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

BUDECORT 200

(Budesonide Inhaler 200 mcg/dose)

Composition
Budecort 200 Inhaler
Each actuation delivers
Budesonide BP.....200 mcg
Suspended in propellant HFA 134a……q.s.

Description
A one piece filled metal container fitted with a valve with plastic stem and printed with product name, batch number and container number. On visual examination there should be no sign of physical damage such as dents, bulged containers bent valve stem and uneven crimping.

Pharmacology
Budesonide is a potent glucocorticoid that when given systemically has standard glucocorticoid activity and binds with high affinity to the glucocorticoid receptor. The drug was developed primarily for topical use. Budesonide, if given systemically, has catabolic and antianabolic effect on proteins in peripheral tissues; it causes resistance to insulin and impairs the peripheral utilization of glucose as well as causing increased calcium loss from bone via the kidney. However, budesonide depends for its effects on the local anti-inflammatory and immunosuppressive activity. It has been shown in animal studies to have a high ratio of topical to systemic activity compared with other corticosteroids including beclomethasone dipropionate, flunisolide, fluocinolone acetonide, and triamcinolone acetonide. Results of a study of hamsters with induced ileitis suggested that the anti-inflammatory effect of budesonide was owing to a local effect rather than a systemic effect. Inhaled glucocorticoids reduce the number of inflammatory cells, such as eosinophils, lymphocytes and mast cells, and restore airway epithelial integrity in bronchial biopsy specimens obtained from mild asthmatic patients. Inhaled budesonide also reduces indices of eosinophil activation in asthma. These effects are likely to result from inhibition of the transcription of several cytokines that are over expressed in asthma, in particular the interleukins IL-3, IL-4 and IL-5 and granulocyte macrophage colony stimulating factor (GM-CSF), especially from activated T cells. Glucocorticoids also inhibit plasma exudation through the endothelial barrier of the bronchial vasculature and, therefore, their administration leads to a reduction in airway edema. Budesonide inhibits phospholipase A_2 activity, and by this means reduces the formation of prostaglandins and leukotrienes in the airway.

Pharmacokinetics
The preferred analytical method is by high performance liquid chromatography in series with radioimmunoassay, which gives a sensitivity of 1 μg/l. There is no interference from endogenous steroids.

Absorption from the gastrointestinal tract is probably complete. Oral bioavailability is approximately 10%, indicating high presystemic metabolism by the liver. Studies with ^{3}H-budesonide show no metabolism in lung or nasal mucosa. Peak plasma levels are reached in about 30 min after nasal application; after inhalation, a plasma peak is found within 5-10 min; after rectal administration peak plasma concentrations were obtained within 1.5 h. Rectal administration of 2 mg budesonide gave a mean maximal plasma concentration of 3 nmol.l^{-1} (range 1-9 nmol.l^{-1}). Plasma half-life is approximately 2 h and the plasma clearance rate is 0.9-1.41.min^{-1}. The metabolites have minimal biological activites. Inhalation gives a high plasma concentration, 2 nmol.l^{-1} after 500 μg budesonide, resembling that obtained after intravenous administration. This suggests effective lung deposition and minimal biotransformation in the lung, since poor lung deposition would give a delayed plasma peak as found with oral administration (10 nmol.l^{-1} 2h after 500 μg budesonide). The volume of distribution after intravenous administration is 301 $\pm$ 421 and there is little or no entry into the CNS. Plasma protein binding is 86-90%, mainly to albumin and not to transcortin.
Budesonide is extensively distributed. Tissue distribution has been studied in the mouse, in which there is some placental transfer, but it is not known for humans. No data on concentrations in breast milk in humans are available. Metabolism is more rapid in small children. Metabolic transformation of budesonide in liver is not affected by drugs which inhibit some forms of cytochrome P450 (e.g. cimetidine).

Oral absorption	≅ 100%
Presystemic metabolism	90%
Plasma half-life mean	2h
Volume of distribution	43 l/kg
Plasma protein binding	86-90%

Pharmacodynamics:
Budesonide is an anti-inflammatory corticosteroid that exhibits potent glucocorticoid activity and weak mineralocorticoid activity. The precise mechanism of corticosteroid action on inflammation in asthma is not known. Corticosteroids have been shown to have a wide range of inhibitory activities against mutiple cell types (mast cells, eosinophils, macrophages & lymphocytes) and mediators (e.g

histamine, eicosanoids, leukotrienes and cytokines) involved in allergic and non-allergic mediated inflammation.

Indications
Bronchial asthma.

DOSAGE AND ADMINISTRATION
For oral inhalation.
The dosage of Budecort 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
Budecort Inhaler is contraindicated in patients with a history of hypersensitivity to budesonide or any of the component of the drug product.

