AUSTRALIAN PRODUCT INFORMATION

ALVESCO®
(ciclesonide) pressurised metered dose inhaler (pMDI)

1 NAME OF THE MEDICINE

ciclesonide

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

ALVESCO is available in the following strengths:

- ALVESCO 80: 80 micrograms ciclesonide per actuation
- ALVESCO 160: 160 micrograms ciclesonide per actuation

Excipient(s) with known effect: ethanol

For the full list of excipients, see Section 6.1 List of excipients.

3 PHARMACEUTICAL FORM

Inhalation, pressurised.

The drug is dissolved in a non-halogenated solution and delivered via a pMDI, resulting in an extra fine aerosol. The main particle fraction ranges from 1.1 microns to 2.1 microns, which ensures high lung deposition (>50% of the ex-actuator dose), and less deposition in the oropharynx than marketed suspension formulations of other ICS.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

ALVESCO is indicated as prophylactic treatment of asthma in adults, adolescents and in children 6 years of age and older.

4.2 Dose and method of administration

ALVESCO is for oral inhalation use only.

Symptoms start to improve with ALVESCO within 24 hours of treatment. However, due to its prophylactic nature, ALVESCO should be taken regularly even when patients are asymptomatic.

Dosing recommendation for children (6-11 years)

The recommended dose of ALVESCO for children is 80 micrograms or 160 micrograms once daily. ALVESCO can be administered as 1 or 2 puffs once daily either in the morning or evening. The use of a spacer is recommended for children 6-11 years (see *Method of administration*). The dose should be adjusted to the lowest dose at which effective control of asthma is maintained.

Dosing recommendation for adults and adolescents aged 12 years and older

The recommended dose range is 80 to 320 micrograms per day in adult and adolescent patients. In certain circumstances the dosage may be increased in adults (see *Adult Patients - Higher doses in certain circumstances* below). Patients should be given a starting dose of ALVESCO which is appropriate to the severity of their disease. Typical starting doses in patients either newly diagnosed or not previously treated with inhaled corticosteroids (ICS) are provided in Table 1.

Table 1 Starting doses in patients either newly diagnosed or not previously treated with inhaled corticosteroid

Asthma severity	Recommended dosage
Mild asthma	160 micrograms once daily
Moderate asthma	160-320 micrograms once daily
Severe asthma	320 micrograms once daily. In certain circumstances in adult patients, this may be increased to 640 micrograms daily, administered as 320 micrograms twice daily (see *Adult Patients - Higher doses in certain circumstances* below).

Patients previously maintained on another ICS may require a higher dose depending on their current maintenance dose. ALVESCO can be administered as 1 or 2 puffs once daily either in the morning or evening. In the case of a higher dose, twice daily administration is recommended (see Adult Patients - Higher doses in certain circumstances). The dose should be adjusted to the lowest dose at which effective control of asthma is maintained.

Adult Patients - Higher doses in certain circumstances

Adults with severe asthma may have their daily dose increased from 320 micrograms once daily to 320 micrograms twice daily. However, the superiority of this higher dose versus 320 micrograms once daily has not been unequivocally established (see Section 5.1 Pharmacodynamic properties, Clinical trials and Section 4.4 Special warnings and precautions for use). The dose should be adjusted to the lowest dose at which effective control of asthma is maintained.

When transferring a patient from an oral steroid to ciclesonide, the patient should be in a relatively stable phase. A high dose of ciclesonide should be given in combination with the oral steroid for about 10 days. The oral steroid should be gradually reduced to the lowest possible level.

Special patient populations

Renal impairment

There is no need to adjust the dose in patients with renal impairment.

Hepatic impairment

There is no need to adjust the dose in patients with hepatic impairment.

Systemic exposure to the active metabolite (M1; 21-des-isobutyryl-ciclesonide) is increased in patients with hepatic impairment (see Section 5.2 Pharmacokinetic properties).

Use in the elderly

There is no need to adjust the dose in elderly patients.

Use in paediatric patients

To date, there is insufficient data available in the treatment of children of 5 years and younger with ALVESCO.

Method of administration

For detailed instructions see the Patient Instruction Leaflet.

The mouthpiece should be cleaned with a dry tissue or cloth weekly, do not wash the inhaler or put any part of the inhaler in water.

Because of the already high lung deposition and low deposition of active corticosteroid in the oropharynx, the use of a spacer with ALVESCO is not routinely recommended for all patients. However, some patients may benefit from the consistent use of a spacer device in conjunction with their metered dose inhaler, particularly those with poor inhaler technique and children (6-11 years) as mentioned above. If a spacer is considered necessary, the AeroChamber Plus is a suitable device for using with ALVESCO. The patient should be instructed to inhale after each actuation of drug into the spacer. Any delay between actuation and inhalation should be kept to a minimum.

