

Summary of Product Characteristics

(S.P.C)

E S O N I D E[®]

B u d e s o n i d e

m. d. nasal spray

1. NAME OF THE MEDICINAL PRODUCT

ESONIDE[®]

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Budesonide 2 mg /ml (100 µg/dose)

Budesonide C₂₅H₃₄O₆

16a,17a - butylidenedioxy - 11β, 21- dixydroypregna - 1, 4 - diene - 3, 20 dione.

3. PHARMACEUTICAL FORM

Metered dose nasal spray (suspension).

4. CLINICAL DATA

4.1. Indications

ESONIDE[®] nasal spray is indicated :

- For the treatment of seasonal or chronic allergic rhinitis in adults and children (≥6 years old) and chronic non allergic rhinitis in adults.
- For the treatment of nasal obstruction related to nasal polyps in adults.

4.2 Posology and method administration

Administration

For nasal use.

Dosage :

The dosage of ESONIDE[®] should be individualised and limited to the lowest possible dosage necessary for controlling the symptoms.

For method of administration see 6.6.

Symptomatic treatment of seasonal or chronic allergic rhinitis :

Adults, elderly and children over 6 years of age :

The recommended initial dose is 200-400 mcg daily. ESONIDE[®] may be given once daily or may be divided in two doses in the morning and in the evening:

200 mcg (2 applications x 100 mcg) into each nostril in the morning

or

100 mcg (1 application x 100 mcg) into each nostril twice daily, in the morning and in the evening.

ESONIDE[®] should not be administered for more than twice daily.

There is no data on ESONIDE[®] administration for this indication in children younger than 6 years of age, therefore it should not be administered in this category of patients.

When good effect has been achieved, usually in 1-2 weeks, the dosage should be reduced to the minimum required for controlling the symptoms.

Treatment of seasonal rhinitis should, if possible, start before exposure to the allergens. Concomitant treatment may sometimes be necessary to counteract eye symptoms caused by the allergy.

Symptomatic treatment of chronic non allergic rhinitis only in adults:

The recommended dose is mentioned above. ESONIDE[®] is not recommended for this indication in children because clinical studies have not included a sufficient number of children.

Symptomatic treatment of nasal obstruction related to nasal polyps in adults:

Recommended dosage is 200 mcg twice daily (1 spray x 100 mcg in each nostril in the morning and in the evening) for a period up to 3 months.

There is no data on ESONIDE[®] use for this indication in children, therefore ESONIDE[®] is administered only in adults.

4.3. Contra-indications

ESONIDE[®] is contra-indicated to patients who have shown hypersensitivity to any of the ingredients.

The following concern all corticosteroids in general :

The following contra-indications include a great number of patients and pathological states. Anticipated benefits should always be weighed against the possible hazards to the patients.

The most important cases of corticosteroids contra-indications are:

Gastro-duodenal ulcer, ocular herpes simplex, glaucoma, osteoporosis, diabetes mellitus, psychoses, right before and after a preventive vaccination, cardiopathy or hypertension with congestive heart failure, systematic mycosis, tuberculosis, severe renopathy, infectious diseases, bleeding predisposition.

4.4. Special warnings and special precautions for use

Overdosage –or long-term therapy- with glucocorticosteroids could lead to symptoms or signs of hypercortisolism, suppression of HPA axis (hypothalamic- pituitary -adrenal) and / or growth retardation in children. Growth retardation has also been reported in children being treated with nasal corticosteroids in the recommended dosages.

The results of long-term therapy with nasal steroids in children are not fully known. Physicians should closely monitor the growth of children taking glucocorticosteroids by any kind of administration for a long time, and weigh the therapeutic benefit and the possibility for growth delay.

Reduced hepatic function affects corticosteroids excretion. However, budesonide pharmacokinetics after intravenous administration is similar to both cirrhotic patients and healthy individuals.

After oral administration, budesonide pharmacokinetics was affected by reduced hepatic function as proven by increased systematic bioavailability. However, this fact is of small clinical significance for ESONIDE[®] nasal spray because after one inhalation, ESONIDE[®] nasal spray's contribution to the systematic bioavailability of budesonide is very small.

Special care may be needed for patients with lung tuberculosis.

Special care is needed in patients with fungal or viral infections in the airways and with bacterial sinusitis for which concomitant treatment with the suitable antibiotics is necessary.

Children under immunosuppressive treatment are more prone to infections than healthy ones. For example, diseases like chickenpox or measles may develop more severely or even lethally in children immunosuppressed with glucocorticoids. In these children or in adults who are not immune to these diseases, potential exposure should be avoided. If exposed, it is indicated to use anasospherin against chickenpox / herpes zoster or anasospherin collected intravenously from many individuals. In case of chickenpox, treatment with antiviral factors can be taken into consideration.

