

SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

Budesonid Mylan 50 micrograms/dose nasal spray, suspension

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Budesonide 50 micrograms/dose.

For the full list of excipients, see section 6.1

3. PHARMACEUTICAL FORM

Nasal spray, suspension

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Seasonal and perennial allergic rhinitis and vasomotor rhinitis

4.2 Posology and method of administration

Adults and children over 6 years of age: 4 sprays (200 micrograms) in each nostril in the morning. When a good effect has been achieved, the dose may be reduced on a trial basis to 2 sprays (100 micrograms) in each nostril in the morning. However, the minimum dose should be used at which effective control of symptoms is maintained.

(for countries where the strength 100 micrograms/dose is marketed)

For high doses, the use of the Budesonid Mylan 100 microgram/dose nasal spray is recommended.

The patient should be informed that the full effect of budesonide is not achieved until after a few days treatment (in rare cases only after 2 weeks). Treatment of seasonal allergic rhinitis should, if possible, start before exposure to allergens.

Symptom relief appears within 24-36 hours after treatment is initiated in some patients.

If there is severe nasal congestion, supplementary treatment with a vasoconstrictor may be needed initially.

Supplementary treatment may sometimes be necessary in order to prevent possible eye symptoms caused by the allergy.

4.3 Contraindications

Hypersensitivity to the active substance or to any of the excipients listed in section 6.1.

4.4 Special warnings and precautions for use

Switching from administration route

Caution must be observed when treating patients that have been transferred from systemically acting corticosteroids to Budesonid Mylan if there is any reason to suppose that adrenal function is impaired. In these patients, there should be a gradual reduction of the systemic steroid dose and consideration of testing the hypothalamus-pituitary-adrenocortical function. There may also need to be additional systemic steroids at times of stress, e.g. surgery, trauma, etc.

Special caution must be taken in patients with active or quiescent pulmonary tuberculosis, and in patients with fungal or viral infections in the airways.

Contact of budesonide with the eyes should be avoided. If budesonide does come in contact with the eyes, rinse with water immediately.

Systemic effects of nasal corticosteroids may occur, particularly at high doses prescribed for prolonged periods. These effects are much less likely to occur than with oral corticosteroids and may vary in individual patients and between different corticosteroid preparations. Potential systemic effects may include Cushing's syndrome, Cushingoid features, adrenal suppression, growth retardation in children and adolescents, cataract, glaucoma and more rarely, a range of psychological or behavioural effects including psychomotor hyperactivity, sleep disorders, anxiety, depression or aggression (particularly in children).

Paediatric population

Influence on growth

The long-term effects of nasal glucocorticosteroids in children are not fully known. Physicians should closely follow the growth of children taking glucocorticosteroids for longer term by any route, and weigh the benefits of the glucocorticosteroid therapy against the possibility of growth suppression.

If growth is slowed, therapy should be reviewed with the aim of reducing the dose of nasal corticosteroid, if possible, to the lowest dose at which effective control of symptoms is maintained. The benefits of the corticosteroid therapy and the possible risks of growth suppression must be carefully weighed. In addition, consideration should be given to referring the patient to a paediatric respiratory specialist.

Growth retardation has been reported in children receiving nasal corticosteroids at licensed doses.

Reduced liver function affects the elimination of corticosteroids, causing lower elimination rate and higher systemic exposure. Be aware of possible systemic side effects.

Budesonide has no anabolic effects. However, because of the steroid component of the substance, the possibility of a false positive result in sports doping tests cannot be excluded.

4.5 Interaction with other medicinal products and other forms of interaction

Budesonide has not been observed to interact with any drug used for the treatment of rhinitis.

The metabolism of budesonide is primarily mediated by CYP3A4. Potent inhibitors of this enzyme, e.g., ketoconazole and itraconazole, can therefore increase systemic exposure to budesonide several times. Since there is no data to support a dosage recommendation, the combination should be avoided. If this is not possible, the period between treatments should be as long as possible and a reduction of the budesonide dose could also be considered.

Other inhibitors of CYP3A4 are also likely to increase plasma levels of budesonide

Raised plasma concentrations of and enhanced effects of corticosteroids have been observed in women also treated with oestrogens and contraceptive steroids, but no effect has been observed with budesonide and concomitant intake of low dose combination oral contraceptives.

Because adrenal function may be suppressed, an ACTH stimulation test for diagnosing pituitary insufficiency might show false results (low values).

4.6 Fertility, pregnancy and lactation

Pregnancy:

Data from approximately 2000 pregnancies have not shown any increased risk for malfunctions after treatment with budesonide. A small increased risk of mild heart malfunctions compared to the expected frequency in the study population was observed in children whose mothers were exposed to budesonide during early pregnancy, but a causal relation to exposure was assessed not likely.

During pregnancy budesonide should be used at the lowest effective dose for the shortest possible duration.

