PRODUCT MONOGRAPH

INCLUDING PATIENT MEDICATION INFORMATION

[Pr]MYLAN-BUDESONIDE AQ

Budesonide Aqueous Nasal Spray
100 mcg per metered dose

Mylan Std.

Corticosteroid for Nasal Use

Mylan Pharmaceuticals ULC
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Etobicoke, Ontario
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PART I: HEALTH PROFESSIONAL INFORMATION

1. INDICATIONS

MYLAN-BUDESONIDE AQ (Budesonide Aqueous Nasal Spray) is indicated for:

- The treatment of seasonal allergic and allergic/ non-allergic perennial and vasomotor rhinitis unresponsive to conventional therapy in patients 6 years and older.
- The treatment of nasal polyps and in the prevention of nasal polyps after polypectomy in patients 12 years and older.

1.1 Pediatrics

Children Under 6 Years of Age: Due to limited clinical data in this age group, the safety and efficacy of MYLAN-BUDESONIDE AQ in pediatric patients under 6 years of age have not been established; therefore, Health Canada has not authorized an indication for this age group.

2. CONTRAINDICATIONS

MYLAN-BUDESONIDE AQ is contraindicated in:

- Patients who are hypersensitive to this drug or to any ingredient in the formulation, including any non-medicinal ingredient, or component of the container. For a complete listing, see Dosage Forms, Strengths, Composition and Packaging.
- Patients with active or quiescent tuberculosis;
- Patients with untreated fungal, bacterial, or viral infections;
- Children under 6 years of age.

3. DOSAGE AND ADMINISTRATION

3.1 Dosing Considerations

Careful attention must be given to patients previously treated for prolonged periods with systemic corticosteroids when transferred to MYLAN-BUDESONIDE AQ (budesonide) (see WARNINGS AND PRECAUTIONS). Initially, MYLAN-BUDESONIDE AQ and the systemic corticosteroid must be given concomitantly, while the dose of the latter is gradually decreased. The usual rate of withdrawal of the systemic steroid is the equivalent of 2.5 mg of prednisone every four days if the patient is under close supervision. If continuous supervision is not feasible, the withdrawal of the systemic steroid should be slower, approximately 2.5 mg of prednisone (or equivalent) every ten days. If withdrawal symptoms appear, the previous dose of the systemic steroid should be resumed for a week before further decrease is attempted.

Patients should be informed that the full effect of MYLAN-BUDESONIDE AQ therapy may not become evident until 2 to 3 days of treatment have been completed. Full therapeutic benefit requires regular usage.

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.

If the nasal passages are severely blocked, the drug may fail to reach the site of action. In such cases, decongestants may be required before initiating MYLAN-BUDESONIDE AQ therapy.

Although systemic effects are negligible at recommended doses, MYLAN-BUDESONIDE AQ treatment should not be continued beyond three weeks in the absence of significant symptomatic improvement. MYLAN-BUDESONIDE AQ should not be used in the presence of untreated localized infections involving the nasal mucosa.

3.2 Recommended Dose and Dosage Adjustment

Treatment of Rhinitis:

Adults and Children (12 Years of Age and Older)

Initial Dose
The recommended starting dose is 4 sprays per day (total daily dose of 400 mcg). The dose can be administered as 2 sprays in each nostril once daily in the morning or divided into two administrations daily of 1 spray in each nostril in the morning and evening.

Maintenance dose
After the desired clinical effect is obtained and symptoms are controlled, the maintenance dose should be reduced to the smallest amount necessary to control the symptoms. The dose can be reduced to 1 spray per nostril once daily in the morning (total daily dose of 200 mcg).

Children (6 Years to Less Than 12 Years of Age)

Initial Dose
The recommended dose is 1 spray in each nostril (total dose 200 mcg) once daily in the morning.

If symptoms do not improve, the dose can be increased up to 2 sprays per nostril (up to 400 mcg total daily dose) once daily in the morning.

Maintenance Dose

Once allergy symptoms improve, the maintenance dose should be reduced to 1 spray in each nostril once daily in the morning.

Parents should talk to their child's physician if the child needs to use the spray for longer than two months a year.

Treatment or Prevention of Nasal Polyps:

Adults and Children (12 Years of Age and Older)

The recommended dose is 1 spray (100 mcg) into each nostril morning and evening (total daily dose of 400 mcg).

Children Under 6 Years

Health Canada has not authorized an indication for children in this age group.

3.3 Administration

MYLAN-BUDESONIDE AQ should be administered by the intranasal route only.

Before taking each dose, the bottle should be inverted 3 to 4 times.

Prior to administration, the nasal spray must be prepared for first time use. The bottle should be inverted 3 to 4 times and the protective cap removed. The pump should be actuated 5 to 10 times away from the face until a fine mist spray appears. If the spray was not used on the prior day, the pump should be prepared by pressing down once away from the face before administration. Illustrated instructions for proper use appear in PART III: PATIENT MEDICATION INFORMATION.

3.4 Missed Dose

If a single dose is missed, instruct the patient to take the dose as soon as possible and then go back to their regular schedule. If it is almost time to take the next dose, instruct the patient to skip the missed dose and to take the next dose at the usual time.

The patient should not take a double dose of MYLAN-BUDESONIDE AQ to make up for a missed dose.

4. OVERDOSAGE

Like any other nasally administered corticosteroid, acute overdosing is unlikely in view of the total amount of active ingredient present. However, when used chronically in excessive doses or

in conjunction with other corticosteroid formulations, systemic corticosteroid effects such as hypercorticism and adrenal suppression may appear. If such changes recur, the dosage of MYLAN-BUDESONIDE AQ (budesonide) should be discontinued slowly consistent with accepted procedures for discontinuation of chronic steroid therapy (see DOSAGE AND ADMINISTRATION).

