BUDECORT Respules (Budesonide)
For the use of a Registered Medical Practitioner or a Hospital or a Laboratory only

Qualitative And Quantitative Composition

BUDECORT 0.5 mg and 1 mg respules
Each 2 ml contains Budesonide IP...... 0.5 mg
Each 2 ml contains Budesonide IP...... 1 mg

Dosage Form And Strength(S)

BUDECORT respules are supplied as a sterile, clear, colorless, aqueous suspension for inhalation in a unit-dose single-use LDPE respule. Each 2 mL respule is available in the strength of 0.5 mg & 1 mg of budesonide.

Clinical Particulars

Therapeutic Indications

BUDECORT respules contain the potent, non-halogenated, corticosteroid, budesonide, indicated for maintenance treatment of asthma and as prophylactic therapy in children 12 months to 8 years of age, where use of a pressurized inhaler or dry powder formulation is unsatisfactory or inappropriate. BUDECORT respules is not indicated for the relief of acute bronchospasm. BUDECORT respules are also recommended for use in infants and children with croup (acute viral upper respiratory tract infection also known as viral laryngotracheobronchitis or laryngitis subglottica), in which hospitalisation is indicated.

Posology and Method of Administration

The dosage of BUDECORT respules should be adjusted to the need of the individual. Dosage schedules: The dose delivered to the patient varies depending on the nebulizing equipment used. The nebulization time and the dose delivered is dependent on flow rate, volume of nebulizer chamber and fill volume. An air-flow rate of 6 - 8 litres per minute through the device should be employed. A suitable fill volume for most nebulizers is 2 - 4 ml. The dosage of BUDECORT respules should be adjusted to the need of the individual. The dose should be reduced to the minimum needed to maintain good asthma control. The highest dose (2 mg/day) for children under 12 years should only be considered in children with severe asthma and during limited periods.

Bronchial asthma
Initiation of therapy

When treatment is started, during periods of severe asthma and while reducing or discontinuing oral glucocorticosteroids, the recommended dose of BUDECORT respules is:
Adults (including the elderly): Usually 1-2 mg twice daily. In very severe cases the dosage may be further increased.

**Pediatric population**

**Children 12 years and older:** Dosage as for adults.

**Children 3 months to 12 years:** 0.5-1 mg twice daily.

**Maintenance**

The maintenance dose should be individualized and be the lowest dose which keeps the patient symptom-free.

Adults (including the elderly and children 12 years and older): 0.5-1 mg twice daily.

**Pediatric population**

**Children 3 months to 12 years:** 0.25-0.5 mg twice daily.

**Patients maintained on oral glucocorticosteroids**

BUDECORT respules may permit replacement or significant reduction in dosage of oral glucocorticosteroids while maintaining asthma control. When transferral from oral steroids BUDECORT respules is started, the patient should be in a relatively stable phase. A high dose of BUDECORT respules 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 the oral steroid with BUDECORT respules.

**Dose division and miscibility**

BUDECORT respules can be mixed with solutions for nebulization of ASTHALIN, LEVOLIN, IPRAVENT, MUCINAC and INHALEX respules. The admixture should be used within 30 minutes. Where an increased therapeutic effect is desired, especially in those patients without major mucus secretion in the airways, an increased dose of BUDECORT respules is recommended, rather than combined treatment with oral corticosteroids, because of the lower risk of systemic effect.

**Croup**

In infants and children with croup, the usual dose is 2 mg of nebulized budesonide. This dose is given as a single administration, or as two 1 mg doses separated by 30 minutes. Dosing can be repeated every 12 hour for a maximum of 36 hours or until clinical improvement.

**Method of administration**

BUDECORT respules should be administered from suitable nebulizers. Instruction for correct use of BUDECORT respules.

The respule should be detached from the strip, shaken gently and opened by twisting off the wing tab. The contents of the respule should be gently squeezed into the nebulizer cup. The empty respule should be thrown away and the top of the nebulizer cup replaced.

BUDECORT respules should be administered via a jet nebulizer equipped with a mouthpiece or suitable face mask. The nebulizer should be connected to an air compressor with an adequate air flow (6-8 L/min), and the fill volume should be 2-4ml.

Note: It is important to instruct the patient to carefully read the instructions for use in the patient information leaflet which are packed together with each nebulizer.

that ultrasonic nebulizers are not suitable for the administration of BUDECORT respules and therefore are not recommended

BUDECORT respules can be mixed with solutions for nebulization of ASTHALIN, LEVOLIN, IPRAVENT, MUCINAC and INHALEX respules. The admixture should be used within 30 minutes.
to minimize the risk of oropharyngeal candida infection, the patient should rinse their mouth out with water after inhaling.

to wash the facial skin with water after using the face mask to prevent facial skin irritation

to adequately clean and maintain the nebulizer according to the manufacturer's instructions

### Contraindications

The use of BUDECORT respules is contraindicated in the following conditions:
- Primary treatment of status asthmaticus or other acute episodes of asthma where intensive measures are required.
- Hypersensitivity to any ingredient of the formulation

### Special Warnings and Precautions for Use

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. After the course of the oral drug, BUDECORT respules alone should be sufficient therapy.

