

PRODUCT MONOGRAPH

 **PULMICORT® TURBUHALER®**

budesonide

Dry Powder for Oral Inhalation
100 mcg, 200 mcg, and 400 mcg / metered dose

Glucocorticosteroid

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Date of Revision:
November 8, 2017

Submission Control No. 207570

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ACTIONS AND CLINICAL PHARMACOLOGY

The active ingredient of PULMICORT TURBUHALER, budesonide, is a potent synthetic glucocorticosteroid with strong topical and weak systemic effects.

PULMICORT TURBUHALER has a high topical anti-inflammatory potency and it is rapidly biotransformed in the liver. This favourable separation between topical anti-inflammatory activity and systemic effect is due to strong glucocorticosteroid receptor affinity and an effective first pass metabolism with a short half-life.

The late reaction can be significantly inhibited if PULMICORT TURBUHALER is given at least 2 hours before a bronchial challenge. Pre-treatment for 1 - 4 weeks with inhaled budesonide may inhibit the immediate bronchial reaction. After initiation of therapeutic use of orally inhaled budesonide, 1 - 2 weeks may pass before the full effect is obtained.

INDICATIONS AND CLINICAL USE

Patients with bronchial asthma:

- In patients who require inhaled steroids;
- In patients for whom a reduction of systemic glucocorticoids is desirable.

CONTRAINDICATIONS

- Status asthmaticus; not to be used in primary treatment of acute episodes of asthma or in patients with moderate to severe bronchiectasis;
- Hypersensitivity to budesonide;
- Active or quiescent pulmonary tuberculosis;

- Untreated fungal, bacterial or viral infections of the respiratory system.

WARNINGS

PULMICORT 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 corticosteroid.

Particular care is needed in patients who are transferred from systemically active corticosteroids to PULMICORT TURBUHALER (budesonide) and in patients who have required high dose emergency corticosteroid therapy. This is important as deaths due to adrenal insufficiency have occurred in asthmatic patients during and after transfer from systemic corticosteroids to inhaled corticosteroids. Patients receiving prolonged treatment at the highest recommended dose of inhaled corticosteroids, may also be at risk for adrenal insufficiency. After withdrawal from systemic corticosteroids, a number of months are required for recovery of hypothalamic-pituitary-adrenal (HPA) function. During this period of HPA suppression, patients may exhibit signs and symptoms of adrenal insufficiency when exposed to severe stress including worsening of asthma attacks, trauma, surgery or infections, particularly gastroenteritis, or other conditions associated with severe electrolyte loss. Additional systemic corticosteroid should be considered during periods of stress or elective surgery.

Although PULMICORT TURBUHALER may provide control of asthmatic symptoms during these episodes, it does NOT provide the systemic steroid which is necessary for coping with these emergencies.

During periods of stress or a severe asthmatic attack, patients who have been withdrawn from systemic corticosteroids should be instructed to resume systemic steroids (in large dosages) immediately and to contact their physicians for further instruction. These patients should also be instructed to carry a warning card indicating that they may need supplementary systemic steroids during periods of stress or a severe asthma attack. To assess the risk of adrenal insufficiency in emergency situations, routine tests of adrenal cortical function, including measurement of early morning and evening cortisol levels, should be performed periodically in all patients. An early morning resting cortisol level may be accepted as normal only if it falls at or near the normal mean level.

Patients previously on high doses of systemic steroids may regain earlier symptoms not related to asthma such as rhinitis and eczema when transferred from oral therapy to PULMICORT TURBUHALER. These allergies should be symptomatically treated with anti-histamine and/or topical preparations, including topical steroids. These symptoms are a result of the generally lower systemic steroid action which will be experienced. Patients may also suffer from tiredness, headache, pain in muscles and joints and, occasionally, nausea and vomiting.

Temporary resumption of systemic steroids may be necessary to treat these conditions.

The development of pharyngeal and laryngeal candidiasis is cause for concern because the extent of its penetration of the respiratory tract is unknown. If oral pharyngeal candidiasis develops, appropriate anti-fungal therapy should be implemented to eradicate the infection. The incidence of candidiasis can generally be held to a minimum by having patients rinse their mouths out with water after each inhalation (See DOSAGE AND ADMINISTRATION).

Glucocorticosteroids may mask some signs of infection and new infections may appear during their use.

There is no evidence that control of asthma can be achieved by administration of PULMICORT TURBUHALER in doses higher than those recommended. During such episodes, patients may require therapy with systemic corticosteroids.

PRECAUTIONS

In transferring patients from a systemic steroid to PULMICORT TURBUHALER (budesonide), the reduction of the systemic steroid must be very gradual and carefully supervised by the physician since systemic withdrawal symptoms (e.g. joint and/or muscular pain, lassitude, depression), may occur in spite of maintenance or improvement of respiratory functions. (See DOSAGE AND ADMINISTRATION).

It is essential that the patient be instructed that PULMICORT TURBUHALER is a preventative agent which must be taken at regular intervals and is not to be used to relieve an acute asthmatic attack.

The long-term effects of budesonide on developmental or immunologic processes in the mouth, pharynx, trachea, eyes, and lung are unknown. With the recommended therapeutic doses of PULMICORT TURBUHALER, there is little risk of adverse systemic effects.