The restoration of the hypothalamic-pituitary-axis may be a slow process and during periods with pronounced physical stress such as severe infections, trauma, and surgical operations, a supplement with systemic steroids may be advisable.

For management of a suspected drug overdose, contact your regional Poison Control Centre immediately.

5. DOSAGE FORMS, STRENGTHS, COMPOSITION AND PACKAGING

MYLAN-BUDESONIDE AQ (budesonide) 100 mcg per dose is a white to off-white, thixotropic suspension of budesonide in water supplied in amber glass bottles provided with a pump spray mechanism, nasal adapter and Patient Instruction leaflet in bottles of 165 doses.

Table 1 – Dosage Forms, Strengths and Composition

Route of Administration	Dosage Form / Strength / Composition	Non-medicinal Ingredients
Intranasal	Nasal Spray / 100 mcg metered dose / Budesonide	Carboxymethylcellulose sodium, disodium Edetate, dextrose, hydrochloric acid, microcrystalline cellulose, potassium sorbate, tween 80 and water

6. WARNINGS AND PRECAUTIONS

General

During transfer of patients from a systemic steroid to MYLAN-BUDESONIDE AQ, the reduction of the systemic steroid must be very gradual and carefully supervised by the physician since systemic withdrawal symptoms (e.g., joint and/or muscular pain, lassitude, depression) may occur in spite of maintenance or improvement of respiratory functions (see DOSAGE AND ADMINISTRATION). In severe cases, adrenal insufficiency may occur necessitating a temporary resumption of systemic steroids.

Careful attention must be given to patients with asthma or other clinical conditions in whom a rapid decrease in systemic steroids may cause a severe exacerbation of their symptoms.

Patients should be advised to inform subsequent physicians of the prior use of glucocorticosteroids.

Treatment with MYLAN-BUDESONIDE AQ should not be stopped abruptly but tapered off gradually.

Ear/Nose/Throat

MYLAN-BUDESONIDE AQ should not be used in the presence of untreated localized infection involving the nasal mucosa.

Concomitant treatment (topical histamines or cromones) may sometimes be required, as an add-on therapy to nasal corticosteroids, to counteract eye symptoms caused by allergy.

The long-term effects of nasal corticosteroids in human subjects are still unknown, in particular, their local effects, and on developmental or immunologic processes. The nasal mucosa of those patients receiving long term, continuous therapy should be inspected at least twice a year. The possibility of atrophic rhinitis and/or pharyngeal candidiasis should be kept in mind.

Following the use of intranasal corticosteroids, instances of nasal septum perforation have been reported very rarely.

Endocrine and Metabolism

Use of excessive doses of, or long-term treatment with, glucocorticosteroids may lead to signs or symptoms of hypercorticism, suppression of HPA function and/or suppression of growth in children. During long-term therapy, pituitary-adrenal function status should be periodically assessed.

Glucocorticosteroid effects may be enhanced in patients with hypothyroidism.

Dose-related suppression of plasma and urinary cortisol has been observed in healthy volunteers after short-term administration of intranasal budesonide. Although no important changes in basal plasma cortisol levels were manifested in patients with rhinitis using intranasal budesonide at recommended doses, caution is advised.

Hematologic:

In hypoprothrombinemia, salicylates (e.g. acetylsalicylic acid) should be used cautiously in conjunction with glucocorticosteroids. During long-term therapy, hematological status should be periodically assessed.

Hepatic/Biliary/Pancreatic

Glucocorticosteroid effects may be enhanced in patients with cirrhosis. Reduced liver function may affect the elimination of corticosteroids. The intravenous pharmacokinetics of budesonide however, are similar in cirrhotic patients and in healthy subjects. The pharmacokinetics after oral ingestion of budesonide were affected by compromised liver function as evidenced by increased systemic availability. This is however, of limited clinical importance for MYLAN-BUDESONIDE AQ, as the oral contribution to the systemic availability is relatively small.

Immune

As with all medications containing a corticosteroid, MYLAN-BUDESONIDE AQ should be administered with caution, and only if necessary, in patients with active or quiescent tuberculosis infections of the respiratory tract; chronic or untreated infections such as systemic fungal, bacterial, viral, or parasitic; or ocular herpes simplex.

Glucocorticosteroids may mask some signs of infections and new infections may appear during their use. A decreased resistance to localized infection has been observed during glucocorticosteroid therapy; this may require treatment with appropriate therapy or stopping the administration of MYLAN-BUDESONIDE AQ.

Patients who are on immunosuppressant drugs are more susceptible to infections than healthy individuals. Chicken pox and measles, for example, can have a more serious or fatal course in children on immunosuppressant corticosteroids. In such children, or in adults who have not had these diseases, particular care should be taken to avoid exposure. How the dose, route, and duration of corticosteroid administration affects 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, therapy with varicella zoster immune globulin (VZIG) or pooled intravenous immunoglobulin (IVIG), as appropriate, may be indicated. If chicken pox develops, treatment with antiviral agents may be considered.

Ophthalmologic

Following the use of intranasal aerosolized corticosteroids, instances of increased intraocular pressure have been reported very rarely.

Visual disturbance may be reported with systemic and topical (including intranasal, inhaled and intraocular) corticosteroid use. The possible causes of visual disturbance may include cataract, glaucoma or rare diseases such as central serous chorioretinopathy (CSCR) which may have been reported after use of systemic and topical corticosteroids. Therefore, close monitoring is warranted in patients with a change in vision or with a history of increased intraocular pressure, glaucoma and/or cataracts.

Peri-operative Considerations

Because of the inhibitory effect of corticosteroids on wound healing in patients who have had recent nasal surgery or trauma, MYLAN-BUDESONIDE AQ should be used with caution until healing has occurred.

