## 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® 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.

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.*

A total of 5535 patients were treated with Alvesco®, 100 to 1600 micrograms per day, in 25 clinical studies ranging in duration from 4 weeks to 1 year. All trials had a randomized, blinded design with the exception of 3 long-term open-label studies.

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 ≥ 1% of patients:

**Table 1 - Common Adverse Reactions[1] (≥1 - <10%) in Placebo-Controlled Clinical Trials**

| | Alvesco® n=1850 (%) | Placebo n= 934 (%) |
|---|---|---|
| **Respiratory** | | |
| Paradoxical bronchospasm[2] | 1.8 | 1.9 |

[1] assessed as possibly related to the treatment by investigator and/or sponsor

[2] Paradoxical 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 (1.7%), Dysphonia (1.1%)

**Uncommon Clinical Trial Adverse Drug Reactions (≥0.1% to <1%)**
**Cardiovascular:** Palpitations (0.1%)
**Eye:** Cataract cortical (0.1%), Cataract nuclear (0.1%), Cataract subcapsular (0.1%), Vision blurred (0.1%)
**Gastrointestinal:** Nausea (0.2%), Dry mouth (0.1%), Dyspepsia (0.1%), Halitosis (0.1%)
**Infections:** Oral candidiasis (0.7%), Candidiasis (0.1%), Laryngitis (0.1%), Oral fungal infection (0.1%), Pharyngitis (0.1%)
**Investigations:** ALT increased (0.1%), Blood pressure increase (0.1%), Gamma-glutamyltransferase increased (0.1%), Weight increased (0.1%)
**Metabolism:** Appetite increased (0.1%)
**Nervous System:** Headache (0.6%), Dysgeusia (0.4%), , Dizziness (0.1%)
**Respiratory, thoracic and mediastinal disorders:** Pharyngolaryngeal pain (0.5%), Throat irritation (0.3%), Dry throat (0.2%), Productive cough (0.1%)
**Skin:** Eczema (0.1%), Rash (0.1%)
**Vascular:** Hypertension (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 Reactions[1] 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 |
| Dry Throat | 0.2 | 0.0 |
| Pharyngitis | 0.1 | 0.0 |
| Throat irritation | 0.1 | 0.0 |

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

**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**

Very 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.

## 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**

- The recommended starting dose of Alvesco® 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.

Symptoms can start to improve with Alvesco® within 24 hours of treatment. Clinically, Alvesco® has been shown to improve lung function as measured by $FEV_1$, peak expiratory flow, improved asthma symptom control, reduced exacerbations, and decreased need for inhaled beta-2 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® 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.

## 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 limit 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% by 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:** Alvesco® is currently not recommended in patients < 18 years of age.

**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 renal 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® be stored at room temperature between 15 - 30 °C. Do not freeze.

## DOSAGE FORMS, COMPOSITION AND PACKAGING

Alvesco® 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.

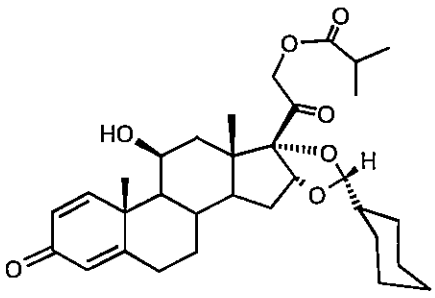
Alvesco® is available in two strengths: 100 mcg per actuation (ex-valve) and 200 mcg per actuation (ex-valve). Alvesco® is available in canisters containing 120 actuations.

## 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);<br>soluble in ethanol, acetone, methylenechloride, chloroform |

## CLINICAL TRIALS

### 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 $FEV_1$, peak expiratory flow, improved asthma symptom control, reduced exacerbations, and decreased need for inhaled beta-2-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 $FEV_1$ (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 4] | $FEV_1$ >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% pred 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
[1]Lack of Efficacy was defined as a clinical exacerbation or defined deteriorations in lung function and/or asthma symptom scores

**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 $FEV_1$, 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.

## 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 ($AUC_{(0, 1h)}$) 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 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 the 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 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 $LD_{50}$ 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 tumorgenic 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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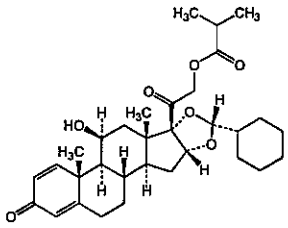
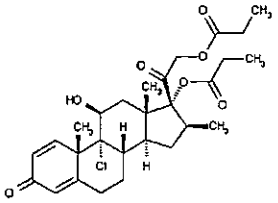
## 1.7　同種同効品一覧表

