PACKAGING RESEARCH & DEVELOPMENT

OXALIS LABS

Restricted Circulation

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ARTWORK / PRINTPROOF APPROVAL FORM

For the use only of a Registered Medical Practitioner or a Hospital or a Laboratory

BUNASE (Budesonide) Pressurised Inhalation BP 200 mcg/ actuation

COMPOSITION

Each actuation from the valve delivers:
Budesonide BP……..200mcg
Suspended in 1,1,1,2 Tetrafluoroethane (Propellant HFA 134A) …….q.s.

PRODUCT DESCRIPTION

Pressurised metered dose inhaler containing suspension aerosol filled in plain aluminum canister fitted with suitable metered valve provided with brown coloured cap and white body colour body. There should be no sign of physical damage or leakage.

PHARMACODYNAMICS

Pharmacodynamic properties

Budesonide is an anti-inflammatory corticosteroid that exhibits potent glucocorticoid activity and weak mineralocorticoid activity. After oral inhalation, it has a local anti-inflammatory effect on the bronchial mucosa.
The precise mechanism of corticosteroid actions on inflammation in asthma is not known. Inflammation is an important component in the pathogenesis of asthma. Corticosteroids have been shown to have a wide range of inhibitory activities against multiple cell types (eg, mast cells, eosinophils, neutrophils, macrophages, and lymphocytes) and mediators (eg, histamine, eicosanoids, leukotrienes, and cytokines) involved in allergic and non-allergic-mediated inflammation. These anti-inflammatory actions of corticosteroids may contribute to their efficacy in asthma.

PHARMACOKINETICS

Absorption

Following Respiratory inhalation via Bunase (Budesonide) Pressurized Inhalation BP 200mcg/actuation, peak plasma concentrations of Budesonide (4.0 nmol/L after a dose of 800 µg) occur within 30 minutes. Maximum plasma concentration and area under the plasma concentration time profile increase linearly with dose, but are slightly (20-30%) higher following repeated doses (3 weeks treatment) than after a single dose. The maximal plasma concentration after inhalation of 1 milligram Budesonide is about 3.5 nmol/L and is reached after about 20 minutes.

Distribution

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

Biotransformation

Budesonide undergoes an extensive degree (approximately 90%) of biotransformation on first passage through the liver to metabolites of low glucocorticosteroid activity. The glucocorticosteroid activity of the major metabolites, 6β-hydroxy Budesonide and 16α- hydroxyprednisolone, is less than 1% of that of Budesonide. The metabolism of Budesonide is primarily mediated by CYP3A, a subfamily of cytochrome p450.

Excretion

The metabolites of Budesonide are excreted as such or in conjugated form mainly via the kidneys. No unchanged Budesonide has been detected in the urine. Budesonide has high systemic clearance (approximately 1.2 L/min) in healthy adults, and the terminal half-life of Budesonide after i.v dosing averages 2-3 hours.

Linearity

The kinetics of Budesonide is dose-proportional at clinically relevant doses.

Paediatric safety data

Budesonide has a systemic clearance of approximately 0.5 L/min in 4-6 years old asthmatic children. Per kg body weight children have a clearance which is approximately 50% ;greater than in adults. The terminal half-life of Budesonide after inhalation is approximately 2.3 hours in asthmatic children. This is about the same as in healthy adults.

INDICATION

BUNASE 200 is indicated in patients with bronchial asthma.

RECOMMENDED DOSAGE AND ROUTE OF ADMINISTRATION

Route of administration: For Respiratory inhalation
The dosage of Bunase (Budesonide) Pressurized Inhalation BP 200mcg/actuation is individual. Initially, at the beginning of inhaled corticosteroid therapy, for therapy during periods of severe asthma or when scaling down or withdrawing oral corticosteroids the dosage should be:
Children aged 2-7 years: 200-400 micrograms per day divided into 2 administrations.
Children aged 7 years and older: 200-800 micrograms per day divided into 2 administrations.
Adults:
200-1600 micrograms per day divided into 2 administrations. For maintenance treatment administration twice daily, morning and evening, is usually sufficient. The maintenance dose should be the lowest possible. Following a single dose an effect may be expected after a few hours. The full therapeutic effect is only achieved after a few weeks of treatment.

