

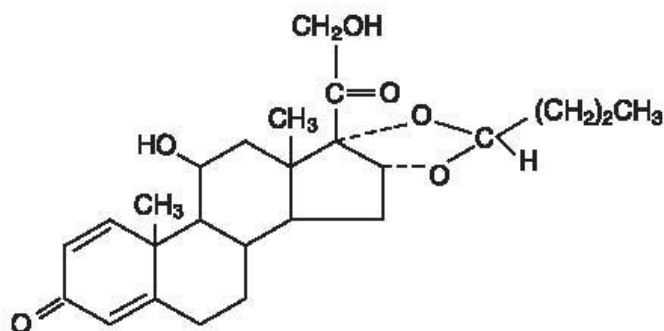
# **PULMICORT® RESPULES®** **(budesonide)**

## **1. NAME OF THE MEDICINAL PRODUCT**

Budesonide

## **2. QUALITATIVE AND QUANTITATIVE COMPOSITION**

The active ingredient, budesonide, is a non-halogenated glucocorticoid structurally related to 16 $\alpha$  hydroxyprednisolone. The chemical name is 16 $\alpha$ , 17 $\alpha$ -22R, S-propylmethylenedioxy-pregna-1, 4-diene-11 $\beta$ , 21-diol-3, 20-dione; MW 430.5.



CAS Number: 51333-22-3

Budesonide is a white to off-white powder, freely soluble in chloroform, sparingly soluble in ethanol and practically insoluble in water and heptane. Budesonide melts with decomposition between 224°C and 231.5°C.

PULMICORT RESPULES contain budesonide 0.5 mg/2 mL or 1.0 mg/2 mL as the active ingredient plus, disodium edetate, sodium chloride, polysorbate 80 (E 433) citric acid - anhydrous (E 330), sodium citrate (E 331) and water for injections.

## **3. PHARMACEUTICAL FORM**

PULMICORT RESPULES nebulising suspension for inhalation is a white to off-white suspension in plastic single dose units.

## **4. CLINICAL PARTICULARS**

### **4.1 Therapeutic indications**

Treatment of bronchial asthma.

PULMICORT may also be used when replacement or reduction in oral steroid therapy is desirable.

PULMICORT RESPULES provide budesonide in a nebulising suspension which is recommended when other modes of steroid therapy are unsuitable.

## **4.2 Posology and method of administration**

### **Bronchial asthma**

#### **PULMICORT RESPULES Nebulising Suspension**

PULMICORT RESPULES should be administered from a suitable nebuliser. The dose delivered to the patient varies between 40-60% of the nominal dose depending on the nebulising equipment used. The nebulisation time and the dose delivered is dependent on flow rate, volume of nebuliser chamber and volume fill. A suitable fill for most nebulisers is 2-4 mL.

Some sedimentation may occur during storage of PULMICORT RESPULES. If this does not readily resuspend completely upon shaking, the RESPULE should be discarded.

#### **Dosage initially, or during periods of severe asthma, or while reducing oral corticosteroids**

##### ***Adults***

1-2 mg twice daily.

##### ***Children***

0.5-1 mg twice daily.

#### **Maintenance**

The maintenance dose should be individualised and should be the lowest dose, which keeps the patient symptom-free. Recommended doses are:

##### ***Adults***

0.5-1 mg twice daily.

##### ***Children***

0.25-0.5 mg twice daily.

### **Patient Instructions**

1. It is essential that the patient be instructed that PULMICORT is a preventative agent, which must be taken regularly and is not to be used as sole therapy to relieve an acute asthma attack.
2. The patient should be instructed in the proper use of the inhaler device considered appropriate for his/her particular needs. A full set of instructions are provided with each pack of PULMICORT.
3. Patients also receiving bronchodilators by inhalation should be advised to use the bronchodilator before PULMICORT in order to enhance its penetration into the bronchial tree. Several minutes should elapse between the use of the two inhalers.

### **Clinical Management**

#### **Patients - not oral corticosteroid dependent**

Treatment with the recommended doses of PULMICORT usually gives a therapeutic effect within 10 days.

In patients with excessive mucus secretion in the bronchi, an initial short course (about 2 weeks) of an oral corticosteroid, commencing with a high dose and gradually reducing, should be given in addition to PULMICORT. Treatment should be continued for at least one month before determining the maximal response to a given dose of PULMICORT.