Electrostatic charge on the walls of the spacer may cause variability in drug delivery. Patients should be instructed to wash the spacer in warm water and detergent and allow it to dry without rinsing or drying with a cloth. This should be performed before initial use of the spacer and at least monthly thereafter. In those patients using a spacer, a change in the make of spacer may be associated with an alteration in the amount of drug delivered to the lungs. The clinical significance of such alterations is uncertain. However, in these situations, the patient should be monitored for any loss of asthma control.

4.3 Contraindications

ALVESCO should not be used in case of known hypersensitivity to any of the ingredients.

4.4 Special warnings and precautions for use

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

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

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

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 must be sought. In this situation, patients should be reassessed and consideration given to the need for increased anti-inflammatory treatment therapy (eg higher doses of ICS or a course of oral corticosteroids). The maximal daily dose is 640 micrograms/day (given as 320 micrograms twice a day but the superiority of this dose over 320 micrograms/day has not been unequivocally demonstrated (see Section 5.1 Pharmacodynamic properties, Clinical trials). Severe asthma exacerbations should be managed according to standard medical practice.

Systemic effects

Inhaled steroid products are designed to direct glucocorticoid delivery to the lungs in order to reduce overall systemic glucocorticoid exposure and side effects. In sufficient doses however, all ICS can have adverse effects, notably depression of the hypothalamic-pituitary-adrenal (HPA) axis,

reduction of bone density, cataract, glaucoma and retardation of growth rate in children and adolescents. In steroid dependent patients, prior systemic steroid usage may be a contributing factor, but such effect can occur amongst patients who use only ICS regularly.

HPA axis suppression and adrenal insufficiency

The lowest dose of ciclesonide that causes suppression of the HPA axis (as indicated by 24-hour urinary cortisol concentrations), effects on bone mineral density or growth retardation in patients has not yet been established.

A controlled study compared 24-hour plasma cortisol AUC in 26 adult asthmatic patients following 7 days of treatment. Compared to placebo, treatment with ciclesonide 320, 640 and 1280 micrograms/day did not statistically lower the 24-hour time averages of plasma cortisol ($AUC_{(0-24)}$/24 hours) nor was a dose-dependent effect seen. Hence, at therapeutic doses, no significant difference was detected between inhaled ciclesonide and placebo on HPA function and serum cortisol levels. However, potential effects on the HPA axis may occur in individual patients particularly at times of physiological stress (eg hot climate, illness or surgery). Similar results were seen in other studies in asthmatic children aged 4 to 12 years.

Growth

It is recommended that the height of children and adolescents receiving prolonged treatment with ICS is regularly monitored. In addition, consideration should be given to referring the patient to a paediatric respiratory specialist.

Visual disturbance

Visual disturbance may be reported with systemic and topical corticosteroid use. If a patient presents with symptoms such as blurred vision or other visual disturbances, the patient should be considered for referral to an ophthalmologist for evaluation of possible causes which may include cataract, glaucoma or rare diseases such as central serous chorioretinopathy (CSCR) which have been reported after use of systemic and topical corticosteroids.

Transfer from oral corticosteroids

The benefits of inhaled ciclesonide should minimise the need for oral corticosteroids. However, patients transferred from oral steroids may remain at risk of impaired adrenal reserve for a considerable time after transferring to inhaled ciclesonide. The possibility of adverse effects may persist for some time. These patients may require specialised advice to determine the extent of adrenal impairment before elective procedures. The possibility of residual impaired adrenal response should always be considered in emergency (medical or surgical) and elective situations likely to produce stress, and appropriate corticosteroid treatment considered. Transfer of patients from systemic corticosteroid therapy to ALVESCO may unmask pre-existing allergic conditions such as allergic rhinitis or eczema, previously suppressed by systemic corticosteroid therapy.

General

Paradoxical bronchospasm with an immediate increase of wheezing or other symptoms of bronchoconstriction after dosing should be treated with an inhaled short-acting bronchodilator, which usually results in quick relief. If the patients find short-acting bronchodilator treatment ineffective, or they need more inhalations than usual, medical attention must be sought. This indicates a worsening of the underlying conditions, and warrants a reassessment of the therapy.

The patient should be assessed and therapy with ALVESCO should only be continued, if after careful consideration the expected benefit is greater than the possible risk. Correlation between severity of asthma and general susceptibility for acute bronchial reactions should be kept in mind (see Section 4.8 Adverse Effects).

The patient should be advised against abrupt discontinuation of therapy with ALVESCO.

Patient inhaler technique should be checked regularly to make sure that inhaler actuation is synchronised with inhalation to ensure optimum delivery to the lungs (see Section 4.2 Dose and method of administration).

