Pulmicort 0.25 mg/ml and 0.5 mg/ml

budesonide

Nebuliser Suspension

Qualitative and Quantitative Composition

Each single-dose unit of 2 ml contains: 0.5 mg or 1 mg budesonide.

Pharmaceutical form

Sterile Nebuliser Suspension.
Whitish suspension in single-dose unit made of plastic.

Therapeutic indications

Bronchial asthma

Posology and method of administration

The dosage of Pulmicort Nebuliser Suspension is individual. In the case of daily doses up to 1 mg the whole dose may be given in one administration. In the case of higher daily doses the dose is divided into two administrations per day.

Initially the dosage should be:
Children from 6 months: 0.25-0.5 mg per day. If necessary, the dose may be increased to 1 mg per day.
Adults: 1-2 mg per day.

For maintenance treatment:
Children from 6 months: 0.25-2 mg per day.
Adults: 0.5 – 4 mg per day. In very severe cases the dose may be increased further.

Dosage table

Dose (mg)	Volume of Pulmicort Nebuliser Suspension	
	0.25 mg/ml	0.5 mg/ml
0.25	1 ml*	-
0.5	2 ml	-
0.75	3 ml	-
1	4 ml	2 ml
1.5	-	3 ml
2	-	4 ml

**should be diluted to 2 ml with 0.9 % saline or solution for nebuliser, see "Instructions for correct use of Pulmicort Nebuliser".*

The maintenance dose should be the lowest possible.

Following a single dose an effect may be expected after a few hours. The full therapeutic effect is achieved only after a few weeks of treatment. Treatment with Pulmicort is prophylactic therapy with no demonstrated effect on acute disorders.

In patients in whom an increased therapeutic effect is desired, in general an increase of the Pulmicort dose is to be recommended in preference to combination treatment with oral corticosteroids because of the lower risk of systemic side effects.

Patients dependent on oral steroids:
When transfer from oral steroids is initiated the patient must be in a relatively stable condition. A high dose of Pulmicort is given in combination with the previously used oral steroid dose for 10 days. After that, the oral dose should be gradually reduced by e.g. 2.5 mg prednisolone or equivalent per month to the lowest possible level. The oral steroid can often be discontinued entirely.

Since budesonide given as Pulmicort Nebuliser Suspension is deposited in the lungs with the aid of inspiration, it is important that the patient inhales calmly and with even breaths through the mouthpiece of the nebuliser.

There is no experience of treatment of patients with impaired hepatic or renal function. Since budesonide is eliminated predominantly through metabolism in the liver, increased exposure may be expected in patients with severe cirrhosis of the liver.

Instructions for correct use of Pulmicort Nebuliser

Pulmicort Nebuliser Suspension should be administered via a jet nebuliser equipped with a mouthpiece or suitable facemask. The nebuliser should be connected to an air compressor with an adequate airflow (5-8 l/min), and the fill volume should be 2-4 ml.

Note It is important to instruct the patient

- to carefully read the instructions for use: “How to use Pulmicort Nebuliser”
- that Ultrasonic nebulisers are not suitable for the administration of Pulmicort Nebuliser Suspension and therefore are not recommended
- Pulmicort Nebuliser Suspension can be mixed with 0.9 % saline and with solutions for nebulisation of terbutaline, salbutamol, fenoterol, acetylcysteine, sodium cromoglycate and ipratropium. The admixture should be used within 30 minutes.
- to rinse the mouth out with water after inhaling the prescribed dose to minimise the risk of oropharyngeal thrush
- to wash the facial skin with water after using the face mask to prevent irritation
- to adequately clean and maintain the nebuliser according to the manufacturer’s instructions

A facemask can be used for children who cannot breathe in through the mouthpiece.

Contraindications
Hypersensitivity to budesonide or any of the other ingredients.

Special warnings and special precautions for use
In order to minimise the risk of Candida infections in the oral cavity and throat, the patient should be instructed to rinse the mouth with water after each dose administration.

Concomitant treatment with ketoconazole, itraconazole or other potent CYP3A4 inhibitors should be avoided. If this is not possible, the interval between administrations of the medications should be as long as possible (see *"Interaction with other medicaments and other forms of interaction"*).

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.

