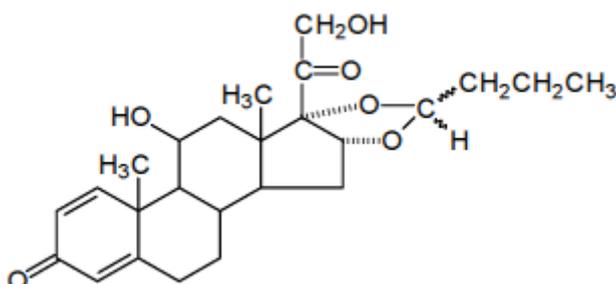


APOHEALTH BUDESONIDE HAYFEVER NASAL INHALATION**NAME OF THE MEDICINE**

Budesonide

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

Structural Formula:



Molecular Formula: C₂₅H₃₄O₆

Molecular Weight: 430.5

CAS Registry Number: 51333-22-3

DESCRIPTION

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.

Budesonide Hayfever is an aqueous nasal suspension, containing 32 μ g budesonide per actuation as the active ingredient.

In addition, each vial contains the following inactive ingredients: glucose, disodium edetate, potassium sorbate, microcrystalline cellulose, sodium carboxymethyl cellulose, polysorbate 80, hydrochloric acid, purified water.

PHARMACOLOGY**Pharmacological Actions**

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.

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.

Pharmacokinetics

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

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 Budesonide Hayfever is 2.7 nmol.h/L in adults and 5.5 nmol.h/L in children.

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

Budesonide is metabolised in the liver by cytochrome p450 3A to more polar metabolites with low glucocorticoid activity (i.e. 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 1.2L/min) and the plasma half-life after i.v. dosing averages 2-3 hours.

CLINICAL TRIALS

The therapeutic efficacy of intranasal budesonide has been evaluated in placebo controlled clinical trials of seasonal and perennial allergic rhinitis of 3-6 weeks duration.

Overall, the results of these clinical trials showed that intranasal budesonide 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 intranasal budesonide. Maximum benefit can take up to 2 weeks after initiation of treatment.

INDICATIONS

For short term (3-6 months) prophylaxis or treatment of seasonal allergic rhinitis in adults and children aged 12 years and over and perennial allergic rhinitis in adults 18 years and over.

CONTRAINDICATIONS

1. Hypersensitivity to any ingredient.
2. Hypersensitivity to other corticosteroids.
3. Severe nasal infections, especially candidiasis.
4. Persons with haemorrhagic diatheses or with a history of recurrent nasal bleeding.

PRECAUTIONS

Clinical response

The full effect of Budesonide Hayfever 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 Budesonide Hayfever is administered to patients already using corticosteroids, care should be taken to ensure that the daily dosage of Budesonide Hayfever is included when determining total daily corticosteroid dose.

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.

Infection

If infection of the respiratory tract, nasal passages or paranasal sinuses is present or occurs during administration of Budesonide Hayfever, adequate antibacterial therapy should be promptly instituted (see also CONTRAINDICATIONS, 2).

Wound healing

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

Reduced liver function:

Reduced liver function may affect the elimination of glucocorticosteroids. The pharmacokinetics after oral ingestion of budesonide were 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.

Adrenocortical function:

Dose-related suppression of plasma and urinary cortisol has been observed in healthy volunteers after short-term administration of Budesonide Hayfever. However, at recommended doses, Budesonide Hayfever does not cause any clinically important changes in basal cortisol levels nor in the response to stimulation with ACTH in patients with rhinitis.

Use in Pregnancy (Category A)

Results from a large prospective epidemiological study and from world-wide post marketing experience indicate that inhaled budesonide during pregnancy has no adverse effects on the health of the foetus or new born child. 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.

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. Breastfeeding can be considered if the potential benefit outweighs any potential risks.

Paediatric Use

Budesonide Hayfever is not recommended for use in children below 12 years of age.

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 50µg /kg/day, those receiving 25 and 50µg/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.

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

INTERACTIONS WITH OTHER MEDICINES

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, (e.g. itraconazole, clarithromycin, erythromycin) may inhibit the metabolism of, and increase the systemic exposure to, budesonide.

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

ADVERSE EFFECTS

Adverse local reactions following intranasal budesonide use are mild and usually transient. Systemic corticosteroid side-effects have not been reported during clinical studies of intranasal budesonide in adults.

Adverse events reported during studies with intranasal budesonide:

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.
Central Nervous System:	Headache, dizziness, tiredness.

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.
Immune system:	Immediate and delayed hypersensitivity reactions including urticaria, rash, dermatitis, angioedema and pruritus.

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.

DOSAGE AND ADMINISTRATION

Seasonal Allergic Rhinitis (adults and children 12 years and over) and Perennial Allergic Rhinitis (adults 18 years and over):

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

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.

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.

Patient instructions:

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

OVERDOSAGE

Symptoms

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

In the unlikely event of prolonged excessive use of Budesonide Hayfever 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).

PRESENTATION AND STORAGE CONDITIONS

APOHEALTH Budesonide Hayfever is intended for nasal inhalation.

Each bottle contains budesonide 32 mg per actuation, as the active ingredient 120 doses per bottle.

White to off-white suspension contained in an amber glass bottle with a metered-dose, manual spray pump for intranasal administration (AUST R 259935)

Storage

Store below 25°C.

Store upright. Do not freeze

NAME AND ADDRESS OF THE SPONSOR

Apotex Pty Ltd
16 Giffnock Avenue
Macquarie Park NSW 2113

POISON SCHEDULE OF THE MEDICINE

S2 – Pharmacy Medicine

DATE OF FIRST INCLUSION IN THE AUSTRALIAN REGISTER OF THERAPEUTIC GOODS (THE ARTG) 19 SEP 2016