# BUDENASE AQ Nasal Spray (Budesonide)

## Composition

Each spray delivers:
Budesonide 100 micrograms

## Dosage Form

Aqueous intranasal spray

## Pharmacology

### Pharmacodynamics

Budesonide is an anti-inflammatory corticosteroid that exhibits potent glucocorticoid activity and weak mineralocorticoid activity. In standard *in vitro* and animal models, budesonide has approximately a 200-fold higher affinity for the glucocorticoid receptor and a 1000-fold higher topical anti-inflammatory potency than cortisol (rat croton oil ear edema assay). The precise mechanism of corticosteroid actions in seasonal and perennial allergic rhinitis is not known. Corticosteroids have been shown to have a wide range of inhibitory activities against multiple cell types (e.g., mast cells, eosinophils, neutrophils, macrophages, and lymphocytes) and mediators (e.g., histamine, eicosanoids, leukotrienes, and cytokines) involved in allergic mediated inflammation.

Corticosteroids affect the delayed (6 hours) response to an allergen challenge more than the histamine-associated immediate response (20 minutes). The clinical significance of these findings is unknown.

### Pharmacokinetics

The pharmacokinetics of budesonide has been studied following nasal, oral, and intravenous administration. Budesonide is relatively well absorbed after both inhalation and oral administration, and is rapidly metabolized into metabolites with low corticosteroid potency. The clinical activity of budesonide aqueous nasal spray is, therefore, believed to be due to the parent drug, budesonide. *in vitro* studies indicate that the two epimeric forms of budesonide do not interconvert.

**Absorption:**
Following intranasal administration of budesonide aqueous, the mean peak plasma concentration occurs at approximately 0.7 hours. Compared to an intravenous dose, approximately 34% of the delivered intranasal dose reaches the systemic circulation, most of which is absorbed through the nasal mucosa. While budesonide is well absorbed from the gastrointestinal tract, the oral bioavailability of budesonide is low (~10%) primarily due to extensive first-pass metabolism in the liver.

**Distribution:**
Budesonide has a volume of distribution of approximately 2-3 L/kg. The volume of distribution for the 22R epimer is almost twice that of the 22S epimer. Protein binding of budesonide *in vitro* is constant (85-90%)
over a concentration range (1-100 nmol/L), which exceeded that achieved after administration of recommended doses. Budesonide shows little to no binding to glucocorticosteroid-binding globulin. It rapidly equilibrates with red blood cells in a concentration-independent manner, with a blood/plasma ratio of about 0.8.

Metabolism:
In humans, budesonide is rapidly and extensively metabolized in the liver. Two major metabolites (16alpha-hydroxyprednisolone and 6beta-hydroxybudesonide) are formed via cytochrome P450 (CYP) isoenzyme 3A4 (CYP3A4)-catalysed biotransformation. Known metabolic inhibitors of CYP3A4 (e.g., ketoconazole), or significant hepatic impairment, may increase the systemic exposure of unmetabolized budesonide. *in vitro* studies on the binding of the two primary metabolites to the glucocorticoid receptor indicate that they have less than 1% of the affinity for the receptor as the parent compound, budesonide. *In vitro* studies have evaluated sites of metabolism and showed negligible metabolism in the skin, lungs, and serum. No qualitative difference between the *in vitro* and *in vivo* metabolic patterns could be detected.

Elimination:
Budesonide is excreted in the urine and the faeces in the form of metabolites. After intranasal administration of a radiolabelled dose, two-thirds of the radioactivity was found in the urine and the remainder in the faeces. The main metabolites of budesonide in the 0-24 hours urine sample, following intravenous administration, are 16alpha-hydroxyprednisolone (24%) and 6beta-hydroxybudesonide (5%). An additional 34% of the radioactivity recovered in the urine was identified as conjugates. The 22R form was preferentially cleared with clearance value of 1.4 L/min versus 1.0 L/min for the 22S form. The terminal half-life of 2-3 hours was similar for both epimers and it appeared to be independent of dose.

### Indications

BUDENASE AQ Nasal Spray is indicated for the management of nasal symptoms of seasonal or perennial allergic rhinitis in adults and children, 6 years of age and older.

BUDENASE AQ Nasal Spray is also indicated for the treatment of nasal polyps.

### Dosage And Administration

#### Adults and Children (6 years of age and older)
Initially, two sprays in each nostril every morning.

For maintenance, one spray in each nostril once daily.

#### Polyps
One spray in each nostril, morning and evening, for up to 3 months.

Not recommended below 6 years of age.

### Contraindications

Budesonide aqueous nasal spray is contraindicated in patients with a hypersensitivity to any of its ingredients.