**Steroid-dependent patients:** When transfer from oral corticosteroid to treatment with BUDECORT respules is initiated, the patient should be in a relatively stable phase. BUDECORT respules 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 mg prednisolone or the equivalent each month), to the lowest possible level. In many cases, it is possible to completely substitute BUDECORT respules for the oral corticosteroid. During transfer from oral therapy to nebulized budesonide, a generally lower systemic corticosteroid 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. A general insufficient glucocorticosteroids 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. Patients should be advised that BUDECORT respules may cause systemic corticosteroid effects of hypercorticism and adrenal suppression. Additionally, patients should be instructed that deaths due to adrenal insufficiency have occurred during and after transfer from systemic corticosteroids. Patients should taper slowly from systemic corticosteroids if transferring to BUDECORT respules. As with other inhalation therapy, paradoxical bronchospasm may occur, with an immediate increase in wheezing after dosing. If a severe reaction occurs, treatment should be reassessed, and an alternative therapy instituted if necessary. 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 cover should be considered during periods of stress or elective surgery. 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 and glaucoma and more rarely, a range of psychological or behavioural effects including psychomotor hyperactivity, sleep disorders, anxiety, depression or aggression (particularly in children). Patients with major risk factors for decreased bone mineral content, such as prolonged immobilization, family history of osteoporosis, poor nutrition, or chronic use of drugs that can reduce bone mass (e.g., anticonvulsants and corticosteroids), should be monitored and
treated with established standards of care. Close monitoring is warranted in patients with a change in vision or with a history of increased intraocular pressure, glaucoma, and/or cataracts. It is important, therefore, that the dose of inhaled corticosteroid is titrated to the lowest dose at which effective control of asthma is maintained. Orally inhaled corticosteroids, including budesonide, may cause a reduction in growth velocity when administered to pediatric patients. Monitor the growth of pediatric patients receiving budesonide respules routinely (e.g., via stadiometry). To minimize the systemic effects of orally inhaled corticosteroids, including budesonide respules, each patient should be titrated to his/her lowest effective dose.

**BUDECORT** respules 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 glucocorticosteroids. Reduced liver function may affect the elimination of glucocorticosteroids, 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 nebulized 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. The nebulizer chamber should be cleaned after every administration. Wash the nebulizer chamber and mouthpiece or face-mask in hot water using a mild detergent. Rinse well and dry, by connecting the nebulizer chamber to the compressor or air inlet.

**Local effects:** In clinical trials with nebulized budesonide, localized infections with *Candida albicans* occurred in the mouth and pharynx in some patients. The incidences of localized infections of *Candida albicans* were similar between the placebo and nebulized budesonide treatment groups. If these infections develop, they may require treatment with appropriate local or systemic antifungal therapy and/or discontinuance of treatment with nebulized budesonide. Patients should rinse the mouth after inhalation of **BUDECORT** respules.

**Hypersensitivity Reactions Including Anaphylaxis:** Hypersensitivity reactions including anaphylaxis, rash, contact dermatitis, urticaria, angioedema, and bronchospasm have been reported with use of budesonide respules. Discontinue **BUDECORT** respules if such reactions occur.

**Eosinophilic Conditions and Churg-Strauss Syndrome:** In rare cases, patients on inhaled corticosteroids may present with systemic eosinophilic conditions. Some of these patients have clinical features of vasculitis consistent with Churg-Strauss syndrome, a condition that is often treated with systemic corticosteroids therapy. These events usually, but not always, have been associated with the reduction and/or withdrawal of oral corticosteroid therapy following the introduction of inhaled corticosteroids. Healthcare providers should be alert to eosinophilia, vasculitis rash, worsening pulmonary symptoms, cardiac complications, and/or neuropathy presenting in their patients. A causal relationship between budesonide and these underlying conditions has not been established.
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.

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.

Pediatric 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 benefits of the corticosteroid therapy and the possible risks of growth suppression must be carefully weighed. In addition, consideration should be given to referring the patient to a paediatric respiratory specialist.

Drug Interactions

The metabolism of budesonide is primarily mediated by CYP3A4, one of the cytochrome p450 enzymes. Inhibitors of this enzyme, e.g. ketoconazole, itraconazole HIV protease inhibitors and cobicistat-containing products, can therefore increase systemic exposure to budesonide. The combination of Pulmicort 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. Care should be exercised when budesonide is co-administered with long-term ketoconazole and other known CYP3A4 inhibitors (e.g., ritonavir, atazanavir, clarithromycin, indinavir, itraconazole, nefazodone, nelfinavir, saquinavir, telithromycin). Limited data on the interaction of high dose inhaled budesonide indicate marked increase 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 mcg). 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. The suppressive effect on adrenal function is additive if used concomitantly with systemic/ intranasal steroids. Because adrenal function may be suppressed, an ACTH stimulation test for diagnosing pituitary insufficiency might show false results (low values).

