to 12 weeks duration and approximately 1700 patients were treated with ALVESCO in five long-term studies up to one year. Most studies were double-blind, some were placebo controlled whereas others used beclomethasone dipropionate, budesonide or fluticasone propionate as an active control. Patients classified as mild, moderate or severe asthmatics were included in these studies. The age of patients ranged from 11 to 88 years and the median age in the ALVESCO group was 43 years. The percentage of male and female patients in the ALVESCO group was 46% and 54%, respectively, and the majority of patients in each group were Caucasian (>90%).

Study results

Clinically, ALVESCO was demonstrated to be well tolerated and effective in treating asthma of varying disease severity.

Placebo-Controlled Trials:

In double-blind, randomized, placebo-controlled studies, ALVESCO was shown to improve lung function versus placebo as measured by FEV₁, peak expiratory flow, improved asthma symptom control, reduced exacerbations, and decreased need for inhaled beta₂-agonists. Treatment with ALVESCO in recommended doses did not cause HPA axis suppression as measured by 24 hour serum and urine cortisol concentrations or after cosyntropin stimulation. See DETAILED PHARMACOLOGY.

The table below presents the outcome of primary endpoints in two randomized double-blind efficacy studies comparing ALVESCO with placebo. Patients with asthma who were pre-treated with beclomethasone dipropionate 400 to 1000 mcg/day or equivalent were randomized to receive either ALVESCO or placebo. Mean morning PEF remained essentially unchanged at the end of 12 weeks of treatment in the ALVESCO groups, but decreased by 18 and 28 L/min, respectively, in the placebo groups. At the end of the study, the differences in morning PEF between the placebo and ALVESCO treatments of 20 to 27 L/min (depending on the dose) were statistically significant ($p \leq 0.0012$). Statistically significant differences vs. placebo were also demonstrated for the percentage of patients who did not experience lack of efficacy (see Table 5) and for the secondary variable FEV₁ (140 to 220 ml, depending on the dose; $p \leq 0.011$).

Table 5 Results of placebo-controlled clinical studies with ALVESCO 12 weeks in duration

	Inclusion	Treatment arms/ dosage ¹ (mcg)	# of patients (ITT)	Change in AM PEF		% of patients with no Lack of Efficacy ¹	
				T _{last} – T ₀ L/min	p value vs placebo	%	p value vs placebo
[Ref 5]	FEV ₁ >60-90% predicted Pre-treatment with ICS	ALV 100 OD	113	2 ± 5	0.0012	62	0.005
		ALV 400 OD	113	3 ± 5	0.0006	77	<0.001
		Placebo	119	-18 ± 5		45	
[Ref 1]	FEV ₁ 60-90% predicted Pre-treated with ICS	ALV 200 OD	104	-4 ± 4	<0.0001	70	<0.0001
		ALV 800 OD	108	-0.7 ± 4	<0.0001	69	<0.0001
		Placebo	109	-28 ± 4		37	

ALV = ALVESCO, ICS = Inhaled Corticosteroid, PEF = Peak Flow

¹Lack of Efficacy was defined as a clinical exacerbation or defined deteriorations in lung function and/or asthma symptom scores

Studies involving adolescent patients demonstrated comparable efficacy between adult and adolescent patients.

Long-Term Studies:

The long-term safety and maintenance of efficacy of ALVESCO was demonstrated in 4 long-term extension studies ranging from 40 weeks to one year in duration. Three of the studies were open-label studies where patients were administered ALVESCO at variable doses according to their needs (range of doses: 100 to 1600 mcg). One study was a 52 week double-blind study where patients were randomized to either variable dose ALVESCO (400-800 mcg) or variable dose HFA-beclomethasone dipropionate (400-800 mcg). It was demonstrated that asthma control achieved in the preceding 12-week studies was maintained over the 40-52 week study duration, as measured by FEV₁, asthma exacerbations, and patients' as well as investigators' effectiveness ratings. In these studies, there was no significant suppression of HPA function, as measured by 24-hour urine and serum cortisol concentrations, over the one year treatment period.

The potential effect of ALVESCO on lens opacification was investigated in a double-blind, 52-week study in which patients with moderate or severe persistent asthma were treated with ALVESCO 800 mcg/day (n=743, mITT) or HFA-beclomethasone dipropionate 800 mcg/day (n=742, mITT). This study demonstrated that there were no significant differences between ALVESCO and HFA-beclomethasone dipropionate with respect to the occurrence of lens opacification. Furthermore, no clinically significant changes from baseline in best-corrected visual acuity score and median intraocular pressure were reported with ALVESCO and the results were comparable to HFA-beclomethasone dipropionate. No single case of glaucoma was reported.