### Warnings And Precautions

Special care is demanded in treatment of patients transferred from oral steroids to budesonide aqueous nasal spray where disturbances of the hypothalamic-pituitary-adrenal (HPA) axis could be expected. Special care is needed in patients with fungal and viral infections of the airways and in patients with lung
tuberculosis.
The patient should be informed that the full effect of budesonide nasal spray is not achieved until after a few
days treatment. 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. In
continuous long-term treatment, the nasal mucosa should be inspected regularly e.g. every 6 months.
Systemic effects of nasal corticosteroids may occur, particularly at high doses prescribed for prolonged
periods. Growth retardation has been reported in children receiving nasal corticosteroids at licensed doses.
It is recommended that the height of children receiving prolonged treatment with nasal corticosteroids is
regularly monitored. 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. In
addition, consideration should also be given to referring the patient to a pediatric specialist.
Treatment with higher than recommended doses may result in clinically significant adrenal suppression. If
there is evidence for higher than recommended doses being used, additional systemic corticosteroid cover
should be considered during periods of stress or elective surgery.
The replacement of a systemic corticosteroid with a topical corticosteroid can be accompanied by signs of
adrenal insufficiency, and in addition some patients may experience symptoms of corticosteroid withdrawal,
e.g., joint and/or muscular pain, fatigue, weakness, nausea, vomiting, hypotension, lassitude, and
depression. Patients previously treated for prolonged periods with systemic corticosteroids should be
weaned off slowly when transferred to topical corticosteroids and carefully monitored for acute adrenal
insufficiency in response to stress. In those patients who have asthma or other clinical conditions requiring
long-term systemic corticosteroid treatment, too rapid a decrease in systemic corticosteroids may cause a
severe exacerbation of their symptoms.
in vivo studies have shown that oral administration of itraconazole and ketoconazole (known inhibitors of
CYP3A4 activity in the liver and in the intestinal mucosa, may cause an increase in the systemic exposure to
budesonide. This is of limited clinical importance for short-term (12 weeks) treatment with itraconazole or
ketoconazole, but should be taken into consideration during long-term treatment.
In case of infections of the nose caused by bacteria or fungi, Budesonide nasal spray suspension should be
used only if concomitant antibacterial or antifungal treatment is carried out.
In continuous long-term treatment, the nasal mucosa should be inspected regularly e.g. every 6 months.
Budesonide nasal spray is not recommended in patients with epistaxis and in patients, with herpetic
infection of oral, nasal or ophthalmic region.
Budesonide nasal spray is not recommended in patients with nasal ulcerations, in cases of recent surgery or
nasal trauma until it is fully recovered.
In clinical studies of 3 to 52 weeks duration epistaxis was observed more frequently in patients treated with
budesonide nasal spray than those who received placebo.
In clinical studies with budesonide administered intranasally, the development of localized infections of the
nose and pharynx with Candida albicans has occurred. When such an infection develops, it may require
treatment with appropriate local or systemic therapy and discontinuation of treatment with BUDENASE AQ
Nasal Spray. Patients using BUDENASE AQ Nasal Spray over several months or longer should be examined
periodically for evidence of Candida infection or other signs of adverse effects on the nasal mucosa.
Instances of nasal septum perforation have been reported following the intranasal application of
corticosteroids, including budesonide.
Because of the inhibitory effect of corticosteroids on wound healing, patients who have experienced recent
nasal septal ulcers, nasal surgery, or nasal trauma should not use a nasal corticosteroid until healing has
occurred.
Hypersensitivity reactions including anaphylactic reaction, urticaria, rash, dermatitis, angioedema and pruritus may occur.

Patients who are on drugs that suppress the immune system are more susceptible to infections than healthy individuals. Chicken pox and measles, for example, can have a more serious or even fatal course in susceptible children or adults using corticosteroids. In such children or adults who have not had these diseases or been properly immunized, particular care should be taken to avoid exposure.

How the dose, route, and duration of corticosteroid administration affect the risk of developing a disseminated infection is not known.

The contribution of the underlying disease and/or prior corticosteroid treatment to the risk is also not known. If exposed to chicken pox, therapy with varicella zoster immune globulin (VZIG) or pooled intravenous immunoglobulin (IVIG), as appropriate, may be indicated. If exposed to measles, prophylaxis with pooled intramuscular immunoglobulin (IG) may be indicated. (See the respective package inserts for complete VZIG and IG prescribing information). If chicken pox develops, treatment with antiviral agents may be considered. Glaucoma, increased intraocular pressure and cataracts have been reported following the intranasal application of corticosteroids, including budesonide. Therefore, close monitoring is warranted in patients with a change in vision or with a history of increased intraocular pressure, glaucoma, and/or cataracts.

