SCHEDULING STATUS: **S 3**

PROPRIETARY NAME (and dosage form):

Pulmicort® Turbuhaler® 100 µg/dose (Inhaler)

Pulmicort® Turbuhaler® 200 µg/dose (Inhaler)

Pulmicort® Turbuhaler® 400 µg/dose (Inhaler)

COMPOSITION:

Each metered dose contains 100 µg, 200 µg or 400 µg budesonide. PULMICORT TURBUHALER is free from propellants, lubricants, preservatives, carrier substances or other additives.

PHARMACOLOGICAL CLASSIFICATION:

A 21.5.1 Corticosteroids and analogues.

PHARMACOLOGICAL ACTION:

PULMICORT TURBUHALER contains the non-halogenated corticosteroid budesonide. Inhaled budesonide has been shown to possess a local anti-inflammatory action.

The exact mechanisms 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.

Absorption:

After inhalation via TURBUHALER approximately 25-35% of the metered dose is deposited in the lungs, which is approximately twice that of pMDI.

The maximal plasma concentration after oral inhalation of a single dose of 800 µg budesonide is approximately 4 nmol/litre, occurring within 30 minutes. Systemic availability of budesonide via TURBUHALER has been estimated to 38% of the metered dose, of which only about 1/6 was derived from swallowed drug.

Distribution:

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

Biotransformation:

Budesonide is inactivated rapidly in the liver. 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.

Studies in healthy volunteers with PULMICORT TURBUHALER have shown dose-related effects on plasma and urinary cortisol.

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 litre/min) and the plasma half-life after iv. dosing averages 2-3 hours.

Linearity:

The kinetics of budesonide are dose-related at clinically relevant doses, i.e. 400-1600 µg.

Studies in healthy volunteers with PULMICORT TURBUHALER have shown dose-related effects on plasma and urinary cortisol.

INDICATIONS:

Prophylaxis of the symptoms of asthma.

CONTRA-INDICATIONS:

Lung tuberculosis. Fungal and viral infections in the airways. Pregnancy. Hypersensitivity to budesonide. The safety and efficacy for children under the age of six years have not been established.

WARNINGS:

The long-term local and systemic effects of PULMICORT TURBUHALER 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.

PULMICORT TURBUHALER 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 who are transferred from systemic to inhaled glucocorticosteroids. During this period of Hypothalamic Pituitary Adrenal (HPA) axis suppression, patients may exhibit signs and symptoms of adrenal insufficiency when

xposed to trauma, surgery, or infection (particularly gastroenteritis) or other conditions associated with severe electrolyte loss.

Although PULMICORT TURBUHALER may provide control of asthma symptoms during these episodes, in recommended doses it supplies less than normal physiological amounts of glucocorticosteroid systemically and does NOT provide the mineralocorticosteroid activity that is necessary for coping with these emergencies.

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

Reduced liver function may affect the elimination of glucocorticosteroids as evidenced by increased systemic availability.

Special consideration may be needed in patients with fungal and viral infections in the airways, including pulmonary tuberculosis.

INTERACTIONS:

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

The metabolism of budesonide is primarily mediated by CYP3A, a subfamily of cytochrome P450. Inhibitors of this enzyme, e.g. ketoconazole, can 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:

Administration during pregnancy should be avoided as in pregnant animals, administration of budesonide causes abnormalities of foetal development. The relevance of this finding to man has not been established.

If treatment with glucocorticosteroids during pregnancy is unavoidable, inhaled glucocorticosteroids may be preferred because of their lower systemic effects compared with equipotent anti-asthmatic doses of oral glucocorticosteroids.

There is no information regarding the passage of budesonide into breast milk.

DOSAGE AND DIRECTIONS FOR USE:

The dosage of PULMICORT TURBUHALER is individual. The recommended starting dose and the highest recommended dose of PULMICORT TURBUHALER, based on prior asthma therapy, are listed in the following table.