A reduction of growth velocity in children or adolescents may occur as a result of inadequate control of chronic diseases such as asthma or from use of corticosteroids for treatment. Physicians should closely follow the growth of children and adolescents taking corticosteroids by any route and weigh the benefits of corticosteroid therapy and asthma control against the possibility of growth suppression if a child/adolescent's growth appears slowed. To minimize the systemic effects, it is important that the dose of inhaled corticosteroid is titrated to the lowest dose at which effective control of asthma is maintained (see DOSAGE AND ADMINISTRATION).

Controlled clinical trials have shown confounding results indicating inhaled corticosteroids may cause a reduction in growth in children and adolescents. In one trial in children aged 3 to 13 years (mean 8.7 years), treated for 3 to 13 years (mean 9.2 years) with budesonide via Turbuhaler[®] at a mean daily dose of 412 mcg, no effect was demonstrated on long-term statural growth compared to nonsteroidal therapy. However, in a long-term, double-blind study, children and adolescents (aged 5 to 12 years) treated for 4 to 6 years (mean 4.3 years)

with inhaled budesonide via Turbuhaler[®] became on average 1.2 cm shorter as adults than those randomized to placebo.

Treatment with PULMICORT TURBUHALER should not be stopped abruptly, but tapered off gradually.

Pulmonary infiltrates with eosinophilia may occur in patients on PULMICORT TURBUHALER therapy. Although this is possible in some patients who are administered inhalational steroids, their causative role cannot be ruled out.

Corticosteroids may mask some signs of infections and new infections may appear. A decreased resistance to localized infection has been observed during corticosteroid therapy. During long-term therapy, pituitary-adrenal function and height (in children) should be periodically assessed.

Patients should be advised to inform subsequent physicians of the prior use of corticosteroids.

There may be enhanced systemic effects of budesonide in patients with an advanced liver cirrhosis, and in those with hypothyroidism. Reduced liver function may affect the elimination of corticosteroids. The intravenous pharmacokinetics of budesonide however, are similar in cirrhotic patients and in healthy subjects. The pharmacokinetics after oral ingestion of budesonide were affected by compromised liver function as evidenced by increased systemic availability. This is however, of limited importance for PULMICORT TURBUHALER, as after inhalation the oral contribution to the systemic availability is very small.

Acetylsalicylic acid should be used cautiously in conjunction with corticosteroids in hypoprothrombinemia.

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 upper respiratory infections cause significantly fewer problems in patients who are on regular treatment with topical glucocorticosteroids.

To ensure the proper dosage and administration of the drug, the patient should be instructed by a physician or other health professional in the use of PULMICORT TURBUHALER.

Adequate oral hygiene is of primary importance in minimizing overgrowth of micro-organisms such as *Candida albicans* (see DOSAGE AND ADMINISTRATION).

Usage During Pregnancy

In experimental animal studies, budesonide was found to cross the placental barrier. Like other glucocorticosteroids, budesonide is teratogenic to rodent species. High doses of budesonide administered subcutaneously produced fetal malformations, primarily skeletal defects, in rabbits, rats and in mice. Results from world-wide post marketing experience indicate inhaled budesonide during pregnancy has no adverse effects on the health of the fetus/new born child. Review of published literature of orally inhaled budesonide, including results from a large case control study performed with cases identified from 3 Swedish health registers showed that there was no association between exposure to inhaled budesonide and overall congenital malformations. Results from a similar study performed with intranasal budesonide, using the same 3 Swedish health registers showed that the use of intranasal budesonide was associated with a subgroup “less severe cardiovascular defects”; however there was no statistically significant association between the use of intranasal budesonide during pregnancy and overall congenital malformations, or overall frequency of cardiovascular defects in the offspring. Budesonide should be used during pregnancy only if the potential benefits clearly outweigh the risk to the fetus. Infants born of mothers who have received substantial doses of corticosteroids, especially oral steroids, during pregnancy should be carefully observed for hypoadrenalism.

Lactation

Nursing Women: Budesonide is excreted in breast milk. The administration of PULMICORT TURBUHALER to women who are breast feeding should only be considered if the expected benefit to the mother is greater than any possible risk to the child.

Children Under 6 Years of Age

PULMICORT TURBUHALER is not presently recommended for children younger than 6 years of age due to limited clinical data in this age group.

Drug Interactions

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

Cimetidine

The kinetics of budesonide were investigated in a study of healthy subjects without and with cimetidine, 1000 mg daily. After a 4 mg oral dose the values for C_{max} (nmol/L) and systemic availability (%) of budesonide without and with cimetidine (3.3 vs 5.1 nmol/L and 10 vs 12%, respectively) indicated a slight inhibitory effect on hepatic metabolism of budesonide, caused by cimetidine. This should be of little clinical importance.

CYP3A4 Inhibitors

The metabolism of budesonide is primarily mediated by CYP3A4, a subfamily of cytochrome P450. CYP3A4 inhibitors like ritonavir and azole antifungals (e.g. ketoconazole and itraconazole) increase the systemic exposure to budesonide. Therefore, concomitant use of budesonide and ritonavir or azole antifungals should be avoided, unless the potential benefit outweighs the risk of systemic corticosteroid side-effects.

Omeprazole

At recommended doses, omeprazole has no effect on the pharmacokinetics of oral budesonide.