#### **Patients - oral corticosteroid dependent**

Transfer of patients dependent on oral corticosteroids to PULMICORT requires special care because of slow normalisation of the disturbed hypothalamic-pituitary-adrenal function caused by extended treatment with oral corticosteroids (see Section 4.4 Special warnings and precautions for use - Oral Corticosteroid usage and Potential systemic effects of inhaled corticosteroids - HPA axis suppression and adrenal insufficiency).

When PULMICORT treatment is initiated, the patient's asthma should be in a relatively stable phase. A high dose of PULMICORT should then be given in combination with the previously used oral corticosteroid dose for about 2 weeks. The dose of oral corticosteroid should then be reduced gradually (for example 1mg prednisolone or equivalent every four days, however, the exact rate of reduction will depend on individual clinical response) to the lowest possible level. The dose of PULMICORT should not be changed while the patient remains on oral corticosteroids.

In many cases, it may be possible to completely replace the oral corticosteroid with inhaled PULMICORT. In other patients, a low oral steroid maintenance dose may be necessary. Some patients may experience uneasiness during the withdrawal of oral corticosteroids due to the decreased systemic corticosteroid effect. The physician may need to actively support the patient and to stress the reason for the PULMICORT treatment.

The length of time needed for the body to regain sufficient natural corticosteroid production is often extended and may be as long as 12 months. Transferred patients should carry a warning card indicating that they may need supplementary systemic corticosteroids during periods of stress, such as severe infection, trauma or surgery. During such times it may be necessary to give additional oral corticosteroids.

During transfer from oral therapy to PULMICORT, a lower systemic steroid action is experienced. Earlier allergic symptoms may recur (eg. rhinitis, eczema, conjunctivitis) or patients may suffer from tiredness, headache, muscle and joint pain, lassitude and depression or occasionally nausea and vomiting. In these cases, further medical support may be required.

### **4.3 Contraindications**

Hypersensitivity to budesonide or any other ingredients.

### **4.4 Special warnings and precautions for use**

#### **Bronchospasm**

PULMICORT is not indicated for rapid relief of bronchospasm. PULMICORT is therefore not suitable as sole therapy for the treatment of status asthmaticus or other acute exacerbations of asthma where intensive measures are required.

If patients find short-acting bronchodilator treatment ineffective, or they need more inhalations than usual, medical attention must be sought. This indicates a worsening of the underlying conditions, and warrants a reassessment of the therapy.

## **Oral corticosteroid usage**

Particular care is needed in patients who are being transferred from oral corticosteroids to PULMICORT, since they may remain at risk of impaired adrenal function for some considerable time (see Section 4.4 Special warnings and precautions for use - Potential systemic effect of inhaled corticosteroids: HPA axis suppression and adrenal insufficiency). These patients should be instructed to carry an appropriate warning card (see Clinical Management: Patients - Oral corticosteroid dependent).

Patients previously receiving high doses of systemic steroids may regain earlier allergic symptoms such as rhinitis and eczema when transferred from oral therapy to PULMICORT due to the reduced systemic steroid effect of budesonide (see Clinical Management: Patients - Oral corticosteroid dependent).

## **Potential systemic effects of inhaled corticosteroids**

Inhaled steroids are designed to direct glucocorticoid delivery to the lungs in order to reduce overall systemic glucocorticoid exposure and side effects. However inhaled steroids may have adverse effects; possible systemic effects of inhaled steroids include depression of the HPA axis, reduction of bone density, cataracts and glaucoma and retardation of growth rate in children. In steroid-dependent patients, prior systemic steroid usage may be a contributing factor (see Section 4.4 Special warnings and precautions for use - Oral corticosteroid usage), but such effects may occur amongst patients who use only inhaled steroids regularly.

### **HPA axis suppression and adrenal insufficiency**

Dose-dependent HPA axis suppression (as indicated by 24 hour urinary and/or plasma cortisol AUC) has been observed with inhaled budesonide, although the physiological circadian rhythms of plasma cortisol were preserved. This indicates that the HPA axis suppression may represent a physiological adaption in response to inhaled budesonide, not necessarily adrenal insufficiency. The lowest dose that results in clinically relevant adrenal insufficiency has not been established. Very rare cases of clinically relevant adrenal dysfunction have been reported in patients using inhaled budesonide at recommended doses.