During transfer from oral steroid therapy to Pulmicort, patients may experience previous symptoms such as muscle and joint pain. In these cases a temporary increase of the oral steroid dose may be necessary. If, in isolated cases, fatigue, headache, nausea, vomiting or similar symptoms occur, a generally unsatisfactory effect of the steroid should be suspected.

Replacement of systemic steroid treatment by Pulmicort sometimes reveals allergies, e.g. rhinitis and eczema, that were previously controlled by the systemic treatment.

Regular monitoring of growth is recommended in children and adolescents receiving long-term treatment with corticosteroids, irrespective of the administration form. The benefits of corticosteroid treatment must be placed in relation to possible risks of inhibition of growth.

As with other inhalation therapy, paradoxical bronchospasm may occur immediately after dosing. If a severe reaction occurs, treatment should be re-assessed and alternative therapy instituted if necessary.

Patients must be instructed to contact their physician if the effect of the treatment generally diminishes, as repeated inhalations for severe asthma attacks must not delay the initiation of other important therapy. If there is a sudden deterioration the treatment must be supplemented with a short course of oral steroids.

Decreased liver function may affect the ability to eliminate budesonide.

Interaction with other medicaments and other forms of interaction

No clinically relevant interactions with asthma agents are known.

Ketoconazole 200 mg once daily increased the plasma concentrations of oral budesonide (3 mg in a single dose) on average six-fold when administered concomitantly. When ketoconazole was administered 12 hours after budesonide, the concentration was increased on average three-fold. Information about this interaction is lacking for inhaled budesonide, but markedly increased plasma levels are also expected in such cases. The combination should be avoided since data to support dose recommendations are lacking. If this is not possible, the time interval between administration of ketoconazole and budesonide should be as long as possible. A reduction of the budesonide dose must also be considered. Other potent inhibitors of CYP3A4, i.e. itraconazole also cause a marked increase in the plasma levels of budesonide.

Use during pregnancy and lactation

Pregnancy

Data from approximately 2000 pregnancies have not revealed any increased risk of malformations as a result of treatment with budesonide. Animal studies have shown that glucocorticosteroids can induce malformations (see "Preclinical safety data), but this is judged not to be relevant for humans with the recommended dosage.

Animal studies have also identified an involvement of excess prenatal glucocorticoids in increased risks for intrauterine growth retardation, adult cardiovascular disease and permanent changes in glucocorticoid receptor density, neurotransmitter turnover and behaviour at exposures below the tetratogenic dose range.

During pregnancy the aim must be the lowest effective dose of budesonide while taking account of the risk of a worsening of the asthma.

Lactation

Budesonide is excreted in breast milk. However, at therapeutic doses of Pulmicort Nebuliser Suspension no effects on the suckling child are anticipated. Pulmicort Nebuliser Suspension can be used during breast feeding.

Effects on ability to drive and use machines

Pulmicort does not affect ability to drive or use machines.

Undesirable effects

Up to 10 % of treated patients may be expected to experience adverse reactions of a local nature.

Common (> 1/100)	*Airways:*	Candida infection in the oropharynx, mild irritation in the throat, coughing, hoarseness
Rare (< 1/1000)	*General:*	Angioedema, anaphylactic reaction
	CNS:	Nervousness, restlessness, depression, behavioural disturbances
	Skin:	Urticaria, rash, dermatitis, skin bruising
	Airways:	Bronchospasm

On account of the risk of Candida infections in the oropharynx the patient must rinse the mouth with water after every dose.

In rare cases 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.

Facial skin irritation has been reported in some cases when a facemask was used. In order to prevent this, the face should be washed when a facemask is used.

Overdose

Acute overdose with Pulmicort Nebuliser Suspension, even high doses, is not expected to cause any clinical problems. If it is used chronically in high doses, systemic effects of glucocorticosteroids such as hypercortisolism and adrenal suppression may occur.

Pharmacodynamic properties

Budesonide is a glucocorticosteroid with a high local anti-inflammatory effect.
Pharmacotherapeutic group: Inhalation drugs for obstructive airway diseases.
ATC-code R03B A02.

The precise mechanism of action of glucocorticosteroids in the treatment of asthma is not fully understood. Anti-inflammatory effects such as inhibited release of inflammatory mediators and inhibition of cytokine-mediated immune response are probably important. The activity of budesonide, measured as affinity for glucocorticosteroid receptors is approx. 15 times higher than that of prednisolone.