CONTRAINDICATIONS

Hypersensitivity to the active substance budesonide

WARNINGS & PRECAUTIONS

Special caution is necessary in patients with active or quiescent pulmonary tuberculosis, and in patients with fungal or viral infections in the airways.
Non steroid-dependent patients: A therapeutic effect is usually reached within 10 days. In patients with excessive mucus secretion in the bronchi, a short (about 2 weeks) additional oral corticosteroid regimen can be given initially.
Steroid-dependent patients: When transferral from oral steroids to Bunase (Budesonide) Pressurized Inhalation BP 200mcg/actuation is started, the patient should be in a relatively stable phase. A high dose of Bunase (Budesonide) Pressurized Inhalation BP 200mcg/actuation is then given in combination with the previously used oral steroid dose for about 10 days.
After that, the oral steroid dose should be gradually reduced (by for example 2.5 milligrams prednisolone or the equivalent each month) to the lowest possible level. In many cases, it is possible to completely substitute Budesonide for the oral steroid.
During transfer from oral therapy to Budesonide, a generally lower systemic steroid action will be experienced which may result in the appearance of allergic or arthritic symptoms such as rhinitis, eczema and muscle and joint pain. Specific treatment should be initiated for these conditions. During the withdrawal of oral steroids, patients may feel unwell in a non-specific way, even though respiratory function is maintained or improved. Patients should be encouraged to continue with Budesonide therapy whilst withdrawing the oral steroid, unless there are clinical signs to indicate the contrary. A general insufficient glucocorticosteroid effect should be suspected if, in rare cases, symptoms such as tiredness, headache, nausea and vomiting should occur. In these cases a temporary increase in the dose of oral glucocorticosteroids is sometimes necessary.
As with other inhalation therapy, paradoxical bronchospasm may occur, with an immediate increase in wheezing after dosing. If this occurs, treatment with inhaled Budesonide should be discontinued immediately, the patient assessed and alternative therapy instituted if necessary.
Patients who have previously been dependent on oral steroids may, as a result of prolonged systemic steroid therapy, experience the effects of impaired adrenal function. Recovery may take a considerable amount of time after cessation of oral steroid therapy; hence oral steroid-dependent patients transferred to Budesonide may remain at risk from impaired adrenal function for some considerable time. In such circumstances, HPA axis functions should be monitored regularly.
Acute exacerbations of asthma may need an increase in the dose of Budesonide or additional treatment with a short course of oral corticosteroid and/or an antibiotic, if there is an infection. The patient should be advised to use a short-acting inhaled bronchodilator as rescue medication to relieve acute asthma symptoms.
Budesonide is not intended for rapid relief of acute episodes of asthma where an inhaled short-acting bronchodilator is required.
If patients find short-acting bronchodilator treatment ineffective or they need more inhalations than usual, medical attention must be sought. In this situation consideration should be given to the need for or an increase in their regular therapy, e.g. higher doses of inhaled Budesonide or the addition of a long-acting beta agonist, or for a course of oral glucocorticosteroid.
Patients, who have required high dose emergency corticosteroid therapy or prolonged treatment at the highest recommended dose of inhaled corticosteroids, may also be at risk of impaired adrenal function. These patients may exhibit signs and symptoms of adrenal insufficiency when exposed to severe stress. Additional systemic corticosteroid treatment should be considered during periods of stress or elective surgery. These patients should be instructed to carry a steroid warning card indicating their needs. Treatment with supplementary systemic steroids or Budesonide should not be stopped abruptly.
Systemic effects may occur with any inhaled corticosteroids, particularly at high doses prescribed for long periods. These effects are much less likely to occur with inhalation treatment than with oral corticosteroids. Possible systemic effects include Cushing's syndrome, Cushingoid features, adrenal suppression, growth retardation in children and adolescents, decrease in bone mineral density, cataract, glaucoma and more rarely, a range of psychological or behavioural effects including psychomotor hyperactivity, sleep disorders, anxiety, depression or aggression (particularly in children). It is important, therefore, that the dose of inhaled corticosteroid is titrated to the lowest dose at which effective control of asthma is maintained.
Reduced liver function affects the elimination of corticosteroids causing lower elimination rate and higher systemic exposure. Be aware of possible systemic side effects.
The plasma clearance following an intravenous dose of Budesonide however was similar in cirrhotic patients and in healthy subjects. After oral ingestion systemic availability of Budesonide was increased by compromised liver function due to decreased first pass metabolism. The clinical relevance of this to treatment with Budesonide is unknown as no data exist for inhaled Budesonide, but increases in plasma levels and hence an increased risk of systemic adverse effects could be expected.
Co-treatment with CYP3A inhibitors, e.g. itraconazole, ketoconazole, HIV protease inhibitors and cobicistat-containing products is expected to increase the risk of systemic corticosteroid side effects. Therefore, the combination should be avoided unless the benefit outweighs this increased risk, in which case patients should be monitored for systemic corticosteroid side effects. This is of limited clinical importance for short-term (1-2 weeks) treatment with itraconazole or ketoconazole or other potent CYP3A inhibitors, but should be taken into consideration during long-term treatment. A reduction in the dose of Budesonide should also be considered.
Oral candidiasis may occur during the therapy with inhaled corticosteroids. This infection may require treatment with appropriate antifungal therapy and in some patients discontinuation of treatment may be necessary.