Particular care is needed in patients who are being transferred from oral corticosteroids to PULMICORT, since they may remain at risk of impaired adrenal function for some considerable time (see Section 4.4 Special warnings and precautions for use - Oral corticosteroid usage). Patients who have required high dose emergency corticosteroid therapy, prolonged treatment at the highest recommended dose of inhaled corticosteroids or patients administering concomitant medication metabolised by CYP3A4 (see Interactions with other drugs) may also be at risk. These patients may exhibit signs and symptoms of adrenal insufficiency when exposed to severe stress such as trauma, surgery, infection (particularly gastroenteritis) or other conditions associated with severe electrolyte loss. Monitoring for signs of adrenal dysfunction is advisable in these patient groups. For these patients additional systemic glucocorticosteroid cover should be considered during periods of stress, severe asthma attack or elective surgery.

### **Bone density**

Whilst corticosteroids may have an effect on bone mass at high doses, long term follow up (3-6 years) studies of budesonide treatment in adults at recommended doses, have not demonstrated a negative effect on bone mass compared to placebo, including one study conducted in patients with a high risk of osteoporosis. The lowest dose that does effect bone mass has not been established.

Bone mineral density measurements in children should be interpreted with caution as an increase in bone area in growing children may reflect an increase in bone volume. In three large medium to long term (12 months - 6 years) studies in children (5-16 years), no effects on bone mineral density were observed after treatment with Pulmicort (189–1322 µg/day) compared to nedocromil, placebo or age matched controls. However, in a randomised 18 month study (n=176; 5-10 years), bone mineral density was significantly decreased by 0.11 g/cm<sup>2</sup> (p=0.023) in the group treated with inhaled budesonide via Turbuhaler compared with the group treated with inhaled disodium cromoglycate. The dose of budesonide was 400 µg twice daily for 1 month, 200 µg twice daily for 5 months and 100 µg twice daily for 12 months and the dose of disodium cromoglycate 10 mg three times daily. The clinical significance of this result remains uncertain.

### **Growth**

Long term studies show that children treated with inhaled budesonide ultimately achieve adult target height. However, an initial reduction of growth velocity (approximately 1 cm) has been observed and is generally within the first year of treatment.

Rare individuals may be exceptionally sensitive to inhaled corticosteroids. Height measurements should be performed to identify patients with increased sensitivity. The potential growth effects of prolonged treatment should be weighed against the clinical benefit. To minimise the systemic effects of inhaled corticosteroids, each patient should be titrated to his/her lowest effective dose (see Section 4.2 Posology and method of administration).

### **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.

### **Infections and tuberculosis**

High doses of glucocorticosteroids may mask some signs of existing infection and new infections may appear during their use. Special care is needed in patients with active or quiescent pulmonary tuberculosis or fungal, bacterial or viral infections of the respiratory system.

### **Hepatic function**

Reduced liver function may affect the elimination of corticosteroids. This may be clinically relevant in patients with severely compromised liver function.

### **Positive pressure delivery systems**

Respiratory drugs should not be used with positive pressure delivery systems (eg. IPPB) in pulmonary conditions involving pneumothorax, air cysts or mediastinal emphysema unless special drainage is performed.

### **Carcinogenicity and mutagenicity**

The carcinogenic potential of budesonide has been evaluated in mouse and rat at oral doses up to 200 and 50 µg/kg/day, respectively. No oncogenic effect was noted in the mouse. One study indicated an increased incidence of brain gliomas in male Sprague-Dawley rats given budesonide, however the results were considered equivocal. Further studies performed in male Sprague-Dawley and Fischer rats showed that the incidence of gliomas in the budesonide-treated rats was low and did not differ from that in the reference glucocorticoid

groups or the controls. It has been concluded that treatment with budesonide does not increase the incidence of brain tumours in the rat.

In male rats dosed with 10, 25 and 50 µg/kg/day, those receiving 25 and 50 µg/kg/day showed an increased incidence of primary hepatocellular tumours. This was observed in all three steroid groups (budesonide, prednisolone, triamcinolone acetonide) in a repeat study in male Sprague-Dawley rats thus indicating a class effect of corticosteroids.

The mutagenic potential of budesonide was evaluated in 6 different test systems. No mutagenic or clastogenic effects of budesonide were found.