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

Use in hepatic impairment

Systemic exposure to the active metabolite (M1) is increased in patients with hepatic impairment (see Section 5.2 Pharmacokinetic characteristics in special patient populations, Use in hepatic impairment). Although no dosage reduction is necessary, prescribers should be aware of the possibility of an increased risk of systemic adverse effects (see Section 4.2 Dose and method of administration, Use in hepatic impairment).

Use in the elderly

Systemic exposure to M1 is also increased in elderly patients (see Section 5.2 Pharmacokinetic characteristics in special patient populations, Use in the elderly). Although no dosage reduction is necessary, prescribers should be aware of the possibility of an increased risk of systemic adverse effects in such patients (see Section 4.2 Dose and method of administration, Use in the elderly).

Paediatric use

See Section 5.1 Pharmacodynamic properties, Clinical trials.

To date, there is insufficient data available in the treatment of children of 5 years and younger with ALVESCO.

Effects on laboratory tests

No data available.

4.5 Interactions with other medicines and other forms of interactions

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

4.6 Fertility, pregnancy and lactation

Effects on fertility

Fertility was not affected in rats given 900 micrograms/kg/day ciclesonide given by oral gavage.

Use in pregnancy – Category B3

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

In animal studies glucocorticoids have been shown to induce malformations. Corticosteroids are known to induce foetotoxic and teratogenic effects in rodent and rabbit studies.

Embryofoetal development studies with daily SC dosing of ciclesonide in rabbits, abnormal foetal development (cleft palate, hind paw flexure, enlarged fontanelle, parchment like skin) was observed at systemic exposure levels (based on plasma AUC) ranging from about 3 to 12 times that anticipated clinically at the maximum recommended human dose.

Embryofoetal development studies in rats showed reduced foetal weight, skeletal anomalies, hydronephrosis and maternotoxicity at oral doses of 300-900 micrograms/kg/day.

Similar studies with these doses extended until weaning revealed maternotoxicity, reduced pup weight gain, changes in pup organ weight and changes in behavioural development tests. The systemic exposure of dams relative to human exposure in these studies is not known, but doses represented 2-6 times the maximum recommended human dose on a body surface area basis.

As with other ICS preparations, ALVESCO is not to be used during pregnancy unless the potential benefit to the mother justifies the potential risk to the mother or foetus. The lowest effective dose of ciclesonide needed to maintain adequate asthma control should be used. Infants born of mothers who received corticosteroids during pregnancy are to be observed carefully for hypoadrenalism.

Use in lactation

The excretion of ciclesonide or its metabolites into human milk has not been investigated.

There was limited excretion of ciclesonide and/or its metabolites into milk in lactating rats after intravenous or oral administration (respective maxima of 0.23% and 0.03% of dose/g tissues). Oral administration of ciclesonide to rats from early pregnancy until weaning was associated with adverse effects on dams and pups (see Use in Pregnancy).

In breastfeeding mothers, the therapeutic benefits of the drug should be weighed against the potential hazards to mother and baby.

4.7 Effects on ability to drive and use machines

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

4.8 Adverse effects (Undesirable effects)

Clinical trial data in adults and adolescents

Approximately 5% of patients experienced adverse reactions in clinical trials with ALVESCO given in the dose range 80 to 1280 micrograms per day. In the majority of cases, these were mild and did not require discontinuation of treatment with ALVESCO.

The table below shows the adverse events reported with a frequency of ≥2% from participants in studies of up to 1-year duration.

Table 2 Adverse events that occurred ≥2% from participants in studies of up to 1-year duration

Preferred term	Ciclesonide (N=9162) (ET=3239.2)			Placebo (N=975) (ET=150.0)			Active comparators (N=4663) (ET=1695.5)		
	n	%	n*	n	%	n*	n	%	n*
Infections & infestations	1856	20.3	2617	144	14.8	163	1064	22.8	1543
Bronchitis	227	2.5	258	9	0.9	9	125	2.7	151
Influenza	253	2.8	274	21	2.2	21	157	3.4	175
Nasopharyngitis	781	8.5	948	55	5.6	63	442	9.5	526
Oral candidiasis	57	0.6	65	4	0.4	4	125	2.7	156
Sinusitis	325	3.5	408	15	1.5	16	176	3.8	200
Upper respiratory tract infection	526	5.7	664	48	4.9	50	289	6.2	335
Musculoskeletal & connective tissue disorders	177	1.9	210	15	1.5	16	96	2.1	117
Back pain	177	1.9	210	15	1.5	16	96	2.1	117
Nervous system disorders	475	5.2	784	77	7.9	127	239	5.1	405
Headache	475	5.2	784	77	7.9	127	239	5.1	405
Respiratory, thoracic & mediastinal disorders	1185	12.9	1441	188	19.3	213	571	12.2	711
Asthma	745	8.1	852	148	15.2	154	283	6.1	326
Cough	175	1.9	186	21	2.2	21	91	2.0	108
Dysphonia	119	1.3	126	6	0.6	6	119	2.6	121
Pharyngolaryngeal pain	249	2.7	277	28	2.9	32	131	2.8	156
All adverse events with frequency ≥2%	*2916*	*31.8*	*5052*	*343*	*35.2*	*519*	*1530*	*32.8*	*2776*

