PRODUCT INFORMATION- BUDAMAX AQUEOUS NASAL SPRAY (BUDESONIDE), SUSPENSION

1 NAME OF THE MEDICINE

Budesonide

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

BUDAMAX contains 32 µg (not available in Australia) or 64 µg budesonide per actuation.

For the full list of excipients, see Section 6.1 List of excipients.

3 PHARMACEUTICAL FORM

Spray suspension.

White to off-white, viscous thixotropic suspension.

4 CLINICAL PARTICULARS

4.1 THERAPEUTIC INDICATIONS

Rhinitis

Prophylaxis and treatment of seasonal and perennial allergic rhinitis

Nasal polyps

Treatment of nasal polyps.

4.2 DOSE AND METHOD OF ADMINISTRATION

There is no evidence that efficacy improves when the recommended dose is exceeded.

For the treatment of seasonal allergic rhinitis in adults and children 6 years and older and perennial allergic rhinitis (adults).

Initially

Total daily dose, 256 micrograms given as either a single daily application of 128 micrograms into each nostril in the morning, or divided into two applications of 64 micrograms into each nostril, morning and evening.

Maintenance – individualisation of dosage

When a satisfactory therapeutic response has been achieved, the maintenance dose should be titrated to the minimum effective dose. This may be a total daily dose of 128 micrograms given as 64 micrograms into each nostril in the morning, however clinical trials suggest that a maintenance dose of 32 micrograms in each nostril in the morning may be sufficient in some patients.

Continuous long-term use in children is not recommended due to the possibility of growth suppression. Whilst no long-term studies are available for intranasal budesonide, long-term studies in a clinical practice environment suggest that children treated with orally inhaled budesonide on average achieve their adult target height . However, in a long-term double-blind study, in which the budesonide dose was generally not titrated to the lowest effective dose, children treated with inhaled budesonide became on average 1.2 cm shorter as adults than those randomised to placebo. (See Section 4.4 Special warnings and precautions for use- Paediatric use)

Patients should be informed that full response may not occur until after 2-3 days of treatment (in rare cases not until after 2 weeks). Ideally, in seasonal allergic rhinitis treatment should start before exposure to the allergen.

Treatment of nasal polyps – Adults (18 years and older)

Total daily dose, 256 µg given as a divided daily application of 64 µg into each nostril, morning and evening.

Patient instructions

Patients should be instructed in the correct use of BUDAMAX. An instruction leaflet is included in each pack of BUDAMAX. Patients should also be advised to clear secretions from nasal passages prior to use and not to exceed the recommended dose.

4.3 CONTRAINDICATIONS

Hypersensitivity to any component of the product.

Hypersensitivity to other corticosteroids.

Severe nasal infections, especially candidiasis.

Persons with haemorrhagic diatheses or with a history of recurrent nasal bleeding.

4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE

If symptoms persist, worsen or if new symptoms occur, patients should stop use and consult a physician

Clinical response

The full effect of BUDAMAX in allergic rhinitis is not achieved until after 2 to 3 days of treatment (in rare cases not until after 2 weeks).

Concomitant treatment

Concomitant treatment may sometimes be necessary to counteract potential eye symptoms caused by the allergy.

Concomitant corticosteroid therapy

If BUDAMAX is prescribed for patients already using corticosteroids, care should be taken to ensure that the daily dosage of BUDAMAX is included when determining total daily corticosteroid dose.

Consult a physician before use if you are using a steroid medicine for conditions such as asthma, allergies or skin rash.

Continuous, long term use

In continuous long-term treatment, care should be exercised to avoid the development of nasal mucosal atrophy. The nasal mucosa should be inspected at least twice per year.

Severe nasal obstruction/congestion

In some patients with severe nasal obstruction and congestion, concomitant treatment with local decongestants should be considered for 2-3 days only. The decongestant should be administered a few minutes before budesonide. Nasal polypectomy may be indicated initially for patients with nasal obstruction due to nasal polyposis.