#### **4.5 Interaction with other medicinal products and other forms of interaction**

The metabolism of budesonide is primarily mediated by CYP3A, a subfamily of cytochrome P450. Inhibitors of this enzyme e.g. ketoconazole and itraconazole, can therefore increase systemic exposure to budesonide. This is of limited clinical importance for short-term (1-2 weeks) treatment with CYP3A inhibitors, but should be taken into consideration during long-term treatment.

#### **4.6 Pregnancy and lactation**

##### **Use in pregnancy - *Category A*\***

The benefits of asthma control outweigh any potential for an adverse pregnancy outcome.

Results from a large prospective epidemiological study and from world-wide post marketing experience indicate that inhaled budesonide during pregnancy has no adverse effects on the health of the foetus or new born child.

Inhaled glucocorticosteroids, such as budesonide, should be considered because of the lower systemic effects of doses, compared to those of oral glucocorticosteroids, required to achieve similar pulmonary responses.

*\*Category A:* Drugs which have been taken by a large number of pregnant women and women of childbearing age without any proven increase in the frequency of malformations or other direct or indirect harmful effects on the foetus having been observed.

##### **Use in lactation**

Budesonide is excreted in breast milk. However, due to the relatively low doses used via the inhalational route the amount of drug present in the breast milk, if any, is likely to be low. Breastfeeding can be considered if the potential benefit outweighs any potential risks.

#### **4.7 Undesirable effects**

PULMICORT is generally well tolerated. Most adverse reactions have been mild and of a local character. Systemic effects and oropharyngeal complications caused by budesonide were found to be dose-dependent.

Clinical signs of steroid excess were present in 50% of patients (n=10) taking 1.6mg or more daily of budesonide alone for long periods.

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

**Common (more than 1%)**

<i>Nose and throat:</i>	hoarseness; sore, irritated throat; irritation of the tongue and mouth; dry mouth; oral candidiasis
<i>Respiratory:</i>	cough

**Uncommon (less than 1%)**

<i>Nose and throat:</i>	irritation of the larynx; bad taste
<i>Gastrointestinal:</i>	diarrhoea; nausea
<i>Hypersensitivity reactions:</i>	immediate and delayed hypersensitivity reactions such as skin reactions (eg. urticaria, rash, dermatitis), bronchospasm, angioedema and anaphylactic reaction.
<i>Central nervous system:</i>	headache; lightheadedness; thirst; tiredness
<i>Metabolic and nutritional disorders:</i>	weight gain

**Unknown**

<i>Eye disorders:</i>	blurred vision
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If oropharyngeal candidiasis develops, it may be treated with appropriate anti-fungal therapy whilst still continuing with PULMICORT therapy. The incidence of candidiasis can generally be held to a minimum by having patients rinse their mouth with water after each inhalation.

Inhaled steroids may have adverse effects in higher than recommended doses; possible systemic effects of inhaled steroids include depression of the HPA axis, reduction of bone density and retardation of growth rate in children (see Section 4.4 Special warnings and precautions for use - Potential systemic effects of inhaled corticosteroids).

- Reduction in growth velocity has been reported in association with administration of inhaled corticosteroids, however studies with budesonide indicate that this is transient and that final adult height may ultimately be achieved (see Section 4.4 Special warnings and precautions for use - Growth).
- Dose-dependent HPA axis suppression has been observed with budesonide, however this may represent a physiological adaption rather than adrenal insufficiency (see Section 4.4 Special warnings and precautions for use - HPA axis suppression and adrenal insufficiency). The lowest dose that results in clinically relevant adrenal insufficiency has not been established.
- No negative effects on bone mass have been observed in adults treated with inhaled budesonide at recommended doses. In children, bone mineral density should be interpreted with caution as an increase in bone area may reflect an increase in bone volume (see Section 4.4 Special warnings and precautions for use - Bone density).

Rare reports of skin bruising have occurred following treatment with inhaled glucocorticosteroids.

Psychiatric symptoms such as behavioural disturbances, nervousness, restlessness and depression have been observed with budesonide as well as other glucocorticosteroids.

Facial skin irritation has occurred in a few cases when a nebuliser with a face mask has been used. To prevent irritation the face should be washed after each use of PULMICORT RESPULES delivered via a nebuliser with a face mask.

Rarely, PULMICORT may provoke bronchoconstriction in hyperreactive patients. Bronchospasm may be treated with an inhaled  $\beta_2$ -agonist.

