APPROVED PACKAGE INSERT

2015/06/30

SCHEDULING STATUS: S3

PROPRIETARY NAME AND DOSAGE FORM:

Pulmicort® Nebulising Suspension 0,25 mg/ml & 0,5 mg/ml (Suspension)

COMPOSITION:

PULMICORT Nebulising Suspension is an aqueous suspension of budesonide adjusted to a pH of 4,5 with buffer. Each ml contains 0,25 mg or 0,5 mg budesonide.

List of excipients: citric acid anhydrous, disodium edetate, polysorbate 80, purified water, sodium chloride and sodium citrate.

PHARMACOLOGICAL CLASSIFICATION:

A 21.5.1 Corticosteroids and analogues

PHARMACOLOGICAL ACTION:

Pharmacodynamic properties:

Budesonide is a glucocorticosteroid with local anti-inflammatory effect.

The exact mechanism of action of glucocorticosteroids in the treatment of asthma is not fully understood. Anti-inflammatory actions involving T-cells, eosinophils and mast cells, such as inhibition of inflammatory mediator release and inhibition of cytokine-mediated immune response are probably important.

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The therapeutic effect of conventional doses of inhaled budesonide may be largely explained by its direct action on the respiratory tract.

Budesonide has been shown to decrease airway reactivity to histamine and methacholine in hyper-reactive patients.

Pharmacokinetic properties:

Absorption:

In adults the systemic availability of budesonide following administration of PULMICORT Nebulising Suspension via a jet nebuliser is approximately 15 % of the nominal dose and 40-70 % of the dose delivered to the patients. A minor fraction of the systemically available medication comes from swallowed budesonide. The maximal plasma concentration, occurring about 10-30 minutes after start of nebulisation is approximately 4 nmol/litre after a single dose of 2 mg.

Distribution:

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

Biotransformation:

Budesonide undergoes an extensive degree (≈ 90 %) of biotransformation on first passage through the liver to metabolites of low glucocorticosteroid activity. The glucocorticosteroid activity of the major metabolites, 6-beta-hydroxybudesonide and 16-alpha-hydroxyprednisolone, is less than 1 % of that of budesonide. The metabolism of budesonide is primarily mediated by CYP3A, a subfamily of cytochrome P450.

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Elimination:

The metabolites of budesonide are excreted as such or in conjugated form mainly via the kidneys. No unchanged budesonide has been detected in the urine. Budesonide has a high systemic clearance (approximately 1,2 litres/min) in healthy adults and the terminal half-life of budesonide after i.v. dosing averages 2-3 hours.

Linearity:

The kinetics of budesonide are dose-proportional at clinically relevant doses.

Children:

In 4-6 years old asthmatic children, the systemic availability of budesonide following administration of PULMICORT Nebulising Suspension via a jet nebuliser is approximately 6 % of the nominal dose and 26 % of the dose delivered to the patients. The systemic availability in children is about half that in healthy adults. The maximal plasma concentration, occurring approximately 20 minutes after start of nebulisation is approximately 2,4 nmol/litre in 4-6 years old asthmatic children after a 1 mg dose.

Budesonide has a systemic clearance of approximately 0,5 litres/min in 4-6 years old asthmatic children. Per kilogram body weight children have a clearance which is approximately 50 % greater than in adults. The terminal half-life of budesonide after inhalation is approximately 2,3 hours in asthmatic children. This is about the same as in healthy adults.

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The exposure (C_{max} and AUC) of budesonide following administration of a single 1 mg dose by nebulisation to 4-6 year old children is comparable to that in healthy adults given the same delivered dose by the same nebulising system.

INDICATIONS:

PULMICORT Nebulising Suspension is indicated for management of asthma in patients inadequately controlled by bronchodilators, thus necessitating additional treatment with steroids and who are unable to use a pressurised metered dose inhaler or unable to inhale the medicine in powder form.

PULMICORT Nebulising Suspension is also recommended for use in infants and children with acute laryngotracheobronchitis-croup.

CONTRAINDICATIONS:

Lung tuberculosis, fungal and viral infections in the airways.

Hypersensitivity to budesonide and any of the ingredients.

Safety and efficacy for children less than 12 months have not been established.

WARNINGS AND SPECIAL PRECAUTIONS:

Facial skin irritation may occur when a nebuliser with face mask is used. To prevent irritation the facial skin should be washed with water after use of the face mask. To minimise oropharyngeal thrush, the patient should rinse the mouth out with water after each dosing occasion.

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PULMICORT Nebulising Suspension 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 increased anti-inflammatory therapy, e.g. higher doses of inhaled budesonide or a course of oral glucocorticosteroid.

Particular care is needed in patients transferring from oral steroids, since they may remain at risk of impaired adrenal function for a considerable time. 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. 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.