Use in Children

Study demographics and trial design

Over 2900 pediatric patients aged 6 to 11 years were treated with ALVESCO in 9 short-term studies of up to 12 weeks duration and approximately 900 pediatric patients were treated with ALVESCO in 4 long-term studies up to one year. Most studies were double-blind, some were placebo controlled whereas others used budesonide or fluticasone propionate as an active control. Patients classified as mild, moderate or severe asthmatics, who were previously treated with inhaled corticosteroids or bronchodilators alone, were included in these studies.

Study results

In double-blind placebo and active-controlled studies, ALVESCO was shown to be superior to placebo and to be comparable to active comparators budesonide and fluticasone propionate in improving FEV₁ and morning home PEF, in decreasing asthma symptoms, in reducing the need of rescue medication, in reducing exacerbations and in improving pediatric asthma quality of life. Efficacy of ALVESCO was comparable to that of fluticasone propionate on a 1:1 microgram basis and to budesonide on a 1:2 basis.

The results of the primary efficacy endpoint of FEV₁ % predicted for two randomized, double-blind studies comparing ALVESCO versus placebo in patients aged 6 to 11 years are presented in Table 6. In the first study, superiority of 100 mcg/d ciclesonide and 200 mcg/d

ciclesonide to placebo was not shown ($p = 0.140$ and 0.248 respectively), however in the second study, the difference between 200 mcg/d ciclesonide and placebo was statistically significant ($p = 0.041$).

Table 6 Results of placebo-controlled trials with ALVESCO, 12 weeks in duration (patients 6-11 years of age) with primary endpoint FEV₁ % predicted

Study No.	Inclusion ¹	Treatment arms/ dosage (mcg)	# of patients (ITT) ²	FEV ₁ % predicted	
				T _{last} – T ₀	p value vs placebo ³
1	FEV ₁ >40-90% predicted Pre-treatment with ICS or bronchodilators alone	ALV 100 OD	114	15	0.140
		ALV 200 OD	103	15	0.248
		Placebo	108	12	
2	FEV ₁ >40-90% predicted Pre-treatment with ICS or bronchodilators alone	ALV 100 OD	112	12	0.232
		ALV 200 OD	127	14	0.041
		Placebo	109	10	

ALV = ALVESCO, ICS = Inhaled Corticosteroid

¹Inclusion criteria for entry into baseline period during which patients were treated with rescue medication only.

²Number of patients with paired values at T_{last} and T₀.

³ANCOVA, two-sided, $\alpha = 0.05$

The results of the primary efficacy endpoint of morning home PEF for a third randomized, double-blind study comparing ALVESCO versus placebo, are presented in Table 7. In this study, a statistically significant improvement versus placebo in morning PEF from baseline to Week 12 was demonstrated for all doses of ALVESCO. The results for the secondary endpoint of FEV₁ % predicted in this study are also provided in Table 7. Explorative analysis showed a statistically significant improvement for ALVESCO versus placebo in FEV₁ % predicted.

Table 7 Results of placebo-controlled trial with ALVESCO, 12 weeks in duration (patients 6-11 years of age) with primary endpoint morning PEF

Study No.	Inclusion ¹	Treatment arms/ dosage (mcg)	# of patients (ITT)	Morning PEF [L/min]		# of patients (ITT)	FEV ₁ % predicted	
				W _{last} – W ₀	p value vs placebo		T _{last} – T ₀	p value vs placebo
3	PEF predicted: >40-90% if pre-treated with bronchodilator alone; 50-100% if pre-treated with ICS or other controller drugs	ALV 100 OD	312	14.8	0.0295	281	5.7	0.0007
		ALV 200 OD	311	17.4	0.0056	270	6.8	<0.0001
		Placebo	146	5.4		124	1.5	

ALV = ALVESCO, ICS = Inhaled Corticosteroid

¹Inclusion criteria for entry into baseline period during which patients were treated with rescue medication only.

The primary efficacy results of the double-blind, randomized studies comparing ALVESCO with either budesonide or fluticasone propionate are presented in Table 8. Increases in FEV₁ were comparable between ALVESCO 200 micrograms and fluticasone propionate 200 micrograms or budesonide 400 micrograms.

Table 8 Results of active-comparator trials with ALVESCO, 12 weeks in duration (patients 6-11 years of age)

Study No.	Inclusion ¹	Treatment arms/ dosage (mcg)	# of patients (PP)	FEV ₁ (L)	
				T _{last} – T ₀	Non-inferior ²
4	FEV ₁ >50-90% predicted Pre-treatment with ICS	ALV 200 OD	317	0.22	Yes
		BUD 400 OD	162	0.25	
5	FEV ₁ predicted: 50 – 90% if pre-treated with bronchodilator alone; 80-100% if pre-treated with ICS; 50-100% if pre-treated with other controller drugs	ALV 200 OD	124	0.16	Yes
		FP 100 BID	122	0.16	
6	FEV ₁ predicted: 50 – 90% if pre-treated with bronchodilator alone; 80-100% if pre-treated with ICS; 50-100% if pre-treated with other controller drugs	ALV 100 OD	214	0.22	No
		ALV 200 OD	212	0.25	Yes
		FP 100 BID	224	0.28	
7 [Ref 11]	FEV ₁ predicted: 50 – 90% if pre-treated with bronchodilator alone; 80-100% if pre-treated with ICS; 50-100% if pre-treated with other controller drugs	ALV 100 BID	176	0.30	Yes
		FP 100 BID	181	0.28	