## **4.8 Overdose**

### **Symptoms**

In most cases, occasional overdosing will not produce any obvious symptoms but will decrease the plasma cortisol level and increase the number and percentage of circulating neutrophils. The number and percentage of lymphocytes and eosinophils will decrease concurrently. Habitual overdosing may cause hypercorticism and hypothalamic-pituitary-adrenal suppression.

### **Treatment**

Withdrawing PULMICORT or decreasing the dose will abolish these effects, although the normalization of the HPA-axis may be a slow process.

## **5. PHARMACOLOGICAL PROPERTIES**

### **5.1 Pharmacodynamic properties**

PULMICORT is a corticosteroid for inhalation use in the treatment and prophylaxis of asthma.

Studies in animals and humans have shown an advantageous ratio between topical anti-inflammatory activity and systemic glucocorticoid effect over a wide dose range. This is explained by the extensive first pass hepatic degradation of budesonide after systemic absorption, approximately 85-90%, in combination with the low potency of formed metabolites.

Budesonide is approximately twice as potent as beclomethasone dipropionate as shown in the skin blanching test for anti-inflammatory activity of topical steroids in humans. Budesonide has, however, less systemic effect than beclomethasone dipropionate, as measured by depression of morning plasma cortisol and effect on differential WBC count. The improved ratio of topical anti-inflammatory activity to systemic effect of budesonide is due to high glucocorticoid receptor affinity combined with a high first pass metabolism and a short half-life.

Doses of 0.8 mg have been found to suppress plasma cortisol levels and urinary cortisol secretion. A single inhalation of 3.2 mg budesonide was found to suppress plasma cortisol levels to a degree similar to 10 mg oral prednisolone.

Budesonide has been shown to counteract the mainly "IgE" but not the mainly "IgG" mediated lung anaphylaxis in guinea pigs. Pre-treatment for one to four weeks with inhaled budesonide 1 mg daily in asthmatic patients inhibited the immediate bronchial reaction to allergen challenge in a time-related manner; the late reaction is inhibited after one week of inhaled treatment.



Inhaled budesonide pre-treatment for 2 to 4 weeks has also been shown to reduce non-specific bronchial hyper-responsiveness in asthmatic patients to both direct (histamine, methacholine) and indirect (exercise) provocative stimuli in a time-related manner.

Budesonide did not potentiate  $\beta$ -receptor-mediated bronchodilation, and did not affect theophylline-induced relaxation of respiratory airway smooth muscle in guinea pigs. In man, single oral inhalations of up to 1.6 mg budesonide produced mild bronchodilation. This effect is maximal at 6 hours after inhalation with a duration of 12 hours.

## **5.2 Pharmacokinetic properties**

Approximately 10% of the discharged dose of PULMICORT aerosol is deposited in the lungs.

The volume of distribution of budesonide in adult man is approximately 300 L and in children is 3.1 to 4.8 L/kg indicating a high tissue affinity. Plasma protein binding is  $88.3 \pm 1.5\%$  in humans.

In adults the plasma half-life following inhalation via aerosol was  $2.0 \pm 0.2$  hours and in children 1.5 hour with peak plasma levels occurring immediately after administration.

Negligible biotransformation was observed in human lung and serum preparations.

PULMICORT is 90% inactivated on first pass through the liver, via metabolism to more polar metabolites with a more than 100-fold lower glucocorticosteroid systemic activity than the parent compound.

In human volunteers who inhaled tritiated budesonide,  $31.8 \pm 7.5\%$  of the discharged dose was recovered in urine and  $15.1 \pm 4.3\%$  in faeces (0-96 h). Plasma clearance of unchanged budesonide was calculated to be 84 L/h in adults and 1.5 to 2 L/h/kg in children.

## **6. PHARMACEUTICAL PARTICULARS**

### **6.1 Shelf-life**

Please refer to expiry date on the outer carton.

Unused Respules should be discarded three months after opening of foil packs.

Opened single dose units should be used within 12 hours. Please note that if only 1 mL is used the remaining volume is not sterile.

### **6.2 Special precautions for storage**

Store in an upright position and protected from light. Stored below 30°C. Do not refrigerate.

### **6.3 Nature and contents of container**

0.25 mg/ml and 0.5 mg/ml sterile nebulising suspension in single dose polyethylene (plastic) units. Pack size: 30 single dose units of 2 mL.

### **Product Owner**

AstraZeneca UK Limited  
1 Francis Crick Avenue  
Cambridge Biomedical Campus  
Cambridge, CB2 0AA  
United Kingdom

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