Use in Special Population

Patient with Hepatic Impairment

Formal pharmacokinetic studies using budesonide respules have not been conducted in patients with hepatic impairment. However, since budesonide is predominantly cleared by hepatic metabolism, impairment of liver
function may lead to accumulation of budesonide in plasma. Therefore, patients with hepatic disease should be closely monitored.

**Pregnant Women**

Most results from prospective epidemiological studies and world-wide post-marketing data have not been able to detect an increased risk for adverse effects for the foetus and newborn child from the use of inhaled budesonide during pregnancy. In animal studies, glucocorticosteroids have been shown to induce malformations. This is not likely to be relevant for humans given recommended doses, but therapy with inhaled budesonide should be regularly reviewed and maintained at the lowest effective dose. It is important for both foetus and mother to maintain an adequate asthma treatment during pregnancy. As with other drugs administered during pregnancy, the benefit of the administration of budesonide for the mother should be weighed against the risks to 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.

**Lactating Women**

Budesonide is excreted in breast milk. However, at therapeutic doses of budesonide respules no effects on the suckling child are anticipated. Budesonide respules can be used during breast feeding. Maintenance treatment with inhaled budesonide (200 or 400 micrograms twice daily) in asthmatic nursing women results in negligible systemic exposure to budesonide in breast-fed infants. In a pharmacokinetic study, the estimated daily infant dose was 0.3% of the daily maternal dose for both dose levels, and the average plasma concentration in infants was estimated to be 1/600th of the concentrations observed in maternal plasma, assuming complete infant oral bioavailability. Budesonide concentrations in infant plasma samples were all less than the limit of quantification. Based on data from inhaled budesonide and the fact that budesonide exhibits linear pharmacokinetic properties within the therapeutic dosage intervals after nasal, inhaled, oral and rectal administrations, at therapeutic doses of budesonide, exposure to the breast-fed child is anticipated to be low.

**Pediatric Patients**

Interaction studies have only been performed in adults. Safety and effectiveness in children six months to 12 months of age has been evaluated but not established. Safety and effectiveness in children 12 months to 8 years of age have been established. A 12-week study in 141 pediatric patients 6 to 12 months of age with mild to moderate asthma or recurrent/persistent wheezing was conducted. All patients were randomized to receive either 0.5 mg or 1 mg of Budesonide respules or placebo once daily. Adrenal-axis function was assessed with an ACTH stimulation test at the beginning and end of the study, and mean changes from baseline in this variable did not indicate adrenal suppression in patients who received Budesonide respules versus placebo. However, on an individual basis, 7 patients in this study (6 in the Budesonide respules treatment arms and 1 in the placebo arm) experienced a shift from having a normal baseline stimulated cortisol level to having a subnormal level at Week 12. Pneumonia was observed more frequently in patients treated with Budesonide respules than in patients treated with placebo, (N = 2, 1, and 0) in the Budesonide respules 0.5 mg, 1 mg, and placebo groups, respectively. A dose dependent effect on growth was also noted in this 12-week trial. Infants in the placebo arm experienced an average growth of 3.7 cm over 12 weeks compared with 3.5 cm and 3.1 cm in the Budesonide respules 0.5 mg and 1 mg arms respectively. This corresponds to estimated mean (95% CI) reductions in 12-week growth velocity between placebo and Budesonide respules 0.5 mg of 0.2 cm (-0.6 to 1.0) and between placebo and Budesonide respules 1 mg of 0.6 cm (-0.2 to 1.4). These findings support that the use of Budesonide respules in infants 6 to 12 months of age may result in systemic effects and are consistent with findings of growth suppression in other studies with inhaled corticosteroids.
Controlled clinical studies have shown that inhaled corticosteroids may cause a reduction in growth velocity in pediatric patients. In these studies, the mean reduction in growth velocity was approximately one centimeter per year (range 0.3 to 1.8 cm per year) and appears to be related to dose and duration of exposure. This effect has been observed in the absence of laboratory evidence of hypothalamic-pituitary-adrenal (HPA)-axis suppression, suggesting that growth velocity is a more sensitive indicator of systemic corticosteroid exposure in pediatric patients than some commonly used tests of HPA-axis function. The long-term effects of this reduction in growth velocity associated with orally inhaled corticosteroids, including the impact on final adult height, are unknown. The potential for “catch up” growth following discontinuation of treatment with orally inhaled corticosteroids has not been adequately studied.

In a study of asthmatic children 5-12 years of age, those treated with budesonide administered via a dry powder inhaler 200 mcg twice daily (n=311) had a 1.1-centimeter reduction in growth compared with those receiving placebo (n=418) at the end of one year; the difference between these two treatment groups did not increase further over three years of additional treatment. By the end of four years, children treated with the budesonide dry powder inhaler and children treated with placebo had similar growth velocities. Conclusions drawn from this study may be confounded by the unequal use of corticosteroids in the treatment groups and inclusion of data from patients attaining puberty during the course of the study. The growth of pediatric patients receiving inhaled corticosteroids, including Budesonide respules, should be monitored routinely (e.g., via stadiometry). The potential growth effects of prolonged treatment should be weighed against clinical benefits obtained and the risks and benefits associated with alternative therapies. To minimize the systemic effects of inhaled corticosteroids, including Budesonide respules, each patient should be titrated to his/her lowest effective dose.