ALV = ALVESCO, ICS = Inhaled Corticosteroid, BUD=Budesonide, FP = Fluticasone Propionate

¹Inclusion criteria for entry into baseline period during which patients were treated with rescue medication only.

²LSMeans

In two placebo-controlled clinical studies conducted in patients 4 to 11 years of age, a low dose (1 microgram) cosyntropin stimulation test was performed in 60 patients after 12 weeks of dosing with 50, 100 or 200 micrograms once daily ALVESCO or placebo. The frequency of non-normal cortisol values after treatment was the same (7%) for ALVESCO treatment groups and placebo. Mean changes in peak cortisol after stimulation were comparable among ALVESCO groups and placebo. In four long-term studies 52 weeks in duration where patients were treated with variable dose ALVESCO (50 – 200 micrograms/day), there was no

evidence of suppression of HPA function, as measured by 24-hour urine and serum cortisol concentrations.

In a one-year study, ciclesonide was shown to have no effect on growth rates when administered to pediatric patients aged 5 to 8.5 years at doses of up to 200 micrograms per day. The point estimate for growth velocity with ciclesonide 200 micrograms was 0.15 cm/year lower than that noted with placebo (95% confidence interval - 0.33 to 0.03 cm/year). It can be concluded that ALVESCO administered once daily at doses up to 200 micrograms was not statistically different from placebo with respect to growth velocity. In addition, no significant difference was observed between ALVESCO and placebo on HPA function as measured by urinary cortisol.

In a 12 week study, body height, as measured by stadiometry, was compared between ALVESCO 200 micrograms/day and budesonide 400 micrograms/day. Mean body height increased in both groups (by 1.2 cm in the ALVESCO 200 micrograms/day group and by 0.7 cm in the budesonide 400 micrograms/day group). A between-treatment comparison showed a significantly greater increase in height in children treated with ALVESCO versus those treated with budesonide ($p=0.0025$).

DETAILED PHARMACOLOGY

HUMAN PHARMACOLOGY

Pharmacodynamics

Mechanism of Action: See ACTION AND CLINICAL PHARMACOLOGY.

Effects on HPA-Axis: At therapeutic doses, no significant difference was detected between inhaled ciclesonide and placebo on hypothalamic-pituitary-adrenal (HPA) function and serum cortisol levels as detailed below.

An active and placebo-controlled study compared 24-hour plasma cortisol AUC in 26 adult asthmatic patients following 7 days of treatment. Compared to placebo, 24-hour time averages of plasma cortisol ($AUC_{(0-24)}/24$ hours) following treatment with ciclesonide 400, 800, and 1600 mcg/day were decreased by 11%, 10% and 11%, respectively. These differences between placebo and the ciclesonide dose groups were not statistically significant.

Ciclesonide was administered by oral inhalation to healthy volunteers at a dosage of 800 micrograms twice daily (total dose of 1600 mcg/day) for 7 days. The response to ACTH stimulation was measured as the AUC serum cortisol over 90 minutes. There was no significant change compared to baseline.

In another active and placebo controlled study involving 164 adult male and female asthmatic patients, ciclesonide was given at doses of 400 micrograms or 800 micrograms/day over 12 weeks. Serum cortisol concentrations were measured before and after low dose (1 mcg) and high dose (25 mcg) cosyntropin stimulation testing. After cosyntropin stimulation, no

significant changes in serum cortisol levels and urinary cortisol excretion were observed between the ciclesonide treatment groups and placebo.

Ciclesonide is a corticosteroid, therefore, at higher doses, plasma cortisol suppression may be observed. If higher than recommended doses are administered continuously over prolonged periods, monitoring of adrenal reserve should be considered.

Pharmacokinetics

Lung and oropharyngeal deposition: Pulmonary deposition of ciclesonide was assessed in healthy subjects by gamma scintigraphy using ^{99m}Tc -labelled ciclesonide via MDI. The deposition of radiolabeled ciclesonide formulation was low in the mouth and pharynx (38%) and high in the lungs with 52% of ciclesonide inhaled via the MDI being deposited in the lungs.

