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

Budesonide Inhalation Suspension

Budecort Respules

1. QUALITATIVE AND QUANTITATIVE COMPOSITION:

Budecort 0.5 mg Respules
Each 2 ml contains
Budesonide USP ..... 0.5 mg

Budecort 1 mg Respules
Each 2 ml contains
Budesonide USP ..... 1 mg

2. PHARMACEUTICAL FORM:
Nebulizer Suspension for Inhalation

3. CLINICAL PARTICULARS:

4.1 Therapeutic indications:
Budesonide Respules contain the potent, non-halogenated, corticosteroid, budesonide, for use in bronchial asthma, in patients where use of a pressurised inhaler or dry powder formulation is unsatisfactory or inappropriate.
Budesonide Respules are also recommended for use in infants and children with acute laryngotracheobronchitis - Group.

4.2 Posology and method of administration:
Dosage schedules: Budesonide Respules should be administered from suitable nebulisers. The dose delivered to the patient varies depending on the nebulising equipment used. The nebulisation time and the dose delivered is dependent on flow rate, volume of nebuliser 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 nebulisers is 2 - 4 ml. The dosage of BudesonideRespules 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 per 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 BudesonideRespules is:
Adults (including elderly): Usually 1 - 2 mg twice daily. In very severe cases the dosage may be further increased.
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 individualised and be the lowest dose which keeps the patient symptom-free.
Adults (including elderly and children 12 years and older): 0.5 - 1 mg twice daily.
Children 3 months to 12 years: 0.25 - 0.5 mg twice daily.

Patients maintained on oral glucocorticosteroids
BudesonideRespules may permit replacement or significant reduction in dosage of oral glucocorticosteroids while maintaining asthma control.

Acute laryngotracheobronchitis – croup
In infants and children with croup, the usual dose is 2 mg of nebulised budesonide. This dose is given as a single administration, or as two 1 mg doses separated by 30 minutes.

Instruction for correct use of BudesonideRespules
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 nebuliser cup. The empty Respule should be thrown away and the top of the nebuliser cup replaced.
BudesonideRespules should be administered via a jet nebuliser equipped with a mouthpiece or suitable face mask. The nebuliser should be connected to an air compressor with an adequate air flow (6-8 L/min), and the fill volume should be 2-4ml.
The dosage of BudesonideRespules should be adjusted to the need of the individual.

4.3 Contraindications:
History of hypersensitivity to budesonide or any of the excipients.

4.4 Special warnings and precautions for use:
Special care is needed in patients with pulmonary tuberculosis and viral infections of 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, BudesonideRespules alone should be sufficient therapy.
Steroid-dependent patients: When transfer from oral corticosteroid to treatment with budesonide is initiated, the patient should be in a relatively stable phase. Budesonide 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 budesonide for the oral corticosteroid.
During transfer from oral therapy to 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 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 a severe reaction occurs, treatment should be reassessed and an alternative therapy instituted if necessary.
Prolonged treatment with high doses of inhaled corticosteroids, particularly higher than the recommended doses, may result in clinically significant adrenal suppression. Additional systemic corticosteroid cover should be considered during periods of stress or elective surgery.
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 the height of children receiving prolonged treatment with inhaled corticosteroids is regularly monitored. If growth is slowed, therapy should be reviewed, with the aim of reducing the dose of inhaled corticosteroid, if possible, to the lowest dose at which effective control of asthma is maintained. In addition, consideration should be given to referring the patient to a paediatric respiratory specialist.
BudesonideRespules 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.
Reduced liver function may affect the elimination of glucocorticosteroids. 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.
In vivo studies have shown that oral administration of ketoconazole and itraconazole (known inhibitors of CYP3A4 activity in the liver and in the intestinal mucosa causes an increase in the systemic exposure to budesonide. Concomitant treatment with ketoconazole and itraconazole or other potent CYP3A4 inhibitors should be avoided (see section 4.5 Interactions). If this is not possible, the time interval between administration of the interacting drugs should be as long as possible. A reduction in the dose of budesonide should also be considered.

4.5 Interaction with other medicinal products and other forms of interaction:
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.

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4.6 Pregnancy and lactation:
Data on approximately 2000 exposed pregnancies indicate no increased teratogenic risk associated with the use of inhaled budesonide. 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.
The administration of budesonide during pregnancy requires that the benefits for the mother be weighed against the risk 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.
Budesonide is excreted in breast milk. However, at therapeutic doses of budesonide respules no effects on the suckling child are anticipated. BudesonideRespules can be used during breast feeding.

4.7 Effects on ability to drive and use machines:
Budesonide does not affect the ability to drive or use machinery.

4.8 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, bronchospasm and anaphylactic reaction. • 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.
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.
Facial skin irritation has occurred in some cases when a nebuliser with a face mask has been used. To prevent irritation, the facial skin should be washed with water after use of the face mask.

4.9 Overdose:
BudesonideRespules contains 0.1 mg/ml disodium edetate which has been shown to cause bronchoconstriction at levels above 1.2 mg/ml. Acute overdose with budesonide should not present a clinical problem.