Tuberculosis

Whenever corticosteroid administration is required in patients with quiescent or active tuberculosis, the therapeutic advantages should be weighed against possible undesirable effects.

Consult a physician before use if patient has been exposed to someone who has tuberculosis, chicken pox or measles.

Infection

If infection of the respiratory tract, nasal passages or paranasal sinuses is present or occurs during administration of BUDAMAX, adequate antibacterial therapy should be promptly instituted (see Section 4.3 Contraindications).

Consult a physician if you develop signs or symptoms of an infection such as a persistent fever.

Wound healing

Because of the inhibitory effect of corticosteroids on wound healing, patients who have experienced recent nasal septal ulcers, nasal surgery or a nose injury that has not healed should not use a nasal corticosteroid until healing has occurred.

Adrenocortical function

Topical corticosteroids may be absorbed in amounts that can have systemic effects. Use of higher than recommended doses may suppress HPA function. However, at recommended doses, BUDAMAX does not cause any clinically important changes in basal cortisol levels. Similar effects have been noted with inhaled budesonide, whilst still retaining the physiological circadian rhythms of plasma cortisol. This indicates that the HPA axis suppression represents a physiological adaption in response to budesonide, not necessarily adrenal insufficiency. This is further supported by inhaled and intranasal budesonide studies, which found that, at

recommended doses, there was no clinically relevant effect on the response to stimulation with ACTH (predictor for clinically manifest adrenal insufficiency).

Clinically important disturbances of the HPA axis and/or adrenal insufficiency induced by stress may be related to budesonide in specific patient populations, particularly patients administering concomitant medication metabolised by CYP3A4 (see Section 4.5 Interactions with other medicines and other forms of interactions). Monitoring for signs of adrenal dysfunction is advisable in this patient group.

Visual disturbance

Visual disturbance may be reported with systemic and topical corticosteroid use. If a patient presents with symptoms such as blurred vision or other visual disturbances, the patient should be considered for referral to an ophthalmologist for evaluation of possible causes which may include cataract, glaucoma or rare diseases such as central serous chorioretinopathy (CSCR) which have been reported after use of systemic and topical corticosteroids.

Stop use and consult a physician if you have any change in vision. Consult a physician before use if you have ever been diagnosed with glaucoma, cataracts or have an eye infection or if you have diabetes.

Use in hepatic impairment

There are no intranasal budesonide pharmacokinetic data available in hepatic impaired patients. With oral administration, compromised liver function may decrease the rate of glucocorticoid elimination. Hepatic impairment increased the systemic availability of budesonide 2-fold after oral ingestion in adults with cirrhosis. However, after intravenous administration, the pharmacokinetics of budesonide were similar in patients with cirrhosis and healthy adults.

Use in the elderly

No data available

Paediatric use

Controlled clinical trials have shown that intranasal corticosteroids may cause a reduction in growth velocity in children. Whilst no long-term studies are available for intranasal budesonide, long-term studies in a clinical practice environment suggest that children treated with orally inhaled budesonide on average achieve their adult target height. However, in a long-term double-blind study, in which the budesonide dose was generally not titrated to the lowest effective dose, children treated with inhaled budesonide became on average 1.2 cm shorter as adults than those randomised to placebo.

Rare individuals may be exceptionally sensitive to intranasal corticosteroids. Height measurements (eg via stadiometry) should be performed to identify patients with increased sensitivity. The potential growth effects of prolonged treatment should be weighed against the clinical benefits and the availability of safe and effective non-corticosteroid alternatives. To minimise the systemic effects of intranasal corticosteroids, each patient should be titrated to his/her lowest effective dose (see Section 4.2 Dose and method of administration).

The continuous long term use of budesonide nasal spray in children is not recommended due to the possibility of reduced growth velocity. Studies of children with seasonal allergic rhinitis did not extend beyond four weeks of treatment.