Oropharyngeal deposition of ciclesonide and subsequent activation to its active metabolite M1 was further evaluated in healthy subjects. The area under the concentration time curve (on a molar basis in a 50% (v/v) ethanol rinsing solution after mouth rinsing) within one hour after drug inhalation ($\text{AUC}_{(0, 1h)}$) was used as the measure for oropharyngeal drug exposure. Healthy subjects ($n = 18$) received 800 micrograms budesonide (ex-valve) and 800 micrograms ciclesonide (ex-valve) via MDI. The activation of ciclesonide to M1 within the oropharynx was low (8%). The oropharyngeal exposure to M1 was 4% of the AUC of budesonide and the exposure to the parent drug was 34% of the AUC of budesonide.

Lung metabolism: Ciclesonide is primarily hydrolysed by esterases to the active metabolite M1. *In vitro* investigations performed in human precision-cut lung tissue slices demonstrated pronounced and reversible formation of fatty acid conjugates of the active metabolite.

Systemic Bioavailability: For inhaled corticosteroids, pulmonary bioavailability (rate and extent to which a drug reaches its site of action) has to be distinguished from the systemic bioavailability (rate and extent to which it reaches the blood circulation). For inhaled corticosteroids, the systemic bioavailability is the sum of oral and pulmonary bioavailabilities.

Extent of oral absorption and bioavailability of ciclesonide and its active metabolite M1 was investigated in healthy male subjects ($n = 6$) to study the contribution of the swallowed portion of the drug to the systemic circulation. The subjects received a single oral dose of 6.9 mg ^{14}C -ciclesonide and a single intravenous dose of 0.64 mg ^{14}C -ciclesonide, using a crossover study design.

Based on the dose-normalized total radioactivity plasma AUCs following oral absorption, the absorption of drug-related radioactivity (^{14}C) was 24.5%. Following oral administration, the concentration of the parent compound ciclesonide in serum was below the lower limit of quantification. The systemic oral bioavailability of M1 was $< 1\%$ (referenced to intravenous administration), indicating a marked first pass effect.

Systemic bioavailability of ciclesonide and M1 was also assessed after oral administration of ciclesonide 10000 micrograms and MDI inhalation of ciclesonide 1600 micrograms (ex-valve) and results referenced to i.v. infusion of ciclesonide 800 micrograms.

After inhalation of ciclesonide via MDI, the systemic bioavailability of M1 was about 50% (referenced to intravenous administration of ciclesonide). As both ciclesonide and M1 are highly protein bound (99% and >98%, respectively) the systemic exposure to unbound drug, which is relevant for systemic effects, is much lower (approximately 1-2% of the pulmonary absorbed dose).

Single and Repeated Dose Studies:

Ascending Single Doses:

Pharmacokinetic parameters of ascending single doses up to 3600 micrograms ciclesonide inhaled via MDI were investigated in healthy male subjects (n = 12). In this study the AUC and C_{max} of the active metabolite M1 and parent drug increased more than dose proportionally.

Repeated Dose:

Healthy subjects (15 male and 3 female) inhaled ciclesonide 400 micrograms once daily via MDI in the morning for 7 days. On Day 1 and Day 7 (steady state), blood samples were collected immediately before and up to 24 h after administration to establish the pharmacokinetic parameters of M1.

After repeated administration (steady state), the pharmacokinetic parameters of M1 were similar to those after a single dose of ciclesonide. No accumulation of M1 occurred over time.

Population Pharmacokinetics: Dose proportionality was seen in a population pharmacokinetic evaluation based on phase I data.

Special Populations:

Elderly:

In a comparison between one study in elderly subjects and another study in young healthy subjects, there was an approximately 2-fold increase in the rate and extent of exposure to the active metabolite in elderly patients. However, in a population pharmacokinetic analysis of 9 studies, age did not impact the clearance or volume of distribution of the active metabolite.

Hepatic Impairment:

In a Phase I study the systemic exposure to ciclesonide/ M1 was compared between healthy and liver impaired patients. The AUC for M1 was increased in patients with liver impairment by factors of up to 2.8.

ANIMAL PHARMACOLOGY

Pharmacodynamics

Ciclesonide has shown glucocorticoid-like activity in a series of *in vitro* systems investigating lymphocyte responses to mitogenic stimuli. The active metabolite M1 is 100 times more potent than its parent compound ciclesonide. The binding of the ciclesonide R- and S-epimers and their active metabolites to glucocorticoid receptors in the cytosol of rat lung tissue were investigated and the binding affinities relative to dexamethasone [relative binding affinity (RBA)=100] were calculated. R-epimer and S-epimer had low affinity binding (RBA = 12 and RBA = 2 respectively), while the active metabolites R-M1 and S-M1 had 100 times higher affinity bindings (RBA = 1200 and RBA = 230). The binding affinity of budesonide to the glucocorticoid receptor in this study was RBA = 900. Although both epimers are converted into more active M1 metabolites, the R-epimer (ciclesonide) was chosen for development because of its 6 times higher affinity for the glucocorticoid receptor compared to the S-epimer.

