PULMICORT® TURBUHALER®
(budesonide)

1. NAME OF THE MEDICINAL PRODUCT

Pulmicort Turbuhaler 100 and 200 micrograms/dose
budesonide
Inhalation powder

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

1 metered dose contains budesonide 100 micrograms or 200 micrograms.

3. PHARMACEUTICAL FORM

Inhalation powder

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Pulmicort Turbuhaler is indicated for patients with bronchial asthma who require maintenance treatment with glucocorticosteroids for control of the underlying airways inflammation.

4.2 Posology and method of administration

The dosage of Pulmicort Turbuhaler is individual.
Initially, at the beginning of inhaled corticosteroid therapy, for therapy during periods of severe asthma or when scaling down or withdrawing oral corticosteroids the dosage should be:

Children 5-7 years: 200-400 micrograms daily divided into 2-4 administrations.

Children 7 years and more: 200-800 micrograms daily divided into 2-4 administrations.

Adults: 200-1600 micrograms daily divided into 2-4 administrations, (less severe cases 200-800 micrograms daily, more severe cases 800-1600 micrograms daily).

Administration twice daily (morning and evening) is usually sufficient.

The maintenance dose is individual and should be the lowest possible. When the maintenance dose is 400 micrograms or lower the dose can be given once daily. The dose may then be given in the morning or in the evening. If deterioration of asthma occurs, the frequency of dosing and the daily dose should be increased.

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

Clinical trials indicate that a larger amount of budesonide is deposited in the lungs when administered with Pulmicort Turbuhaler, compared with Pulmicort pMDI. If a patient in a

stable phase is transferred from Pulmicort pMDI to Pulmicort Turbuhaler a reduction in dose may therefore be appropriate.

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

Patients dependent on oral steroids:
When transfer from oral steroids to Pulmicort Turbuhaler is initiated the patient must be in a relatively stable condition. For 10 days, a high dose of Pulmicort Turbuhaler is given in combination with the previously used oral steroid. 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.

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

Instructions for correct use of Turbuhaler

It is important that the inhaler is used correctly.

Turbuhaler is inspiratory flow-driven which means that, when the patient inhales through the mouthpiece, the substance will follow the inspired air into the airways.

Note It is important to instruct the patient

- To carefully read the instructions for use: “How to use Pulmicort Turbuhaler”
- To breathe in forcefully and deeply through the mouthpiece to ensure that an optimal dose is delivered to the lungs
- Never to breathe out through the mouthpiece
- To rinse the mouth out with water after inhaling the prescribed dose to minimise the risk of oropharyngeal thrush

The patient may not taste or feel any medication when using Pulmicort Turbuhaler due to the small amount of drug dispensed.

4.3 Contraindications

Hypersensitivity to budesonide.

4.4 Special warnings and special precautions for use

Special care is needed in patients with lung tuberculosis and fungal and viral infections. Children who are on immunosuppressant drugs are more susceptible to infections than healthy children. Chicken pox and measles, for example, can have a more serious or fatal course in children on immunosuppressant corticosteroids. In such children, or in adults who have not had these diseases, particular care should be taken to avoid exposure. If exposed, therapy with varicella zoster immune globulin (VZIG) or pooled intravenous immunoglobulin (IVIG), as appropriate, may be indicated. If chicken pox develops, treatment with antiviral agents may be considered. If, however, a viral upper respiratory infection is present, the patient should adhere to the regular asthma medication. In patients who are known to deteriorate rapidly when they have a viral respiratory infection, a short course of oral corticosteroid therapy should be considered.

Clinical studies have shown that viral infections cause significantly less problems in patients who are on regular treatment with topical glucocorticosteroids.

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 the administrations of the drugs should be as long as possible (see Interactions with other medicinal products and other forms of interaction).

Particular care is needed in patients transferring from oral glucocorticosteroids, since they may remain at risk of impaired adrenal function for a considerable time. Patients, who have required high dose emergency glucocorticosteroid therapy or prolonged treatment at the highest recommended dose of inhaled glucocorticosteroids, may also be at risk. These patients may exhibit signs and symptoms of adrenal insufficiency when exposed to severe stress. Additional systemic glucocorticosteroid cover should be considered during periods of stress or elective surgery.

During the transfer from oral steroid therapy to Pulmicort Turbuhaler, patients may experience the return of previous symptoms such as muscle and joint pain. In these cases a temporary increase of the oral steroid dose may sometimes 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 Turbuhaler 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. 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.

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.
Acute exacerbations of asthma may need complementary treatment with a short oral steroid regimen.

Decreased liver function may affect the ability to eliminate budesonide.

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.

4.5 Interactions with other medicinal products and other forms of interaction

No clinically relevant interactions with other agents for asthma 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. Since there is an absence of data to permit dosage recommendations, the combination should be avoided.

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.

4.6 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, 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 teratogenic 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 Turbuhaler no effects on the suckling child are anticipated. Pulmicort Turbuhaler can be used during breastfeeding.

4.7 Effects on ability to drive and use machines

Pulmicort Turbuhaler does not affect ability to drive or use machines.

4.8 Undesirable effects

Up to 10% of patients treated 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:*	Angiooedema, anaphylactic reaction
	CNS:	Nervousness, restlessness, depression, behavioural disturbances
	Skin:	Urticaria, rash, dermatitis, skin bruising
	Airways:	Bronchospasm
Unknown	*Eye:*	Blurred vision

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.