Safety and effectiveness of BUDAMAX in children below 6 years of age has not been established.

This product may slow the growth rate in some children when used in combination with other steroids.

Effects on laboratory tests

No data available

4.5 INTERACTIONS WITH OTHER MEDICINES AND OTHER FORMS OF INTERACTIONS

The metabolism of budesonide is primarily mediated by CYP3A, a subfamily of cytochrome P450. After oral administration of ketoconazole, a potent inhibitor of cytochrome P450 3A, the mean plasma concentration of budesonide increased by more than seven fold. Concomitant administration of other known inhibitors of this enzyme, (eg itraconazole, clarithromycin, erythromycin, ritonavir, atazanavir, indinavir, nefazodone, nelfinavir, saquinavir, telithromycin, itaconazole) may inhibit the metabolism of, and increase the, the concentration of budesonide in the plasma leading to increased risk of systemic side-effects such as Cushing's syndrome and adrenal suppression. If used, close monitoring of patients is advised for any systemic effects. Otherwise, the combination should be avoided unless the benefit outweighs the risk.

Cimetidine, primarily an inhibitor of cytochrome P450 1A2, caused a slight decrease in budesonide clearance and corresponding increase in its oral bioavailability.

4.6 FERTILITY, PREGNANCY AND LACTATION

Effects on fertility

There are insufficient data available to determine whether intranasal administration of budesonide has the potential to impair fertility. This product should not be used during pregnancy or lactation unless the potential benefit of treatment to the mother outweighs the possible risks to the developing fetus or breastfeeding infant. Ask a physician before use if you are pregnant or breastfeeding

Use in pregnancy – Pregnancy Category A

It is not known if budesonide can cross the placenta but due to its relatively low molecular weight, placental transfer may be possible. When given at therapeutic doses, systemic exposure after intranasal administration is low. As with other drugs the administration of budesonide during pregnancy requires that the benefits for the mother be weighed against the risks for the foetus.

Inhaled glucocorticosteroids such as budesonide, should be considered because of the lower systemic effects, compared to oral glucocorticosteroids.

Ask a physician before use if you are pregnant.

Use in lactation

Budesonide is excreted in breast milk. However, due to the relatively low doses used via the intranasal route the amount of drug present in the breast milk, if any, is likely to be low. There is a linear relationship between budesonide concentration in plasma and breast milk, where the concentration of budesonide in breast milk is less than plasma concentration. Breastfeeding can be considered if the potential benefit outweighs any potential risks.

Ask a physician before use if you are breastfeeding

4.7 EFFECTS ON ABILITY TO DRIVE AND USE MACHINES

The effects of this medicine on a person's ability to drive and use machines were not assessed as part of its registration. However, adverse effects of Budamax include blurred vision which could affect the ability to drive or use machines (see Section 4.8 Adverse Effect (Undesirable Effects).

4.8 ADVERSE EFFECTS (UNDESIRABLE EFFECTS)

Adverse local reactions following BUDAMAX use are mild and usually transient. Systemic corticosteroid side-effects have not been reported during clinical studies of BUDAMAX in adults (refer to Section 4.4 Special warnings and precautions for use – Paediatric use for details relating to children). Growth suppression has been reported in association with administration of intranasal corticosteroids. Whilst no long-term studies are available for intranasal budesonide, long-term studies in a clinical practice environment suggest that children treated with orally inhaled budesonide on average achieve their adult target height. However, in a long-term double-blind study, in which the budesonide dose was generally not titrated to the lowest effective dose, children treated with inhaled budesonide became on average 1.2 cm shorter as adults than those randomised to placebo. See Section 4.4 Special warnings and precautions for use – Paediatric use.

