1. NAME OF THE MEDICINAL PRODUCT

Alvesco® 160 Inhaler

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

1 actuation (delivered dose from the mouthpiece) contains 160 micrograms of ciclesonide.

For a full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Pressurised inhalation, solution

Clear and colourless

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Treatment to control persistent asthma in adults and adolescents (12 years and older).

4.2 Posology and method of administration

The medicinal product is for inhalation use only.

Dosing recommendation for adults and adolescents:

The recommended dose of Alvesco is 160 micrograms once daily, which leads to asthma control in the majority of patients. However in severe asthmatics, a 12 week study has shown that a dose of 640 micrograms/day (given 320 micrograms twice daily) has demonstrated a reduction in the frequency of exacerbations but without an improvement in lung function (see section 5.1). Dose reduction to 80 micrograms once daily may be an effective maintenance dose for some patients.

Alvesco should preferably be administered in the evening although morning dosing of Alvesco has also been shown to be effective. The final decision on evening or morning 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 individualised and titrated to the minimum dose needed to maintain good 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 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. a higher dose of Alvesco for a short period [see section 5.1] or a course of oral corticosteroids). Severe asthma exacerbations should be managed the usual way.

To address specific patient needs, such as finding it difficult to press the inhaler and breathe in at the same time, Alvesco can be used with the AeroChamber Plus spacer device.

<u>Specific patient groups:</u>

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

To date, there are insufficient data available in the treatment of children under 12 years of age with ciclesonide.

Instructions for use / handling:

The patient needs 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.
During inhalation, the patient should preferably sit or stand, and the inhaler should be held upright with the thumb on the base, below the mouthpiece.
Instruct the patient to remove the mouthpiece cover, place the inhaler into their mouth, close their lips around the mouthpiece, and breathe in slowly and deeply. While breathing in through the mouth, the top of the inhaler should be pressed down. Then, patients should remove the inhaler from their mouth, and hold their breath for about 10 seconds, or as long as is comfortable. The patient is not to breathe out into the inhaler. Finally, patients should breathe out slowly and replace the mouthpiece cover.
The mouthpiece should be cleaned with a dry tissue or cloth weekly. The inhaler should not be washed or put in water.

For detailed instructions see Patient Information Leaflet.

4.3 Contraindications

Hypersensitivity to ciclesonide or any of the excipients.

4.4 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, viral or bacterial infections, and only if these patients are adequately treated.

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.

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, and more rarely, a range of psychological or behavioural effects including psychomotor hyperactivity, sleep disorders, anxiety, depression or aggression (particularly in children). It is therefore important that the dose of inhaled corticosteroid is titrated to the lowest dose at which effective control of asthma is maintained.

It is recommended that the height of children and adolescents receiving prolonged treatment with inhaled corticosteroids is regularly monitored. If growth is slowed, therapy should be reviewed with the aim of reducing the dose of inhaled corticosteroid, if possible to the lowest dose at which effective control of asthma is maintained. In addition, consideration should be given to referring the patient to a paediatric respiratory specialist.

There is no 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.

The benefits of inhaled ciclesonide should minimise 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 ciclesonide. The possibility of respective symptoms 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 an emergency (medical or surgical) and elective situations likely to produce stress, and appropriate corticosteroid treatment considered.

For the transfer of patients being treated with oral corticosteroids:

The transfer of oral steroid-dependent patients to inhaled ciclesonide, 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 dose by 1 mg prednisolone per week, 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 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 inhaled ciclesonide 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.

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 4.8).

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

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).

4.5 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 CYP 3A4 (e.g. ketoconazole, itraconazole and ritonavir or nelfinavir) should be avoided unless the benefit outweighs the increased risk of systemic side effects of corticosteroids.

4.6 Pregnancy and lactation

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

In animal studies glucocorticoids have been shown to induce malformations (see section 5.3). This is not likely to be relevant for humans given recommended inhalation doses.

As with other glucocorticoids, ciclesonide should only be used during pregnancy if the potential benefit to the mother justifies the potential risk to the fetus. 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.

It is unknown whether inhaled ciclesonide is excreted in human breast milk. Administration of ciclesonide to women who are breast-feeding should only be considered if the expected benefit to the mother is greater than any possible risk to the child.

4.7 Effects on ability to drive and use machines

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

4.8 Undesirable effects

Approximately 5% of patients experienced adverse reactions in clinical trials with Alvesco given in the dose range 40 to 1280 micrograms per day. In the majority of cases, these were mild and did not require discontinuation of treatment with Alvesco.

Frequency / **System Organ Class**	**Uncommon (>1/1,000, <1/100)**	**Rare (1/10,000 – 1/,1000)**	**Unknown**
Cardiac Disorders		Palpitations**	
Gastrointestinal Disorders	Nausea, vomiting* Bad taste	Abdominal pain* Dyspepsia*	
General disorders and administration site conditions	Application site reactions Application site dryness		
Immune System Disorders		Angioedema Hypersensitivity	
Infections and infestations	Oral fungal infections*		
Nervous System Disorders	Headache*		
Psychiatric Disorders			Psychomotor hyperactivity, sleep disorders, anxiety, depression, aggression, behavioural changes (predominantly in children)
Respiratory, thoracic	Dysphonia		

and mediastinal disorders	Cough after inhalation* Paradoxical bronchospasm*		
Skin and subcutaneous tissue disorders	Eczema and rash		
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 medicinal products, which may be related to the active substance, the excipient, or evaporation cooling in the case of metered dose inhalers. In severe cases, withdrawal of Alvesco should be considered.