4.9 Overdose

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

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Inhalation drugs for obstructive airway diseases.
ATC code: R03BA02

Budesonide is a glucocorticosteroid with a high local anti-inflammatory effect.

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

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.

Asthma, like inhaled corticosteroids, can delay growth. An initial small but generally transient reduction in growth (approximately 1 cm) has been observed, which usually occurs within the first year of treatment. Long-term studies in a clinical practice environment suggest that children and adolescents treated with inhaled budesonide on average achieve their adult target height. However, in a long-term double-blind study, in which the budesonide dose was generally not titrated to the lowest effective dose, children and adolescents treated with inhaled budesonide became on average 1.2 cm shorter as adults than those randomised to placebo. See Special warnings and special precautions for use about titration to the lowest effective dose and about monitoring the growth in children.

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

5.2 Pharmacokinetic properties

Absorption

Inhaled budesonide is rapidly absorbed. The peak plasma concentration is reached within 30 minutes after inhalation. In studies, the average deposition of budesonide in the lungs after inhalation via Turbuhaler has been shown to be 25-35% of the metered dose. The systemic bioavailability is approx. 38% of the metered dose.

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.

5.3 Preclinical safety data

In toxicity studies budesonide 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 in humans at the recommended doses.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Pulmicort Turbuhaler contains no excipients.

6.2 Incompatibilities

Not relevant.

6.3 Shelf-life

Please refer to expiry date on outer carton.

6.4 Special precautions for storage

Do not store above 30°C.
Must be stored with the protective cap in place.

6.5 Nature and content of container

Pulmicort Turbuhaler is an inspiration-driven multi-dose powder inhaler made of plastic.

6.6 Pack size

Please refer to outer carton for pack size.

Product Owner

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

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7. INSTRUCTIONS FOR USE/HANDLING

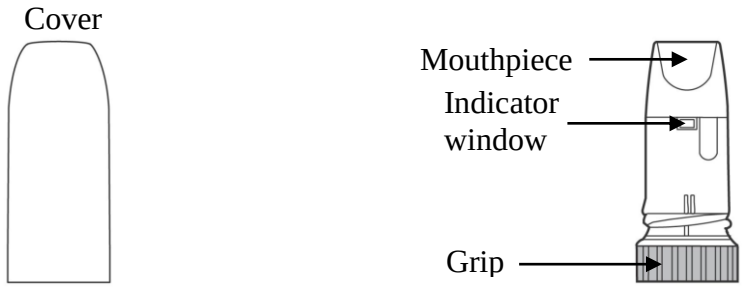
Please read the complete instructions carefully before you start to take your medication.

Turbuhaler is a multidose inhaler from which very small amounts of powder are administered (Figure 1). 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.

How to prepare a new inhaler for use

Before using Turbuhaler **for the first time** you need to prepare the inhaler for use.

Unscrew and lift off the cover (Figure 1).



Hold the inhaler upright with the grip downwards (Figure 2). Do not hold the mouthpiece when you turn the grip. **Turn the grip as far as it will go in one direction, and then back again in the opposite direction as far as it will go**. It does not matter which way you turn first. During this procedure you will hear a click. Perform the procedure twice.

Figure 2

The inhaler is now prepared for use, and **you should not repeat the above procedure again**. To take a dose, please continue according to the instructions below.

HOW TO USE PULMICORT TURBUHALER

To administer one dose, simply follow the instructions below.

1. Unscrew and lift off the cover (Figure 1).

2. **Hold the inhaler upright** with the grip downwards (Figure 2). Do not hold the mouthpiece when you turn the grip. To load the inhaler with a dose, **turn the grip as far as it will go in one direction, and then back again in the opposite direction as**

far as it will go. It does not matter which way you turn first. During this procedure you will hear a click.

3. Hold the inhaler away from your mouth. **Breathe out**. Do **not** breathe out through the mouthpiece.

4. Place the mouthpiece gently between your teeth, close your lips and **inhale forcefully** and deeply through the device (Figure 3). Do not chew or bite on the mouthpiece. Do not use Turbuhaler if it has been damaged or if the mouthpiece has become detached.

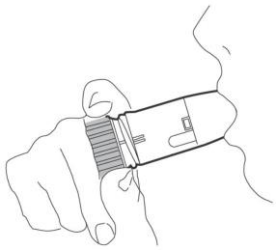


Figure 3

5. **Remove the inhaler from your mouth before breathing out.**
If more than one dose has been prescribed, repeat steps 2-5.

6. Replace the cover by screwing it back on tightly.

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 (Figure 4). 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 (Figure 5). The sound heard as you shake the inhaler is not produced by the medication but by a drying agent.

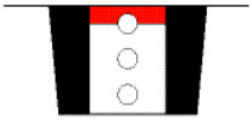


Figure 4

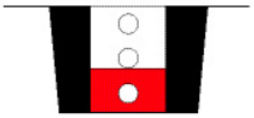


Figure 5

Disposal

Always be sure to dispose of your used Turbuhaler responsibly in the recommended way, since some of the medicine will remain inside it. Ask your pharmacist for advice.