Adverse events reported during studies with BUDAMAX

Common (more than 1%)	Nose and throat	Nasal irritation, itching of throat and larynx, sore throat, dry mucous membranes, dry mouth, sneezing after spraying, increased sputum, haemorrhagic secretion, epistaxis (nose bleeding), nasal crust, sinusitis
	Respiratory	Cough, dyspnoea, asthma, epistaxis, oropharyngeal pain, upper respiratory tract infection, rhinitis,

	Central Nervous System	Headache, dizziness, tiredness, pyrexia
	Skin and appendages	Rash
	Gastrointestinal	Abdominal discomfort
	Injury, poisoning and procedural complications	Head injury
Uncommon (less than 1%)	Nose and throat	Strong smell of spray, bad taste, earache
	Gastrointestinal	Loss of appetite, stomach disorder, nausea
	Skin and appendages	Skin itching
	Central Nervous System	Tremor, sedation
	Infection	Urinary tract infection
	Immune system	Immediate and delayed hypersensitivity reactions including urticaria, rash, dermatitis, angioedema and pruritus.
	Injury, poisoning and procedural complications	Injury
Rare (less than or equal to 0.2%)		Ear itching, joint aches, sexual dysfunction.
Very rare cases of ulcerations of the mucous membrane, nasal septal perforations and anaphylactic reactions have been reported following the use of intranasal corticosteroids.		

Laboratory variables

All changes in haematology, biochemistry and urinalysis were within the normal range and were not considered clinically significant.

Post Marketing Data

Adverse drug reactions (ADRs) identified during Post-marketing experience with budesonide are included in the following table. The frequencies are provided according to the following convention:

Very common	≥1/10
Common	≥1/100 and < 1/10
Uncommon	≥1/1,000 and <1/100
Rare	≥1/10,000 and <1/1,000
Very rare	<1/10,000

Not known (cannot be estimated from the available data)

Adverse Drug Reactions Identified During Post-Marketing Experience with Budesonide by Frequency Category Estimated from Clinical Trials or Epidemiology Studies

SOC Frequency Category	Adverse Event Preferred Term
Immune System Disorders	
Not known	Anaphylactic reaction
Not known	Hypersensitivity
Respiratory, Thoracic and Mediastinal Disorders	
Not known	Epistaxis
Not known	Nasal discomfort (nasal irritation)
Not known	Nasal septum perforation
Skin and subcutaneous tissue disorders	
Not known	Angioedema[a]
Not known	Dermatitis[a]
Not known	Erythema[a]
Not known	Pruritus[a]
Not known	Rash[a]
Not known	Urticaria[a]
General Disorders and Administration Site Conditions	
Not known	Mucosal ulceration (ulcerations of the mucous membrane

a: Immediate and delayed hypersensitivity reactions

Adverse Drug Reactions Identified During Post-Marketing Experience with Budesonide by Frequency Category Estimated from Spontaneous Reporting Rates

SOC Frequency Category	Adverse Event Preferred Term
Immune System Disorders	
Very rare	Anaphylactic reaction
Uncommon	hypersensitivity reaction
Respiratory, Thoracic and Mediastinal Disorders	
Common	Haemorrhagic secretion and Epistaxis
Common	Nasal discomfort (nasal irritation)
Very rare	Nasal septum perforation
Skin and subcutaneous tissue disorders	
Uncommon	Angioedema[a]
Uncommon	Dermatitis[a]
Uncommon	Erythema[a]
Uncommon	Pruritus[a]
Uncommon	Rash[a]
Uncommon	Urticaria[a]
General Disorders and Administration Site Conditions	
Very rare	Mucosal ulceration (ulcerations of the mucous membrane)
Eye disorders	
Rare	Vision blurred

a: Immediate and delayed hypersensitivity reactions

Reporting suspected adverse effects

Reporting suspected adverse reactions after registration of the medicinal product is important. It allows continued monitoring of the benefit-risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions at: www.tga.gov.au/reporting-problems.

4.9 OVERDOSE

Acute overdosage with BUDAMAX, even in excessive doses, is not expected to be a clinical problem.