In vivo, ciclesonide inhibits bradykinin-induced tracheal mucosal leakage more potently than budesonide following topical administration. In several rat models of allergic asthma ciclesonide was able to reduce allergen induced early phase symptoms, cell influx into the airways, lung tissue and airway hyperresponsiveness in a dose dependent manner following intrapulmonary administration or inhalation. Ciclesonide and M1 inhibited cotton pellet induced granuloma formation, sephadex-induced lung edema and croton oil induced ear edema formation following topical administration. In addition, in the cotton pellet test, the local/systemic activity ratio was 4.6 for budesonide and >150 for ciclesonide when the thymus involution was considered as a measure of systemic effect. Therefore, ciclesonide is expected to produce local potency with little systemic effects.

Pharmacokinetics

Following intravenous and oral administration of 1mg/kg radiolabelled ciclesonide to male rats, total radioactivity was eliminated biphasically with a mean terminal half-life of 7 to 8 hours. Based on serum AUC data of total radioactivity, about 28% of the oral dose was absorbed.

Quantitative tissue distribution studies in the rat showed a pronounced affinity of the radiolabelled ciclesonide to the lung. Most of this radioactivity can be attributed to the biologically active metabolite and to its lipophilic fatty ester conjugates.

Regardless of the species or route of administration, drug related radioactivity was excreted predominately in the faeces (80-87% of the administered dose). Most of the radioactivity was excreted within 24 hours in the rat and 48 hours in the dog. Total recovery of radioactivity was 89-91% of the dose in the rat and 90-92% of the dose in the dog.

TOXICOLOGY

Toxicology studies conducted with ciclesonide showed effects typically associated with administering high doses of glucocorticoids; no unexpected effects were found in the toxicology studies conducted with ciclesonide.

Acute toxicity

Oral and intraperitoneal acute toxicity studies were performed in rats and mice.

The approximate LD₅₀ values are significantly higher than doses that would be administered to humans:

Species	Route	Doses (mg/kg)	LD ₅₀ (mg/kg)
Mouse	Intraperitoneal	0, 50, 100, 200	>200
Mouse	Oral	0, 2000	>2000
Rat	Intraperitoneal	0, 50, 100, 200	>200
Rat	Oral	0, 2000	>2000

Chronic Toxicity

Inhalation administration of ciclesonide was evaluated in a series of studies of up to 6 months duration in rats and 12 months duration in dogs, and the no observed adverse effect levels (NOAEL) were determined.

Species	Duration	Application form	NOAEL (mcg/kg/day)
Rat	4 week	Powder	50.5
Rat	4 week	MDI	Males: 50.3; Females 55.2
Rat	6 months	Powder	Males: 44.5; Females 49.6
Dog	4 week	Powder	50
Dog	4 week	MDI	61
Dog	4 week	MDI	15 (highest dose studied)
Dog	13 week	MDI	53
Dog	12 month	Powder	47

In the rat, comparable and typical glucocorticoid-like effects were observed which were completely or partially reversible during the recovery periods – slight reductions in body, spleen and thymus weights and minor alterations in erythrocytes, lymphocytes, differential blood cell picture, serum urea, serum creatinine, serum corticosterone and urine electrolyte levels, increased development of alveolar structures in the mammary gland, atrophy of lymphocytic components in thymus, spleen, and lymph nodes, atrophy of adrenal cortex.

Dogs similarly showed only exaggerated glucocorticoid-like effects – atrophy of lymphocytic components in thymus, spleen and lymph nodes, suppression of serum cortisol levels, atrophy of adrenal cortex.

The recommended maximum dose of ciclesonide in adults and adolescents is 400 mcg twice daily. Assuming a deposition rate of 50%, this total daily dose of 800 mcg corresponds to 8 mcg/kg/day for a 50 kg human, approximately one sixth the NOAELs in these repeated-dose toxicity studies. Comparisons of exposures in human to the ciclesonide active metabolite at the NOAELs determined during chronic exposure in animals demonstrate a sufficient range of exposure ratios of 2.1 to 3.

The initial effects seen in these toxicity studies – decrease of body-weight gain, lymphoid tissue depletion, adrenal atrophy, and, in rats, activation of erythrocyte parameters – result from an excess of pharmacological glucocorticoid activity, demonstrating the continuum of actions recognized for corticosteroids and seen with other glucocorticoids. Because of the need for the enzymatic conversion of ciclesonide ester to its active metabolite and the high plasma protein binding of both ciclesonide and its metabolite, the results suggest that ciclesonide can be used in humans at therapeutic doses that are expected to be devoid of both local (mouth, esophagus, stomach) and systemic glucocorticoid effects.