ADVERSE REACTIONS

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

- The most common side effects were cough, throat irritation and hoarseness (2-4%).
- Bad taste, headache, nausea and dryness of the throat were reported less frequently. Other side effects reported on occasion during budesonide treatment were tiredness, thirst, and diarrhea. Rare cases of anaphylactic reaction have been reported following the use of PULMICORT TURBUHALER. Skin reactions (urticaria, rash, dermatitis, angioedema, etc.) may, in rare cases, occur in association with local corticosteroid therapy. In rare cases, skin bruising has been reported following treatment with inhaled glucocorticosteroids.
- Psychiatric symptoms such as nervousness, restlessness and depression, as well as behavioural disturbances in children, have been observed.
- As with other inhalation therapy, the potential for paradoxical bronchospasm should be kept in mind. If it occurs, the preparation should be discontinued immediately and alternative therapy be instituted.
- In rare cases, signs or symptoms of systemic glucocorticosteroid effect including hypofunction of the adrenal gland and oropharyngeal complications and reduction of growth velocity may occur, depending on dose, exposure time, concomitant and previous steroid exposure, and individual sensitivity. Candidiasis has been reported by some patients and may occur at therapeutic doses.
- Cases of growth suppression have been reported for PULMICORT TURBUHALER.
- In patients in whom systemic steroids are reduced or stopped, withdrawal symptoms due to decreased systemic activity occur frequently (See DOSAGE AND ADMINISTRATION: CLINICAL MANAGEMENT).

SYMPTOMS AND TREATMENT OF OVERDOSAGE

Occasional overdosing will not give any obvious symptoms in most cases but it will decrease the plasma cortisol level. Other pharmacological effects are an increase in the number and percentage of circulating neutrophils, while the number and percentage of eosinophils will decrease concurrently. Stopping the treatment or decreasing the dose will abolish the induced effects.

Habitual overdosing may cause hypercorticism and hypothalamic-pituitary-adrenal suppression. Decreasing the dose or stopping the therapy will abolish these effects, although the restitution of the HPA-axis may be a slow process and during periods with pronounced physical stress (severe infections, trauma, surgical operations, etc.) it may be advisable to supplement with systemic steroids.

DOSAGE AND ADMINISTRATION

Adults and Children over 12 Years of Age

When treatment with inhaled glucocorticosteroids is started, during periods of severe asthma, and while reducing or discontinuing oral glucocorticosteroids the dosage should be 400-2400 mcg daily divided into 2-4 administrations.

The maintenance dose is usually 200-400 mcg twice daily but higher doses may be necessary for longer or shorter periods of time in some patients. The dose of PULMICORT TURBUHALER (budesonide) should be individualized to the patient's need and should be the lowest possible dose that fills the therapeutic objective.

Once daily dosing may be considered in patients who require a dosage of 400 mcg budesonide per day. 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.

Treatment with PULMICORT TURBUHALER should not be stopped abruptly, but tapered off gradually.

Children 6-12 Years

When starting therapy with budesonide in children, during periods of severe asthma and while reducing or discontinuing oral corticosteroids, the dosage should be 200-400 mcg daily, given in divided doses twice daily at 100 to 200 mcg per inhalation.

The maintenance dose is individual and should be the lowest dose which keeps the patient symptom-free. Administration twice daily is usually adequate in stable asthmatics.

Children Under 6 Years of Age

PULMICORT TURBUHALER is not recommended for children in this age group.

Clinical studies in man have shown an improved efficacy for the same amount of budesonide delivered via Turbuhaler[®] inhaler as compared with the pressurized aerosol with Nebuhaler[®]

spacer device. It may be possible to reduce the dose of PULMICORT TURBUHALER when the patient is in a stable phase.

In patients where an increased therapeutic effect is desired, an increased dose of PULMICORT TURBUHALER is recommended because of the lower risk of systemic effects as compared with a combined treatment with oral glucocorticosteroids.

Since the effect of PULMICORT TURBUHALER depends on its regular use and on the proper technique of inhalation, patients must be instructed to use their PULMICORT TURBUHALER daily, as prescribed by their physician and not as they feel necessary. They must also be instructed in the correct method which is described in the INFORMATION FOR THE PATIENT section.

Turbuhaler®

Turbuhaler® is a breath-activated dry powder inhaler. It contains only the active ingredient budesonide – no propellants or preservatives. NOTE: The patient may not taste or feel any medication when inhaling from PULMICORT TURBUHALER. This lack of feeling does not mean that the patient is not receiving benefit from PULMICORT TURBUHALER.

Clinical Management

Patients - Non-Steroid Dependent

Treatment with the recommended doses of PULMICORT TURBUHALER usually gives a therapeutic effect within 10 days. However, certain patients might have an excessive collection of mucous secretion in the bronchi which reduces the penetration of the active substance in PULMICORT TURBUHALER into the bronchial mucosa. In these cases, it is desirable to initially give a short (about 2 weeks) oral corticosteroid regimen in addition to PULMICORT TURBUHALER. The oral treatment is started on a rather large dose which is then gradually reduced. Thereafter, treatment with PULMICORT TURBUHALER only is sufficient. Exacerbations of the asthma caused by bacterial infections are controlled by adequate antibiotic regimens and also by increasing the PULMICORT TURBUHALER dosage.