Pneumonia in patients with COPD

An increase in the incidence of pneumonia, including pneumonia requiring hospitalisation, has been observed in patients with COPD receiving inhaled corticosteroids. There is some evidence of an increased risk of pneumonia with increasing steroid dose but this has not been demonstrated conclusively across all studies.
There is no conclusive clinical evidence for intra- class differences in the magnitude of the pneumonia risk among inhaled corticosteroid products.
Physicians should remain vigilant for the possible development of pneumonia in patients with COPD as the clinical features of such infections overlap with the symptoms of COPD exacerbations.
Risk factors for pneumonia in patients with COPD include current smoking, older age, low body mass index (BMI) and severe COPD.

Paediatric population

Influence on growth
It is recommended that the height of children receiving prolonged treatment with inhaled corticosteroids is regularly monitored. If growth is slowed, therapy should be re-evaluated with the aim of reducing the dose of inhaled corticosteroid, if possible, to the lowest dose at which effective control of asthma is maintained. The benefit of the corticosteroid therapy and the possible risk of growth suppression must be carefully weighed. In addition, consideration should be given to referring the patient to a paediatric respiratory specialist.

INTERACTIONS WITH OTHER MEDICAMENTS

The metabolism of Budesonide is primarily mediated by CYP3A4. Co-treatment with CYP3A inhibitors, e.g. itraconazole, ketoconazole, HIV protease inhibitors and cobicistat-containing products, are expected to increase the risk of systemic side effects.
The combination of Budesonide with potent CYP3A inhibitors should be avoided unless the benefit outweighs the increased risk of systemic corticosteroid side effects, in which case patients should be monitored for systemic corticosteroid side effects. If Budesonide is co-administered with anti-fungals (such as itraconazole and ketoconazole), the period between treatments should be as long as possible. A reduction of the Budesonide dose could be considered.
Limited data about this interaction for high-dose inhaled Budesonide indicate that marked increases in plasma levels (on average four- fold) may occur if itraconazole, 200 mg once daily, is administered concomitantly with inhaled Budesonide (single dose of 1000 µg).
Raised plasma concentrations of and enhanced effects of corticosteroids have been observed in women also treated with oestrogens and contraceptive steroids, but no effect has been observed with Budesonide and concomitant intake of low dose combination oral contraceptives. Because adrenal function may be suppressed, an ACTH stimulation test for diagnosing pituitary insufficiency might show false results (low values).

Paediatric population

Interaction studies have only been performed in adults.

PREGNANCY AND LACTATION

Pregnancy
As with other drugs the administration of Budesonide during pregnancy requires that the benefits for the mother are weighed against the risks for the foetus.
Inhaled glucocorticosteroids should be considered in preference to oral glucocorticosteroids because of the lower systemic effects at the doses required to achieve similar pulmonary responses.
Lactation
Budesonide is excreted in breast milk. However, at therapeutic doses no effects on the suckling child are anticipated. Budesonide 200 micrograms can be used during breast feeding.
Maintenance treatment with inhaled Budesonide (200 or 400 microg twice daily) in asthmatic nursing women results in negligible systemic exposure to Budesonide in breast-fed infants.
Based on data from inhaled Budesonide and the fact that Budesonide exhibits linear PK properties within the therapeutic dosage intervals after nasal, inhaled, oral and rectal administrations, at therapeutic doses of Budesonide, exposure to the suckling child is anticipated to be low

SIDE EFFECTS

Adverse events are listed below by system organ class and frequency.
Frequencies are defined as:
Very common; Common; Uncommon; Rare; Very rare; Not known (cannot be estimated from the available data)
System organ class:
Infections and Infestations
Common: Oropharyngeal candidiasis, Pneumonia (in COPD patients)
Immune System Disorders
Rare: Immediate and delayed hypersensitivity reactions including rash, contact dermatitis, urticaria, angioedema and anaphylactic reaction.
Endocrine Disorders
Rare: Signs and symptoms of systemic corticosteroid effects including adrenal suppression and Growth retardation*
Psychiatric Disorders
Uncommon: Anxiety, Depression
Rare: Psychomotor hyperactivity, Sleep disorders, Aggression, Behavioural changes (predominantly in children)
Nervous System Disorders
Uncommon: Tremor**
Eye Disorders
Uncommon: Cataract, Vision blurred
Not known: Glaucoma
Respiratory, Thoracic and Mediastinal Disorders
Common: Hoarseness, Cough, Throat irritation
Rare: Bronchospasm, Dysphonia, Hoarseness***
Skin and Subcutaneous Tissue Disorders
Rare: Bruising
Musculoskeletal, Connective Tissue and Bone Disorders
Uncommon: Muscle spasm
• * refer to Paediatric population, below
• ** based on the frequency reported in clinical trials
• *** rare in children

Paediatric population

Due to the risk of growth retardation in the paediatric population, growth should be monitored.