N = number of patients in specified treatment group; n = number of patients; n* = number of events

ET = number of patient years of exposure

% = percentage of patients with specified event based on N

The following adverse reactions have also been reported in clinical trials with ALVESCO:

Table 3 Adverse reactions also reported in clinical trials with ALVESCO

Frequency	Event
Uncommon (>1/1,000, <1/100)	nausea, vomiting*, bad taste, application site reactions, application site dryness, eczema, rash, cough after inhalation*, paradoxical bronchospasm*
Rare (1/10,000 – 1/1,000)	palpitations**, dyspepsia*, abdominal pain*, angioedema, hypersensitivity, hypertension

* Similar or lower incidence when compared with placebo

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

Paradoxical bronchospasm may occur immediately after dosing and is an unspecific acute reaction to all inhaled medications, which may be related to the drug, the excipient, or evaporation cooling in the case of metered dose inhalers. In the majority of cases, this reaction is mild and does not require withdrawal of ALVESCO. In severe cases, withdrawal of ALVESCO should be considered.

Clinical trial data in children

In children, the overall frequency of treatment-emergent adverse events seen with ALVESCO treatment was lower than that seen with placebo treatment. There was no evidence of any negative effect of ALVESCO on short or long-term growth velocity.

The following adverse reactions were recorded during clinical trials in children (N=2827) with ALVESCO, regardless of causality.

Table 4 Adverse reactions recorded during clinical trials with children (regardless of causality)

Frequency	Event
Common (>1%)	headache, pyrexia, sinusitis, pharyngitis, influenza, bronchitis, pharyngolaryngeal pain, rhinitis, cough, asthma, nasopharyngitis, upper respiratory tract infection, otitis media, vomiting, ear infection, rhinitis allergic, upper abdominal pain, acute bronchitis, viral infection, viral upper respiratory tract infection, gastroenteritis, tonsillitis, nasal congestion, ear pain, pharyngitis streptococcal, epistaxis, diarrhoea, respiratory tract infection, viral gastroenteritis, rash, toothache, conjunctivitis, rhinorrhoea, varicella.
Uncommon (<1%)	abdominal pain, pain in extremity, viral respiratory tract infection, viral pharyngitis, laryngitis, arthralgia, pneumonia, arthropod bite, urinary tract infection.

Post marketing experience

Very rare cases of immediate or delayed hypersensitivity reactions such as angioedema with swelling of lips, tongue and pharynx have been reported from spontaneous reporting with ALVESCO.

There have been very rare reports of psychiatric symptoms such as agitation, insomnia, depression, anxiety and behavioural changes with ciclesonide as well as with other ICS.

Systemic effects of ICS may occur, particularly at doses higher than recommended. Possible systemic effects include Cushing's syndrome, Cushingoid features, adrenal suppression, growth retardation in children and adolescents and decrease in bone mineral density (see Section 4.4 Special warnings and precautions for use, Systemic effects).

Eye disorders with frequency unknown, such as blurred vision, cataract or glaucoma, have been reported with systemic and topical corticosteroid use (see Section 4.4 Special warnings and precautions for use, Systemic effects).

Reporting suspected adverse effects

Reporting suspected adverse reactions after registration of the medicinal product is important. It allows continued monitoring of the benefit-risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions at www.tga.gov.au/reporting-problems.

4.9 Overdose

For information on the management of overdose, contact the Poison Information Centre on 131126 (Australia).

Acute

Inhalation by healthy volunteers of a single dose of 2880 micrograms of ciclesonide was well tolerated. The potential for acute toxic effects following overdose of inhaled ALVESCO is low. After acute overdosage no specific treatment is necessary.

Chronic

After prolonged administration of 1280 micrograms of ciclesonide no significant clinical signs of adrenal suppression were observed. However, if higher than recommended dosage is continued over prolonged periods, some degree of adrenal suppression cannot be excluded. Monitoring of adrenal reserve may be necessary. In cases of ciclesonide overdose, therapy may still be continued at a suitable dosage for symptom control.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Mechanism of action

Ciclesonide (pure R-epimer) belongs to a new class of on-site activated non-halogenated ICS. Ciclesonide is an ester pro-drug with approximately 100-fold lower affinity for the glucocorticoid receptor than its active metabolite (M1; 21-des-isobutyryl-ciclesonide) and budesonide and fluticasone. Endogenous activation occurs primarily via esterases located in the lung, to give M1.