Patients - Steroid Dependent

Transferal of patients dependent upon oral steroids to treatment with PULMICORT TURBUHALER demands special care mainly because of the slow restitution of the disturbed hypothalamic-pituitary-adrenal function caused by extended treatment with oral corticosteroids. When PULMICORT TURBUHALER treatment is initiated, the patient should be in a relatively stable phase. PULMICORT TURBUHALER is then given in combination with the previously used oral steroid dose for about 10 days. After this period of time, reduction of the oral corticoid dose may be started gradually. The oral dose is thus reduced to the lowest level which, in combination with PULMICORT TURBUHALER, gives a stable respiratory capacity.

In adults, the usual rate of withdrawal of the systemic corticosteroid is the equivalent of 2.5 mg of prednisone every four days if the patient is under close observation. If continuous supervision is not feasible, the withdrawal of the systemic steroid should be slower, approximately 2.5 mg of prednisone (or equivalent) every ten days. A slow rate of withdrawal cannot be overemphasized. If withdrawal symptoms appear, the previous dosage of the systemic drug should be resumed for a week before further decrease is attempted. During withdrawal, some patients may experience symptoms of systemically active steroid withdrawal, e.g. joint and/or muscular pain, lassitude, and depression, despite maintenance or even improvement of respiratory function. Such patients should be encouraged to continue with PULMICORT TURBUHALER, but should be watched carefully for objective signs of adrenal insufficiency such as hypotension and weight loss. If evidence of adrenal insufficiency occurs, the systemic steroid dosage should be boosted temporarily and thereafter further withdrawal should continue more slowly.

In many cases it may be possible to completely replace the oral steroid with PULMICORT TURBUHALER treatment. In other patients, a low oral steroid maintenance dosage may be required. The length of time needed for the body to regain its natural production of corticosteroid in sufficient quantity is often extended. Thus, during severe asthma attacks or physically stressing situations such as severe infections, trauma, and surgical operations, it is necessary to resume systemic steroids (in large dosages) in order to avoid adrenocorticoid insufficiency. Acute exacerbations, especially in connection with increased viscosity and mucous plugging, may require complementary treatment with a short course of oral corticosteroids which are gradually tapered as symptoms subside. During transfer from oral therapy to PULMICORT, a lower general steroid action is experienced. The patients might regain earlier symptoms (rhinitis, eczema) or suffer from tiredness, headache, pain in muscles and joints and, occasionally, nausea and vomiting. In these cases, further medical support may be required.

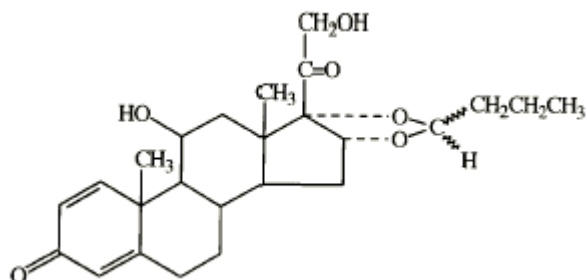
NOTE: **The medication from PULMICORT TURBUHALER is delivered to the lungs as the patient inhales and, therefore, it is important to instruct the patient to breathe in forcefully and deeply through the mouthpiece. When prescribing PULMICORT TURBUHALER to young children it is necessary to ascertain that they can follow the instructions for use. The patient may not taste or feel any medication when using PULMICORT TURBUHALER due to the small amount of drug dispensed.**

Patients should be instructed to rinse their mouths out with water after each inhalation. This will help prevent the occurrence of candidiasis. Cleansing dentures has the same effect.

PHARMACEUTICAL INFORMATION

Drug Substance

Chemical Structure:



Generic Name: Budesonide

Chemical Name: Budesonide is a mixture of two isomers:

1. Pregna-1,4-diene-3,20-dione,16,17-butyldienebis(oxy)-11,21-dihydroxy-, [11 β ,16 α (R)]

and

2. Pregna-1,4-diene-3,20-dione,16,17-butyldienebis(oxy)-11,21-dihydroxy-, [11 β ,16 α (S)]

Molecular Formula: C₂₅H₃₄O₆

Molecular Weight: 430.5

Description: Budesonide is a glucocorticosteroid and consists of a 1:1 mixture of two epimers, 22R and 22S. It is a white to off-white crystalline powder and is freely soluble in chloroform, sparingly soluble in ethanol, practically insoluble in water and in heptane. Budesonide melts at 224°C to 231.5°C, with decomposition.

Composition

PULMICORT TURBUHALER

Ingredient: Budesonide

Strength (mcg/inhalation): 100, 200 or 400

Stability and Storage Recommendations

PULMICORT TURBUHALER should be stored with the cover tightened, at room temperature (15 - 30°C).

AVAILABILITY OF DOSAGE FORMS

PULMICORT TURBUHALER is a dry powder inhaler containing 200 doses of 100 mcg, 200 mcg, and 400 mcg of micronized budesonide. Each inhalation from PULMICORT TURBUHALER will provide either 100 mcg, 200 mcg or 400 mcg of budesonide active substance; no additives or carrier substances are included. PULMICORT TURBUHALER cannot be re-filled and should be discarded when empty.