Psychiatric

Although very rare, there is a potential risk of psychological or behavioural effects (psychomotor hyperactivity, sleep disorders, anxiety, depression and aggression) that have been reported.

6.1 Special Populations

6.1.1 Pregnant Women

In experimental animal studies, budesonide was found to cross the placental barrier. Like other glucocorticosteroids, budesonide is teratogenic to rodent species. High doses of budesonide administered subcutaneously produced fetal malformations, primarily skeletal defects, in rabbits, rats, and in mice. Results from world-wide post marketing experience indicate inhaled budesonide during pregnancy has no adverse effects on the health of the fetus/new born child. Review of published literature of orally inhaled budesonide, including results from a large case control study performed with cases identified from 3 Swedish health registers showed that there was no association between exposure to inhaled budesonide and overall congenital malformations. Results from a similar study performed with intranasal budesonide, using the same 3 Swedish health registers showed that the use of intranasal budesonide was associated with a subgroup "less severe cardiovascular defects"; however, there was no statistically significant association between the use of intranasal budesonide during pregnancy and overall congenital malformations, or overall frequency of cardiovascular defects in the offspring. Budesonide should be used during pregnancy only if the potential benefits clearly outweigh the risk to the fetus. Infants born of mothers who have received substantial doses of corticosteroids, especially oral steroids, during pregnancy should be carefully observed for hypoadrenalism.

6.1.2 Breast-feeding

Budesonide is excreted in breast milk. The administration of MYLAN-BUDESONIDE AQ to women who are breastfeeding should only be considered if the expected benefit to the mother is greater than any possible risk to the child.

6.1.3 Pediatrics

MYLAN-BUDESONIDE AQ is not presently recommended for children younger than 6 years of age due to limited clinical data in this age group.

Children who are on immunosuppressant drugs are more susceptible to infections than healthy children. Chicken pox and measles, for example, can have a more serious or fatal course in children on immunosuppressant corticosteroids. In such children, particular care should be taken

to avoid exposure. If exposed, therapy with varicella zoster immune globulin (VZIG) or pooled intravenous immunoglobulin (IVIG), as appropriate, may be indicated. If chicken pox develops, treatment with antiviral agents may be considered.

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. Until greater clinical experience has been gained, the continuous, long term treatment of children is not recommended.

7. ADVERSE REACTIONS

7.1 Adverse Reaction Overview

The adverse reactions reported with budesonide are consistent with those expected when applying a topical treatment to an already inflamed membrane. All side effects were transient.

The most commonly reported side effects include: nasal and throat irritation, nasal bleeding and crusting. Other adverse events reported are itching throat, sore throat, cough, fatigue, nausea/dizziness, and headache.

When patients are transferred to MYLAN-BUDESONIDE AQ from a systemic steroid, allergic conditions such as asthma or eczema may be unmasked.

7.2 Clinical Trial Adverse Reactions

Because clinical trials are conducted under very specific conditions, the adverse 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 reaction information from clinical trials is useful for identifying drug-related adverse events and for approximating rates.

The safety of budesonide from clinical trial data is based on data from 15 placebo-controlled randomized studies in the treatment of allergic rhinitis.

Tables 2 and 3 include adverse events that occurred where greater than one event was reported, and the incidence was greater than placebo and in 1% of patients or more.

Table 2 – AEs Reported by >1% Budesonide-treated Subjects (Adults and Children 12 Years and Over) with Allergic Rhinitis in Placebo-Controlled Clinical Trials

System Organ Class	Budesonide Nasal Spray Dose			
Preferred Term	64 mcg (N=171)	128 mcg (N=615)	256 mcg (N=1292)	Placebo (N=1172)

	% (Frequency)	% (Frequency)	% (Frequency)	% (Frequency)
Infections and infestations				
Urinary tract infection	1.2 (Common)	0.2 (Uncommon)	0.2 (Uncommon)	0.1 (Uncommon)
Upper respiratory tract infection	7.0 (Common)	1.5 (Common)	1.5 (Common)	2.2 (Common)
Respiratory, thoracic and mediastinal disorders				
Asthma	1.2 (Common)	4.9 (Common)	2.3 (Common)	2.0 (Common)
Epistaxis	4.7 (Common)	5.2 (Common)	9.0 (Common)	3.7 (Common)
Oropharyngeal pain	6.4 (Common)	2.0 (Common)	2.2 (Common)	1.3 (Common)

Table 3 – AEs Reported by > 1% Budesonide treated Subjects (Children Age 6 to less than 12 Years) with Allergic Rhinitis in Placebo Controlled Clinical Trials

System Organ Class	**Budesonide Nasal Spray Dose**			
Preferred Term	64 mcg (N=32) % (Frequency)	128 mcg (N=102) % (Frequency)	256 mcg (N=36) % (Frequency)	Placebo (N=106) % (Frequency)
Gastrointestinal disorders				
Abdominal discomfort	0	0	5.6 (Common)	0
General disorders and administration site conditions				
Pyrexia	0	2.0 (Common)	2.8 (Common)	0.9 (Uncommon)
Infections and Infestations				
Otitis media	0	2.0 (Common)	0	0
Pharyngitis	3.1 (Common)	2.0 (Common)	0	1.9 (Common)
Rhinitis	0	2.0 (Common)	2.8 (Common)	0
Upper respiratory tract infection	6.3 (Common)	2.9 (Common)	2.8 (Common)	0
Bronchitis	0	2.9 (Common)	0	0.9 (Uncommon)

System Organ Class	Budesonide Nasal Spray Dose			
Preferred Term	64 mcg (N=32) % (Frequency)	128 mcg (N=102) % (Frequency)	256 mcg (N=36) % (Frequency)	Placebo (N=106) % (Frequency)
Respiratory tract infection	0	2.9 (Common)	0	1.9 (Common)
Sinusitis	3.1 (Common)	2.0 (Common)	5.6 (Common)	1.9 (Common)
Tonsillitis	0	3.9 (Common)	0	1.9 (Common)
Nervous system disorders				
Headache	6.3 (Common)	3.9 (Common)	8.3 (Common)	3.8 (Common)
Asthma	0	5.9 (Common)	0	4.7 (Common)
Cough	0	6.9 (Common)	8.3 (Common)	4.7 (Common)
Epistaxis	3.1 (Common)	4.9 (Common)	2.8 (Common)	5.7 (Common)
Oropharyngeal pain	9.4 (Common)	2.0 (Common)	5.6 (Common)	0.9 (Uncommon)
Skin and subcutaneous tissue disorders				
Rash	0	1.0 (Common)	5.6 (Common)	1.9 (Common)

7.3 Post-Market Adverse Reactions

The following adverse reactions have been reported during post-approval use of budesonide.