Budesonide has anti-inflammatory effects shown as reduced bronchial obstruction during both the early and the late phase of an allergic reaction. In hyper-reactive patients budesonide reduces the histamine and metacholine reactivity in the airways.

Studies have shown that the earlier budesonide treatment is initiated after the onset of asthma, the better lung function can be expected.

Studies in healthy volunteers with Pulmicort Turbuhaler have shown dose-related effects on plasma and urinary cortisol. At recommended doses, Pulmicort Turbuhaler, causes significantly less effect on the adrenal function than prednisone 10 mg, as shown by ACTH tests.

In children over the age of 3 years, no systemic effects have been detected with doses up to 400 micrograms per day. In the range 400-800 micrograms per day biochemical signs of a systemic effect may occur. With daily doses in excess of 800 micrograms such signs are common. This information applies to Pulmicort administered as inhalation spray and inhalation powder.

Asthma itself, like inhaled corticosteroids, can delay growth. Long-term studies show that 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.

Inhalation therapy with budesonide is effective in preventing exercise-induced asthma.

Pharmacokinetic properties

Absorption
Inhaled budesonide is rapidly absorbed. The peak plasma concentration is reached within 30 minutes after the start of nebulisation.

Distribution and metabolism
Plasma protein binding is approx. 90 %. The volume of distribution is approx. 3 l/kg. Budesonide undergoes extensive (approx. 90 %) first pass metabolism in the liver to metabolites with low glucocorticosteroid activity. The glucocorticosteroid activity of the major metabolites, 6β-hydroxybudesonide and 16α-hydroxyprednisolone, is less than 1 % of that of budesonide.

Elimination
Budesonide is eliminated through metabolism, catalysed primarily by the enzyme CYP3A4. The metabolites are excreted in the urine in unchanged or conjugated form. Only negligible amounts of unchanged budesonide are recovered in the urine. Budesonide has a high systemic clearance (approx. 1.2 l/min), and the plasma half-life after intravenous administration is on average 4 hours. The pharmacokinetics of budesonide is proportional to the dose at relevant dosages.

The pharmacokinetics of budesonide in children and in patients with impaired renal function is unknown. Exposure to budesonide may be increased in patients with hepatic disease.

Preclinical Safety Data

In toxicity studies budesonide has caused only the expected glucocorticoid effects.

Budesonide has not exhibited any genotoxic effects.

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 seem to be relevant to humans at the recommended doses.

List of excipients

Disodium edetate
Sodium chloride
Polysorbate 80
Anhydrous citric acid
Sodium citrate
Water for injections

Incompatibilities

Pulmicort Nebuliser Suspension should not be mixed with drugs other than those mentioned in "Instructions for correct use of Pulmicort Nebuliser".

Shelf-life

Please refer to expiry date on outer carton.

Special precautions for storage

Do not store above 30°C. Do not freeze.
Store in an upright position and protected from light.
After opening of the aluminium foil envelope, the unused single-dose units should be kept in the envelope to protect them from light.
Single-dose units that are stored in an opened envelope must be used within 3 months. The contents of an opened single-dose unit must be used within 12 hours. Observe that if only 1 ml has been used the remaining volume is not sterile.

Pack size

Please refer to outer carton for pack size.

Date of revision of the text

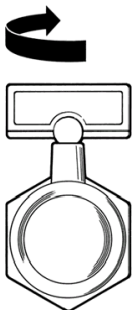
October 2011

RITA.000-032-484.5.0

How to use Pulmicort Nebuliser

1. Before use, re-suspend the contents of the single dose unit by using a gently swirling motion.

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



3. 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 (Pulmicort 0.25 mg/ml and 0.5 mg/ml only). This line 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 level of the liquid reaches the indicator line.

Store the opened single dose unit protected from light. Opened single dose units must be used within 12 hours.

Please note that if only 1 mL is used the remaining volume is not sterile.

Before using the rest of the liquid, re-suspend the contents of the single dose unit by using a gently swirling motion.

NOTE:

1. Rinse your mouth out with water after each dosing occasion.
2. If you use a facemask, make sure that the mask fits tightly while you are inhaling. Wash your face after treatment.

Cleaning

The nebuliser chamber and the mouthpiece, or the facemask, should be cleaned after each use. Wash the parts in hot tap water using a mild detergent or according to the instructions supplied by the manufacturer of the nebuliser. Rinse well and dry by connecting the nebuliser chamber to the compressor or air inlet.