Alvesco®

Package Insert
for
Alvesco® 80 and 160 Inhaler

PRESENTATIONS
ALVESCO® 80 mcg inhaler is a metered-dose inhaler which delivers 80 micrograms of ciclesonide per actuation.

ALVESCO® 160 mcg Inhaler is a metered-dose inhaler which delivers 160 micrograms of ciclesonide per actuation.

INDICATIONS
Alvesco® is indicated as prophylactic treatment of asthma in adults, adolescents and children over 6 years.

DOSAGE AND ADMINISTRATION
The recommended dose range for adults, elderly patients and adolescents over 12 years of age with mild to moderate asthma is 160 to 640 mcg per day.

In severe asthma, this dose range may be increased to 1280 mcg per day. The recommended dose range for children over 6 years is 80 mcg to 160 mcg per day. For once daily dosing, Alvesco® should preferably be administered in the evening although morning dosing of Alvesco® has also been shown to be effective. The final decision on morning or evening dosing should be left to the discretion of the physician.

Symptoms start to improve with Alvesco® within 24 hours of treatment.

Once control is achieved, the dose of Alvesco® should be individualized and titrated to the minimum dose needed to maintain good asthma control.

Alvesco® can be used with or without a spacer (i.e., AeroChamber Plus™).

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

Adolescent and adult patients taking chronic oral corticosteroid therapy:
When 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 no faster than 2.5 mg/day on a weekly basis to the lowest possible level.

INSTRUCTIONS FOR USE/HANDLING
Patients need to be instructed how to use the inhaler correctly. If the inhaler is new or has not been used for one week or more, three puffs should be released into the air. No shaking is necessary as this is a solution aerosol. Instruct patients to remove the mouthpiece cover, breath out as long as they comfortably can, place the inhaler into their mouth, close their lips around the mouthpiece, and breathe in slowly and deeply as long as is comfortable. While breathing in through their mouth, patients must press down on the top of the inhaler. Then, patients should remove the inhaler from their mouth, and hold their breath for about 10 seconds, or longer if comfortable. Finally, patients should breathe out slowly and replace the mouthpiece cover.

The patient is not to breathe out into the inhaler. The mouthpiece should be cleaned with a dry tissue or cloth weekly. The inhaler should not be washed or put in water.

CONTRAINDICATIONS
Alvesco® should not be used in patients with known hypersensitivity to any of the ingredients.

SPECIAL WARNINGS AND PRECAUTIONS FOR USE
As with all inhaled corticosteroids, Alvesco® should be administered with caution in patients with active or quiescent pulmonary tuberculosis, fungal, bacterial or viral infections of the respiratory system.

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

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

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

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

The long-term effect of inhaled steroids in children has not been fully clarified. Generally, the physician should closely monitor the growth development of children treated with glucocorticoids over a prolonged period.

The benefits of inhaled Alvesco® should minimize the need for oral steroids. However, patients transferred from oral steroids remain at risk of impaired adrenal reserve for a considerable time after transferring to inhaled Alvesco®. The possibility of oral steroid adverse effects may persist for some time.

These patients may require specialized 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.

Lack of response or severe exacerbations of asthma should be treated by increasing the dose of inhaled ciclesonide and, if necessary, by giving a systemic steroid and/or an antibiotic if there is an infection.

Treatment with Alvesco® should not be stopped abruptly.

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

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

For the transfer of patients being treated with oral corticosteroids:
The transfer of oral steroid-dependent patients to Alvesco®, and their subsequent management, needs special care as recovery from impaired adrenocortical function, caused by prolonged systemic steroid therapy, may take a considerable time.

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

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

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

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

Replacement of systemic steroid treatment with inhaled therapy sometimes unmasks allergies such as allergic rhinitis or eczema previously controlled by systemic drug. These allergies should be symptomatically treated with antihistamine and/or topical preparations, including topical steroids.

INTERACTION WITH OTHER MEDICINAL PRODUCTS AND OTHER FORMS OF INTERACTION
In vitro data indicate that CYP3A4 is the major enzyme involved in the metabolism of the active metabolite of ciclesonide M1 in man. In a drug-drug interaction study at steady state with ciclesonide and ketoconazole as a potent CYP3A4 inhibitor, the exposure to the active metabolite M1 increased approximately 3.5-fold, whereas the exposure to ciclesonide was not affected. Therefore the concomitant administration of potent inhibitors of CYP3A4 (e.g. ketoconazole, itraconazole and ritonavir or nelfinavir) should be avoided unless the benefit outweighs the increased risk of systemic side effects of corticosteroids.

An interaction study with ciclesonide and the CYP3A4 substrate erythromycin has not revealed any interactions between the two substances.

PREGNANCY AND LACTATION
There are no adequate and well-controlled studies with Alvesco® 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. The excretion of ciclesonide or its metabolites into human milk has not been investigated.

As with other inhaled corticosteroid preparations, Alvesco® is not to be used during pregnancy or lactation unless the potential benefit to the mother justifies the potential risk to the mother or fetus or baby. Infants born of mothers who received corticosteroids during pregnancy are to be observed carefully for hypoadrenalism.

EFFECTS ON ABILITY TO DRIVE AND USE OF MACHINES
Alvesco® has no influence on ability to drive and use machines.