## 1.7　同種同効品一覧表

### 表 1.7-1 同種同効品一覧表(1)

| | 申請薬剤 | 対照比較薬 |
|---|---|---|
| 一般的名称 | シクレソニド | プロピオン酸ベクロメタゾン |
| 販売名 | オルベスコ 50/100/ 200 μg インヘラー 112 吸入用<br>オルベスコ 200 μg インヘラー 56 吸入用 | [redacted] |
| 会社名 | 帝人ファーマ | |
| 承認年月日 | — | |
| 再審査年月日<br>再評価年月日 | — | |
| 規制区分 | — | |
| 化学構造式 |  |  |
| 剤形・含量 | エアゾール剤、50, 100, 200 μg/1 回噴射 | [redacted] |
| 効能・効果 | 気管支喘息 | |
| 用法・用量 | 成人には、通常、シクレソニドとして 100～400 μg を 1 日 1 回吸入投与する。なお、症状により適宜増減するが、1 日の最大投与量は 800 μg とする。<br>また、1 日に 800 μg を投与する場合は、朝、夜の 1 日 2 回に分けて投与する。 | |
| 使用上の注意 | **【禁忌（次の患者には投与しないこと）】**<br>1. 有効な抗菌剤の存在しない感染症、深在性真菌症の患者［症状を増悪するおそれがある。］<br>2. 本剤の成分に対して過敏症の既往歴のある患者<br><br>**【原則禁忌(次の患者には投与しないことを原則とするが、特に必要とする場合には慎重に投与すること)】**<br>結核性疾患の患者［症状を増悪するおそれがある。］<br><br>**【用法・用量に関連する使用上の注意】**<br>(1)喘息症状の緩解がみられた場合は、治療上必要最小限の用量を投与すること。<br>(2) 1 日 1 回投与の場合には、本剤を夜に投与することが望ましい。<br><br>**【使用上の注意】**<br>**1. 慎重投与(次の患者には慎重に投与すること)**<br>感染症（急性呼吸器感染症を除く）の患者［症状を増悪するおそれがある］<br>**2. 重要な基本的注意**<br>(1) 本剤は気管支拡張剤並びに全身性ステロイド剤のように**既に起きている発作を速やかに軽減する薬剤ではない**ので、毎日規則正しく使用すること。 | |

1.7　同種同効品一覧表

| | 申請薬剤 | 対照比較薬 |
|---|---|---|
| 一般的名称 | シクレソニド | プロピオン酸ベクロメタゾン |
| 使用上の注意 | (2) **本剤の投与開始前には、患者の喘息症状を比較的安定な状態にしておくこと。特に、**喘息発作重積状態又は喘息の急激な悪化状態**のときには原則として本剤は使用しないこと。**<br>(3) 気管支粘液の分泌が著しい患者では、本剤の肺内での作用を確実にするため本剤の吸入に先立って、分泌がある程度減少するまで他剤を使用することが望ましい。<br>(4) 本剤の投与期間中に**急性の発作が発現**した場合は、**発作発現時に短時間作用性吸入$\beta_2$刺激薬**等の他の適切な薬剤を使用するよう患者を指導すること。また、その薬剤の**使用量が増加**したり、効果が**十分でなくなってきた**と感じられたら、喘息の管理が十分でないことが考えられるので、可及的速やかに**医療機関を受診**し治療を求めるよう患者を指導すること。このような状態は喘息の管理が不十分になっていることを示唆し、患者の生命を脅かす可能性があるので、**本剤の増量**あるいは**気管支拡張剤・全身性ステロイド剤**を短期間併用し、症状の軽減に合わせて併用薬剤を徐々に減量すること。<br>(5) 本剤の投与を**突然中止すると喘息の急激な悪化**を起こすことがあるので、投与を中止する場合には患者の**喘息症状を観察しながら徐々に減量**すること。<br>(6) 全身性ステロイド剤と比較し可能性は低いが、吸入ステロイド剤の投与により**全身性の作用**（副腎皮質機能抑制、小児の成長遅延、骨密度の低下、白内障、緑内障を含む）が発現する可能性があるので、吸入ステロイド剤の投与量は患者毎に喘息をコントロールできる**最少用量**に調節すること。特に**長期間、大量**投与の場合には**定期的に検査**を行い、全身性の作用が認められた場合には患者の**喘息症状を観察しながら徐々に減量**するなど適切な処置を行うこと。<br>(7) **全身性ステロイド剤の減量**は本剤の吸入開始後症状の安定をみて徐々に行うこと。減量にあたっては一般のステロイド剤の減量法に準ずる。<br>(8) **長期又は大量の全身性ステロイド療法**を受けている患者では**副腎皮質機能不全**が考えられるので、本剤投与後の全身性ステロイド剤の減量中並びに離脱後も**副腎皮質機能検査**を行い、外傷、手術、重症感染症等の侵襲には十分に注意を払うこと。また、必要があれば一時的に全身性ステロイド剤の増量を行うこと。<br>(9) 本剤を含む吸入ステロイド剤投与後に、潜在していた基礎疾患である Churg-Strauss 症候群にみられる好酸球増多症がまれにあらわれることがある。この症状は通常、**全身性ステロイド剤の減量並びに離脱**に伴って発現しており、本剤との直接的な因果関係は確立されていないが、本剤の投与期間中は、好酸球数の推移や、他の Churg-Strauss 症候群症状（しびれ、発熱、関節痛、肺の浸潤等の血管炎症状等）に注意すること。<br>(10) **全身性ステロイド剤の減量並びに離脱**に伴って、鼻炎、湿疹、蕁麻疹、眩暈、動悸、倦怠感、顔のほてり、結膜炎等の症状が発現・増悪することがある。このような症状があらわれた場合には適切な処置を行うこと。 | [redacted] |