**Geriatric Patients**

Of the 215 patients in 3 clinical trials of Budesonide respules in adult patients, 65 (30%) were 65 years of age or older, while 22 (10%) were 75 years of age or older. No overall differences in safety were observed between these patients and younger patients, and other reported clinical or medical surveillance experience has not identified differences in responses between the elderly and younger patients.

**Effects of Ability to Drive and Use Machines**

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

**Undesirable Effects**

The following definitions apply to the incidence of undesirable effects: Frequencies are defined as: very common (≥1/10); common (≥1/100 to <1/10); uncommon (≥1/1,000 to <1/100); rare (≥1/10,000 to <1/1,000); very rare (<1/10,000).

**Endocrine Disorders**

Rare: Signs and symptoms of systemic corticosteroid effects, including adrenal suppression and growth retardation**.

**Eye Disorders**

Uncommon: Cataracts, Vision blurred
Unknown: glaucoma

**Immune System Disorders**

Rare: Immediate and delayed hypersensitivity reactions* including, anaphylaxis and anaphylactic reaction, angioedema, bronchospasm, rash, contact dermatitis, and urticaria

**Infection and Infestation**

Common: Pneumonia (in COPD patients), oropharyngeal candidiasis

**Musculoskeletal and Connective Tissue Disorders**
Uncommon Muscle spasm

Nervous System Disorders
Uncommon: Tremor***

Psychiatric Disorders
Uncommon: Anxiety, Depression
Rare: psychomotor hyperactivity, Sleep disorders, Aggression and behavioural changes (predominantly in children).

Respiratory, Thoracic and Mediastinal Disorders
Common: Cough, hoarseness and throat irritation.
Rare: Bronchospasm, Dysphonia, Hoarseness****

Skin and Subcutaneous Tissue Disorders
Rare: Skin bruising,

* refer to Description of selected adverse reactions; facial skin irritation, below
** refer to Paediatric population, below
*** based on the frequency reported in clinical trials
**** rare in children.

Occasionally, signs or symptoms of systemic glucocorticosteroid-side effects may occur with inhaled glucocorticosteroids, probably depending on dose, exposure time, concomitant and previous corticosteroid exposure, and individual sensitivity.

Description of selected adverse reactions
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. As with other inhalation therapy, paradoxical bronchospasm may occur in very rare cases. Facial skin irritation, as an example of a hypersensitivity reaction, has occurred in some cases when a nebulizer with a face mask has been used. To prevent irritation, the facial skin should be washed with water after use of the face mask. In placebo-controlled studies, cataract was also uncommonly reported in the placebo group. Clinical trials with 13119 patients on inhaled budesonide and 7278 patients on placebo have been pooled. The frequency of anxiety was 0.52% on inhaled budesonide and 0.63% on placebo; that of depression was 0.67% on inhaled budesonide and 1.15% on placebo.

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

If case of any side effects, talk to your doctor or pharmacist or write to drugsafety@cipla.com. You can also report side effects directly via the national pharmacovigilance program of India by calling on 1800 180 3024 or you can report to Cipla Ltd on 18002677779. By reporting adverse events, you can help provide more information on the safety of this product.

Overdosage
BUDECORT respules contains 0.1 mg/ml disodium edetate which has been shown to cause bronchoconstriction at levels above 1.2mg/ml. Acute overdosage with budesonide respules, even in excessive doses, is not expected to be a clinical problem.

Pharmacological Properties

Mechanism of Action
Budesonide is an anti-inflammatory corticosteroid that exhibits potent glucocorticoid activity and weak...
mineralocorticoid activity. In standard in vitro and animal models, budesonide has approximately a 200-fold higher affinity for the glucocorticoid receptor and a 1000-fold higher topical anti-inflammatory potency than cortisol (rat croton oil ear edema assay). As a measure of systemic activity, budesonide is 40 times more potent than cortisol when administered subcutaneously and 25 times more potent when administered orally in the rat thymus involution assay. The clinical significance of these findings is unknown. The activity of budesonide respules is due to the parent drug, budesonide. In glucocorticoid receptor affinity studies, the 22R form was two times as active as the 22S epimer. In vitro studies indicated that the two forms of budesonide do not interconvert. The precise mechanism of corticosteroid actions on inflammation in asthma is not well 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 (e.g., mast cells, eosinophils, neutrophils, macrophages, and lymphocytes) and mediators (e.g., histamine, eicosanoids, leukotrienes, and cytokines) involved in allergic- and non-allergic-mediated inflammation. The anti-inflammatory actions of corticosteroids may contribute to their efficacy in asthma. Studies in asthmatic patients have shown a favorable ratio between topical anti-inflammatory activities and systemic corticosteroid effects over a wide dose range of inhaled budesonide in a variety of formulations and delivery systems including an inhalation-driven, multi-dose dry powder inhaler and the inhalation suspension for nebulization. This is explained by a combination of a relatively high local anti-inflammatory effect, extensive first pass hepatic degradation of orally absorbed drug (85-95%) and the low potency of metabolites.