WARNING & PRECAUTIONS
Budecort Inhaler is not designed to relieve acute symptoms for which an inhaled short-acting bronchodilator is required. Patients should be made aware of the prophylactic nature of therapy with inhaled budesonide and that it should be taken regularly. Systemic effects of inhaled corticosteroids may occur, particularly at high doses prescribed for prolonged periods. These effects are much less likely to occur than with oral corticosteroids. Possible systemic effects include adrenal suppression, growth retardation in children and adolescents, decrease in bone mineral density, cataract and glaucoma. It is important therefore that the dose of inhaled corticosteroid is titrated to the lowest dose at which effective control of asthma is maintained. It is recommended that height of children receiving prolonged treatment with inhaled corticosteroids be regularly monitored. As with all inhaled corticosteroids, special care is necessary in patients with active or quiescent pulmonary tuberculosis. 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 even a fatal course in children on immunosuppressant corticosteroids. Replacement of systemic steroid treatment with inhaled therapy sometimes unmasks allergies such as allergic rhinitis or eczema previously controlled by the systemic drug. These allergies should be symptomatically treated with anti histamine and/or topical preparations including steroids.

For transfer of patients being treated with oral corticosteroids:
The transfer of oral steroid-dependent patients to **Budecort Inhaler** and their subsequent management needs special care as recovery from impaired adrenocortical function, caused by prolonged systemic steroid therapy, may take a considerable time. Gradual withdrawal of the systemic steroid is recommended. In these patients, the possibility of residual impaired adrenal response should always be considered in emergency (medical or surgical) and elective situations likely to produce stress and appropriate corticosteroid treatment considered.

Drug Interactions
The metabolism of budesonide is primarily mediated by CYP3A4, one of the cytochrome p450 enzymes. Inhibitors of this enzyme, e.g. ketoconazole and itraconazole, can therefore increase systemic exposure to budesonide. Other potent inhibitors of CYP3A4 are also likely to markedly increase plasma levels of budesonide.

PREGNANCY
Budesonide has been labeled as pregnancy category B. The possibility of fetal harm is remote if the drug is used during pregnancy. Nevertheless, because the studies in humans cannot rule out the possibility of harm, budesonide should be used during pregnancy only if clearly needed.

Lactation
It is not known whether budesonide is distributed into milk; however, other corticosteroids are distributed into milk. Because of the potential for serious adverse reactions from corticosteroids in nursing infants, a decision should be made whether to discontinue nursing or budesonide, taking into account the importance of the drug to the woman.

Undesirable effects
Clinical trials, literature reports and post-marketing experience suggest that the following adverse drug reactions may occur:

Common (>1/100, <1/10)	• Mild irritation in the throat • Candida infection in the oropharynx • Hoarseness • Coughing
Rare (>1/10 000, <1/1 000)	• Nervousness, restlessness, depression, behavioural disturbances • Immediate and delayed hypersensitivity reactions including rash, contact dermatitis, urticaria, angioedema and bronchospasm • Skin bruising

The candida infection in the oropharynx is due to drug deposition. Advising the patient to rinse the mouth out with water after each dosing will minimise the risk and also minimize the effect of bitter taste of the drug.
As with other inhalation therapy, paradoxical bronchospasm may occur in very rare cases.
Systemic effects of inhaled corticosteroids may occur, particularly at high doses prescribed for prolonged periods. These effects are much less likely to occur than with oral corticosteroids. Possible systemic effects include adrenal suppression, growth retardation in children and adolescents, decrease in bone mineral density, cataract and glaucoma. The effect is probably dependent on dose, exposure time, concomitant and previous steroid exposure, and individual sensitivity.

Overdose:
Acute overdosage with Budecort Inhaler may lead to temporary suppression of adrenal function. This does not necessitate emergency action being taken. In these patients treatment with Budecort by inhalation should be continued at a dose sufficient to control asthma; adrenal function recovers in a few days and can be verified by measuring plasma cortisol. Chronic over dosage may lead to adrenal suppression. Monitoring of adrenal reserve may be indicated. Treatment with inhaled budesonide should be continued at a dose sufficient to control asthma.

Storage:
Store below 30^{o} C,
Do not freeze

Shelf life:
2 years

Packing/Pack size:
Aerosol of 300 metered dose

Presentation: -
Aerosol of 300 metered dose

Registration holder in Malaysia
CIPLA MALAYSIA SDN BHD
(Company No. 1039096-P)
Suite 1101, Amcorp Tower,
Amcorp Trade Centre,
18 Persiaran Barat,
46 050 Petaling Jaya,
Selangor, Malaysia

Mfd. for
Cipla LTD.
At Medispray Laboratories Pvt Ltd
344/345 Kundaim Industrial Estate
Kundaim, Goa-403115, India.

Date of Revision
December 2014