In the unlikely event of prolonged excessive use of BUDAMAX which could possibly lead to adrenal suppression, treatment should be discontinued. Overdosage may give rise to signs of Cushing's syndrome, such as increased bodyweight, lethargy, hypertension, hirsutism, cutaneous striae, personality change, ecchymosis, oedema, polyuria and polydipsia. In severe cases, the dosage of the corticosteroid should be gradually withdrawn to prevent the possibility of adrenal failure.

For information on the management of overdose, contact the Poisons Information Centre on 13 11 26 (Australia).

Keep out of reach of children. In the event of overdose, seek medical attention immediately.

5 PHARMACOLOGICAL PROPERTIES

5.1 PHARMACODYNAMIC PROPERTIES

Mechanism of action

The mechanism of action of intranasally administered budesonide has not yet been completely defined, however budesonide has been shown to counteract the mainly "IgE", mediated lung anaphylaxis in guinea pigs.

Clinical trials

Studies in animals and humans have shown an advantageous ratio between topical anti-inflammatory activity and systemic glucocorticoid effect over a wide dose range.

Budesonide is approximately twice as potent as beclomethasone dipropionate as shown in the skin blanching test for anti-inflammatory activity of topical steroids in humans. Budesonide has, however, less systemic effect than beclomethasone dipropionate, as measured by depression of morning plasma cortisol and effect on differential WBC count. The improved ratio of topical anti-inflammatory activity to systemic effect of budesonide is due to high glucocorticoid receptor affinity combined with a high first pass metabolism and a short half-life.

Pre-treatment for one week with intranasal budesonide 400 micrograms daily in asymptomatic patients with seasonal rhinitis, significantly inhibited the immediate reaction to allergen challenge.

Seasonal and perennial allergic rhinitis

The therapeutic efficacy of BUDAMAX nasal spray has been evaluated in placebo-controlled clinical trials of seasonal and perennial allergic rhinitis of 3-6 weeks duration. The number of patients (aged 6 years and above) treated with BUDAMAX nasal spray in these 8 studies was 1653.

Overall, the results of these clinical trials showed that BUDAMAX nasal spray administered once daily provides statistically significant reduction in the severity of nasal symptoms of seasonal and perennial allergic rhinitis including runny nose, sneezing, and nasal congestion. In some studies, improvement versus placebo has been shown to occur within 24 hours of initiating treatment with BUDAMAX nasal spray. Maximum benefit can take up to 2 weeks after initiation of treatment.

Nasal polyps

A randomised, double blind placebo controlled study evaluated the efficacy of BUDAMAX nasal spray 128 µg bd over a 6 week treatment period in patients (n=46) with moderate to severe nasal polyps. After 6 weeks polyp size was significantly reduced and nasal symptoms improved compared to placebo (n=47).

5.2 PHARMACOKINETIC PROPERTIES

The systemic availability of budesonide from BUDAMAX, with reference to the metered dose, is 33%. Negligible biotransformation occurs in human nasal mucosa

Absorption

After nasal application of 256 micrograms budesonide peak plasma concentrations of approximately 0.63 nmol/L in adults and 1.53 nmol/L in children were observed within 45 minutes. The area under the curve (AUC) after administration of 256 µg budesonide from BUDAMAX is 2.7 nmol.h/L in adults and 5.5 nmol.h/L in children.

Distribution

Budesonide has a volume of distribution of approximately 3 L/kg. Plasma protein binding averages 85-90%.

Metabolism

Budesonide is metabolised in the liver by cytochrome p450 3A to more polar metabolites with low glucocorticoid activity (ie 100 fold lower than the parent compound). The metabolites are inactive and excreted 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 plasma half-life after i.v. dosing averages 2-3 hours.

5.3 PRECLINICAL SAFETY DATA

Genotoxicity

The mutagenic potential of budesonide was evaluated in 6 different test systems. No mutagenic or clastogenic effects of budesonide were found.