Pharmacodynamic Properties

The therapeutic effects of conventional doses of orally inhaled budesonide are largely explained by its direct local action on the respiratory tract. To confirm that systemic absorption is not a significant factor in the clinical efficacy of inhaled budesonide, a clinical study in adult patients with asthma was performed comparing 400 mcg budesonide administered via a pressurized metered dose inhaler with a tube spacer to 1400 mcg of oral budesonide and placebo. The study demonstrated the efficacy of inhaled budesonide but not orally administered budesonide, even though systemic budesonide exposure was comparable for both treatments, indicating that the inhaled treatment is working locally in the lung. Thus, the therapeutic effect of conventional doses of orally inhaled budesonide are largely explained by its direct action on the respiratory tract. Improvement in the control of asthma symptoms following inhalation of budesonide respules can occur within 2-8 days of beginning treatment, although maximum benefit may not be achieved for 4-6 weeks. Budesonide administered via a dry powder inhaler has been shown in various challenge models (including histamine, methacholine, sodium metabisulfite, and adenosine monophosphate) to decrease bronchial hyperresponsiveness in asthmatic patients. The clinical relevance of these models is not certain. Pre-treatment with budesonide administered as 1600 mcg daily (800 mcg twice daily) via a dry powder inhaler for 2 weeks reduced the acute (early-phase reaction) and delayed (late-phase reaction) decrease in FEV following inhaled allergen challenge.

HPA Axis Effect: BUDECORT respules like other inhaled corticosteroid products, may impact the HPA axis, especially in susceptible individuals, in younger children, and in patients given high doses for prolonged periods.

Pharmacokinetic Properties

Absorption

In asthmatic children, 4-6 years of age, the total absolute bioavailability (i.e., lungs + oral) following administration of budesonide respules via a jet nebulizer was approximately 6% of the labelled dose. In children, a peak plasma concentration of 2.6 nmol/L was obtained approximately 20 minutes after nebulization of a 1 mg dose. Systemic exposure, as measured by AUC and C_{max}, is similar for young children
and adults after inhalation of the same dose of budesonide respules.

**Distribution**

In asthmatic children, 4–6 years of age, the volume of distribution of budesonide at steady state was 3 L/kg, approximately the same as in healthy adults. Budesonide is 85-90% bound to plasma proteins, the degree of binding being constant over the concentration range (1-100 nmol/L) achieved with, and exceeding, recommended doses. Budesonide showed little or no binding to corticosteroid-binding globulin. Budesonide rapidly equilibrated with red blood cells in a concentration-independent manner, with a blood/plasma ratio of about 0.8.

**Metabolism**

*In vitro* studies with human liver homogenates have shown that budesonide is rapidly and extensively metabolized. Two major metabolites, formed via cytochrome P450 (CYP) isoenzyme 3A4 (CYP3A4)-catalysed biotransformation, have been isolated and identified as 16-alpha-hydroxyprednisolone and 6-beta-hydroxybudesonide. The corticosteroid activity of each of these two metabolites is less than 1% of that of the parent compound. No qualitative difference between the in vitro and in vivo metabolic patterns has been detected. Negligible metabolic inactivation was observed in the human lungs and in serum preparations.

**Excretion**

Budesonide is excreted in the urine and the faeces in the form of metabolites. In adults, approximately 60% of an intravenous radiolabelled dose was recovered in the urine. No unchanged budesonide was detected in the urine.

**Special Populations**

No differences in pharmacokinetics due to race, gender, or age have been identified.

*Hepatic Insufficiency:*

Reduced liver function may affect the elimination of corticosteroids. The pharmacokinetics of budesonide were affected by compromised liver function as evidenced by a doubled systemic availability after oral ingestion. The intravenous pharmacokinetics of budesonide were, however, similar in cirrhotic patients and in healthy adults.

*Nursing Mothers:*

The disposition of budesonide when delivered by inhalation from a dry powder inhaler at doses of 200 or 400 mcg twice daily for at least 3 months was studied in eight lactating women with asthma from 1 to 6 months postpartum. Systemic exposure to budesonide in these women appears to be comparable to that in non-lactating women with asthma from other studies. Breast milk obtained over eight hours post-dose revealed that the maximum concentration of budesonide for the 400 and 800 mcg doses was 0.39 and 0.78 nmol/L, respectively, and occurred within 45 minutes after dosing. The estimated oral daily dose of budesonide from breast milk to the infant is approximately 0.007 and 0.014 mcg/kg/day for the two dose regimens used in this study, which represents approximately 0.3% to 1% of the dose inhaled by the mother. Budesonide levels in plasma samples obtained from five infants at about 90 minutes after breast-feeding (and about 140 minutes after drug administration to the mother) were below quantifiable levels (<0.02 nmol/L in four infants and <0.04 nmol/L in one infant).

**Drug-Drug Interactions**

*Inhibitors of cytochrome P450 enzymes*

Ketoconazole: Ketoconazole, a strong inhibitor of cytochrome P450 (CYP) isoenzyme 3A4 (CYP3A4), the main metabolic enzyme for corticosteroids, increased plasma levels of orally ingested.