Some patients feel unwell in a non-specific way during the withdrawal phase, e.g. pain in muscles and joints. A general insufficient glucocorticosteroid effect should be suspected if 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.

Replacement of systemic steroid treatment with inhaled therapy sometimes unmasks allergies, e.g. rhinitis and eczema, which were previously controlled by the systemic medicine. These allergies should be symptomatically controlled with an antihistamine and/or topical preparations.

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

The long-term local and systemic effects of PULMICORT Nebulising Suspension in human subjects are not completely known. The dose should be titrated to the lowest effective maintenance dose once control of asthma is achieved. Physicians should closely monitor the growth of children and adolescents taking corticosteroids by any route and weigh the benefit of corticosteroid therapy and asthma control against the possibility of growth suppression.

Special consideration may be needed in patients with pulmonary tuberculosis.

On prolonged administration signs or symptoms of systemic glucocorticosteroid effect, including hypofunction of the adrenal gland and reduction of growth velocity, may occur with inhaled glucocorticosteroids, probably depending on dose, exposure time, concomitant and previous steroid exposure, and individual sensitivity.

Effects on ability to drive and use machines:

PULMICORT Nebulising Suspension has no effect on the ability to drive and use of machines.

INTERACTIONS:

Budesonide has not been observed to interact with any medicine used for the treatment of asthma.

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The metabolism of budesonide is primarily mediated by CYP3A4, a subfamily of cytochrome P450. Inhibitors of this enzyme, e.g. ketoconazole and itraconazole, therefore increase systemic exposure to budesonide.

At recommended doses, cimetidine has slight but clinically insignificant effect on the pharmacokinetics of oral budesonide.

PREGNANCY AND LACTATION:

Pregnancy:

Safety in pregnancy has not been established.

Lactation:

Safety in lactation has not been established.

Budesonide is excreted in breast milk. However, at maternal therapeutic doses of PULMICORT Nebulising Suspension, the budesonide plasma levels in infants are at or below minimal measurable concentrations.

DOSAGE AND DIRECTIONS FOR USE:

Instruction for correct use of PULMICORT Nebulising Suspension:

PULMICORT Nebulising Suspension 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 (5-8 litres/minute), and the fill volume should be 2-4 ml. Carefully read the section, "Instruction for correct use of PULMICORT Nebulising Suspension", added to this package insert.

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Ultrasonic nebulisers are not suitable for the administration of PULMICORT Nebulising Suspension and therefore are not recommended.

The dosage of PULMICORT Nebulising Suspension is individual, and should be titrated to the lowest effective maintenance dose once control of asthma is achieved.

Asthma:

Adults:

Initial Dose:

0,5-1 mg twice daily. In some cases the dose may be further increased.

Children:	*12 months-6 years:*	*6 years and older:*
Previous therapy	Recommended starting dose	
Bronchodilators alone	0,25 mg twice daily	0,25-0,5 mg twice daily
Inhaled corticosteroids	0,25 mg twice daily	0,25-0,5 mg twice daily
Oral corticosteroids	0,5 mg twice daily	0,25-1 mg twice daily
Maintenance dose	0,25-0,5 mg twice daily	

In patients where an increased therapeutic effect is required, an increased dose of PULMICORT Nebulising Suspension should be considered.

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Maintenance dose:

The maintenance dose is individual. After the desired clinical effect has been obtained, the maintenance dose should be gradually reduced to the smallest amount necessary to control symptoms.

Patients dependent on oral steroids:

Initially, PULMICORT Nebulising Suspension should be used concurrently with the patient's usual maintenance dose of oral glucocorticosteroid. After approximately 1 week the oral dose is gradually reduced to the lowest possible level, e.g. by about 2,5 mg prednisolone every 2 weeks. A slow rate of withdrawal is strongly recommended.

In a proportion of cases, it is possible to completely substitute the oral glucocorticosteroid with PULMICORT Nebulising Suspension.

During withdrawal, some patients may experience symptoms of systemic corticosteroid withdrawal, e.g. joint and/or muscular pain, lassitude and depression, despite maintenance or even improvement in pulmonary function. Such patients should be encouraged to continue with PULMICORT Nebulising Suspension but should be monitored for objective signs of adrenal insufficiency. If evidence of adrenal insufficiency occurs, the systemic corticosteroid doses should be increased temporarily and thereafter withdrawal should be continued more slowly. During periods of stress or during a severe asthma attack, transfer patients may require supplementary treatment with systemic corticosteroids.

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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.