Immune System Disorders: Anaphylactic reaction (very rare). Type I hypersensitivity reaction, Type IV hypersensitivity reaction (immediate and delayed hypersensitivity reactions, including Erythema, Urticaria, Rash, Dermatitis, Angioedema, and Pruritus) (uncommon)

Respiratory, Thoracic and Mediastinal Disorders: Hemorrhagic secretion and Epistaxis, Nasal discomfort (nasal irritation) (common), Nasal septum perforation (very rare)

General Disorders and Administrative Site Conditions: Mucosal ulceration (ulcerations of the mucous membrane) (very rare)

8. DRUG INTERACTIONS

8.1 Overview

To date budesonide has not been observed to interact with other drugs used for the treatment of rhinitis.

8.2 Drug-Drug Interactions

Cimetidine

The kinetics of budesonide were investigated in a study in healthy subjects without and with cimetidine, 1000 mg daily. After a 4 mg oral dose the values for C_{max} (nmol/L) and systemic availability (%) of budesonide without and with cimetidine (3.3 vs 5.1 nmol/L and 10 vs 12%, respectively) indicated a slight inhibitory effect on hepatic metabolism of budesonide, caused by cimetidine. This should be of low clinical importance.

Other medicinal products and/or CYP3A4 inhibitors

The metabolism of budesonide is primarily mediated by CYP3A4, a subfamily of cytochrome P450. CYP3A4 inhibitors like ritonavir, atazanavir, clarithromycin, indinavir, nefazodone, nelfinavir, saquinavir, telithromycin, cobicistat-containing products and azole antifungals (e.g. ketoconazole and itraconazole) increase the systemic exposure to budesonide. Therefore, concomitant use of budesonide and these medicinal products should be avoided unless the potential benefit outweighs the risk of systemic corticosteroids side-effects.

Omeprazole

At recommended doses, omeprazole has no effect on the pharmacokinetics of oral budesonide.

Table 4 – Established or Potential Drug-Drug Interactions

Proper Name	Source of Evidence	Effect	Clinical comment
Cimetidine	CT	Slight inhibitory effect on hepatic metabolism of budesonide	Effect should be of little clinical importance
Inhibitors of CYP3A4	T	Increased systemic exposure to budesonide	Concomitant use of budesonide and strong CYP3A4 inhibitors (e.g., ketoconazole, itraconazole, clarithromycin, indinavir, nefazodone, atazanavir, nelfinavir, saquinavir, ritonavir, cobicistat-containing products) should be avoided unless the potential benefit

			to the patient outweighs the risk of systemic corticosteroids side-effects.

Legend: CT = Clinical Trial; T = Theoretical

9 ACTION AND CLINICAL PHARMACOLOGY

9.1 Mechanism of Action

Budesonide is a potent synthetic glucocorticosteroid with strong topical and weak systemic effects.

Budesonide has a high topical anti-inflammatory potency and it is rapidly biotransformed in the liver. This favourable separation between topical anti-inflammatory activity and systemic effect is due to strong glucocorticosteroid receptor affinity and an effective first-pass metabolism with a short half-life. The mechanism of action of intranasally administered budesonide has not yet been completely defined.

9.2 Pharmacodynamics

Studies with animals have shown that budesonide has a 2-10 times better ratio between topical anti-inflammatory and systemic glucocorticosteroid effects than that obtained with beclomethasone dipropionate or triamcinolone acetonide. In the blanching test for topical anti-inflammatory activity in humans, budesonide was about twice as potent as beclomethasone dipropionate. Beclomethasone dipropionate was, however, more active than budesonide with regard to systemic activity as measured by depression of morning plasma cortisol. The favourable topical anti-inflammatory activity to systemic effect ratio demonstrated by budesonide is due to its high glucocorticosteroid receptor affinity and high first pass metabolism with a short half-life.

Budesonide has been shown to counteract the mainly "IgE" mediated lung anaphylaxis in guinea pigs. No significant bronchorelaxing activity, either *in vitro* or *in vivo,* could be demonstrated. Budesonide did not potentiate beta-mediated bronchorelaxation and did not affect theophylline-induced relaxation or respiratory airway smooth muscle in guinea pigs.

Budesonide exhibits typical glucocorticosteroid effects in that subcutaneous administration to adrenalectomised rats induced glycogen deposition in the liver, increased urinary volume and only slightly affected sodium excretion. Whole body autoradiography in mice has shown budesonide and its metabolites to have a similar distribution pattern to other glucocorticosteroids with a high distribution to endocrine organs.

9.3 Pharmacokinetics

Absorption:

The systemic bioavailability of oral budesonide in humans is low (about 10%). With reference to the metered dose, the systemic availability of budesonide from MYLAN-BUDESONIDE AQ is 33%. After application of budesonide in solution directly on the nasal mucosa, all of the dose is systemically available, indicating that budesonide does not undergo local metabolism in the nose. The maximal plasma concentration after administration of 400 mcg budesonide from MYLAN-BUDESONIDE AQ is 1.0 nmol/L and is reached within 0.7 hours.