| | 申請薬剤 | 対照比較薬 |
|---|---|---|
| 一般的名称 | シクレソニド | プロピオン酸ベクロメタゾン |
| 使用上の注意 | **3. 相互作用**<br>本剤はエステラーゼによる代謝を受けて活性代謝物である脱イソブチリル体に変換される。脱イソブチリル体は主として肝チトクローム P-450 3A4 (CYP3A4)で代謝される。<br><br>〔**併用注意**〕(併用に注意すること)<br>薬剤名等 / 臨床症状・措置方法 / 機序・危険因子<br>CYP3A4 阻害作用を有する薬剤 イトラコナゾール、リトナビル等 / 副腎皮質ステロイド剤を全身投与した場合と同様の症状があらわれる可能性がある。 / CYP3A4による代謝が阻害されることにより、本剤の活性代謝物である脱イソブチリル体の血中濃度が上昇する可能性がある。[【薬物動態】の項参照]<br><br>**4. 副作用**<br>承認時までの安全性評価対象 588 例中 35 例 (6.0%) に自他覚的副作用がみられた。その主な症状は、呼吸困難 5 例 (0.9%)、嗄声 5 例 (0.9%)、発疹 3 例 (0.5%) 等であった。副作用としての臨床検査値の異常は、尿中蛋白 4 例(0.7%)、AST(GOT)の増加 3 例(0.5%)、ALT(GPT)の増加 3 例 (0.5%) 等であった。<br><br>以下のような副作用があらわれた場合には、症状に応じて適切な処置を行うこと。<br>種類＼頻度 / 頻度不明 / 1%未満<br>過敏症[注1] / 血管浮腫等の過敏症状[注2] / 発疹、そう痒<br>口腔・呼吸器 / / 咽喉頭症状 (不快感、疼痛)、嗄声、口渇、口腔カンジダ症、味覚異常、声のかすれ<br>肝臓 / / AST(GOT), ALT(GPT)の増加<br>精神神経系 / / 倦怠感、頭痛<br>その他 / 気管支痙攣[注3] / 呼吸困難[注4]、尿中蛋白、胸部不快感[注4]、胸痛[注4]、気分不快、浮腫、動悸<br>注 1) このような場合には投与を中止すること。<br>注 2) 外国のみで報告が認められている。<br>注 3) 外国のみで報告が認められている。短時間作用性気管支拡張剤を投与するなどの適切な処置を行うこと。<br>注 4) 気管支痙攣が疑われる場合は、短時間作用性気管支拡張剤を投与するなどの適切な処置を行うこと。 | [redacted] |