Special care is also needed in patients changing from systematically administered corticoids to ESONIDE[®] nasal spray because HPA axis disorders may occur. Concomitant treatment with ESONIDE[®] and other inhaler steroids could increase the risk of sign occurrence or overdose symptoms from corticosteroids and /or suppression of HPA axis. If another inhaler corticosteroid is used, the sum of the nasal and inhaler dosage should be adjusted, in order that possible side-effects of corticosteroids are avoided, especially for children.

In continuous long - term treatment, the nasal mucosa should be inspected regularly, every 6 months. Until more experience is obtained, long - term therapy in children is not recommended

The following concern all corticosteroids in general :

Long-term administration of glucocorticoids results, as mentioned above, in HPA axis suppression, that is suspension of adrenal function. The degree of this suspension depends on the dosage, the strength of the administered corticosteroid, the frequency and the time of administration during the 24 hours, its half-life in the tissues and the therapy's total duration. It is noted that glycocorticoid suppressing activity on the HPA axis is more intense and more prolonged when they are administered during night time. In normal people, a dexamethazone dose of 1 mg taken at night suspends the excretion of adrenal hormone for 24 hours.

Sudden reduction of glucocorticoid dosage may cause «withdrawal syndrome» characterized by acute adrenal insufficiency with muscular weakness, hypotension, hypoglycaemia, nausea, vomiting, myalgia, arthralgia and malaise. In some instances, withdrawal symptoms may simulate a clinical relapse of the disease for which the patient has been undergoing treatment. Therefore, after the desirable therapeutic effect has been achieved, the dosage should be gradually reduced to the lowest effective dose

It should also be individualized according to the increase and decrease of the disease symptoms, the individual patient's response and the exposure to pathetic or natural stress (infections, surgical operations, traumas etc.). After withdrawal for about one year, the patient has the potential risk of developing adrenal insufficiency in cases of stress and should be treated with high doses.

4.5. Interaction with other medicaments and other forms of interaction

There are no reported interactions of budesonide with any of the drugs used for the treatment of rhinitis.

Budesonide is mainly metabolized by the CYP3A4, a subgroup of cytochrome P450. This enzyme's inhibitors, for example ketokonazole, may increase systematic exposure to budesonide. However, the concomitant use of ketokonazole with ESONIDE[®] nasal spray for a small period of time has limited clinical significance.

In recommended doses, cimetidine has a slight effect, without clinical significance, on the pharmacokinetics of orally administered budesonide.

The following interactions concern all corticosteroids in general :

Phenytoin, phenobarbital, ephedrine and rifampicin reduce the activity of corticosteroids.

Alcohol and non steroidal anti-inflammatory drugs enhance the likelihood of ulcer formation with corticosteroids.

Potassium depleting diuretics cause / enhance hypokalaemia, which may lead to paraesthesia. They reduce or enhance the activity of coumarin anticoagulants. With insulin or orally taken antidiabetics, a dosage increase is required.

4.6. Administration during Pregnancy and Lactation

Pregnancy :

In pregnant animals, administration of budesonide caused abnormalities of foetal development, as with other glucocorticosteroids. The relevance of this to man has not been established. ESONIDE[®] nasal spray may be administered during pregnancy only if the benefits for the mother are greater than the risks for the foetus.

Lactation :

There is no information available regarding the passage of budesonide into breast milk. Use in lactation requires that the therapeutic benefit to the mother is greater than the potential risk to the neonate.

4.7. Effects in driving ability and in ability to operating machines

ESONIDE[®] nasal spray does not affect the ability to drive and operate machinery.

4.8. Side - effects

Possible side – effects should include:

- Nasal irritation
- Slight haemorrhagic secretion and epistaxis
- Direct and belated hypersensitivity reactions including itching, rash, dermatitis, angioedema.

Topical symptoms, such as dryness, sneezing and stinging may occur right after the product's use. Ulceration of mucous membrane and nasal septum perforation have been reported following the use of intranasal aerosol corticosteroids, but these are very rare.

It is possible to develop mycosis and atrophy of mucous membrane.

The following apply for all corticosteroids in general:

Natural corticosteroids as well as their synthetic derivatives given in equivalent doses have equal side-effects.

Therefore, the long-term use could lead to severe side-effects, the most important of which are : Cushing's syndrome, sodium and water retention, hypokalaemia, hypertension, negative nitrogen and calcium balance with osteoporosis, peptic ulcer, psychotic symptoms (as nervousness, anxiety, depression), increase of intra-ocular pressure and glaucoma, cataracts, increased susceptibility to fungal and/or microbial infections, growth suppression in children, benign intra-cranial hypertension, deregulation of diabetes mellitus, suppression of the hypothalamic-pituitary-adrenal (HPA) axis function, suppression of acute surgical abdomen (unknown peritonitis in cases of perforation).

4.9. Overdosage

Acute overdose with ESONIDE[®] nasal spray should not present clinical problems.