Bronchial inflammation is known to be an important component in the pathogenesis of asthma. Inflammation occurs in both large and small airways and also causes an associated increase in airway responsiveness to a variety of inhaled stimuli. In clinical trials, ciclesonide has been shown to reduce airway reactivity to adenosine monophosphate in hyperreactive patients. Pre-treatment with ciclesonide for seven days significantly attenuated the early and late phase reactions following inhaled allergen challenge. Inhaled ciclesonide treatment was also shown to attenuate the increase in inflammatory cells (total eosinophils) and inflammatory mediators in induced sputum.

Clinical trials

Clinical trials in adults and adolescents

Forty-two studies with ALVESCO pMDI were initiated in Europe, Canada, Japan, USA and South Africa. Over 14,000 patients were evaluated including adolescents (12-17 years), adults and elderly patients (65-75 years). 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.

ALVESCO was demonstrated to be well tolerated and effective in treating asthma of varying disease severity in adults and adolescents. Safety and efficacy was maintained over 12 months.

Treatment with ALVESCO in recommended doses did not cause HPA axis suppression as measured by 24-hour serum and urine cortisol concentrations or cosyntropin tests.

The tables below present the outcome of primary endpoints in efficacy studies comparing ALVESCO with placebo, budesonide and fluticasone propionate. All studies were a randomised (evenly) parallel group design of 12 weeks duration.

Table 5 ALVESCO versus placebo (ITT-analysis)

Study	N	Inclusion	Treatment	Primary endpoint results (12w-baseline)			
				AM PEFR (L/min)		% pts with no LOE	
				Diff	P vs placebo		P vs placebo
FK1 101	345	Asthma, FEV_1 60-90% pred. Pre-treated with ICS	ALV 80 micrograms OD	+2±5	0.0012	62	0.0052
			ALV 320 micrograms OD	+3±5	0.0006	77	<0.0001
			Placebo	-18±5	-	45	-
FK1 102	321	Asthma; FEV_1 60-90% pred. Pre-treated with ICS	ALV 160 micrograms OD	-4±4	<0.0001	70	<0.0001
			ALV 640 micrograms OD	-0.7±4	<0.0001	69	<0.0001
			Placebo	-28±4	-	37	-

ALV = ALVESCO, Pred. = predicted, ICS = Inhaled corticosteroid, LOE = Lack of Efficacy

Table 6 ALVESCO versus budesonide (PP-analysis)

Study	N	Inclusion	Treatment	FEV_1 results (12 weeks – baseline)	
				Diff (L/min)	P vs BUD
FK1 110	433	Asthma; FEV_1 >50% pred. Pre-treatment with ICS allowed	ALV 80 micrograms OD	+0.263	0.0727
			ALV 320 micrograms OD	+0.273	0.0924
			BUD 200 micrograms BD	+0.355	-
FK1 113	281	Asthma; FEV_1 65-90% pred. Pre-treated with ICS	ALV 320 micrograms OD	-0.178	0.1246
			BUD 400 micrograms OD	-0.232	-
FK1 114	314	Asthma; FEV_1 >50% pred. Pre-treated with SABA only	ALV 320 micrograms OD	+0.411	0.0374
			BUD 400 micrograms OD	+0.319	-
MI-139	357	Asthma, FEV_1 pred. 50-80% for adolescents pre-treated with ICS	ALV 320 micrograms OD	+0.518	0.6124
			BUD 800 micrograms OD	+0.533	-

ALV = ALVESCO, BUD = Budesonide (Turbuhaler®), ICS = Inhaled corticosteroid, Pred. = predicted, SABA = Short acting β-agonist

Table 7 ALVESCO versus fluticasone (PP-analysis)

Study	N	Inclusion	Treatment	FEV_1 results	
				Diff (L/min)	P vs FP
				12 weeks - baselines	
FK1 118	427	Asthma, FEV_1 50-90% pred. Pre-treatment with ICS	ALV 160 micrograms OD	0.506	0.4766
			FP 100 micrograms BD	0.536	-
M1 133	363	Asthma, FEV_1 :>60 pred. Pre-treatment with ICS allowed., ≥85% pred. Pretreated with ICS & LABA	ALV 320 micrograms OD	+0.199	0.7471
			FP 200 micrograms BD	+0.231	-
				24 weeks - baselines	
M1 134	371	Asthma, FEV_1 ≥80% pred. Pre-treatment with ICS	ALV 320 micrograms BD	+0.011	0.7862
			FP 375 micrograms BD	+0.038	

ALV = ALVESCO, FP = fluticasone propionate, ICS = Inhaled corticosteroid, Pred. = predicted, SABA = Short acting β-agonist, LABA = Long acting β-agonists