ARTWORK APPROVAL

SITE CODE **3100028124**	REPLACES: **3100010219**
COLORS: **1** BLACK	DWG: **PE00137_V4** 180mm x 315mm PHARMACODE: **868**

REGULATORY:

PACK TECH:

QUALITY:

REASON FOR CHANGE:
MAT

CREATION DATE: **23 March 2021** R2

Body text size	Smallest text size
7.5 pt	7.5 pt

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

Organ System/ Frequency	Uncommon (>1/1,000, < 1/100)	Rare (1/10,000 - 1/1,000)
Cardiac Disorders		Palpitations**
Gastrointestinal Disorders	Nausea, vomiting* Bad taste	Abdominal pain* Dyspepsia*
General disorders and administration site conditions	Application site reactions such as burning, inflammation and irritation; Application site dryness	
Immune System Disorders		Angioedema Hypersensitivity
Infections and Infestations	Oral fungal infections*	
Nervous System Disorders	Headache*	
Respiratory, thoracic and mediastinal disorders	Dysphonia Cough after inhalation* Paradoxical bronchospasm*	
Skin and subcutaneous tissue disorders	Rash and eczema	
Vascular disorders		Hypertension

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

Paradoxical bronchospasm may occur immediately after dosing and is an unspecific acute reaction to all inhaled 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 the withdrawal of Alvesco®. It may even subside with Alvesco® (see also section Special warnings and special precautions for use).

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

OVERDOSE
Acute:
Inhalation by healthy volunteers of a single dose of 2880 mcg of Alvesco® was well tolerated.
The potential for acute toxic effects following overdose of inhaled ciclesonide is low. After acute overdosage no specific treatment is necessary.

Chronic:
After prolonged administration of 1280 mcg of Alvesco®, no clinical signs of adrenal suppression were observed. However, if higher than recommended dosage is continued over prolonged periods, some degree of adrenal suppression cannot be excluded. In these cases, monitoring of adrenal reserve may be necessary. In cases of Alvesco® overdose, therapy may still be continued at a suitable dosage for symptom control.

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

Absorption:
Studies with oral and intravenous dosing of radiolabeled ciclesonide have shown an incomplete extent of oral absorption (24.5%) of drug related substance. The oral bioavailability of both ciclesonide and the active metabolite is negligible (<0.5% for ciclesonide, <1% for the metabolite) due to a high first pass metabolism. Based on gγ-scintigraphy studies, lung deposition in healthy subjects and patients is >50%. In line with this figure, the systemic bioavailability for the active metabolite is >50% by using the ciclesonide metered dose inhaler. As the oral bioavailability for the active metabolite is <1%, the swallowed portion of the inhaled drug does not contribute to systemic exposure.

Distribution:
Following intravenous administration to healthy subjects, the initial distribution phase for ciclesonide was rapid and consistent with its high lipophilicity. The volumes of distribution of ciclesonide and des-ciclesonide were approximately 2.9 L/kg and 12.1 L/kg.
The percentage of ciclesonide bound to human plasma proteins averaged 99%, and that of the active metabolite 98-99%, indicating an almost complete binding of circulating ciclesonide/active metabolite to plasma proteins. Only the free fraction of a drug in the systemic circulation is available for a further pharmacodynamic effect.

Metabolism:
Ciclesonide is primarily hydrolyzed to its biologically active metabolite by esterase enzymes in the lung. Investigation of the enzymology of further metabolism by human liver microsomes showed that this compound is mainly metabolized to hydroxylated inactive metabolites by CYP3A4 catalysis. The clearance of ciclesonide and the apparent clearance of des-ciclesonide (approximately 152 L/h and 228 L/h, respectively) indicate a high hepatic extraction.

Excretion:
Ciclesonide is predominantly excreted via the feces, after oral and intravenous administration, indicating that excretion via the bile is the major route of elimination.

Pharmacokinetic characteristics in patients
Asthmatic patients:
Ciclesonide shows no pharmacokinetic changes in mild asthmatic patients compared to healthy subjects.

Renal or Hepatic Insufficiency, Elderly:
In view of the pharmacokinetic characteristics obtained in elderly and in patients with hepatic insufficiency, dose adjustment is not necessary in these populations.

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

In patients with hepatic insufficiency, a slightly extended half-life and a slight increase in exposure were reported. Based on the current data, accumulation at high doses cannot therefore be ruled out.

Children:
In two clinical safety and efficacy studies conducted in patients 4 to 11 years of age with asthma, serum samples were obtained in 53 patients for pharmacokinetic analysis. The observed pharmacokinetic parameters of des-ciclesonide were similar between children and adults.

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

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

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 Alvesco® 320, 640, and 1280 mcg/day were lowered by 11%, 10%, and 11%, respectively, ($p \geq 0.05$).

PRECLINICAL SAFETY DATA
The non-CFC propellant HFA-134a is considered by the Committee of Proprietary Medicinal Products (CPMP) to be a suitable alternative to chlorofluorocarbons in metered dose inhalers.

The spray concentrations were well above the doses used by patients and have shown no toxic effects of HFA-134a.

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

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

COMPOSITION
Active ingredient: ciclesonide

Inactive ingredients: ethanol, norflurane (HFA-134a).

INCOMPATIBILITIES
None

SPECIAL PRECAUTIONS FOR STORAGE
The container contains a pressurized liquid. Do not expose to temperatures higher than 50°C. Do not pierce the canister. Store below 30°C.

MANUFACTURER
Kindeva Drug Delivery Ltd
Derby Road, Loughborough,
Leicestershire, LE11 5SF,
United Kingdom

SHELF LIFE
Please see outer pack.

PACKAGING
Alvesco Inhalers are metered-dose inhalers which contain 60 and 120 actuations.

DATE OF REVISION
February 2021
Doc ID-003726565 V2

COVIS
3100028124

ARTWORK APP ROVAL

SITE CODE **3100028124** REPLACES: **3100010219**

COLORS: **1**
BLACK

DWG: **PE00137_V4**
180mm x 315mm
PHARMACODE: **868**

REGULATORY:

PACK TECH:

QUALITY:

REASON FOR CHANGE:
MAT

CREATION DATE: **23 March 2021** R2

Body text size	Smallest text size
7.5 pt	7.5 pt