Mutagenicity

Ciclesonide was negative in the conducted *in vitro* test for genotoxicity:

- in the Ames test for gene mutation in bacteria;
- in the HPRT test for gene mutation in bacteria;
- in the test for chromosome aberrations in human lymphocytes and the *in vitro* micronucleus test in Chinese hamster V79 cells.

Moreover, racemic ciclesonide was also negative in an Ames test.

Four independent *in vivo* micronucleus tests were performed in mice covering a range of orally administered doses of glucocorticoids including ciclesonide. Threshold doses were found for all glucocorticoids tests at a dose which induced micronuclei *in vivo*. This induction of micronuclei is known from the literature. A positive response at high doses of glucocorticoids in the *in vivo* micronucleus assays is not indicative for a genotoxic potential.

Carcinogenicity

Two, 2-year carcinogenicity studies were performed with ciclesonide; one study was conducted in mice (oral gavage) and the other in rats (inhalation).

Doses in the mouse study were 150, 450, and 900 mcg/kg/day administered by oral gavage. Histology showed small, focal and solitary gastric adenomas at a very low incidence (one

male and three female in the high dose group, one male each in the low and mid dose group). A higher incidence of focal hyperplastic lesions of the antral mucosa or at its junction with the duodenum was observed, particularly in male mice of the mid and high dose group. Additionally, there was a slightly higher incidence of focal squamous metaplasia at the antral junction in females from the mid and high dose groups. No compound related malignant tumors were reported. The benign gastric adenomas in mice would be unlikely to represent a safety concern to humans since these benign neoplastic findings were only present in one species (mouse), only in one site (the antrum of the stomach), only by one route of administration (oral gavage) and at dosages markedly higher than those that will be swallowed by humans. Mice dosed at 900 mcg/kg/day in the carcinogenicity study received >100 times the anticipated maximum. Moreover, the effects of the vehicle PEG 400 combined with ciclesonide may have resulted in an altered gastric environment that would not be expected in humans administered ciclesonide by inhalation. Thus, the benign neoplastic findings in the antrum are unlikely to present a safety concern for humans receiving ciclesonide without using this vehicle.

Inhalation doses in the rat carcinogenicity study were for males/females, 14/16.2, 34.9/40.4, and 89.3/99.1 mcg/kg/day administered by MDI over one hour. After 2 years of daily exposure, the results of the rat inhalation carcinogenicity study indicate the absence of a tumorigenic potential of inhaled ciclesonide.

Reproduction and Teratology

No effects were observed in rats on fertility, embryofoetal development, or pre/post natal studies apart from a reduction in body weight or body weight gain in animals receiving 300 mcg/kg/day and 900 mcg/kg/day (all studies were conducted with 100/300/900 mcg/kg/day). In rabbits, embryotoxic effects (reduced litter weight, incomplete ossification) and teratogenic effects (like cleft palate, flexure of paw, enlarged fontanelle, parchment-like skin) were observed over the dose range of 5 to 100 mcg/kg/day given subcutaneously. The effects observed with ciclesonide in rabbits are those reported for other glucocorticosteroids. The no-effect for maternal toxicity in rabbits was established at 25 mcg/kg/day and for embryofoetal development at 1 mcg/kg/day.

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PART III: CONSUMER INFORMATION

 **ALVESCO**[®]

ciclesonide inhalation aerosol

This leaflet is part III of a three-part "Product Monograph" published when ALVESCO was approved for sale in Canada and is designed specifically for Consumers. This leaflet is a summary and will not tell you everything about ALVESCO. Contact your doctor or pharmacist if you have any questions about the drug.

ABOUT THIS MEDICATION

What the medication is used for:

ALVESCO is used to help breathing problems in asthmatic patients 6 years of age and older.

Asthma is a chronic inflammatory disease of the lungs. People with asthma have episodes of difficulty in breathing. The airways in their lungs are very sensitive. During an asthma attack, the airways get smaller, making it difficult for air to flow in and out of the lungs.

Control of asthma requires avoiding irritants that cause asthma attacks and taking the appropriate medications. For example patients should avoid exposure to house dust mites, mould, pets, tobacco smoke and pollens.

What it does:

ALVESCO is an inhaled (breathed in) medicine. ALVESCO is a corticosteroid that can help ease breathing problems. It relieves swelling and irritation in the small air passages in the lungs.

When it should not be used:

- Do not use this medication if you are allergic to any of the ingredients used in ALVESCO (See "What the medicinal ingredient is" and "What the non-medicinal ingredients are").
- Do not use this medication to treat a sudden attack of breathlessness. You will probably need a different kind of medicine (ie. a fast acting relief medication) in a different colour puffer than may already have been given to you. If you have more than one medicine, be careful not to confuse them.
- Do not use this medication if you have an untreated fungal, bacterial or tuberculosis infection in the respiratory tract.

What the medicinal ingredient is:

ALVESCO contains the medicinal ingredient ciclesonide.