Distribution:
The distribution volume (V_d) of budesonide is 301.3 ± 41.7 L, indicating the high issue affinity of the drug. Plasma protein binding is estimated at 88.3 ± 1.5%.

Metabolism:
In vitro studies with human liver have shown that budesonide is rapidly metabolised to more polar compounds than the parent drug. Two major metabolites have been isolated and identified as 6β-hydroxybudesonide and 16α-hydroxyprednisolone. The metabolism of budesonide in the liver is primarily mediated by cytochrome P450 3A (CYP3A4). The glucocorticosteroid activity of these two metabolites was at least 100-fold lower than the parent compound as shown in the rat ear edema test. No qualitative differences between the *in vitro* and *in vivo* metabolic patterns could be detected. Negligible biotransformation was observed in human lung and serum preparations.

Elimination:
After nasal administration of tritiated budesonide in human volunteers, 56.1% ± 2.6% of the discharged dose was recovered in the urine (0 - 96 hours) while during the same period, 33.4 ± 2.0% of the dose could be recovered in the feces. In those subjects who took the compound intravenously, 56.7 ± 1.2% was recovered in the urine, 34.0 ± 3.0% in the feces.

10 STORAGE, STABILITY AND DISPOSAL

Stability and Storage Recommendations

MYLAN-BUDESONIDE AQ should be stored at room temperature (15°C - 30°C).

PART II: SCIENTIFIC INFORMATION

11. PHARMACEUTICAL INFORMATION

Drug Substance

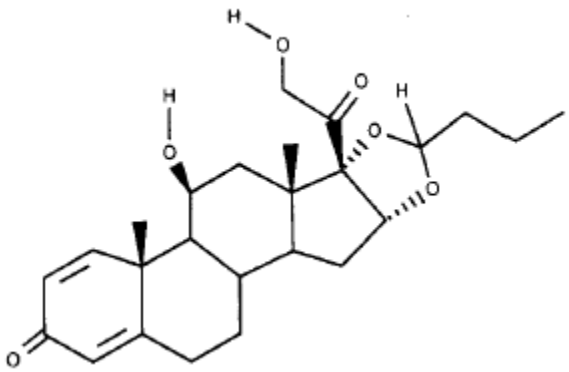
Generic Name: Budesonide

Chemical Name: Budesonide is a mixture of two isomers:

1. Pregna-1,4-diene-3,20-dione,16,17-butylidenebis(oxy)-11,21-dihydroxy, [11β,16α (R)] and

2. Pregna-1,4-diene-3,20-dione,16,17-butylidenebis(oxy)-11,21-dihydroxy,[11β,16α (S)].

Chemical Structure:



Molecular Formula: $C_{25}H_{34}O_6$

Molecular Weight: 430.5 g/mol

Physiochemical Properties: Budesonide is a non-halogenated glucocorticosteroid and consists of a 1:1 mixture of two epimers, 22R and 22S. It is a white to off-white crystalline powder and is freely soluble in chloroform, sparingly soluble in ethanol, practically

insoluble in water and in heptane. Budesonide melts at 224 °C to 231.5°C, with decomposition.

12. NON-CLINICAL TOXICOLOGY

Acute Toxicity

Species	Sex	Route	LD_{50} (mg/kg) After 3 Weeks
mouse	Male	s.c.	35 ± 18
mouse	male	p.o.	> 800
mouse	female	p.o.	>800
rat	male	s.c	15.1 ± 4.4
rat	female	s.c.	20.3 ± 7.1
rat	male	p.o.	≈ 400

Surviving animals exhibited a marked decrease in body weight gain.

Toxicity After Repeated Administration of Budesonide to Rats, Rabbits and Dogs

Animal		Number and Sex Per Group	No. of Dose Groups	Daily Dose Levels		Route of Administration	Duration	Toxic Effects
Species	Strain			mg/kg	mg/animal			
rat	Sprague-Dawley	6 males 6 females	4	0.05 0.5 5.0 50.0		p.o.	1 month	Atrophy of adrenal gland and lymphoid system. Gastric ulceration.
rat	Wistar	10 males 10 females	3	0.02 0.10 0.2-0.5		inhalation	3 months	Hair loss, dose related reduction in lymphocytes, leukocytes, increase in neutrophils. In high dose group, reduced adrenal, thymic, splenic and hepatic weights. No pulmonary impairment observed.
rat	Wistar	40 males 40 females	3	0.005 0.01 0.05		inhalation	12 months	As above.
rabbit	New Zealand White	3 males 3 females	2		0.025 0.1	s.c	1 month	High dose caused slight liver mass increase, slight decrease in adrenal mass, thymal regression.
dog	Beagle	1 male 1 female	3	0.01 0.1 1.0		p.o.	1 month	High dose - typical steroid effects - adrenal, lymphoid system atrophy, increased fat in myocardium glycogen in liver.
dog	Beagle	2 males 2 females	3	0.02 0.06 0.2		inhalation	6 weeks	High dose - induced thymal atrophy, adrenal atrophy. No changes in respiratory system observed.

Toxicity After Repeated Administration of Budesonide to Rats, Rabbits and Dogs

dog	Beagle	5 males 5 females	3		0.20 0.60 2.00	inhalation	6 months	High dose - decreased plasma cortisol, cortical atrophy of the adrenal gland, thymal regression. Slight visceral obesity.
dog	Beagle	5 males 5 females	3		0.20 0.60 2.00	inhalation	12 months	High dose - obesity, alopecia, females showed no evidence of estrous cycle. Systemic steroid effects - lymphoid and adrenal atrophy.

All effects observed were consistent with those expected during prolonged corticosteroid exposure.