Breast-feeding:

Budesonide is excreted in breast milk. However, at therapeutic doses of Budesonide no effects on the suckling child are anticipated since the systemic exposure of the breast-feeding infant to budesonide is negligible.

Budesonid Mylan can be used during breast-feeding.

4.7 Effects on ability to drive and use machines

Budesonid Mylan has no influence on the ability to drive and use machines.

4.8 Undesirable effects

About 5% of the patients treated may expect side effects in the form of local irritation.

The following definitions apply to the incidence of undesirable effects:

very common ($\geq 1/10$);

common ($\geq 1/100$ to $< 1/10$);

uncommon ($\geq 1/1000$ to $< 1/100$);

rare ($\geq 1/10000$ to $< 1/1000$);

very rare ($< 1/10000$);

not known (frequency cannot be estimated from available data)

<i>System organ class</i>	<i>Common</i>	<i>Uncommon</i>	<i>Rare</i>	<i>Very rare</i>	<i>Not Known</i>
Immune system disorders		Immediate and delayed hypersensitivity reactions, including urticaria, rash, dermatitis, angioedema and pruritus		Anaphylactic reaction	
Endocrine disorders			Signs and symptoms of systemic corticosteroid effects, including adrenal suppression and growth retardation		
Eye disorders					Cataract, glaucoma

<i>System organ class</i>	<i>Common</i>	<i>Uncommon</i>	<i>Rare</i>	<i>Very rare</i>	<i>Not Known</i>
Respiratory, thoracic and mediastinal disorders	Sneezing, haemorrhagic secretion and epistaxis, nasal Irritation			Perforation of the nasal septum, ulceration of the mucous membrane, dysphonia	

Systemic effects of nasal corticosteroids may occur, particularly when prescribed at high doses for prolonged periods (see section 4.4)

Paediatric Population

Growth retardation has been reported in children receiving intranasal steroids.

Due to the risk of growth retardation in the paediatric population, growth should be monitored as described in section 4.4.

4.9 Overdose

Acute overdosage with budesonide, even in excessive doses, is not expected to be a clinical problem. When used chronically in high doses, the systemic effects of the glucocorticosteroids like hypercortisolism and adrenocortical suppression may appear.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Glucocorticoids.

ATC-code: R01AD05

Budesonide is a glucocorticosteroid with a strong local anti-inflammatory effect. The exact mode of action for glucocorticosteroids in treatment of rhinitis is not fully elucidated. Anti-inflammatory effects, such as inhibited release of inflammatory mediators and inhibition of cytokine-mediated immune response, are probably important. The activity of budesonide, measured as affinity to glucocorticosteroid receptors, is about 15 times higher than that for prednisolone.

Budesonide, administered for prevention before nasal provocation has been shown to protect from migration of eosinophils and hyperreactivity.

At recommended doses, budesonide does not produce any clinically important changes; either in the basal plasma cortisol level or in the response to stimulation with ACTH. However, dose-related suppression of plasma- and urine cortisol has been observed in healthy volunteers after short-term administration of budesonide.

Paediatric population

Clinical efficacy

The therapeutic efficacy of Budesonide Aqua Nasal Spray has been evaluated in several thousand adults and children. Most studies were conducted with delivered doses of Rhinocort Aqua of 32 to 256 µg intranasal once daily. Examples of representative studies evaluating the use of Rhinocort Aqua for the treatment of children with seasonal and perennial allergic rhinitis studies are provided below. The primary efficacy variable was the combined nasal symptoms score (CNSS), which is the sum of the individual nasal symptom scores for three nasal symptoms (congestion, runny nose and sneezing, each rated on a scale of 0-3).

Seasonal allergic rhinitis

Paediatric population

A 2-week randomized double-blind, placebo-controlled, parallel-group study evaluated the efficacy and safety of Rhinocort Aqua 16, 32 and 64 µg once daily in 400 children (aged 2 to 5 years) with allergic rhinitis (seasonal or perennial). There was a marked reduction from baseline CNSS in all treatment groups, including placebo. The difference between Rhinocort Aqua 64 µg and placebo treatment was not statistically significant.

Perennial allergic rhinitis

Paediatric population

A 6-week randomized double-blind, placebo-controlled, parallel-group study evaluated the efficacy and safety of Rhinocort Aqua 128 µg once daily in 202 children (aged 6-16 years) with perennial allergic rhinitis. Primary efficacy variables were CNSS and values of peak nasal inspiratory flow (PNIF) measurements. Rhinocort Aqua improved the CNSS and PNIF statistically significantly more than placebo. Onset of action for Rhinocort Aqua was 12 hours after first dose for CNSS and 48 hours for PNIF.

Clinical safety

Paediatric population

In a randomized, double-blind, placebo-controlled growth study, 229 pre-pubertal children ages 4 years to 8 years received Rhinocort Aqua 64 mcg once daily or placebo for 12 months after a 6-month baseline period. In this study, growth velocity was similar between Rhinocort Aqua and placebo treatment groups after 12 months of therapy: the mean difference in growth velocity (placebo-Rhinocort Aqua) was 0.27 cm/year (95% confidence interval: -0.07 to 0.62).