What the non-medicinal ingredients are:

ALVESCO contains ethanol and HFA-134a (a propellant).

What dosage forms it comes in:

ALVESCO comes in two strengths: per spray, 100 micrograms and 200 micrograms.

WARNINGS AND PRECAUTIONS

If you notice the following warning signs, you should contact your physician as soon as possible or go to the nearest hospital:

- A sudden worsening of your shortness of breath and wheezing shortly after using your fast-acting relief medication or after using ALVESCO inhalation aerosol.
- You do not feel relief within 10 minutes after using your fast-acting medication or the relief does not last for at least 3 hours.
- Measurement from your peak flow meter indicates a value less than 60 percent of predicted or personal best.
- You are breathless at rest.
- Your pulse is more than 120 beats per minute.

The following warning signs indicate that your asthma is getting worse and that your treatment needs to be reassessed by your physician:

- A change in your symptoms such as more coughing, attacks of wheezing, chest tightness, or an unusual increase in the severity of the breathlessness.
- You wake up at night with chest tightness, wheezing or shortness of breath.
- You use increasing amounts of your fast-acting relief medication.
- Measurement from your peak flow meter indicates a value between 60 and 80 percent of predicted or personal best.

Pregnancy:

Do not use this medication if you are pregnant, plan to become pregnant or are breastfeeding without first discussing with your doctor.

BEFORE you use ALVESCO talk to your doctor or pharmacist:

- About all health problems you have now or have had in the past.
- If you are suffering from any chest infection (e.g. cold, bronchitis).
- About all the medicines you take, including ones you can get without a prescription.
- If you ever had to stop taking other medicines for asthma because you were allergic to them or had other problems with them.
- If you have a history of tuberculosis (TB) infections.
- If you are taking or have previously taken other steroid medicine by mouth or by inhalation (breathing in).
- If you ever had thrush (a fungal infection) in your mouth.
- If you are taking drugs that suppress the immune system.
- If you have thyroid abnormalities (hypothyroidism).

IMPORTANT: PLEASE READ

- If you have glaucoma or are at risk of developing glaucoma.
- If you have cirrhosis (liver disease).
- If you are taking oral corticosteroids. In rare cases, the withdrawal of oral corticosteroid therapy following the beginning of an inhaled corticosteroid such as ALVESCO, has led to serious hematologic conditions.
- If you have hypoprothrombinemia and are taking acetylsalicylic acid.

INTERACTIONS WITH THIS MEDICATION

Drugs containing ketoconazole (an azole antifungal) have been shown to interact with ALVESCO.

Drugs containing itraconazole (an azole antifungal), or ritonavir and nelfinavir (medicines used to treat HIV infection or AIDS) may interact with ALVESCO.

PROPER USE OF THIS MEDICATION

Usual dose:

Your doctor has explained when and how to take ALVESCO. Follow your doctor's directions carefully.

Adults and Adolescents 12 years of age and older:

The usual dosage for ALVESCO ranges from 100 to 400 micrograms per day. ALVESCO can be taken as 1 or 2 puffs once daily either in the morning or evening.

Some patients with more severe asthma will require 800 micrograms daily, administered as 400 micrograms twice daily.

Children 6-11 years of age:

The recommended dose range is 100 to 200 micrograms per day taken as 1 or 2 puffs once daily either in the morning or evening.

Your doctor will tell you how much ALVESCO to take and how often to take it. You should take ALVESCO daily.

It is very important that you use your medicine regularly to control your asthma. You should continue to take ALVESCO regularly even when you don't have symptoms.

Do not take more doses or use your inhaler more often than your doctor advises.

Do not adjust your dosage without talking to your doctor, even if you think your asthma is under control.

Contact your doctor immediately if your asthma symptoms get worse, or if you need to use your rescue medication more often.

If your doctor decides to stop your treatment, do not keep any leftover medicine unless your doctor tells you to.

Your asthma symptoms can start to improve within 24 hours of starting to use ALVESCO. If your symptoms do not improve within 1-2 weeks, you should talk to your doctor. You should continue to take ALVESCO regularly even when you don't have symptoms. **Do not stop taking ALVESCO suddenly** – even if you feel better. Your doctor can provide you with information about how to slowly stop the medication if necessary.

How to Use ALVESCO Properly:

If your inhaler is new, or if it has not been used for one week or more, you should release three puffs into the air to ensure that it works properly.

You do not need to shake ALVESCO before you use it.

1. Remove the mouthpiece cover.



2. Place the inhaler in your mouth and close your lips around the mouthpiece.
3. Start to breathe in slowly and deeply through your mouth.
4. As you breathe in through your mouth, press down on the top of the inhaler.



5. Move the inhaler away from your mouth and hold your breath for about 10 seconds or as long as is comfortable.
6. Breathe out slowly. Replace the mouthpiece cover. Do not breathe out into the inhaler.