Teratology and Reproduction Studies

Effects on Pregnancy

Rat

Daily doses of 20, 100, and 500 mcg/kg body mass were administered subcutaneously to pregnant rats during days 6-15 of gestation. In the high dose group, all of the rats showed a deteriorated general condition including piloerection, drowsiness, decreased food consumption and decreased body mass gain. Fetal loss was increased and pup masses decreased in comparison to the control group. The frequency of fetal abnormalities was also increased. Doses in excess of 100 mcg/kg must be considered teratogenic in the rat.

Daily doses of 0.01, 0.05 and 0.1- 0.25 mg/kg were administered by inhalation to pregnant rats during days 6-15 of gestation. At the highest dose a slight significant reduction in fetal weight gain was observed, but there was no evidence of any effect on fetal development attributable to budesonide at any dose level.

Rabbit

Daily doses of 5, 25, and 125 mcg/kg body mass were administered subcutaneously during days 6-18 of gestation. In the low and medium dose groups, food consumption and body mass gain were decreased during the fourth gestational week.

Some does also showed signs of diarrhea and vaginal bleeding. In the high dose group, all does aborted at the end of the gestation period. In the medium dose group, a marked increase in the frequency of abnormalities, mainly skeletal defects, was observed. Most commonly, defects were skull and vertebral abnormalities.

Effects on Fertility and General Reproductive Performance

Rat

To evaluate the effect of budesonide on fertility and general reproductive performance, daily doses of 0.01, 0.05, and 0.19 μmol/kg were given subcutaneously to males for 9 weeks prior to and throughout mating. Females received the same doses for two weeks before, throughout gestation and up to 21 days postpartum. The offspring of the high dose group showed a decrease of peri- and post-natal viability. Dams showed a decrease in body mass gain.

Mutagenicity Studies

Budesonide showed no mutagenic activity in the Ames Salmonella/microsome plate test or in the mouse micronucleus test.

Carcinogenicity
The carcinogenic potential of budesonide was evaluated in long term mouse and rat studies.

Chronic Drinking Water Study in Mice

Budesonide was administered in the drinking water for 91 weeks to three groups of CD® - 1 mice at dose levels of 10, 50 and 200 mcg/kg/day.

A statistically significant dose-related decrease in survival was noted for the males only. All other evaluation criteria were comparable in all groups. Upon microscopic examination, a variety of spontaneous lesions was observed which were not related to treatment. No carcinogenic effect was present.

Chronic Drinking Water Study (104 Weeks) with Budesonide in Rats

Three rat carcinogenicity studies have been performed. In the first study, budesonide was administered for 104 weeks in doses of 10, 25 and 50 mcg/kg/day.

A small but statistically significant increase in gliomas was noted in male animals from the high dose group. These results were considered equivocal since the S-D rat is very variable with regard to spontaneous glioma incidence.

To elucidate these results, two further 104 week carcinogenicity studies with budesonide 50 mcg/kg/day were performed, one using male S-D rats, and one using male Fischer rats (which have a lower and less variable incidence of gliomas). Prednisolone and triamcinolone acetonide were used as reference glucocorticosteroids in both studies.

The results from these new carcinogenicity studies in male rats did not demonstrate an increased glioma incidence in budesonide treated animals, as compared to concurrent controls or reference glucocorticosteroid treated groups.

13. SUPPORTING PRODUCT MONOGRAPHS

McNeil Consumer Healthcare, Rhinocort® Aqua (Budesonide Aqueous Nasal Spray) 64 mcg per metered dose Product Monograph, dated of revision: August 12, 2019, submission control number: 226546.

READ THIS FOR SAFE AND EFFECTIVE USE OF YOUR MEDICINE
PATIENT MEDICATION INFORMATION

PrMYLAN-BUDESONIDE AQ
Budesonide Aqueous Nasal Spray

Read this carefully before you start taking MYLAN-BUDESONIDE AQ and each time you get a refill. This leaflet is a summary and will not tell you everything about this drug. Talk to your healthcare professional about your medical condition and treatment and ask if there is any new information about MYLAN-BUDESONIDE AQ.

What is MYLAN-BUDESONIDE AQ used for?
- seasonal allergic rhinitis (hay fever) and perennial (year-round) rhinitis in patients 6 years and older
- nasal polyps and to prevent new nasal polyps from appearing after surgery (polypectomy) in patients 12 years and older.

How does MYLAN-BUDESONIDE AQ work?
MYLAN-BUDESONIDE AQ reduces and prevents inflammation in the lining of the nose (rhinitis).

What are the ingredients in MYLAN-BUDESONIDE AQ?
Medicinal ingredient: Budesonide

Non-medicinal ingredients: Dextrose, Disodium Edetate, Hydrochloric Acid, Microcrystalline Cellulose, Carboxymethylcellulose sodium, Potassium Sorbate, Tween 80 and Water.

MYLAN-BUDESONIDE AQ comes in the following dosage forms:
MYLAN-BUDESONIDE AQ comes as a nasal spray: 100 mcg of budesonide per spray. The bottle will deliver 165 sprays.

Do not use MYLAN-BUDESONIDE AQ if you:
- are allergic to budesonide or any of the other ingredients;
- have an untreated fungal (yeast), bacterial or viral infection;
- have or have had tuberculosis;
- are under the age of 6 years.

To help avoid side effects and ensure proper use, talk to your healthcare professional before you take MYLAN-BUDESONIDE AQ Talk about any health conditions or problems you may have, including if you:
- have or have had any other recent infection. MYLAN-BUDESONIDE AQ may hide some symptoms of infection or may cause the symptoms of infection to worsen. You may be more likely to get an infection while taking MYLAN-BUDESONIDE AQ

- have asthma;
- have thyroid problems;
- have open wounds after recent nasal surgery or trauma
- have or had liver problems;
- are on drugs that suppress the immune system;
- have ever been diagnosed with glaucoma, cataracts or have an eye infection, or if you have diabetes;
- are taking, or have previously taken steroids either as an injection or by mouth within the past several months;
- are pregnant or planning to become pregnant. MYLAN-BUDESONIDE AQ should only be used during pregnancy if the potential benefits to the mother outweigh the risk to the unborn baby.
- are breastfeeding. Budesonide will transfer to the mother's breast milk. It should only be used if the benefit to the mother outweighs the potential risk to the baby.
- have a rare blood disorder called hypoprothrombinemia.