*Cimetidine:* At recommended doses, cimetidine, a non-specific inhibitor of CYP enzymes, had a slight but clinically insignificant effect on the pharmacokinetics of oral budesonide.
Nonclinical Properties

Carcinogenesis, Mutagenesis, Impairment of Fertility

In a two-year study in Sprague-Dawley rats, budesonide caused a statistically significant increase in the incidence of gliomas in male rats at an oral dose of 50 mcg/kg (approximately 0.5 and 0.1 times, respectively, the maximum recommended human daily inhalation dose (MRHDID) in adults and children 12 months to 8 years of age on a mcg/m² basis). No tumorigenicity was seen in male rats at oral doses up to 25 mcg/kg (approximately 0.2 and 0.04 times, respectively, the MRHDID in adults and children 12 months to 8 years of age on a mcg/m² basis) and in female rats at oral doses up to 50 mcg/kg (approximately 0.5 and 0.1 times, respectively, MRHDID in adults and children 12 months to 8 years of age on a mcg/m² basis). In two additional two-year studies in male Fischer and Sprague-Dawley rats, budesonide caused no gliomas at an oral dose of 50 mcg/kg (approximately 0.5 and 0.1 times, respectively, the MRHDID in adults and children 12 months to 8 years of age on a mcg/m² basis). However, in the male Sprague-Dawley rats, budesonide caused a statistically significant increase in the incidence of hepatocellular tumors at an oral dose of 50 mcg/kg (approximately 0.5 and 0.1 times, respectively, the MRHDID in adults and children 12 months to 8 years of age on a mcg/m² basis). The concurrent reference corticosteroids (prednisolone and triamcinolone acetonide) in these two studies showed similar findings. In a 91-week study in mice, budesonide caused no treatment-related carcinogenicity at oral doses up to 200 mcg/kg (approximately equivalent to and 0.1 times, respectively, the MRHDID in adults and children 12 months to 8 years of age on a mcg/m² basis). Budesonide was not mutagenic or clastogenic in six different test systems: Ames Salmonella/microsome plate test, mouse micronucleus test, mouse lymphoma test, chromosome aberration test in human lymphocytes, sex-linked recessive lethal test in Drosophila melanogaster, and DNA repair analysis in rat hepatocyte culture. Fertility and reproductive performance were unaffected in rats at subcutaneous doses up to 80 mcg/kg approximately equivalent to the MRHDID in adults on a mcg/m² basis. However, it caused a decrease in prenatal viability and viability in the pups at birth and during lactation, along with a decrease in maternal body-weight gain, at subcutaneous doses of 20 mcg/kg and above approximately 0.2 times than the MRHDID in adults on a mcg/m² basis. No such effects were noted at 5 mcg/kg (approximately 0.05 times the MRHDID in adults on a mcg/m² basis).

Animal Toxicology or Pharmacology

The acute toxicity of budesonide is low and of the same order of magnitude and type as that of the reference glucocorticosteroids studied (beclomethasone dipropionate, fluocinolone acetonide). Results from subacute and chronic toxicity studies show that the systemic effects of budesonide are less severe than, or similar to, those observed after administration of other glucocorticosteroids, e.g. decreased body-weight gain and atrophy of lymphoid tissues and adrenal cortex. An increased incidence of brain gliomas in male rats, in a carcinogenicity study, could not be verified in a repeat study in which the incidence of gliomas did not differ between any of the groups on active treatment (budesonide, prednisolone, triamcinolone acetonide) and the control groups. Liver changes (primary hepatocellular neoplasms) found in male rats in the original carcinogenicity study were noted again in the repeat study with budesonide, as well as with the reference glucocorticosteroids. These effects are most probably related to a receptor effect and thus represent a class effect. Available clinical experience shows that there are no indications that budesonide, or other glucocorticosteroids, induce brain gliomas or primary hepatocellular neoplasms in man. In animal reproduction studies, corticosteroids such as budesonide have been shown to induce malformations (cleft palate, skeletal malformations). However, these animal experimental results do not appear to be relevant in humans at the recommended doses. Animal studies have also identified an involvement of excess prenatal
glucocorticosteroids, in increased risk for intrauterine growth retardation, adult cardiovascular disease and permanent changes in glucocorticoid receptor density, neurotransmitter turnover and behaviour at exposures below the teratogenic dose range.

**Description**

Budesonide is a corticosteroid designated chemically as (RS)-11β, 16α, 17, 21-tetrahydroxypregna-1, 4-diene-3, 20-dione cyclic 16, 17-acetal with butyraldehyde. Budesonide is provided as a mixture of two epimers (22R and 22S). The empirical formula of budesonide is $C_{25}H_{34}O_6$ and its molecular weight is 430.5. Its structural formula is:

![Structural formula of budesonide](image)

Budesonide is a white to off-white, tasteless, odorless powder that is practically insoluble in water and in heptane, sparingly soluble in ethanol, and freely soluble in chloroform.