Dose finding studies to support 640 micrograms/day

In the original registration data set, efficacy studies did not find a dose effect between ciclesonide 160 micrograms/day and 640 micrograms/day doses (FK1 102) or between ciclesonide 80 micrograms/day and 320 micrograms/day doses (FK1 101) in patients with mild to moderate asthma. Lack of efficacy was present in 66 out of 110 placebo group patients in FK1 102 compared with 31 out of 107 patients on 160 micrograms/day and 32 out of 112 patients on 640 micrograms/day ciclesonide. FK1 104 did not show superiority (PEFR or FEV_1) of 1280 micrograms/day ciclesonide/day over 640 micrograms/day in patients with severe asthma. Study FK1 104 did not use a comparator dose of ciclesonide 320 micrograms/day. It does not provide evidence to support a dose exceeding 640 micrograms/day. Study 193/2000 compared ciclesonide 80 or 320 micrograms/day with budesonide 400 micrograms/day – both doses were non-inferior.

Late studies that examined dose-response of ciclesonide over 320 micrograms/day were studies M1 140 (ciclesonide 160 micrograms/day versus 640 micrograms/day) and XRP 323/324 (640 and 320 micrograms/day and fluticasone propionate 880 micrograms/day).

Study M1 140 – the objective of this randomised, parallel group study (n=680 patients) was to show superiority of ciclesonide 320 micrograms twice a day over ciclesonide 160 micrograms/day. There were two primary variables over the 12-week treatment phase: time to first asthma exacerbation (loss of efficacy) and change in FEV_1 from T0 to T end/last. First asthma exacerbation/loss of efficacy was defined as worsening asthma which required treatment with additional asthma medications other than increased use of rescue medication. After a 2-week baseline period when the patients received fluticasone propionate 250 micrograms twice a day, randomization occurred if FEV_1 were ≤70% predicted, asthma symptom scores ≥4 for the 4 of the last 7 days before randomization or ≥puffs of rescue medication were used in the last 4 days before randomization. Six hundred and eighty patients were randomised to (ratio 1:1):341 to ciclesonide 640 micrograms/day and 339 to ciclesonide 160 micrograms/day; 595 of them completed the study (ciclesonide 640 micrograms/day 91.2% and ciclesonide 160 micrograms/day 71.1%). Ciclesonide 640 micrograms/day (320 micrograms twice daily) was superior to ciclesonide 160 micrograms/day with regard to time to occurrence of a first exacerbation (p=0.005) 12.7% of patients in the ciclesonide 160 micrograms/day group and 6.7% of patients in the ciclesonide 640 micrograms/day experienced exacerbation. For the second primary efficacy variable, FEV_1 (L/min) from T0 to T end/last, this increased in both treatment groups; ciclesonide 160 micrograms/day 0.269 and ciclesonide 320 micrograms twice a day 0.332 (both p<0.0001) but superiority of ciclesonide 320 micrograms twice a day over ciclesonide 160 micrograms/day was not shown. Ciclesonide 320 micrograms twice a day – ciclesonide 160 micrograms/day Δ0.062 (p=0.0639). This study did not use a comparator dose of ciclesonide 320 micrograms/day. The added benefit of 320 micrograms twice a day over 320 micrograms/day was not examined.

Study XRP 323/324 was a phase III double-blind, double-dummy, parallel-group, multicentre, placebo-controlled, efficacy and safety study of ciclesonide pMDI 320 micrograms/day, 640 micrograms/day and Flovent pMDI (fluticasone propionate) 880 micrograms/day (ex-actuator) administered twice daily for 12-weeks in the treatment of severe persistent asthma in adolescents and adults. Patients were required to have been on ≥500 micrograms fluticasone propionate or equivalent for at least one month prior to baseline and used β_2-agonist >twice per week. During baseline the patients took 50 or 25% of their usual ICS dose. At randomization, FEV_1 was ≥40% and ≤65% predicted and a reduction of ≥10% from the actual FEV_1 value at entry to baseline. The primary efficacy variable was change in FEV_1 from baseline to week 12 and the primary efficacy analysis was the treatment difference between active treatments and placebo. The first comparison was between ciclesonide 640 micrograms/day and placebo followed by the comparison between ciclesonide 320 micrograms/day and placebo. The intent to treat population totalled 527 patients.