SYMPTOMS AND TREATMENT OF OVERDOSAGE

Acute overdose with **BUNASE 200** micrograms, even in excessive doses, is not expected to be a clinical problem.
The only harmful effect that follows inhalation of large amounts of the drug over a short period is suppression of hypothalamic-pituitary-adrenal (HPA) function.
Management
No special emergency action needs to be taken. Treatment with Bunase (Budesonide) Pressurized Inhalation BP 200mcg/actuation should be continued at the recommended dose to control the asthma.

EFFECTS ON ABILITY TO DRIVE AND USE MACHINE

Budesonide has no or negligible influence on the ability to drive and use machines.

INSTRUCTIONS FOR USE:

How to use your inhaler

Budesonide Pressurised Inhalation is used by breathing the medicine contained in the inhaler in through your mouth. It is important that you do not rush using your inhaler. At first, you may need to practise using the inhaler in front of the mirror. Any mist coming from the top of the inhaler or from the mouthpiece may mean that you have not inhaled the medicines properly. Young children may need help from their parent or carers to use the inhaler. Your doctor, asthma nurse or pharmacist will regularly check how you use your inhaler.
Every time you need to take an inhalation, follow the instruction below;
1. Remove the dust cap from the plastic adapter. Check that the mouth piece is clean and not blocked. **Shake the inhaler vigorously so that the content of the aerosol canister are properly mixed before each use.**
2. Hold your Bunase (Budesonide) Pressurized Inhalation BP 200mcg/Actuation. Breathe out as far as possible.
3. Place the mouth piece between your lips. Do not chew or bite on the mouthpiece. Start to breathe in slowly and deeply through your mouth. Keep breathing in and press the canister firmly to release a puff from inahaler. You may need to use both hands to release a puff from your inhaler. Keep breathing in for a short while after pressing the canister.
4. Hold your breath for 10 seconds, or for as long as is comfortable. Hold your inhaler away from your mouth. Then breathe out slowly, if you are to take a second puff, wait atleast half a minute. Then shake the inhaler vigorously and repeat steps 2, 3 and 4.
5. After use, replace the dust cap on the plastic adapter. Store your inhaler so that it is sitting upright on its brown plastic base.
6. Rinse your mouth out with water and spit it out.

Cleaning your inhaler

Clean the inhaler once a week. Remove the dust cap and the aerosol canister. Clean the plastic actuator and dust cap with a dry cloth or tissue. Then relapse the aerosol canister and dust cap. Do not put the inhaler into water.

If you take more Bunase (Budesonide) Pressurized Inhalation BP 200mcg/Actuation than you should

If too much Bunase (Budesonide) Pressurized Inhalation BP 200mcg/Actuation is used on a single occasion no harmful effects should occur. If too much Budesonide Pressurised Inhalation is used over a long period (weeks or months)
It is possible that side effects may arise. If you use more Bunase (Budesonide) Pressurized Inhalation BP 200mcg/Actuation than you should, contact your doctor, asthma nurse or pharmacist for advice as soon as possible.

STORAGE CONDITIONS

• Store below 30°C. Do not freeze. Protect from frost and direct sunlight.
• Store the inhaler with the mouthpiece down.
• Do not remove Budesonide Pressurised Inhalation from the outer carton until you are ready to use it. Store the carton in the position indicated.
• Always replace the cap after using your inhaler.
• Always store Budesonide Pressurised Inhalation so that it is sitting upright on its brown plastic base.
• Do not use Budesonide Pressurised Inhalation after the expiry date printed on the label and carton. The expiry date refers to the last day of the month.
• Medicines should not be disposed of via waste water or house hold waste. Ask your pharmacist how to dispose of medicines that are no longer required. This will help to protect the environment.

DOSAGE FORMS AND PACKAGING AVAILABLE

Pack of one aluminium plain canister in a carton.

Warning: The canister contains a pressurised liquid. Do not expose to temperatures higher than 50°C. Do not pierce the canister. The canister should not be broken, punctured or burnt, even when it seems to be empty.

PRODUCT OWNER:
MACLEODS PHARMACEUTICALS LTD.
Off.: Atlanta Arcade, Marol Church Road,
Andheri (E), Mumbai - 400 059.

MANUFACTURED BY:
OXALIS LABS
Village Theda, P.O. Lodhimajra,
Tehsil Baddi, Distt. Solan
(H.P) 174101 India.

PRODUCT REGISTRATION HOLDER:
Macleods Pharmaceutical Sdn. Bhd.,
A2-27-1 Soho Suites KLCC, Jalan Perak, 50450
Kuala Lumpur, Malaysia.

Date of Preparation: 24-6-2022.

PM00405001