**Pharmaceutical Particulars**

- **Incompatibilities**
  
  BUDECORT respules can be mixed with solutions for nebulization of ASTHALIN, LEVOLIN, IPRAVENT, MUCINAC and INHALEX respules. The admixture should be used within 30 minutes.

- **Shelf-life**
  
  As on the pack

- **Packaging Information**
  
  BUDECORT respule 0.5 mg is available as unit-dose vial of 2 ml. Available in a pack of 5 strips. Each strip contains 8 unit-dose vials of 2ml.
  
  BUDECORT respule 1 mg is available as unit-dose vial of 2 ml. Available in a pack of 5 strips. Each strip contains 4 unit-dose vials of 2ml.

- **Storage and Handling Information**
  
  Store below 25°C. Do not freeze. Store the respules in the foil envelope to protect them from light. The respule should be opened immediately before use and any solution remaining after use should be discarded.

- **Patient Counselling Information**
  
  Read all of this leaflet carefully before you start using this medicine because it contains important information for you.
  
  Keep this leaflet. You may need to read it again.
If you have any further questions, ask your doctor or pharmacist. This medicine has been prescribed for you only. Do not pass it on to others. It may harm them, even if their signs of illness are the same as yours. If you get any side effects, talk to your doctor or pharmacist. This includes any side effects not listed in this leaflet.

1. What BUDECORT respules are and what they are used for?

BUDECORT respules contain a medicine called budesonide. This belongs to a group of medicines called ‘corticosteroids’. It works by reducing and preventing swelling and inflammation in your lungs. BUDECORT respules are used to treat asthma. They are also used to treat croup in infants and children.

A Respule is a small plastic container that contains a liquid. The liquid is put into a machine called a nebulizer. This machine turns the medicine into a fine mist which you breathe in through a face mask or mouthpiece.

2. What you need to know before you use BUDECORT respules?

Do not use BUDECORT respules:
- If you are allergic to budesonide or any of the other ingredients of this medicine.

Warnings and precautions

Talk to your doctor or pharmacist before using BUDECORT respules, tell your doctor or pharmacist if:
- You have a lung infection.
- You have a cold or chest infection.
- You have liver problems.

Contact your doctor if you experience blurred vision or other visual disturbances.

Other medicines and BUDECORT respules

Tell your doctor or pharmacist if you are taking, have recently taken or might take any other medicines. This includes medicines that you buy without a prescription and herbal medicines. This is because BUDECORT respules can affect the way some medicines work and some medicines can have an effect on BUDECORT respules and your doctor may wish to monitor you carefully.

In particular, tell your doctor or pharmacist if you are taking any of the following medicines:
- Steroid medicines.
- Medicines to treat fungal infections (such as itraconazole and ketoconazole).
- HIV medicines (such as ritonavir or cobicistat-containing products).

Pregnancy, breast-feeding and fertility

If you are pregnant or breast-feeding, think you may be pregnant or are planning to have a baby, ask your doctor or pharmacist for advice before using this medicine - do not use BUDECORT respules unless your doctor tells you to.

If you get pregnant while using BUDECORT respules, do not stop using BUDECORT respules but talk to your doctor immediately.

Driving and using machines

BUDECORT respules are not likely to affect you being able to drive or use any tools or machines.

3. How to use BUDECORT respules?

Always use this medicine exactly as your doctor or pharmacist has told you. Check with your doctor or pharmacist if you are not sure.

The solution in a respule must be put into a nebulizer and made into a fine mist before it can be breathed in. It is then inhaled through a face mask or mouthpiece. Instructions for using your nebulizer are given after the section ‘How much to take’.
Note: Do not use an ultrasonic nebulizer with BUDECORT respules.

Your asthma may improve within 2 days. However, it can take up to 4 weeks for the medicine to have its full effect. It is important to use BUDECORT respules every day, even if you have no asthma symptoms at the time.

How much to take?

Asthma

Your doctor will tell you how much to take. This will depend on how severe your asthma is. Your doctor may lower your dose as your asthma improves.

The recommended starting dose in adults and children over 12 years is 1 mg to 2 mg (milligrams), twice a day.

Children under 12 years are usually prescribed a lower dose of 0.5 mg to 1 mg, twice a day.

Croup

The recommended dose for infants and children is 2 mg a day. This may be given all in one go, or 1 mg may be given followed by another 1 mg 30 minutes later.

Instructions for using BUDECORT respules

1. Break off a respule from the strip. Leave the rest in the foil envelope.
2. Shake the respule gently.
3. Hold upright. Twist off the top of the respule to open.
4. Place the open end of the respule firmly inside the nebulizer cup. Squeeze slowly to put the liquid in the cup.
5. Throw the empty respule away. Put the top back on the nebulizer cup.
6. Connect one end of the cup to the face mask or mouthpiece.
7. Connect the other end of the cup to the air pump.
8. Gently shake the cup.
9. Turn on the nebulizer and breathe in the mist calmly and deeply using the face mask or mouthpiece.
   - If you are using a face mask, make sure the face mask fits tightly.
10. You will know when your treatment is complete because the fine mist will stop coming out of your mask or mouthpiece.
11. How long it takes to nebulize all the medicine depends on the type of equipment you use. It will also depend on the amount of medicine to be used.
12. Rinse your mouth with water. Spit out the water. Do not swallow it. If you have used a face mask, wash your face as well.
13. After each use, you must wash the nebulizer cup and mouthpiece (or face mask) in warm soapy water and rinse well. After washing, dry these parts by connecting to the air outlet or the compressor and blow air through them.