5. PHARMACOLOGICAL DATA

5.1. Pharmacodynamic properties

Budesonide is a glucocorticoid with strong topical anti-inflammatory action.

The exact mechanism of glucocorticoids' action in the treatment of rhinitis is not fully understood. Anti-inflammatory actions, such as inhibition of the release of inflammatory mediators and of the immunological reaction raised by the intervention of cytokines are probably important. The endogenous activity of budesonide, measured as the degree of chemical relation to glucocorticoid receptors, is almost 15 times higher than the one of prednisolone.

A clinical study of seasonal rhinitis, where the action of intra-nasal administered (nasal spray under pressure (pMDI) budesonide versus oral budesonide and placebo, showed that the therapeutic effect of budesonide might be completely explained by the topical action of the substance.

For patients with rhinitis, ESONIDE[®] nasal spray in the recommended doses does not cause clinically significant changes neither at the main cortisol plasma levels nor at the response after epinephrine stimulation by administrating ACTH. However, there has been observed a dose-dependent suppression of cortisol in plasma and urine after short-term administration in healthy volunteers.

5.2. Pharmacokinetic properties

Absorption

In relation to the dosimetric administration, the systemic bioavailability of nasal administered budesonide is 33%. In adults, after the administration of 400 µg nasal administered Budesonide, the maximum plasma concentration is 0,99 nmole /L and is achieved in 0,7 hours. The area under the curve (AUC) after administration of 400 µg nasal administered Budesonide is 4.2 nmol/h/L in adults.

Distribution

The distribution volume of budesonide is about 3 L/kg. The binding with the plasma proteins is between 85 and 90%.

Biotransformation

The substance undergoes extended biotransformation (about 90%) already from its first pass through the liver into metabolites of low glucocorticoid activity.

The glucocorticoid activity of the main budesonide metabolites (6β-hydroxybudesonide and 16α-hydroxy-prednisolone) is lower than 1% of the administered substance. Budesonide is mainly metabolized by enzyme CYP3A4, a subgroup of cytochrome P450. Budesonide does undergo topical metabolic inactivation in the nose.

Excretion

The metabolites of budesonide are excreted unchangeable or in conjugated form mainly from the kidneys. There has been no trace of unchangeable budesonide in urine. Budesonide shows high systemic clearance (about 1,2 L/min) and its elimination half-life in the plasma after intravenous administration is between 2-3 hours.

Linearity

The kinetics of budesonide in clinically significant doses is dose-dependent.

Children

The area under the curve (AUC) after administration of 400 mcg nasal budesonide in children is 8.6 nmol/h/L, which indicates greater systemic exposure of children to glucocorticosteroids.

5.3. Preclinical data for safety

Results from acute, subacute and chronic toxicity studies show that the systemic effects of budesonide, such as decreased body-weight gain and atrophy of lymphoid tissues and adrenal cortex, are less severe or similar to those observed after administration of the other glucocorticosteroids.

Budesonide was evaluated in 6 different studies and has not shown any mutagenic or clastogenic effect.

An increased incidence of brain gliomas in male rats in a carcinogenicity study could not be verified in a repeat study in which the incidence of gliomas did not differ between any of the groups with active treatment (budesonide, prednisolone, triamcinolone acetonide) and the control groups.

Liver changes (primary hepatocellular neoplasms) found in male rats in the original carcinogenicity study were noted again in the repeat study with budesonide as well as with the reference glucocorticosteroids. These effects are most probably related to a receptor effect and thus represent a class effect.

Available clinical experience shows no indication that budesonide or other glucocorticosteroids induce brain gliomas or primary hepatocellular neoplasms in man.

6. PHARMACEUTICAL DATA

6.1. List of excipients

Cellulose microcrystalline & Carmellose sodium, Glucose anhydrous, Polysorbate 80, Edetate disodium, Potassium sorbate, Hydrochloric acid, Purified water.

6.2. Incompatibilities

Not known.

6.3. Shelf life

The shelf life of the product is 36 months when stored at normal conditions.

6.4. Special precautions for storage

ESONIDE[®] nasal spray should be stored at room temperature ($\leq 25^{\circ}\text{C}$).

Keep out of the reach of children.

6.5. Nature and contents of container

White suspension in an amber glass bottle closed with special metered dose caps, with a label printed with the product and batch characteristics.

Each bottle contains 10 ml of solution (200 doses).

In each box there is one bottle and a patient information leaflet.

6.6. Instructions for use and handling

Before using ESONIDE[®] nasal spray, read the instructions and follow them carefully.

Children should use ESONIDE[®] nasal spray only under an adult's supervision, in order to reassure the correct use and dosage of the product.

Keeping the ESONIDE[®] nasal spray clean

The upper plastic parts of the nasal spray should be regularly cleaned. Remove the protective brown cover and pull the white nozzle. Wash all plastic parts of the nasal spray with hot water and then dry well before its next use.

7. MARKETING AUTORISATION HOLDER

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