PHARMACOLOGY

Studies with animals have shown that budesonide has a 2-10 times better ratio between topical anti-inflammatory and systemic glucocorticoid effects than that obtained with beclomethasone dipropionate or triamcinolone acetonide. In the blanching test for topical anti-inflammatory activity in humans, budesonide was about twice as potent as beclomethasone dipropionate. Beclomethasone dipropionate was, however, more active than budesonide with regard to systemic activity as measured by depression of morning plasma cortisol. The favourable topical anti-inflammatory activity to systemic effect ratio demonstrated by budesonide is most probably due to its high glucocorticoid receptor affinity and high first pass metabolism with a short half-life.

Budesonide has been shown to counteract the mainly "IgE" mediated lung anaphylaxis in guinea pigs.

No significant bronchorelaxing activity, either *in vitro* or *in vivo*, could be demonstrated. Budesonide did not potentiate beta-mediated bronchorelaxation, and did not affect theophylline-induced relaxation of respiratory airway smooth muscle in guinea pigs.

Budesonide exhibits typical glucocorticoid effects in that subcutaneous administration to adrenalectomized rats induced glycogen deposition in the liver, increased urinary volume and only slightly affected sodium excretion.

Whole body autoradiography in mice has shown budesonide and its metabolites to have a similar distribution pattern to other glucocorticosteroids with a high distribution to endocrine organs.

Human Pharmacokinetics

The maximal plasma concentration after inhalation of 1 mg budesonide from PULMICORT TURBUHALER (budesonide) is about 3.5 nmol/L and is reached after about 20 minutes. The plasma half-life of budesonide is 2.0 ± 0.2 hours, similar to that found after intravenous administration (2.8 ± 1.1 h). Approximately 30% of the metered dose is deposited in the lungs. The systemic bioavailability of budesonide after inhalation from PULMICORT TURBUHALER is 49% of the dose retained by the patient. After oral administration, peak plasma concentrations of unchanged compound were found after about 3 hours. The oral bioavailability is calculated to be $10.7 \pm 4.3\%$. Since budesonide acts locally in the lung, plasma levels are not predictive of therapeutic efficacy or safety.

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

In human volunteers who inhaled tritiated budesonide (via metered dose aerosol) 31.8±7.5% of the discharged dose was recovered in the urine (0-96 hours) while during the same period, 15.1±4.3% of the dose could be recovered in the feces. In those subjects who took the compound orally, 45.0±5.0% was recovered in the urine, 29.6±2.5% in the feces.

In vitro studies with human liver have shown that budesonide is rapidly metabolized to more polar compounds than the parent drug. Two major metabolites have been isolated and identified as 6β-hydroxybudesonide and 16α-hydroxyprednisolone. The glucocorticoid activity of these two metabolites was at least 100-fold lower than the parent compound as shown in the rat ear edema test. No qualitative differences between the *in vitro* and *in vivo* metabolic patterns could be detected. Negligible biotransformation was observed in human lung and serum preparations.

TOXICOLOGY

Acute Toxicity

Species	Sex	Route	LD ₅₀ (mg/kg) After 3 Weeks
mouse	male	s.c.	35±18
mouse	male	p.o.	>800
mouse	female	p.o.	>800
rat	male	s.c.	15.1±4.4
rat	female	s.c.	20.3±7.1
rat	male	p.o.	≈400

Surviving animals exhibited a marked decrease in body weight gain.

Toxicity After Repeated Administration of Budesonide To Rats, Rabbits, And Dogs.

Animal		Number and Sex Per Group	No. of Dose Groups	Daily Dose Levels		Route of Administration	Duration	Toxic Effects
Species	Strain			mg/kg	mg/animal			
rat	Sprague-Dawley	6 males 6 females	4	0.05 0.5 5.0 50.0		p.o.	1 month	Atrophy of adrenal glands and lymphoid system. Gastric ulceration.
rat	Wistar	10 males 10 females	3	0.02 0.10 0.2-0.5		inhalation	3 months	Hair loss. Dose related reduction in lymphocytes, leukocytes. Increase in neutrophils. In high dose group, reduced adrenal, thymic, splenic and hepatic weights. No pulmonary impairment observed.
rat	Wistar	40 males 40 females	3	0.005 0.01 0.05		inhalation	12 months	As above.
rabbit	New Zealand White	3 males 3 females	2		0.025 0.1	s.c.	1 month	High dose caused slight liver mass increase, slight decrease in adrenal mass, thymal regression.
dog	Beagle	1 male 1 female	3	0.01 0.1 1.0		p.o.	1 month	High dose - Typical steroid effects - adrenal, lymphoid system atrophy, increased fat in myocardium, glycogen in liver.
dog	Beagle	2 males 2 females	3	0.02 0.06 0.2		inhalation	6 weeks	High dose - Induced thymal atrophy, adrenal atrophy. No changes in respiratory system observed.
dog	Beagle	5 males 5 females	3		0.20 0.60 2.00	inhalation	6 months	High dose - Decreased plasma cortisol, cortical atrophy of the adrenal gland, thymal regression. Slight visceral obesity.
dog	Beagle	5 males 5 females	3		0.20 0.60 2.00	inhalation	12 months	High dose -Obesity, alopecia, females showed no evidence of estrous cycle. Systemic steroid effects - lymphoid and adrenal atrophy.