	Previous Therapy	**Recommended Starting Dose**	**Highest Recommended Dose**
Adults and elderly	Nonsteroid treatment	100 to 400 µg twice daily	800 µg twice daily
	Inhaled glucocortico-steroids	100 to 400 µg twice daily	800 µg twice daily
	Oral glucocortico-steroids	400 to 800 µg twice daily	800 µg twice daily
Children 6 years and above	Nonsteroid treatment	100 to 200 µg twice daily	400 µg twice daily

	Inhaled glucocortico-steroids	100 to 200 µg twice daily	400 µg twice daily
	Oral glucocortico-steroids	200 to 400 µg twice daily	400 µg twice daily

In severe asthma and during exacerbations some patients may benefit from dividing the daily dose into 3-4 administrations per day.

Maintenance dose:

In all patients it is desirable to titrate to the lowest effective maintenance dose once control of asthma is achieved.

Dose-range maintenance dose:

Adults and elderly: 100-1600 µg daily

Children: 100-800 µg daily

Onset of effect:

Improvement in asthma control following inhaled administration of PULMICORT TURBUHALER can occur within 24 hours of initiation of treatment, although maximum benefit may not be achieved for 1 to 2 weeks or longer after starting treatment.

Patients not receiving glucocorticosteroids:

Patients who require maintenance therapy of their asthma may benefit from treatment with PULMICORT TURBUHALER at the doses recommended in the dosing table. For patients who do not respond adequately to the starting dose, higher doses may provide additional asthma control.

Patients maintained on inhaled glucocorticosteroids:

Clinical studies in man have shown an improved efficacy for the same amount of budesonide delivered via TURBUHALER compared with the pressurised aerosol (pMDI). Thus, when patients treated with PULMICORT pMDI have been transferred to PULMICORT TURBUHALER and control of asthma is good, it may be possible to reduce the dose of the pMDI dose. Also in patients transferred from other inhaled glucocorticosteroids, a dose reduction with PULMICORT TURBUHALER may be considered after the patient initially has been given a similar dose as prior to transferral.

Patients maintained on oral glucocorticosteroids:

PULMICORT TURBUHALER may permit replacement or significant reduction in the dosage of oral glucocorticosteroids with maintained or improved asthma control.

Initially, PULMICORT TURBUHALER should be used concurrently with the patient's usual maintenance dose of oral glucocorticosteroid. After approximately one week the oral dose is gradually reduced to the lowest possible level. A slow rate of withdrawal is strongly recommended. In many cases it is possible to completely substitute the oral glucocorticosteroid with PULMICORT TURBUHALER.

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 TURBUHALER 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 continue more slowly. During periods of stress or a severe asthma attack, transfer patients may require supplementary treatment with systemic corticosteroids.

SIDE EFFECTS AND SPECIAL PRECAUTIONS:

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

The following frequency rating has been used:

Common: □ 1/100; Uncommon: □□1/1000 and < 1/100

Rare: < 1/1000 and □□1/10 000; Very rare: < 1/10 000

Common (>1/100, <1/10)	• Respiratory tract:	• Irritation in the throat. • Candida infection in the mouth and throat due to drug deposition in the oral cavity. To minimise oropharyngeal thrush the patient should rinse the mouth out with water after each dosing occasion. • Hoarseness. • Coughing.
Rare (>1/10 000, <1/1 000)	• Central nervous system:	• Psychiatric symptoms such as nervousness, restlessness, depression and behavioural disturbances.
	• Skin:	• Immediate and delayed hypersensitivity reactions including rash, contact dermatitis, urticaria, angioedema. • Skin bruising.
	• Respiratory tract:	• Bronchospasm.

Signs or symptoms of systemic glucocorticosteroid effect, including hypofunction of the adrenal gland and reduction of growth rate, may occur with inhaled glucocorticosteroids, probably depending on dose, exposure time, concomitant and previous glucocorticosteroid exposure, and individual sensitivity.

KNOWN SYMPTOMS OF OVERDOSE AND PARTICULARS OF ITS TREATMENT:

Acute overdosage with PULMICORT TURBUHALER, even in excessive doses, is not expected to be a clinical problem. When used chronically in excessive doses, systemic glucocorticosteroid effects, such as glucocorticosteroid excessiveness and adrenal suppression, may occur.