Systemic effects of inhaled corticosteroids may occur, particularly at high doses prescribed for prolonged periods. Possible systemic effects include Cushing's syndrome, Cushingoid features, adrenal suppression, growth retardation in children and adolescents, decrease in bone mineral density, cataract, glaucoma (see also section 4.4).

4.9 Overdose

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 ciclesonide is low. After acute overdosage no specific treatment is necessary.

Chronic:
After prolonged administration of 1280 micrograms of ciclesonide, 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. Monitoring of adrenal reserve may be necessary.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Other drugs for obstructive airway diseases, Inhalants, Glucocorticoids, ATC Code: R03B A08

Ciclesonide exhibits low binding affinity to the glucocorticoid-receptor. Once orally inhaled, ciclesonide is enzymatically converted in the lungs to the principal metabolite (C21-des-methylpropionyl-ciclesonide) which has a pronounced anti-inflammatory activity and is thus considered as the active metabolite.

In four clinical trials, ciclesonide has been shown to reduce airway hyperresponsiveness to adenosine monophosphate in hyperreactive patients with maximal effect observed at the dose of 640 micrograms. 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.

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

1,280 micrograms/day did not statistically significantly lower the 24-hour time averages of plasma cortisol ($AUC_{(0-24)}$/24 hours) nor was a dose-dependent effect seen.

In a clinical trial involving 164 adult male and female asthmatic patients, ciclesonide was given at doses of 320 micrograms or 640 micrograms/day over 12 weeks. After stimulation with 1 and 250 micrograms cosyntropin, no significant changes in plasma cortisol levels were observed versus placebo.

Double-blind placebo-controlled trials of 12-weeks duration in adults and adolescents have shown that treatment with ciclesonide resulted in improved lung function as measured by FEV_1 and peak expiratory flow, improved asthma symptom control, and decreased need for inhaled beta-2 agonist.

In a 12-week study of 680 severe asthmatics, previously treated with 500-1,000 micrograms fluticasone propionate per day or equivalent, 87.3% and 93.3% of patients remained exacerbation-free during treatment with 160 or 640 micrograms of ciclesonide, respectively. At the end of the 12 week study period, the results showed a statistically significant difference between the doses of 160 micrograms and 640 micrograms/day ciclesonide with regard to the occurrence of an exacerbation after the first day of the study: 43 patients/339 (= 12.7%) in the 160 micrograms/day group and 23 patients/341 (6.7%) in the 640 micrograms/day group (Hazard ratio=0.526; p= 0.0134). Both ciclesonide doses resulted in comparable FEV1 values at 12 weeks. Treatment-related adverse events were seen in 3.8% and 5% of patients treated with 160 or 640 micrograms per day of ciclesonide respectively. No study was performed to compare 160 micrograms, 320 micrograms and 640 micrograms daily dose in patients with severe asthma.

5.2 Pharmacokinetic properties

Ciclesonide 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%). The oral bioavailability of both ciclesonide and the active metabolite is negligible (<0.5% for ciclesonide, <1% for the metabolite). Based on a γ-scintigraphy experiment, lung deposition in healthy subjects is 52%. 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 ciclesonide does not contribute to systemic absorption.

Distribution:
Following intravenous administration to healthy subjects, the initial distribution phase for ciclesonide was rapid and consistent with its high lipophilicity. 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 averaged 99%, and that of the active metabolite 98-99%, indicating an almost complete binding of circulating ciclesonide/active metabolite to plasma proteins.

Metabolism:
Ciclesonide is primarily hydrolysed 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. Furthermore, reversible lipophilic fatty acid ester conjugates of the active metabolite were detected in the lung.

Excretion:
Ciclesonide is predominantly excreted via the faeces (67%), 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
According to population pharmacokinetics, age has no impact on the systemic exposure of the active metabolite.

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 to the active metabolite was observed.

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

5.3 Preclinical safety data

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

A treatment-related effect on the ovaries (namely atrophy) was observed at the top dose in two 12-month studies in dogs. This effect occurred at systemic exposures 5.27-8.34 times those noted at the 160 µg daily dose. The relevance of this finding to humans is unknown.

Animal studies with other glucocorticoids indicate that administration of pharmacological doses of glucocorticoids during pregnancy may increase the risk for intrauterine growth retardation, adult cardiovascular and/or metabolic disease and/or permanent changes in glucocorticoid receptor density, neurotransmitter turnover and behaviour. The relevance of these data to humans administered ciclesonide by inhalation is unknown.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Norflurane (HFA-134a)
Ethanol, anhydrous

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

30 metered actuations – 1 year
60 and 120 metered actuations – 3 years

6.4 Special precautions for storage

This medicinal product does not require any special storage conditions.

The container contains a pressurised liquid. Do not expose to temperatures higher than 50°C.

The container should not be punctured, broken or burnt even when apparently empty.

6.5 Nature and contents of container

The inhaler comprises a pressurised container made from aluminium and is sealed with a metering valve, mouthpiece, and cap.

30 metered actuations
60 metered actuations
120 metered actuations

Hospital packs:
10 x 30 metered actuations
10 x 60 metered actuations
10 x 120 metered actuations

Not all pack sizes may be marketed.

6.6 Instructions for use and handling

Patients should be carefully instructed in the proper use of their inhaler (see Patient Information Leaflet).

As with most inhaled medicinal products in pressurised containers, the therapeutic effect of this medicinal product may decrease when the container is cold. However, Alvesco delivers a consistent dose from –10°C to 40°C.

7. MARKETING AUTHORISATION HOLDER

Takeda GmbH
Byk-Gulden-Str. 2
D-78467 Konstanz
Germany

8. MARKETING AUTHORISATION NUMBER(S)

PL 31752/0006

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

16 April 2004/28 September 2009

10. DATE OF REVISION OF THE TEXT

30th November 2012