Influence on plasma cortisol concentration:

In the recommended dosages Rhinocort Nevel does not cause clinical relevant changes in basal plasma cortisol concentrations or to ACTH stimulation. In healthy volunteers a dose dependent suppression of plasma cortisol- and urinary cortisol concentrations were seen after short term administration of Rhinocort Nevel.

5.2 Pharmacokinetic properties

Absorption

The systemic availability of budesonide with reference to the metered dose is 33% of measured dose.

In adults, the maximal plasma concentration after administration of 256 micrograms budesonide from Rhinocort Aqua is 0.64 nmol/l and is reached within 0.7 hours. The Area Under Curve (AUC) after administration of 256 micrograms budesonide from Rhinocort Aqua is 2.7 nmol*h/l in adults.

Distribution

Budesonide has a volume of distribution of about 3 l/kg. The plasma protein binding is 85-90%.

Biotransformation

Budesonide undergoes an extensive degree (~90%) of biotransformation on first passage through the liver to metabolites with low glucocorticosteroid activity. The glucocorticosteroid activity of the major metabolites, 6-beta-hydroxy budesonide and 16-alpha-hydroxy prednisolone, is less than 1% of that of budesonide. The metabolism of budesonide is primarily mediated by CYP3A, a subfamily of cytochrome P450. Budesonide does not undergo local metabolism in the nose.

Elimination

The metabolites are excreted as such or in conjugated form mainly via the kidneys. No intact budesonide has been detected in the urine. Budesonide has a high systemic clearance (approximately 1.2 l/min) and the half-life in plasma after intravenous dosing is approximately 2-3 hours.

Linearity

The kinetics of budesonide are dose-proportional at clinically relevant doses.

Paediatric population

Budesonide has a systemic clearance of approximately 0.5 l/min in 4-6 years old asthmatic children. Per kg body weight children have a clearance which is approximately 50% greater than in adults. The terminal half-life of budesonide after inhalation is approximately 2.3 hours in asthmatic children. This is about the same as in healthy adults. The Area Under Curve (AUC) after administration of 256 micrograms budesonide from Rhinocort Aqua is 5.5 nmol*h/l in children, indicating a higher systemic glucocorticosteroid exposure in children than in adults. At clinically recommended doses, the pharmacokinetics of budesonide are dose-proportional and plasma exposure is correlated to the weight of the patient. Therefore this should be taken into account when establishing paediatric doses.

5.3 Preclinical safety data

Results from acute, sub-acute and chronic toxicity studies show that the systemic effects of budesonide, e.g. reduced increase in body weight and atrophy of lymphoid tissue and adrenal gland cortex, are less than or of similar degree of severity to those observed after administration of other glucocorticoids.

Budesonide, when evaluated in six different test systems did not show any mutagenic or clastogenic effects.

An increased incidence of cerebral glioma in male rats in a carcinogenicity study could not be verified in a repeated study, in which the incidence of glioma 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 was observed again in a repeated study, with both budesonide and the reference corticosteroids. These effects are most probably related to a receptor effect and therefore represent a class effect.

From the clinical experience gathered, there is nothing that implies that budesonide or other glucocorticoids induce cerebral glioma or primary hepatocellular neoplasms in humans.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Disodium edetate
Glucose
Hydrochloric acid
Potassium sorbate (preservative)
Cellulose, microcrystalline
Sodium carboxymethyl cellulose
Polysorbate
Water, purified

6.2 Incompatibilities

Not applicable.

6.3 Shelf-Life

2 years

Shelf-life after opening: 2 months.

6.4 Special precautions for storage

Do not store above 25°C. Do not freeze.

6.5 Nature and contents of container

Amber glass bottles with a nasal spray unit containing nasal spray 50 micrograms/dose: 10 ml (200 sprays) and 2 x 10ml (400 sprays).

The product may be marketed in packs of one or two bottles.

6.6 Special precautions for disposal

Before Budesonid Mylan is used for the first time, the nasal applicator must be primed with the drug. To achieve this, shake the bottle and spray in the air until an even douche is achieved. The effect of this remains for about 24 hours. If a longer period elapses until the next dose, the nasal applicator must be reloaded with the drug.

This time one spray in the air is enough.

Instructions for the patient on how to use Budesonid Mylan are fully described in the package insert.

Contact of Budesonid Mylan with the eyes should be avoided. If Budesonid Mylan does come in contact with the eyes, the patient must immediately rinse them with water.

7. MARKETING AUTHORISATION HOLDER

[To be completed nationally]

8. MARKETING AUTHORISATION NUMBER

[To be completed nationally]

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

[To be completed nationally]

10. DATE OF REVISION OF THE TEXT

2014-09-16

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