Other warnings you should know about:
Local corticosteroids such as MYLAN-BUDESONIDE AQ may cause:
- slower growth in children. Continuous long-term use in children is not recommended as the effects are not fully known. Talk to your child's physician if your child needs to use the spray for longer than two months a year. Your child's doctor should regularly monitor their growth while they are taking MYLAN-BUDESONIDE AQ.
- symptoms of Cushing's syndrome, such as thinning fragile skin that bruises easily, rapid weight gain around the body and face, excess sweating, and muscle and bone weakness.
- development of unintentional and purposeless motions and restlessness, sleep disorders, anxiety, depression and aggression.

Changes in vision
Changes in vision can occur with the use of corticosteroids. The changes can include:
- Cataracts: clouding of the lens in the eye, blurry vision, eye pain;
- Glaucoma: an increased pressure in your eyes, eye pain. Untreated, it may lead to permanent vision loss;
- Central serous chorioretinopathy (CSCR): blurry vision or other changes in your vision.

If you notice any changes in your vision while taking MYLAN-BUDESONIDE AQ, tell your doctor right away. Your doctor may monitor your eyes during your treatment.

Exposure to measles or chicken pox:
You should avoid coming into contact with people who have measles or chicken pox while taking MYLAN-BUDESONIDE AQ. If you are exposed, tell your doctor right away.

Transfer to MYLAN-BUDESONIDE AQ from an oral corticosteroid

If you have been prescribed MYLAN-BUDESONIDE AQ and are taking oral steroid medication, your doctor may gradually reduce the dose of your tablets. This may happen over a period of weeks or months.

You should contact your doctor if you get symptoms such as:
- headache
- tiredness
- muscle and joint pain
- nausea or vomiting
- depression
- rash
- runny nose
- coughing, especially at night, during exercise or when laughing
- difficulty breathing
- chest tightness
- shortness of breath
- wheezing.

Tell your doctor if:
- your symptoms have not improved after 2 weeks of taking MYLAN-BUDESONIDE AQ
- your nose becomes irritated or you have severe or frequent nose bleeds
- you develop signs or symptoms of an infection such as persistent fever
- you have a yellow or green discharge from your nose

If symptoms persist or worsen, or if new symptoms occur, stop use and consult a doctor.

Tell your healthcare professional about all the medicines you take, including any drugs, vitamins, minerals, natural supplements or alternative medicines.

The following drugs may interact with MYLAN-BUDESONIDE AQ:
- ritonavir, atazanavir, indinavir, nelfinavir, saquinavir and cobicistat-containing products used to treat HIV or AIDS
- ketoconazole, itraconazole used to treat fungal infections
- clarithromycin, telithromycin used to treat bacterial infections
- nefazodone used to treat depression

How to take MYLAN-BUDESONIDE AQ

- MYLAN-BUDESONIDE AQ is for use in the nose only. **Do not** use it in your eyes or mouth.
- It may take 2-3 days (and up to 2 weeks) to work. Take it each day without missing a dose to get the best results.
- It works best if it is started before allergy season begins.

- It does not relieve allergy symptoms in the eyes. Tell your doctor if your eyes bother you and they can give you additional medicine to help.
- If your nose is blocked, you can use decongestant nose drops during the first 2-3 days of the treatment.
- Stop taking MYLAN-BUDESONIDE AQ if it does not relieve your symptoms after 3 weeks of regular treatment.

Take MYLAN-BUDESONIDE AQ exactly as recommended by your doctor. **Follow your doctor's directions carefully. They may differ from the information in this leaflet.**

Do not stop taking MYLAN-BUDESONIDE AQ unless your doctor told you to, even if you feel better. Do not stop treatment with MYLAN-BUDESONIDE AQ abruptly, it should be tapered off gradually.

Always supervise children when they are using MYLAN-BUDESONIDE AQ. This will help them get the correct dose.

Usual dose:

Depending on how MYLAN-BUDESONIDE AQ works for you, your doctor may change your dose.

Rhinitis in patients 12 years and older:

MYLAN-BUDESONIDE AQ can be taken once a day or twice a day.

- **Usual once a day starting dose***:* 2 sprays into each nostril once a day (in the morning)
- **Usual twice a day starting dose:** 1 spray into each nostril twice a day (in the morning and evening)
- **Maintenance dose:** Use the lowest effective dose necessary to control symptoms. The usual maintenance dose is 1 spray into each nostril in the morning only.

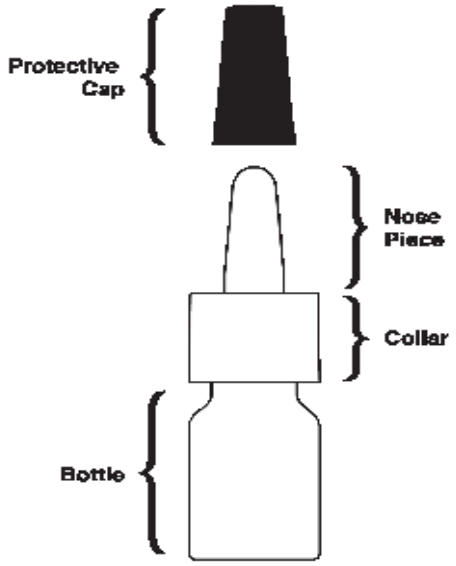
Rhinitis in patients 6 to 11 years of age:

- **Usual dose**: 1 spray into each nostril once a day (in the morning)
- If symptoms do not improve, 2 sprays per nostril once a day (in the morning) can be used.
- **Maintenance dose:** Once allergy symptoms improve, the maintenance dose is 1 spray in each nostril once daily in the morning.