- **Effects on Ability to Drive and Use Machines**

  Budesonide nasal spray suspension has no influence on the ability to drive or use machines.

- **Drug Interactions**

  Concomitant administration of oral ketoconazole 200 mg once daily and oral budesonide (3 mg single dose) increased the plasma concentrations of budesonide on average 6-fold. When ketoconazole was administered orally 12 hours after the budesonide dose, the concentrations of budesonide increased on average 3-fold. There is no information about this interaction following nasal administration of budesonide, but increased plasma concentrations are expected. The combination should be avoided as there are no dose recommendations for the combination, but if not possible the time interval between the administrations of the two drugs should be as long as possible. A reduction of the dose may also be considered. Concomitant administration of other potent inhibitors of CYP3A4 (e.g.: ketoconazole, ciclosporin, ethinylestradiol and troleandomycin) is likely to result in a marked increase of budesonide plasma concentrations.

- **Geriatric Use**

  No specific pharmacokinetic study has been undertaken in subjects >65 years of age.

- **Paediatric**

  After administration of budesonide aqueous nasal spray, the time taken to reach peak drug concentrations and plasma half-life was similar in children and in adults. Children had plasma concentrations approximately twice those observed in adults, primarily due to differences in weight between the children and the adults. Safety and effectiveness in pediatric patients below 6 years of age have not been established.

- **Gender**

  No specific pharmacokinetic study has been conducted to evaluate the effect of gender on budesonide pharmacokinetics. However, following administration of 400 mcg of budesonide aqueous nasal spray to 7 male and 8 female volunteers in a pharmacokinetic study, no major gender differences in the pharmacokinetic parameters were found.

- **Race**
No specific study has been undertaken to evaluate the effect of race on budesonide pharmacokinetics.

Renal Impairment:

The pharmacokinetics of budesonide has not been investigated in patients with renal impairment.

Hepatic Impairment

Reduced liver function may affect the elimination of corticosteroids. The pharmacokinetics of orally administered budesonide was affected by compromised liver function as evidenced by a doubled systemic availability. The relevance of this finding to intranasally administered budesonide has not been established.

Pregnancy

Results from prospective epidemiological studies and from worldwide post marketing experience indicate no increased risk for overall congenital malformations from the use of inhaled or intranasal budesonide during early pregnancy. As with other drugs the administration of BUDENASE AQ Nasal Spray during pregnancy requires that the benefits for the mother are weighed against the risk for the foetus.

Lactation

Budesonide is excreted in breast milk. However, at therapeutic doses of budesonide nasal spray no effects on the breast fed child are anticipated. Budesonide nasal spray can be used during breast feeding. Based on data from inhaled budesonide and the fact budesonide exhibits linear PK properties within the therapeutic dosage intervals after nasal, inhaled, oral and rectal administrations at therapeutic doses of budesonide, exposure to the breast-fed child is anticipated to be low. Dosing considerations include prescription or titration to the lowest clinically effective dose and use of budesonide nasal spray immediately after breastfeeding to maximize the time interval between dosing and breastfeeding to minimize infant exposure.

Undesirable Effects

Systemic and intranasal corticosteroids use may result in the following:

- Epistaxis, Candida albicans infection, nasal septum perforation, and impaired wound healing.
- Hypersensitivity Including Anaphylaxis.
- Immunosuppression.
- Hypercorticism and Adrenal Suppression.
- Growth Effect.
- Glaucoma and Cataracts.

In clinical trials with patients 6 years and above the reported adverse effects which occurred at a frequency of ≥ 2% were: epistaxis, pharyngitis, bronchospasm, coughing and nasal irritation.

If recommended doses are exceeded, or if individuals are particularly sensitive, symptoms of hypercorticism, i.e., Cushing’s syndrome, could occur.

Adverse events reported from postmarketing experience include: immediate and delayed hypersensitivity reactions (including anaphylactic reaction, urticaria, rash, dermatitis, angioedema and pruritus), glaucoma, increased intraocular pressure, cataracts, nasal septum perforation, pharynx disorders (throat irritation, throat pain, swollen throat, burning throat, and itchy throat), wheezing, haemorrhagic secretion and epistaxis, angi-oedema, anosmia, and palpitations, nasal irritation (sneezing, stinging and dryness), ulceration of mucous membrane.

Cases of growth suppression have been reported for intranasal corticosteroids, including BUDENASE AQ Nasal Spray.
Overdosage

Acute overdose with Budesonide Nasal Spray should not present clinical problems. Inhalation of high doses of corticosteroids may lead to suppression of the hypothalamic-pituitary-adrenal (HPA) axis function.

Packaging Information

BUDENASE AQ Nasal Spray: Each sales pack contains 150 metered doses

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