All effects observed were consistent with those expected during prolonged corticosteroid exposure.

Teratology and Reproduction Studies

Effects on Pregnancy

Rat: Daily doses of 20, 100, and 500 mcg/kg body mass were administered subcutaneously to pregnant rats during days 6-15 of gestation. In the high dose group, all of the rats showed a deteriorated general condition including piloerection, drowsiness, decreased food consumption and decreased body mass gain. Fetal loss was increased and pup masses decreased in comparison to the control group. The frequency of fetal abnormalities was also increased. Doses in excess of 100 mcg/kg must be considered teratogenic in the rat.

Daily doses of 0.01, 0.05 and 0.1 - 0.25 mg/kg were administered by inhalation to pregnant rats during days 6-15 of gestation. At the highest dose a slight significant reduction in fetal weight gain was observed, but there was no evidence of any effect on fetal development attributable to budesonide at any dose level.

Rabbit: Daily doses of 5, 25, and 125 mcg/kg body mass were administered subcutaneously during days 6-18 of gestation. In the low and medium dose groups, food consumption and body mass gain were decreased during the fourth gestational week. Some doses also showed signs of diarrhea and vaginal bleeding. In the high dose group, all doses aborted at the end of the gestation period. In the medium dose group, a marked increase in the frequency of abnormalities, mainly skeletal defects, was observed. Most commonly, defects were skull and vertebral abnormalities.

Effects on Fertility and General Reproductive Performance

Rat: To evaluate the effect of budesonide on fertility and general reproductive performance, daily doses of 0.01, 0.05, 0.19 mcg/kg were given subcutaneously to males for 9 weeks prior to and throughout mating. Females received the same doses for two weeks before, throughout gestation and up to 21 days postpartum. The offspring of the high group showed a decrease of peri- and post-natal viability. Dams showed a decrease in body mass gain.

Mutagenicity Studies

Budesonide showed no mutagenic activity in the Ames Salmonella/microsome plate test or in the mouse micronucleus test.

Carcinogenicity

The carcinogenic potential of budesonide was evaluated in long term mouse and rat studies.

Chronic Drinking Water Study in Mice

Budesonide was administered in the drinking water for 91 weeks to three groups of CD[®]-1 mice at dose levels of 10, 50 and 200 mcg/kg/day.

A statistically significant dose-related decrease in survival was noted for the males only. All other evaluation criteria were comparable in all groups. Upon microscopic examination, a variety of spontaneous lesions was observed which were not related to treatment. No carcinogenic effect was present.

Chronic Drinking Water Study (104 Weeks) with Budesonide in Rats

Three rat carcinogenicity studies have been performed. In the first study, budesonide was administered for 104 weeks in doses of 10, 25 and 50 mcg/kg/day.

A small but statistically significant increase in gliomas was noted in male animals from the high dose group. These results were considered equivocal since the S-D rat is very variable with regard to spontaneous glioma incidence.

To elucidate these results, two further 104 week carcinogenicity studies with budesonide 50 mcg/kg/day were performed, one using male S-D rats, and one using male Fischer rats (which have a lower and less variable incidence of gliomas). Prednisolone and triamcinolone acetonide were used as reference glucocorticoids in both studies.

The results from these new carcinogenicity studies in male rats did not demonstrate an increased glioma incidence in budesonide treated animals, as compared to concurrent controls or reference glucocorticosteroid treated groups.

Compared with concurrent control male S-D rats there was also an increased incidence of liver tumors in the mid and high dose groups in the original study. This finding was confirmed in all three steroid groups (budesonide, prednisolone, triamcinolone acetonide) in the repeat study in male S-D rats thus indicating a class effect of glucocorticosteroids.

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PART III: CONSUMER INFORMATION

Pr PULMICORT[®] TURBUHALER[®]

budesonide dry powder for oral inhalation

This leaflet is part III of a three-part "Product Monograph" published when PULMICORT TURBUHALER was approved for sale in Canada and is designed specifically for Consumers. This leaflet is a summary and will not tell you everything about PULMICORT TURBUHALER. Contact your doctor or pharmacist if you have any questions about the drug.

ABOUT THIS MEDICATION

This medicine is for you. Only a doctor can prescribe it for you. Never give it to someone else. It may harm them even if their symptoms are the same as yours.

What the medication is used for:

PULMICORT TURBUHALER is used in adults and children 6 years of age and older to treat asthma, which is caused by inflammation in the airways.

PULMICORT TURBUHALER is not meant to relieve an asthma attack that has already started. Other inhalers containing fast-acting bronchodilators provide rapid relief. If your doctor prescribed one of these, follow their directions when you have an acute attack of asthma.

What it does:

PULMICORT TURBUHALER contains the medicine budesonide, which belongs to a group of medicines called glucocorticosteroids. It reduces and prevents inflammation in the airways.

When it should not be used:

You should not use PULMICORT TURBUHALER:

- if you are allergic to budesonide;
- to treat a sudden attack of breathlessness. You will probably need a different kind of medicine (ie. a fast-acting relief medication) in a different colour puffer than may already have been given to you. If you have more than one medicine, be careful not to confuse them;
- if you have an untreated infection (fungal, bacterial, or viral) or tuberculosis in the respiratory tract.

What the medicinal ingredient is:

Budesonide.