Important information about your asthma symptoms

Contact your doctor immediately if:

- Your breathing is getting worse or you often wake up at night with asthma.
- Your chest starts to feel tight in the morning or your chest tightness lasts longer than usual.

These signs could mean that your condition is not being properly controlled and you may need different or additional treatment immediately.

If you use more BUDECORT respules than you should

It is important that you take your dose as stated on the pharmacist’s label or as advised by your doctor. You
should not increase or decrease your dose without seeking medical advice. If you use more BUDECORT respules than you should, contact your doctor or pharmacist for advice.

If you forget to use BUDECORT respules
If you forget to take a dose, skip the missed dose and take the next dose as usual.
If you have any further questions on the use of this medicine, ask your doctor or pharmacist.

4. Possible side effects
Like all medicines, this medicine can cause side effects, although not everybody gets them.

If either of the following happen to you, stop using BUDECORT respules and talk to your doctor immediately:

- Swelling of your face, particularly around your mouth (with possible swelling of the lips, tongue, eyes, ears), rash, itching, contact dermatitis (a skin problem), hives and bronchospasm (tightening of the muscles in the airways which causes wheezing). This may mean that you are having an allergic reaction. This happens rarely, affecting less than 1 in 1,000 people.
- Sudden wheezing after inhaling your medicine. This happens very rarely, affecting less than 1 in 10,000 people.

Other possible side effects:

**Common (may affect up to 1 in 10 people)**
- Thrush (a fungal infection) in the mouth. This is less likely if you rinse your mouth out with water after using BUDECORT respules.
- Mild sore throat, coughing and a hoarse voice.
- Pneumonia (infection of the lung) in COPD patients.

Tell your doctor if you have any of the following while taking budesonide, they could be symptoms of a lung infection:

- fever or chills
- increased mucus production, change in mucus colour
- increased cough or increased breathing difficulties.

**Uncommon (may affect up to 1 in 100 people)**
- Feeling worried, restless and nervous.
- Depression.
- Trembling and shaking.
- Cataract (clouding of the lens in the eye).
- Muscle cramps.
- Blurred vision.

**Rare (may affect up to 1 in 1,000 people)**
- Rash on the face after using the face mask. You can stop this from happening by washing your face after using the face mask.
- Sleeping problems, feeling over-excited or irritable. These effects are more likely to occur in children.
- Bruising of the skin.
- Loss of voice.
- Hoarse voice (in children).

Inhaled corticosteroids can affect the normal production of steroid hormones in your body, particularly if you use high doses for a long time. The effects include:

- changes in bone mineral density (thinning of the bones)
- glaucoma (increased pressure in the eye)
- a slowing of the rate of growth of children and adolescents (rare). If high doses are given over several years, final height may be reduced by about 1 cm.
an effect on the adrenal gland (a small gland next to the kidney) (rare).
These effects are much less likely to happen with inhaled corticosteroids than with corticosteroid tablets.

**Reporting of side effects**
If you get any side effects talk to your doctor or pharmacist. This includes any side effects not listed in this leaflet.

To report SUSPECTED ADVERSE REACTIONS, contact doctor or pharmacist or write to drugsafety@cipla.com.
You can also report side effects directly via the national pharmacovigilance program of India by calling on 1800 180 3024 or you can report to Cipla Ltd on 18002677779. By reporting adverse events, you can help provide more information on the safety of this product.

5. How to store BUDECORT respules?

Keep this medicine out of the sight and reach of children.
Do not use this medicine after the expiry date which is stated on the carton and foil envelope. The expiry date refers to the last day of that month.
Do not store above 30°C. Do not freeze. Store in an upright position. Store BUDECORT respules in their original carton and foil, and out of direct sunlight.
Once a foil envelope has been opened, the respules inside should be used within 3 months. Note: It is best to mark the opening date on the foil envelope to help you remember.
If only some of the suspension is used, the remaining suspension in the respule should be thrown away immediately.

6. Contents of the pack and other information

What does BUDECORT respule 0.5 mg & 1 mg contain?
The active substance is budesonide. Each BUDECORT respule of 0.5 mg & 1 mg contains and 0.5mg & 1 mg of the active ingredient, budesonide.
The other ingredients are disodium edetate, sodium chloride, polysorbate 80, citric acid, sodium citrate and water for injections.

**Details Of Manufacturer**

Mfg By Cipla Ltd
Registered Office: Cipla House,
Peninsula Business Park, Ganpatrao Kadam Marg,
Lower Parel, Mumbai – 400 013, India

**Details Of Permission Or Licence Number With Date**

M/447/2007 dated: 12/01/2012

**Date Of Revision**

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**BUDECORT Respules**

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