Budesonide

Budecort Turbuhaler®

200 mcg/dose

Inhalation powder

Anti-asthma

1. FORMULATION

1 metered dose contains budesonide 200 mcg.

2. PHARMACEUTICAL FORM

Inhalation powder

3. CLINICAL PARTICULARS

3.1 Therapeutic indication

Bronchial asthma

3.2 Dosage and method of administration

The dosage of Budesonide (BUDECORT 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 aged 6 years and older:
100-800 micrograms per day, divided into 2-4 inhalations. With daily doses up to 400 micrograms the full dose may be given in one administration.

Adults:
The normal dose range is 200-800 micrograms per day, divided into 2-4 inhalations. In more severe cases daily doses of up to 1600 micrograms may be needed. With daily doses up to 400 micrograms the full dose may be given in one administration.

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 only achieved after a few weeks of treatment. Treatment with Budesonide (BUDECORT 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 Budesonide (BUDECORT Turbuhaler), compared with Budesonide (BUDECORT pMDI). If a patient in a stable phase is transferred from Budesonide

(BUDECORT pMDI) to Budesonide (BUDECORT 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 Budesonide (BUDECORT Turbuhaler) 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 Budesonide (BUDECORT) 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.

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
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 Budesonide (BUDECORT Turbuhaler)
- To breathe in forcefully and deeply through the mouthpiece to ensure that an optimal dose is delivered to the lungs
- Never to breath out through the mouthpiece
- To rinse the mouth out with water after inhaling the prescribed dose to minimise the risk of oropharyngeal thrush

It is possible that the patient will not taste or perceive any medicine when Budesonide (BUDECORT Turbuhaler) is used; this is because such a small amount of substance is dispensed.

3.3 Contraindications

Hypersensitivity to budesonide.

3.4 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 the administrations of the drugs should be as long as possible.

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.

Caution must be observed in treatment of patients who are transferred from systemically acting corticosteroids to Budesonide (BUDECORT) and in cases of suspected disturbance of pituitary-adrenocortical function. In these patients there should be a cautious reduction of the dose of systemic steroid, and tests of hypothalamic-pituitary-adrenocortical function should be considered. They may also require the adjunct of systemic steroids in connection with periods of stress, e.g. surgery, trauma, etc.

During the transfer from oral steroid therapy to Budesonide (BUDECORT 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 Budesonide (BUDECORT 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.

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.

3.5 Interactions

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. 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.

3.6 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.

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
It is not known whether budesonide passes into breast milk.

3.7 Effects on ability to drive and use machines

Budesonide (BUDECORT Turbuhaler) does not affect ability to drive or use machines.

3.8 Adverse Reactions

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, irritation in the throat, coughing, hoarseness
Rare (<1/1000)	*General:*	Angiooedema
	Skin:	Urticaria, rash, dermatitis
	Airways:	Bronchospasm

Occasional cases of nervousness, restlessness, depression and behavioural disturbances have been observed. On account of the risk of Candida infections in the oropharynx the patient must rinse the mouth with water after every dose.

In isolated cases signs or symptoms of systemic glucocorticoid effects may occur, including adrenal hypofunction.

Isolated cases of bruising have occurred.

3.9 Overdose

Acute overdose with Budesonide (BUDECORT 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.

4. PHARMACOLOGIC PROPERTIES

4.1 Pharmacodynamic properties

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. 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 Budesonide (BUDECORT Turbuhaler) have shown dose-related effects on plasma and urinary cortisol. At recommended doses, Budesonide (BUDECORT 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. However, studies in children and adolescents who were treated with budesonide for a long period (up to 11 years) show that the patients reach the expected adult height.

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

4.2 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. PHARMACEUTICAL PARTICULARS

5.1 Shelf-life
Please refer to outer carton.

5.2 Storage conditions

Store at a temperature not exceeding above 30°C.
Store with the cover tightly closed.

5.3 Availability
Budesonide (BUDECORT Turbuhaler) 200 mcg per dose Inhalation Powder – 1 x 100 Doses

6. INSTRUCTIONS FOR USE, HANDLING AND DISPOSAL

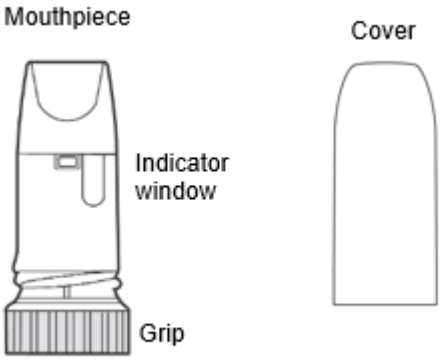
How to use Budesonide (BUDECORT Turbuhaler)

Note: In the printed leaflet, clarifying pictures are included in this part.

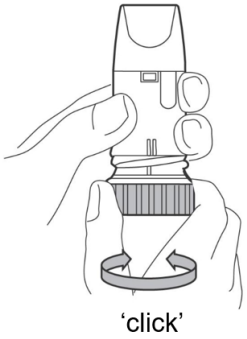
Turbuhaler is a multidose inhaler from which the drug is administered without the use of additives. When you breathe in through Turbuhaler the powder is delivered to the lungs. It is therefore important that you inhale forcefully and deeply through the mouthpiece.

Turbuhaler is very easy to use. Simply follow the instructions given below.

1 Unscrew and lift off the cover.

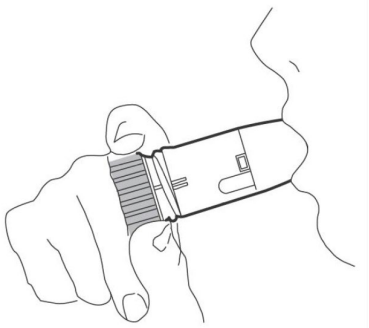


2 **Hold the inhaler upright** with the grip downwards. Load the inhaler with a dose by turning the grip as far as it will go and then back to the original position.



3 **Breathe out.** Do **not** breathe out **through** the inhaler.

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.**

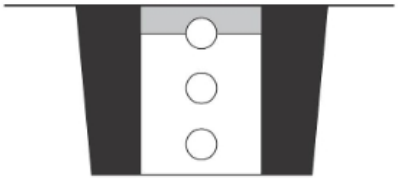
NOTE!
Never breathe out through the mouthpiece.
Always replace the cover properly after use.

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.

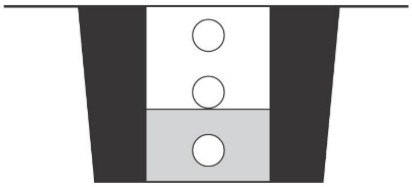
Dose indicator
When a red mark is first seen in the indicator window there are approximately 20 doses left. When the red mark has reached the lower edge of the window the inhaler will no longer deliver the correct amount of medicine, and should be discarded. The sound heard as you shake the inhaler is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

This indicates that there are 20 doses remaining.



20 doses left

This indicates that the inhaler is empty.



empty

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

7. REGISTRATION NUMBER
DR-XY13867

8. DATE OF FIRST AUTHORIZATION

2 July 1991

Caution

Foods, Drugs, Devices, and Cosmetics Act prohibits dispensing without prescription.

For suspected adverse drug reaction, please report to the Food and Drug Administration (FDA) at www.fda.gov.ph and to AstraZeneca at patientsafety.ph@astrazeneca.com. The patient should seek medical attention immediately at the first sign of any adverse drug reaction.

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