What are the nonmedicinal ingredients:

PULMICORT TURBUHALER contains no other ingredients.

What dosage forms it comes in:

Dry powder for oral inhalation: 100 mcg, 200 mcg, or 400 mcg per dose. Each inhaler contains 200 metered doses.

WARNINGS AND PRECAUTIONS

BEFORE you use PULMICORT TURBUHALER talk to your doctor or pharmacist:

- about **all** health problems you have now or have had in the past, especially if you have had lung tuberculosis or any other recent infection or liver problems;
- if you take, or have taken steroid medicines within the past several months;
- if you have ever had a bad, unusual or allergic reaction to budesonide;
- if you are pregnant, plan to become pregnant or are breast feeding.

All cortisone-type medicines, especially when used for a long time, may possibly interfere with the usual growth pattern in growing adolescents. It is recommended that children being treated with steroids, including PULMICORT TURBUHALER have their height checked regularly by their doctor.

If you develop an infection or a respiratory infection, contact your doctor to see if you can continue taking PULMICORT TURBUHALER.

INTERACTIONS WITH THIS MEDICATION

As with most medicines, interactions with other drugs are possible. Tell your doctor, nurse, or pharmacist about all the medicines you take, including drugs prescribed by other doctors, vitamins, minerals, natural supplements, or alternative medicines.

Drugs that may interact with PULMICORT TURBUHALER include:

- ritonavir (used to treat HIV infection or AIDS);
- some antifungals used to treat fungal infections (such as ketoconazole and itraconazole).

PROPER USE OF THIS MEDICATION

The dosage of PULMICORT TURBUHALER is individual.

Follow your doctor's instructions carefully. They may differ from the information in this leaflet. It is important that you use PULMICORT TURBUHALER daily at the intervals recommended by your doctor.

IMPORTANT: DO NOT EXCEED THE DOSE PRESCRIBED BY YOUR DOCTOR. IF DIFFICULTY IN BREATHING PERSISTS, CONTACT YOUR DOCTOR OR PHARMACIST.

DO NOT STOP TAKING PULMICORT TURBUHALER ON YOUR OWN. Treatment with PULMICORT TURBUHALER should not be stopped abruptly, but tapered off gradually. Follow your doctor's directions.

Suggested **starting doses** are:

Adults and Children 12 Years of Age and Older: 400-2400 mcg daily, divided into 2-4 administrations.

Children 6 to 12 Years Old: 200-400 mcg daily, divided into 2 administrations.

Maintenance Dose:

Adults and Children 12 Years of Age and Older: 200-400 mcg daily, divided into 2 administrations. Your doctor will prescribe the lowest dose necessary to control symptoms.

In adults who require 400 mcg daily, PULMICORT TURBUHALER may be taken once daily, either in the morning or evening.

Children 6 to 12 Years Old: Your doctor will prescribe the lowest dose necessary to control symptoms.

You may notice that your symptoms improve after the first dose of PULMICORT TURBUHALER. However, 1 - 2 weeks may pass before the full effect is achieved. Don't forget to take it even when you feel well.

If you have been prescribed PULMICORT TURBUHALER and are still using "cortisone" tablets, your doctor may gradually (over a period of weeks or months) reduce your dose of tablets. You may even be able to eventually stop using the tablets.

If your medication is changed from "cortisone" tablets to PULMICORT TURBUHALER, you may temporarily regain symptoms which may have bothered you earlier, e.g. runny nose, rash, pain in muscle and joints. If any of these symptoms bothers you, or if you get symptoms such as headache, tiredness, nausea or vomiting, contact your doctor.

Missed dose:

If you miss a dose of PULMICORT TURBUHALER and remember within 6 hours, you should take your usual dose as soon as possible. Then go back to your regular schedule. If it has been more than 6 hours, do not take the missed dose. Just take the next dose on time.

Never take a double dose of PULMICORT TURBUHALER to make up for missed doses. If you are still unsure, check with your doctor or pharmacist to see what you should do.

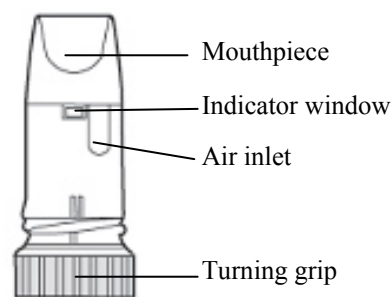
Overdose:

In case of drug overdose, contact a health care practitioner, hospital emergency department or regional Poison Control Centre immediately, even if there are no symptoms.

HOW TO USE YOUR PULMICORT TURBUHALER INHALER

Before you start using PULMICORT TURBUHALER for the first time it is important that you read the instructions below and follow them carefully.

TURBUHALER is a multidose inhaler from which very small amounts of powder are administered. When you breathe in through PULMICORT TURBUHALER the powder is delivered to the lungs. It is therefore important that you **inhale as deeply and strongly** as you can through the mouthpiece.



Before you use a **NEW** inhaler for the first time you must prepare the inhaler for use. Follow the steps under "**A. How to prepare a NEW inhaler for use:**".

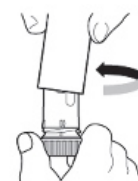
For regular use of your inhaler follow the steps under "**B. How to take a dose:**".