Dosage table:

Dosage in mg	**Volume of PULMICORT Nebulising Suspension**	
	0,25 mg/ml	**0,5 mg/ml**
0,25 mg	1 ml	-
0,5 mg	2 ml	1 ml
0,75 mg	3 ml	-
1 mg	-	2 ml
1,5 mg	-	3 ml
2 mg	-	4 ml

PULMICORT Nebulising Suspension can be mixed with 0,9 % saline and with solutions for nebulisation of terbutaline, salbutamol, fenoterol, acetylcysteine, sodium cromoglycate or ipratropium bromide. The admixture should be used within 30 minutes.

SIDE EFFECTS:

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

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Clinical trials:

Common (≥ 1/100, < 1/10)	*Respiratory, thoracic and mediastinal disorders*	Mild irritation in the throat, hoarseness, coughing
	Infections and infestations	Candida infection in the oropharynx
Rare (≥ 1/10 000, < 1/1 000)	*Skin and subcutaneous tissue disorders*	Skin bruising

Post marketing experience:

Psychiatric disorders:

Nervousness, restlessness, depression, behavioural disturbances

Immune system disorders:

Immediate and delayed hypersensitivity reactions including rash, contact dermatitis, urticaria, angioedema, bronchospasm and anaphylactic reaction

In rare cases, through unknown mechanisms, medicines for inhalation, such as PULMICORT Nebulising Suspension, may cause bronchospasm.

KNOWN SYMPTOMS OF OVERDOSAGE AND PARTICULARS OF ITS TREATMENT:

Acute overdosage with PULMICORT Nebulising Suspension, even in excessive doses, is not expected to be a clinical problem. Treatment should be discontinued and appropriate measures taken to protect the patient against stress situations.

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IDENTIFICATION:

An easily resuspendable white to off-white suspension filled into single-dose units made of plastic.

Each unit is marked in black colour with PULMICORT 0,25 mg/ml or PULMICORT 0,5 mg/ml on the container body, with 2 ml (0,5 mg or 1,0 mg) and the batch number on the flat tab (same side).

Sheets of 5 units.

PRESENTATION:

Each single-dose unit contains 2 ml suspension. Sheets of 5 units are packed in an envelope of foil laminate. Four foil envelopes are packed per unit carton.

STORAGE INSTRUCTIONS:

Store at or below 30 °C. Always keep unopened single dose units in the foil envelope so they are well protected from light. Single units in an open foil envelope should be used within 3 months. If you do not use a full unit for each dose, store the opened container protected from light. The contents of an opened container should be used within 12 hours. Keep out of reach of children.

REGISTRATION NUMBERS:

PULMICORT Nebulising Suspension 0,25 mg/ml: 30/21.5.1/0017

PULMICORT Nebulising Suspension 0,5 mg/ml: 30/21.5.1/0016

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NAME AND BUSINESS ADDRESS OF THE HOLDER OF THE CERTIFICATE OF REGISTRATION:

AstraZeneca Pharmaceuticals (Pty) Limited

Building 2, Northdowns Office Park

17 Georgian Crescent West,

Bryanston, Johannesburg

2191, South Africa

DATE OF PUBLICATION OF THE PACKAGE INSERT:

20 April 2012

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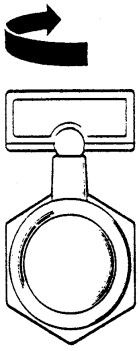
Instructions for correct use of PULMICORT Nebulising Suspension:

Not to be used for injection. For use only in a nebuliser.



Shake the contents gently using a swirling motion.

Hold the single dose unit upright (see picture) and open by twisting off the wing.

Place the open end of the unit well into the reservoir of the nebuliser and squeeze slowly.

The single dose unit is marked with a line which indicates the 1 ml volume when the single dose unit is held up-side down. If only 1 ml is to be used, empty the contents until the surface of the liquid reaches the indicator line. Store the opened container protected from light. Before using the rest of the suspension, shake the contents carefully by using a gentle swirling motion.

The contents of an opened single dose unit should be used within 12 hours.

Single dose units in an opened envelope should be used within 3 months.

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NB:

Rinse the mouth out with water after inhaling the prescribed dose to minimise the risk of oropharyngeal thrush.

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

Cleaning instructions:

Adequately clean and maintain the nebuliser according to the manufacturer's instructions.

AstraZeneca Logo

Ref: Pulmicort Nebulising Suspension Range – EPI (02-02-2015)

CDS: June 2008

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Pulmicort Nebulising Suspension 0,25 mg/ml NAMIBIA: NS2 Reg. No.: 08/21.5.1/0159	Pulmicort Nebulising Suspension 0,5 mg/ml NAMIBIA: NS2 Reg. No.: 08/21.5.1/0160

Pulmicort Nebulising Suspension 0,25 mg/ml BOTSWANA: S2 Reg. No.: BOT 0200479	Pulmicort Nebulising Suspension 0,5 mg/ml BOTSWANA: S2 Reg. No.: BOT 0600889

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