5.PHARMACOLOGICAL PROPERTIES:
Pharmacodynamic properties:
Budesonide is a glucocorticosteroid which possesses a high local anti-inflammatory action, with a lower incidence and severity of adverse effects than those seen with oral corticosteroids.
Pharmacotherapeutic group: Other drugs for obstructive airway diseases, inhalants, glucocorticoids. ATC Code: RO3B A02.

Topical anti-inflammatory effect
The exact mechanism of action of glucocorticosteroids in the treatment of asthma is not fully understood. Anti-inflammatory actions, such as inhibition of inflammatory mediator release and inhibition of cytokine-mediated immune response are probably important.
A clinical study in asthmatics comparing inhaled and oral budesonide at doses calculated to achieve similar systemic bioavailability demonstrated statistically significant evidence of efficacy with inhaled but not oral budesonide compared with placebo. Thus, the therapeutic effect of conventional doses of inhaled budesonide may be largely explained by its direct action on the respiratory tract.
In a provocation study pre-treatment with budesonide for four weeks has shown decreased bronchial constriction in immediate as well as late asthmatic reactions.

Onset of effect
After a single dose of orally inhaled budesonide, delivered via dry powder inhaler, improvement of the lung function is achieved within a few hours. After therapeutic use of orally inhaled budesonide delivered via dry powder inhaler, improvement in lung function has been shown to occur within 2 days of initiation of treatment although maximum benefit may not be achieved for up to 4 weeks.

Airway reactivity
Budesonide has also been shown to decrease airway reactivity to histamine and methacholine in hyperreactive patients.

Exercise-induced asthma
Therapy with inhaled budesonide has effectively been used for prevention of exercise-induced asthma.

Growth
Limited data from long-term studies suggest that most children and adolescents treated with inhaled budesonide ultimately achieve their adult target height. However, an initial small but transient reduction in growth (approximately 1 cm) has been observed. This generally occurs within the first year of treatment.

5.1 Pharmacokinetic properties:
Budesonide undergoes an extensive biotransformation in the liver, to metabolites of low glucocorticosteroid activity. The glucocorticosteroid activity of the major metabolites, 6 β-hydroxybudesonide and 16α-hydroxyprednisolone, is less than 1% of that of budesonide. The metabolism of budesonide is primarily mediated by CYP3A4, one of the cytochrome p450 enzymes.
In a study, 100 mg ketoconazole taken twice daily, increased plasma levels of concomitantly administered oral budesonide (single dose of 10 mg) on average, by 7.8-fold. Information about this interaction is lacking for inhaled budesonide, but marked increases in plasma levels could be expected.
Of the fraction of budesonide which is swallowed, approximately 90% is inactivated at first passage through the liver. The maximal plasma concentration after inhalation of 1 mg budesonide, delivered via dry powder inhaler, is about 3.5 nmol/L and is reached after about 20 minutes.

5.2 Preclinical safety data:
The acute toxicity of budesonide is low and of the same order of magnitude and type as that of the reference glucocorticosteroids studied (beclomethasonedipropionate, fluocinoloneacetonide).
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.

Storage:
Store upright at controlled room temperature 20-25°C (68-77°F) and protected from light. Do not freeze.

Presentation
Budecort 0.5 mg respules
Carton containing 6 combipacks having 5 respules of 2.0ml

Budecort 1 mg respules
Carton containing 6 combipacks having 5 respules of 2.0ml

Cipla

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RESPULES

PACKAGING DEVELOPMENT

Product Name: Budecort Respules	**Material No.:** 21061532	**Version:** 01	**Item:** Leaflet	**Co-ordinator:** Sandhya	**Artist:** Vaibhav	**Date:** 21-3-17
Colours: BLUE WOOL TEST VALUE 5-8 (LIGHT FASTENING DATA) ■ **Black**				**INK:** Oil based Ink from DIC OR MICRO		
Design: Folded		**Supersedes/Reference:** 9451 U		**Software:** Illustrator CC		
Fonts: –––-			**Links:** NA			
Actual Size: 190 x 180 mm	**Size after folding:** 48 x 45 mm	**Pharmacode : 6470_STD**		**Grain Direction :** Parallel to length		**Screen : #** __
Material: 54 GSM Maplitho Paper				**Varnish:**	**Artwork Print Size:** ☐ actual ☐ scaled	
Path: PC: F:\Vaibhav\April 2016 to March 2017\Sandhya\21061532 Budecort Respules Leaflet Iran.ai						

- **Instructions / Remark:**
- Any deviation must be brought to the notice of packaging development co-ordinator immediately.
- For any clarification, please contact packaging development co-ordinator immediately.
  NO CHANGES IN ARTWORK SHOULD BE DONE BY THE PRINTER
- The printer should verify the e-proof against the approved artwork before submitting for approval and the e-proof should have printer details .

Checked by	Artist	Cordinator	file loaded in Server	Section Head
Pharma Code	☐	☐		
2D Code	☐	☐		
QR Code	☐	☐		
Bar Code	☐	☐		
Artwork	☐	☐		
Spell check	☐	☐		