FEV1, improved significantly from T0 to T12 for all treatments: 0.25 L/min for placebo, 0.36 L/min for ciclesonide 320 micrograms, 0.43 L/min for ciclesonide 640 micrograms, and 0.50 L/min for FP 880 micrograms. There was a statistically significant difference in FEV_1 for ciclesonide 640 micrograms vs. placebo, (Δ0.18, p=0.0008), ciclesonide 320 micrograms/day vs. placebo (Δ0.11, p=0.0374) and fluticasone 880 vs. placebo (0.24, p=0.0001). The treatment differences between ciclesonide 640 micrograms and 320 micrograms and ciclesonide 640 micrograms and fluticasone 880 micrograms treatment groups were not significant clinically or statistically but some dose-related trends were seen.

Study FK1 102 was a placebo controlled, parallel group study that compared 12 weeks treatment with 160 or 640 micrograms/day ciclesonide or placebo – the primary efficacy variables were change in morning peak expiratory flow from initial to last observation and the fraction of patients with predefined loss of efficacy up to week 12. The adults enrolled had mild to moderate asthma. This was a superiority study of ciclesonide 640 micrograms/day and then ciclesonide 160 micrograms/day compared to placebo. The first comparison did not show superiority. Note: This study did not use a comparator dose of ciclesonide 320 micrograms/day. Added benefit of 640 micrograms/day over ciclesonide 160 micrograms/day was not shown in mild to moderate asthma.

Clinical trials in children (under 12 years of age)

In four active-controlled studies of 12 weeks duration in children comparable efficacy to the respective active control was shown for lung function as measured by FEV_1 and peak expiratory flow, asthma symptom scores, and need for inhaled β_2-agonist. In two of these studies ciclesonide was administered with a spacer.

The effect on growth in 609 children aged 5 to 9 years was investigated in a placebo-controlled multi-centre, double-blind, randomised parallel-group study of 12 months duration. In the modified intention-to-treat (mITT) analysis, the mean growth velocities observed during the double-blind treatment period were 5.76 cm/year in the placebo group, 5.75 cm/year in the 40 micrograms ciclesonide group, and 5.60 cm/year in the 160 micrograms ciclesonide group. It can be concluded that doses of ciclesonide administered at 40 micrograms or 160 micrograms once daily were non-inferior to placebo with respect to growth velocity. In addition, no significant difference was observed between ciclesonide and placebo as measured by 24-hour urinary free cortisol in 292 patients who were studied for HPA axis function.

Growth was also assessed by stadiometry in one of the double-blind, double-dummy, randomised parallel group 12-week studies in a subset of patients (ciclesonide 160 micrograms od with spacer: N=58, budesonide 400 micrograms od administered by DPI: N=26). Height increased by 1.2 cm in the ciclesonide group and by 0.7 cm in the budesonide group. A between-treatment comparison showed superiority of ciclesonide over treatment with budesonide (p=0.0025).

5.2 Pharmacokinetic properties

Ciclesonide is dissolved in a non-halogenated solution which results in a finer aerosol and less oropharyngeal deposition than suspension formulations of other ICS. In addition, ciclesonide is delivered as a pro-drug, with a low level of conversion to the active metabolite (M1) in the oropharynx.

In the following all doses of ALVESCO are given as ex-actuator. 160 micrograms ALVESCO ex-actuator corresponds to 200 micrograms ex-valve. Doses for other ICS are given as ex-valve.

In a study comparing oropharyngeal deposition, the AUC (in nmol x hr/L) of M1 recovered from the oropharynx after a 640 micrograms dose of ALVESCO was 4% of the AUC of budesonide recovered after an 800 micrograms (ex-valve) dose of a suspension formulation of budesonide.

Similarly, the AUC of M1 recovered from the oropharynx after a 640 micrograms dose of ALVESCO was 8% of the AUC of fluticasone recovered after a 1000 micrograms dose (ex-valve) of a suspension formulation of fluticasone.

Based upon a γ-scintigraphy experiment in healthy subjects 52% of the dose leaving the ALVESCO pMDI is deposited in the lungs. In line with this figure, the mean systemic bioavailability for M1 is ≥50%. Systemic exposure to M1 is approximately proportional to dose.

Studies with oral and intravenous dosing of radiolabelled drug have shown an incomplete extent of oral absorption (24.5%). With a powder capsule formulation of ciclesonide, the oral bioavailability of both ciclesonide and M1 is low (<0.5% for ciclesonide, <1% for M1). The swallowed portion of the inhaled drug is not expected to contribute significantly to systemic absorption.

Distribution

Following IV administration of ciclesonide the volume of distribution was estimated at 2.9 L/kg for ciclesonide and 12.1 L/kg for M1. Ciclesonide and M1 are highly bound to plasma proteins (98-99%).

Metabolism

Ciclesonide is primarily hydrolysed to M1 by esterase enzymes in the lung. Studies with human liver microsomes showed that M1 is metabolised predominantly by CYP3A4 catalysis to hydroxylated metabolites, which have a lower affinity (4-15 fold) than M1 for the glucocorticosteroid receptor. Furthermore, in studies in rats, lipophilic fatty acid ester conjugates of the M1 in the lung were detected. This could maintain levels of the active principle due to C21-ester hydrolysis in the lung.

