NEW ZEALAND DATA SHEET

BUTACORT

Budesonide (50 µg & 100 µg per actuation)

Aqueous Nasal Suspension

Presentation

Budesonide aqueous spray 50µg and 100µg per metered actuation.

50 µg/actuation: An almost white opaque suspension, almost odourless. Amber glass bottle fitted with a metered pump device delivering 50 µg budesonide per actuation. Delivery of valve: 50 µl (each 50 µl contains 50 µg of budesonide).

100 µg/actuation: An almost white opaque suspension, almost odourless. Amber glass bottle fitted with a metered pump device delivering 100 µg budesonide per actuation. Delivery of valve: 50 µl (each 50 µl contains 100 µg of budesonide).

Uses

Actions

Budesonide is a potent non-halogenated corticosteroid. In investigations in animals and humans, budesonide has shown an advantageous ratio between topical anti-inflammatory activity and systemic glucocorticoid effect over a wide dosage range. This improved ratio is due to budesonide's high glucocorticoid receptor affinity combined with a high first pass metabolism with short half-life. 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.

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.

Pharmacokinetics

Due to extensive first-pass metabolism in the liver, the oral bioavailability of budesonide is low (approximately 10%). After nasal administration of a large dose (1mg) of budesonide from a metered dose aerosol the systemically available fraction is approximately 15%. Negligible biotransformation occurs in human nasal mucosa.

The maximal plasma concentration after nasal application of 100 µg budesonide is less than 0.2 nmol/L and is reached within 45 minutes. Budesonide has a volume of distribution of approximately 3 L/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 found in the urine. Budesonide has a high systemic clearance (approximately 1.2L/min) and the plasma half-life of budesonide in humans after nasal inhalation is 2.9 $\pm$ 0.4 hours, and the plasma clearance of unchanged budesonide is 55.2 $\pm$ 7.8 L/h.

Indications

BUTACORT 50 Aqueous Nasal Spray is indicated for the short-term prevention and treatment of seasonal allergic rhinitis (hayfever).

BUTACORT 100 Aqueous Nasal Spray is indicated for the prevention and treatment of seasonal and perennial allergic rhinitis and vasomotor rhinitis.

BUTACORT 100 Aqueous Nasal Spray is also indicated for the symptomatic relief of nasal polyposis.

Dosage and Administration

BUTACORT 50

For adults and children over 12 years:

Initially one or two sprays into each nostril twice a day (morning and night), then after 2 to 3 days, one spray into each nostril twice a day.

BUTACORT 100

For adults and children over 6 years:

Initially one or two sprays into each nostril in the morning, then after 2 to 3 days, one spray into each nostril in the morning.

For patients with only mild initial symptoms, a total daily dose of 200 micrograms may be sufficient.

For long term treatment, the lowest dose which keeps the patient symptom-free should be used. Continuous long term use in children is not recommended.

Patient Instructions:

Patients should be instructed in the correct use of BUTACORT. Patients should be informed that full response may not occur until after 2-3 days of treatment. Patients should also be advised to clear nasal passages of secretions prior to use and not to exceed the recommended dose. In seasonal allergic rhinitis, treatment ideally should start before exposure to the allergen. Do not use for more than 6 months except on medical advice.

Contraindications

Hypersensitivity to any ingredient (see Further Information).

Severe nasal infections, especially candidiasis.

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

Warnings and Precautions

Clinical Response:

The full effect of BUTACORT in allergic rhinitis is not achieved until at least 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 BUTACORT is prescribed for patients already using corticosteroids, care should be taken to ensure that the daily dosage of BUTACORT is included when determining total daily corticosteroid dose.

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 a year.

Systemic effects of nasal corticosteroids may occur, particularly at high doses prescribed for prolonged periods. These effects are much less likely to occur than with oral corticosteroids and may vary in individual

patients and between different corticosteroid preparations. Potential systemic effects may include Cushing's syndrome, Cushingoid features, adrenal suppression, growth retardation in children and adolescents (see Paediatric Use), cataract, glaucoma and more rarely, a range of psychological or behavioural effects including psychomotor hyperactivity, sleep disorders, anxiety, depression or aggression (particularly in children).

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 BUTACORT, adequate antibacterial therapy should be promptly instituted (see Contraindications).

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:

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, BUTACORT 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 Interactions with other drugs). Monitoring for signs of adrenal dysfunction is advisable in this patient group.

Paediatric Use

Controlled clinical studies have shown that intranasal corticosteroids may cause a reduction in growth velocity in paediatric patients. 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 (e.g. 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 minimize the systemic effects of intranasal corticosteroids, each patient should be titrated to his/her lowest effective dose (see Dosage and 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 intranasal budesonide in children below 6 years of age has not been established.

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 medications the administration of budesonide during pregnancy requires that the benefits for the mother be weighed against the risks for the foetus.

Intranasal 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 budesonide present in the breast milk, if any, is likely to be low. Breastfeeding can be considered if the potential benefit outweighs any potential risks

Carcinogenicity/Mutagenicity

The carcinogenic potential of budesonide has been evaluated in mouse and rat at oral doses up to 200 and 50 µg/kg/day, respectively. 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. No oncogenic effect was noted in the mouse. The mutagenic potential of budesonide was evaluated in 6 different test systems. No mutagenic or clastogenic effects of budesonide were found.

Do not use BUTACORT 50 for children under 12 years of age without first consulting with a doctor.

If hayfever symptoms do not improve within 7 days of treatment with BUTACORT 50, consult with a doctor.

Adverse Effects

Adverse local reactions following budesonide use are mild and usually transient. Systemic side effects may occur, particularly at high doses prescribed for prolonged periods (see Warnings and Precautions). 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 Warnings and Precautions).

Adverse events reported during studies with budesonide aqueous nasal sprays:

Common (more than 1%):

Nose and throat:

Nasal irritation, itching of throat and larynx, sore throat, dry mucous membranes, dry mouth, increased sputum, haemorrhagic secretion, epistaxis (nose bleeding), sneezing after spraying, 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.

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 (e.g. itraconazole, clarithromycin, erythromycin) may inhibit the metabolism of, and therefore increase systemic exposure to budesonide. As a result of the CYP3A4 inhibition caused by such medications there may be an increased risk of developing Cushing's syndrome.

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

Overdosage

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

In the unlikely event of prolonged excessive use of BUTACORT, 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 further advice on management of overdose please contact the National Poisons Information Centre (0800 POISON or 0800 764 766).

Pharmaceutical Precautions

BUTACORT 50 µg/dose and 100 µg/dose should be protected from the light and stored below 25°C. Do not refrigerate.

Discard three months after first using the spray.

Medicine Classification

BUTACORT 50: Pharmacy Medicine

BUTACORT 100: Prescription Medicine.

Package Quantities

Round amber glass bottle fitted with a metering, atomising pump and nasal applicator. The pump is fitted with a 50 µl valve and a nasal adaptor. Both dosage strengths provide 200 actuations.

Further Information

List of excipients: glucose (anhydrous), dispersible cellulose, potassium sorbate, disodium edetate, polysorbate, hydrochloric acid and purified water.

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Date of Preparation

20 July 2016