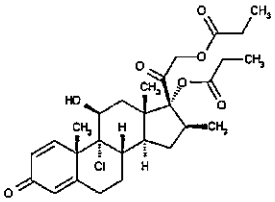
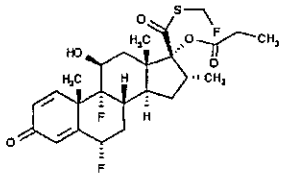
1.7　同種同効品一覧表

| | 申請薬剤 | 対照比較薬 |
|---|---|---|
| 一般的名称 | シクレソニド | プロピオン酸ベクロメタゾン |
| 使用上の注意 | **5. 高齢者への投与**<br>高齢者での薬物動態試験で、活性代謝物である脱イソブチリル体の血中濃度が非高齢者に比べて高くなることが認められているので、患者の状態を観察しながら慎重に投与すること。[【薬物動態】の項参照]<br>**6. 妊婦・産婦・授乳婦等への投与**<br>(1)妊婦又は妊娠している可能性のある婦人には、治療上の有益性が危険性を上まわると判断される場合にのみ投与すること。[本薬は動物実験（ラット、ウサギ）で胎盤通過性が報告されている。また、本薬は動物実験（ウサギ）で副腎皮質ステロイド剤に共通した催奇形作用が報告されている。]<br>**(2)授乳中の婦人には、本剤投与中は授乳を避けさせることが望ましい。[本薬は動物実験（ラット）で乳汁中に移行（静脈内投与において投与量の0.044%以下）することが報告されている。]**<br>**7. 小児等への投与**<br>低出生体重児、新生児、乳児、幼児又は小児に対する安全性は確立していない。[国内での使用経験がない。]<br>**8. 過量投与**<br>長期間の過量投与（【用法・用量】の範囲を超えた量等）により、副腎皮質機能抑制等の全身性の作用がみられることがあるので、このような場合には、患者の症状を観察しながら徐々に減量するなど適切な処置を行うこと。<br>**9. 適用上の注意**<br>(1) 本剤は口腔内への吸入投与にのみ使用すること(内服しても効果はみられない)。<br>(2) 本剤吸入後に、うがいを実施するよう指導すること（口腔内カンジダ症又は嗄声の予防のため)。ただし、うがいが困難な患者には、うがいではなく、口腔内をすすぐよう指導すること。 | [redacted] |

## 1.7 同種同効品一覧表

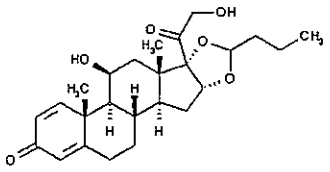
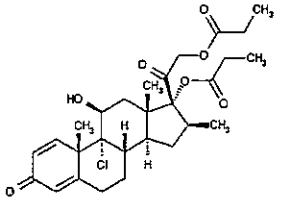
| | 申請薬剤 | 対照比較薬 |
|---|---|---|
| 一般的名称 | シクレソニド | プロピオン酸ベクロメタゾン |
| 使用上の注意 | | [redacted] |
| 添付文書作成年月日 | (案) 2007年3月 | |

表 1.7-2 同種同効品一覧表(2)

| | 既承認薬(後発医薬品) | 既承認薬 |
|---|---|---|
| 一般的名称 | プロピオン酸ベクロメタゾン | プロピオン酸フルチカゾン |
| 販売名 | [redacted] | |
| 会社名 | | |
| 承認年月日 | | |
| 再審査年月日<br>再評価年月日 | | |
| 規制区分 | | |
| 化学構造式 |  |  |
| 剤形・含量 | | |
| 効能・効果 | | |
| 用法・用量 | | |
| 使用上の注意 | | |

| | 既承認薬(後発医薬品) | 既承認薬 |
|---|---|---|
| 一般的名称 | プロピオン酸ベクロメタゾン | プロピオン酸フルチカゾン |
| 使用上の注意 | [redacted] | |
| 添付文書作成年月日 | | |

表 1.7-3 同種同効品一覧表(3)

| | 既承認薬 | 既承認薬 |
|---|---|---|
| 一般的名称 | ブデソニド | プロピオン酸ベクロメタゾン |
| 販売名 | [redacted] | |
| 会社名 | | |
| 承認年月日 | | |
| 再審査年月日<br>再評価年月日 | | |
| 規制区分 | | |
| 化学構造式 |  |  |
| 剤形・含量 | [redacted] | |
| 効能・効果 | | |
| 用法・用量 | | |
| 使用上の注意 | | |

1.7　同種同効品一覧表

| | 既承認薬 | 既承認薬 |
|---|---|---|
| 一般的名称 | ブデソニド | プロピオン酸ベクロメタゾン |
| 使用上の注意 | [redacted] | |
| 添付文書作成年月日 | | |