Nasal Polyps in patients 12 years and older:
Usual Dose: 1 spray into each nostril twice a day (in the morning and evening).

How to use your MYLAN-BUDESONIDE AQ
Before you start using MYLAN-BUDESONIDE AQ for the first time, it is important that you read the instructions below and follow them carefully.

Parts of the Spray Bottle:



A. Before using MYLAN-BUDESONIDE AQ for the first time:

You must prepare MYLAN-BUDESONIDE AQ before you use it. Follow the steps below:

1 Turn the bottle upside-down 3 to 4 times. Remove the protective cap from the nose piece.

2 Load the pump by pressing downwards on the collar. Use your index and middle fingers while supporting the base of the bottle with your thumb (Figure 1). Press down 5 to 10 times away from the face until a fine mist spray appears. Avoid spraying the mist in your eyes.

Figure 1

The spray is now ready for use.

B. How to take a dose:

Follow these instructions for daily use of MYLAN-BUDESONIDE AQ:

1 Turn the bottle upside-down 3 to 4 times. Remove the protective cap from the nose piece.

2 If you did not use your spray yesterday, make sure you prepare the pump by pressing down once only (Figure 1). Avoid spraying the mist in your eyes.

3 Gently blow your nose. Hold the bottle as shown. Tilt your head forward slightly. Close one nostril with a finger and gently insert the tip of the nose piece into the other nostril (Figure 2).

Figure 2

4 For each spray your doctor has instructed you to take, press firmly downwards once on the collar. Breathe gently inwards through the nostril, then breathe out through the mouth.

5 Repeat the procedure for the other nostril.

6 Replace the protective cap on the nose piece. Keep the bottle in an upright position.

C. How to clean MYLAN-BUDESONIDE AQ

Clean the nose piece and protective cap regularly. To clean the nose piece, remove the protective cap, press upwards on the collar and the nose piece will come off. Wash the nose piece and protective cap under lukewarm water. Air dry and replace the nose piece and the protective cap back on the bottle and reload as in Step #2. **Do not try to clean the nasal applicator by using a pin or sharp object.**

Overdose:

If you think you have taken too much MYLAN-BUDESONIDE AQ, contact your healthcare professional, hospital emergency department or regional poison control centre immediately, even if there are no symptoms.

Missed Dose:

- If you miss a dose take it as soon as possible. Then go back to your regular schedule.
- If it is almost time to take your next dose, skip the missed dose and take the next dose at the usual time.
- **Do NOT take a double dose of MYLAN-BUDESONIDE AQ to make up for a missed dose.** If you are still unsure, check with your doctor or pharmacist to see what you should do.

What are possible side effects from using MYLAN-BUDESONIDE AQ

These are not all the possible side effects you may feel when taking MYLAN-BUDESONIDE AQ. If you experience any side effects not listed here, contact your healthcare professional.

Common side effects are:
- nose and throat irritation,
- nose bleeding and crusting
- stomach pain
- ear, nose and/or throat infection
- rash

Other side effects include:
- itchy and sore throat
- cough
- fatigue
- nausea/dizziness
- headache

Uncommon side effects that may occur when also taking an oral steroid:
- asthma
- skin rash
- itching or swelling in the face
- Cushing's syndrome (hypercorticism)
- small holes or ulcers in the skin inside the nose

SERIOUS SIDE EFFECTS AND WHAT TO DO ABOUT THEM				
Symptom / effect		Talk to your healthcare professional		Stop taking drug and get immediate medical help
		Only if severe	In all cases	
Uncommon	**Cushing's Syndrome:** (hypercorticism) Rapid weight gain especially around the body and face; round "moon" face, Excess sweating; thinning of the skin with easy bruising and dryness; muscle and bone weakness		X	
Very rare	Small holes or ulcers in the skin inside the nose		X	
	Allergic reactions, including Anaphylactic reactions: such as swelling of the face, lips, tongue, and/or throat (which may cause difficulty in breathing or swallowing), hives, rash and itching			X
Unknown	**Cataracts:** glare, reduced vision		X	
	Glaucoma: increased pressure in your eyes, eye pain			X
	Nasal perforation: constant whistling sound when you breathe from your nose			X
	Vision blurred			X

If you have a troublesome symptom or side effect that is not listed here or becomes bad enough to interfere with your daily activities, talk to your healthcare professional.

Reporting Side Effects

You can report any suspected side effects associated with the use of health products to Health Canada by:

- Visiting the Web page on Adverse Reaction Reporting (https://www.canada.ca/en/health-canada/services/drugs-health-products/medeffect-canada/adverse-reaction-reporting.html) for information on how to report online, by mail or by fax; or
- Calling toll-free at 1-866-234-2345.

NOTE: Contact your health professional if you need information about how to manage your side effects. The Canada Vigilance Program does not provide medical advice.

Storage:
Keep MYLAN-BUDESONIDE AQ out of the reach and sight of children.

Store the bottle at room temperature (15°C - 30°C). Always replace the protective cap after using MYLAN-BUDESONIDE AQ.

Do not keep or use MYLAN-BUDESONIDE AQ after the expiry date indicated on the label.

If you want more information about Mylan-Budesonide AQ:

- Talk to your healthcare professional
- Find the full product monograph that is prepared for healthcare professionals and includes this Patient Medication Information by visiting the Health Canada website (https://health-products.canada.ca/dpd-bdpp/index-eng.jsp); or by calling 1-844-596-9526

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