Carcinogenicity

The carcinogenic potential of budesonide has been evaluated in mouse and rat at oral doses up to 200 and 50 µg/kg/day, respectively. No oncogenic effect was noted in the mouse. One study indicated an increased incidence of brain gliomas in male Sprague-Dawley rats given budesonide, however the results were considered equivocal.

Further studies performed in male Sprague-Dawley and Fischer rats showed that the incidence of gliomas in the budesonide treated rats was low and did not differ from that in the reference glucocorticoid groups or the controls. It was concluded that treatment with budesonide does not increase the incidence of brain tumours in the rat.

In male rats dosed with 10, 25 and 50 µg/kg/day, those receiving 25 and 50 µg/kg/day showed an increased incidence of primary hepatocellular tumours. This was observed in all three steroid groups (budesonide, prednisolone, triamcinolone acetonide) in a repeat study in male Sprague-Dawley rats thus indicating a class effect of corticosteroids.

6 PHARMACEUTICAL PARTICULARS

6.1 LIST OF EXCIPIENTS

Disodium edetate, potassium sorbate, glucose, dispersible cellulose, polysorbate 80, hydrochloric acid (for pH adjustment) and purified water.

6.2 INCOMPATIBILITIES

Incompatibilities were either not assessed or not identified as part of the registration of this medicine. Refer to section 4.5: Interactions with other medicines and other forms of interactions.

6.3 SHELF LIFE

In Australia, information on the shelf life can be found on the public summary of the Australian Register of Therapeutic Goods (ARTG). The expiry date can be found on the packaging.

6.4 SPECIAL PRECAUTIONS FOR STORAGE

Store below 30°C. Do not freeze.

6.5 NATURE AND CONTENTS OF CONTAINER

BUDAMAX nasal spray is available in a amber glass (Type II) bottle with pump spray equipment and nasal adaptor.

Pack sizes:

32 µg strength: 1 x 120 doses in 10mL

64 µg strength: 1x 50 doses (sample pack)in 10mL, 120 doses (1x120 dose in 10mL bottle) and 240 doses (2x120 dose in 10mL bottles)

Not all pack sizes may be available in Australia.

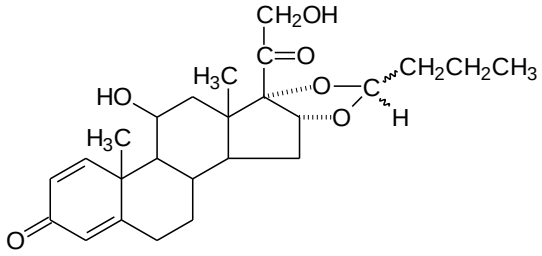
6.6 SPECIAL PRECAUTIONS FOR DISPOSAL

In Australia, any unused medicine or waste material should be disposed of by taking to your local pharmacy.

6.7 PHYSICOCHEMICAL PROPERTIES

The active ingredient, budesonide, is a non-halogenated glucocorticoid structurally related to 16α hydroxyprednisolone. Budesonide is a white to off-white powder, freely soluble in chloroform, sparingly soluble in ethanol and practically insoluble in water and heptane. Budesonide melts between 224°C and 231.5°C with decomposition.

Chemical structure



Chemical Name: 16α, 17α-22 R, S-propylmethylenedioxypregna-1, 4- diene-11β, 21-diol-3, 20-dione; MW 430.5

CAS number 51333-22-3

7 MEDICINE SCHEDULE (POISONS STANDARD)

Prescription only medicine (Schedule 4)

8 SPONSOR

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New Zealand: 0800 446 147
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9 DATE OF FIRST APPROVAL

24 August 2000

10 DATE OF REVISION

09 March 2023

SUMMARY TABLE OF CHANGES

Section Changed	Summary of new information
4.4	Additional warning
4.5	Revision of text/ additional warnings
4.6	Revision of text/additional warnings
4.9	Additional warnings