Excretion

Following IV administration of ciclesonide, clearance of ciclesonide was 152 L/hr and clearance of M1 was estimated at 228 L/hr. Half-life was estimated at 0.94 hours for ciclesonide and 2.8 hours for M1.

Ciclesonide and its metabolites are predominantly excreted via the faeces, after oral and intravenous administration, indicating that biliary excretion is the major route of elimination.

Pharmacokinetic characteristics in special patient populations

Hepatic impairment

Following a single inhaled dose of 1280 micrograms of ALVESCO in patients with moderate or severe cirrhosis, plasma concentrations of M1 were increased approximately two-fold compared to healthy subjects.

Use in the elderly

Following a single inhaled dose of 1280 micrograms of ALVESCO in healthy elderly male subjects, plasma concentrations of M1 were increased approximately two-fold compared to healthy young male subjects.

5.3 Preclinical safety data

Genotoxicity

Ciclesonide did not induce gene mutations in bacterial or mammalian assays in vitro, nor induce chromosomal aberrations in CHO cells or human lymphocytes in vitro. However, ciclesonide induced micronuclei in mouse bone marrow in vivo in oral doses ≥75 mg/kg in females and >1000 mg/kg in males. The estimated systemic exposure (plasma AUC) to the active metabolite at the no effect dose level was ≥6 times that expected in humans at the maximum clinical dose. Positive in vivo clastogenicity results have also been observed with other corticosteroids and may result from effects on erythrocyte differentiation. The clinical relevance of these clastogenicity findings is unknown.

Carcinogenicity

Carcinogenicity was investigated in a 2-year inhalation study in rats receiving up to 104 micrograms/kg/day (females) or 90 micrograms/kg/day (males) ciclesonide and in a 2-year oral study in mice receiving up to 900 micrograms/kg/day ciclesonide respectively.

Gastric adenomas (benign tumour) were significantly increased in female mice receiving a 70-fold higher dose (on a mg/kg basis) compared to the amount of the maximal recommended clinical inhalation dose estimated to be swallowed per day. This effect may arise from a local action in the antrum.

There were no significant tumorigenic effects of low doses of ciclesonide in the rat 2-year inhalation study (systemic exposure based on plasma AUC that is similar to that expected in humans given the maximum daily dose).

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Ethanol and norflurane ((HFA-134a) a propellant, which does not contain chlorofluorocarbons (CFCs)).

6.2 Incompatibilities

Incompatibilities were either not assessed or not identified as part of the registration of this medicine

6.3 Shelf life

In Australia, information on the shelf life can be found on the public summary of the Australian Register of Therapeutic Goods (ARTG). The expiry date can be found on the packaging.

6.4 Special precautions for storage

Store below 25°C. Do not refrigerate or freeze. Do not puncture or incinerate even when empty as canister may explode.

6.5 Nature and contents of container

ALVESCO is registered* in the following pack sizes:

- ALVESCO 80: 60 or 120 inhalations
- ALVESCO 160: 60 or 120 inhalations

*not all presentations may be available in Australia.

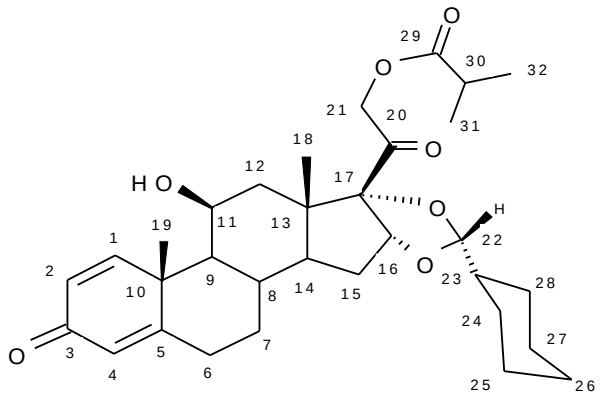
6.6 Special precautions for disposal

In Australia, any unused medicine or waste material should be disposed of by taking to your local pharmacy.

6.7 Physicochemical properties

Chemical name: [11β,16α(R)]-16,17-[(Cyclohexylmethylene)bis(oxy)]-11-hydroxy-21-(2-methyl-1-oxopropoxy)pregna-1,4-diene-3,20-dione

Figure 1 Chemical structure of ciclesonide



CAS number: 126544-47-76

Molecular formula: $C_{32}H_{44}O_7$

7 MEDICINE SCHEDULE (POISONS STANDARD)

Prescription only medicine (Schedule 4)

8 SPONSOR

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8	Change of sponsor and contact details.
All	Editorial changes throughout the document.