Clean the mouthpiece once a week with a dry tissue, both inside and out. Using a dry, folded tissue, wipe over the front of the small hole where the medicine comes out. Do not use water or any other liquids.

Remember: This medicine is only for you. Only a doctor can prescribe it for you. Never give it to someone else. It may harm them even if their symptoms are the same as yours.

Overdose:

IMPORTANT: PLEASE READ

In case of drug overdose, contact a health care practitioner, hospital emergency department or regional Poison Control Centre immediately, even if there are no symptoms.

Missed dose:

It is very important that you use ALVESCO daily.

However, if you miss one dose, do not worry - just take the next dose when it is due. Do not double dose.

SIDE EFFECTS AND WHAT TO DO ABOUT THEM

Very occasionally, some people find that their throat or tongue becomes sore after taking this medicine or that their voice becomes a little hoarse. In some people, an infection of the mouth and throat called candidiasis (thrush) may occur. Tell your doctor but do not stop treatment unless told to do so. Rinsing your mouth and gargling with water immediately after taking each dose may help. Do not swallow the water after rinsing. Cleaning dentures may also help.

Some patients who take corticosteroids may experience side effects. Side effects are more likely to happen if a patient is taking a high dose of this type of medication. Side effects are also more likely to happen with steroid tablets than with inhaled steroids. Possible side effects are: rounded face, loss of bone density and increased risk of fractures and eye problems.

It is very important that you use your medicine regularly to control your asthma.

Most people who take ALVESCO have no problems. When the drug was tested, some people reported mild, self-limiting side effects. They did not have to stop taking ALVESCO.

Some patients reported:

- hoarseness and difficulty in speaking.
- cough after inhalation.
- nausea or vomiting.
- fungal infection in the mouth.
- headache.
- bad taste, burning, inflammation, irritation, dryness of the mouth or throat.
- skin rash or eczema.

This is not a complete list of side effects. For any unexpected effects or if you feel unwell or have any symptoms that you do not understand while taking ALVESCO, contact your doctor or pharmacist.

SERIOUS SIDE EFFECTS, HOW OFTEN THEY HAPPEN AND WHAT TO DO ABOUT THEM

Symptom / effect	Talk with your doctor or pharmacist	Stop taking drug and call your
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		Only if severe	In all cases	doctor or pharmacist
Common	Sudden wheeziness and chest pain or tightness			X
Rare	Allergic reaction, for example: <ul style="list-style-type: none"> • Swelling of eyelids, face, lips, tongue or throat • Lumpy skin rash or “hives” anywhere on the body 			X
Uncommon	Irregular heart beat (palpitations)		X	
Rare	High blood pressure	X		
Rare	Discomfort or pain in the abdomen	X		

If you notice a sudden worsening of your shortness of breath and wheeze shortly after using your ALVESCO, tell your doctor as soon as possible. As with other medicines taken by inhaling, patients may have increased wheezing immediately after inhaling the drug. In clinical tests with ALVESCO, these reactions have been mostly mild and have disappeared quickly. Use your fast-acting relief medication to treat this reaction.

Some people can be allergic to medicines. If you have any of the following symptoms soon after taking ALVESCO, **stop** taking this medicine and tell your doctor immediately:

- Sudden wheeziness and chest pain or tightness.
- Swelling of eyelids, face, lips, tongue or throat.
- Lumpy skin rash or “hives” anywhere on the body.

HOW TO STORE IT

The canister contains pressurized liquid. Do not pierce or burn it. Store at room temperature (15-25°C) and protect from temperatures above 50°C. Do not freeze. Keep out of the reach and sight of children.

REPORTING SUSPECTED SIDE EFFECTS

You can report any suspected adverse reactions associated with the use of health products to the Canada Vigilance Program by one of the following 3 ways:

- Report online at www.healthcanada.gc.ca/medeffect
- Call toll-free at 1-866-234-2345
- Complete a Canada Vigilance Reporting Form and:
 - Fax toll-free to 1-866-678-6789, or
 - Mail to: Canada Vigilance Program
Health Canada
Postal Locator 1908C
Ottawa, ON
K1A 0K9

Postage paid labels, Canada Vigilance Reporting Form and the adverse reaction reporting guidelines are available on the MedEffect™ Canada Web site at www.healthcanada.gc.ca/medeffect.

NOTE: Should you require information related to the management of side effects, contact your health professional. The Canada Vigilance Program does not provide medical advice.

MORE INFORMATION

NOTE: This CONSUMER INFORMATION leaflet provides you with the most current information at the time of printing.

The Consumer Information Leaflet plus the full Product Monograph, prepared for health professionals can be found at:

www.covispharma.com,

or by contacting the sponsor, Covis Pharma B.V. at:

Questions or concerns: 1-833-523-3009.

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