IDENTIFICATION:

PULMICORT TURBUHALER contains white to off white rounded granules, which disintegrate to a fine powder upon slight pressure.

The PULMICORT TURBUHALER 100 µg/dose is light-brown and the bottom of the turning grip is embossed with the words "Budesonide 100".

The PULMICORT TURBUHALER 200 µg/dose is brown and the bottom of the turning grip is embossed with the words "Budesonide 200".

The PULMICORT TURBUHALER 400 µg/dose is dark brown and the bottom of the turning grip is embossed with the words "Budesonide 400".

PRESENTATION:

PULMICORT TURBUHALER is a multidose, inspiratory flow driven dry powder inhaler.

The inhaler is made of plastic parts.

PULMICORT TURBUHALER 100 µg/dose contains 200 doses of 100 µg budesonide.

PULMICORT TURBUHALER 200 µg/dose contains 200 doses of 200 µg budesonide.

PULMICORT TURBUHALER 400 µg/dose contain 50 or 100 doses of 400 µg budesonide.

STORAGE INSTRUCTIONS:

Store below 30ºC with the cover tightened. Keep out of reach of children.

REGISTRATION NUMBER:

PULMICORT TURBUHALER 100 µg/dose: Y/21.5.1/171

PULMICORT TURBUHALER 200 µg/dose: Y/21.5.1/172

PULMICORT TURBUHALER 400 µg/dose: Z/21.5.1/266

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

AstraZeneca Pharmaceuticals (Pty) Limited

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DATE OF PUBLICATION OF THIS PACKAGE INSERT:

April 2004

AstraZeneca Logo

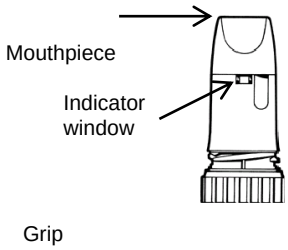
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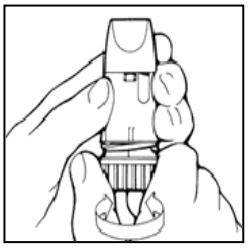
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INSTRUCTIONS FOR USE/HANDLING



HOW TO USE PULMICORT TURBUHALER

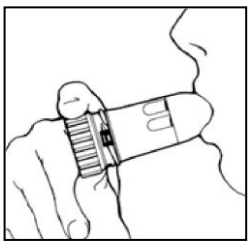
TURBUHALER is a multidose inhaler from which the medicine is administered without the use of additives. When you breathe in through TURBUHALER the powder is delivered to the lungs. It is therefore important that you inhale forcefully and deeply through the mouthpiece. TURBUHALER is very easy to use. Simply follow the instructions given below.



1. Unscrew and lift off the cover.

2. Hold the inhaler upright with the grip downwards. Load the inhaler with a
   dose by turning the grip as far as it will go and then back to the original position.

3. Breathe out. Do not breathe out through the mouthpiece.



4. Place the mouthpiece gently between your teeth, close your lips and breathe
   in forcefully and deeply through your mouth. Do not chew or bite on the mouthpiece. Do not use TURBUHALER if it has been damaged or

if the mouthpiece has become detached.

5. Before breathing out, remove the inhaler from your mouth.

   If more than one dose has been prescribed, repeat steps 2-5.

6. Replace the cover.

7. Rinse your mouth out with water after inhaling your prescribed dose.

NOTE!

Never breathe out through the mouthpiece.

Always replace the cover properly after use.

As the amount of the powder dispensed is very small, you may not be able to taste it after inhalation. However, you can still be confident that the dose has been inhaled if you have followed the instructions.

Cleaning:

Clean the outside of the mouthpiece regularly (weekly) with a dry tissue.

Do not use water for cleaning the mouthpiece.

Dose indicator:





When a red mark is first seen in the indicator window there are approximately 20 doses left. When the red mark has reached the lower edge of the window the inhaler will no longer deliver the correct amount of medicine, and should be discarded. The sound heard as you shake the inhaler is not produced by the medication but by a drying agent.

Disposal:

Always be sure to dispose of your used TURBUHALER responsibly/in the recommended way, since some of the medicine will remain inside it.