A. How to prepare a NEW inhaler for use:

You only need to prepare your **NEW** inhaler for use **once**. You do not need to repeat these steps even if your inhaler is not used regularly.

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

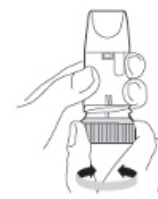
Figure 1



STEP 2 Hold the inhaler upright. Do not hold the inhaler by the mouthpiece.

Figure 2

- Turn the **brown grip** as far as it will go in one direction (clockwise or counter-clockwise, it does not



matter which way you turn it first).

- Then turn the brown grip as far as it will go in the opposite direction (Figure 2).
- At some point when you are turning the grip you will hear a “click”. This is part of the preparation process.

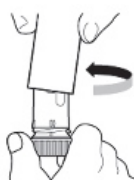
STEP 3 **Repeat STEP 2** one more time. Then follow the steps under “**B. How to take a dose:**”, starting at **STEP 2**.

B. How to take a dose:

To properly take a dose, follow these 4 steps:

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

Figure 1



STEP 2 Hold the inhaler upright. Do not hold the inhaler by the mouthpiece.

- Turn the **brown grip** as far as it will go in one direction (clockwise or counter-clockwise, it does not matter which way you turn it first).
- Then turn the brown grip as far as it will go in the opposite direction (Figure 2).

Figure 2



A dose has now been loaded.

- At some point when you are turning the grip you will hear a “click”. This is part of the loading process.

NOTE: If you accidentally **drop, shake or breathe out** into PULMICORT TURBUHALER after the dose has been loaded, you will lose your dose. If this happens, repeat STEP 2 to load a new dose.

STEP 3 **Breathe out**, with your mouth away from the mouthpiece (Figure 3). Then, place the mouthpiece gently between your teeth.

Figure 3



STEP 4 Now close your lips over the mouthpiece. Do not bite or chew the mouthpiece.

- **Inhale as deeply and strongly** as you can (Figure 4).
- You may not feel or taste the medication when inhaling. This is common.
- Before you exhale, remember to remove the inhaler from your mouth.

Figure 4



Repeat STEPS 2-4 if more than one dose has been prescribed. When you have taken the prescribed amount of doses, **replace the cover of the inhaler by screwing it back on.** With each inhalation some medication may stick to the inside of your mouth and throat. To reduce the risk of side effects rinse your mouth with water, and do not swallow.

Note: Do not try to remove the mouthpiece or to twist it unnecessarily. It is fixed to the inhaler and must not be taken off. Do not use PULMICORT TURBUHALER if it has been damaged or if the mouthpiece has become detached.

I cannot remember how many times I turned the brown grip. What should I do?

The TURBUHALER is designed to load only one dose at a time. If you can't remember how many times you have turned the brown grip, you can start the process again. Follow the steps below. You will not end up loading two doses.

If you are using a **NEW** inhaler for the first time, start at the beginning of STEP 2 under the section "**A. How to prepare a NEW inhaler for use:**".

If you are already regularly using your inhaler, start at the beginning of STEP 2 under the section "**B. How to take a dose:**".

How do I know my dose has been loaded?

By turning the brown grip all the way in **BOTH** directions, you will properly load a dose of your medication. At some point when you are turning the grip you will hear a "click". This is part of the loading process. If you are not sure you heard the "click", repeat from the beginning of STEP 2 under the section "**B. How to take a dose:**". This will not result in two doses being loaded. The TURBUHALER is designed to load only one dose at a time. If you do not hear the "click" sound when the turning grip is rotated, you will not receive any medication. If this problem persists, you need to replace the PULMICORT TURBUHALER.

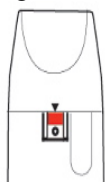
How do I clean my inhaler?

Clean the outside of the mouthpiece once a week with a **dry** tissue. **Never** use water or any other fluid. If fluid enters the inhaler it may not work properly.

How do I know when to start a new inhaler?

PULMICORT TURBUHALER has a dose indicator. When a red mark first appears in the little window underneath the mouthpiece, there are approximately 20 doses left (Figure 5). Now is the time to obtain your next inhaler. When the red mark reaches the bottom of the window, you should throw out your inhaler and start a new inhaler. The sound you hear if you shake the inhaler is made by a drying agent, not the medication. PULMICORT TURBUHALER cannot be refilled with drug and should be thrown away when it is empty.

Figure 5



Approximately 20 doses left



EMPTY

The most common side effects are:

- cough;
- throat irritation;
- thrush (fungal infection) in the mouth;
- hoarseness.

Other side effects are:

- bad taste;
- headache;
- nausea;
- dryness of the throat.

There have been occasional reports of:

- tiredness;
- thirst;
- diarrhea;
- throat or mouth infections.

Rare side effects include:

- skin reactions like rash;
- skin bruising;
- increase in chest tightness;
- nervousness, restlessness, depression;
- behavioural disturbances in children.

If you take PULMICORT TURBUHALER for a long period and at higher doses you may develop symptoms of adrenal insufficiency. If you develop symptoms such as tiredness, headache, nausea, vomiting, pain in muscles and joints, contact your doctor.

SERIOUS SIDE EFFECTS, HOW OFTEN THEY HAPPEN AND WHAT TO DO ABOUT THEM

Symptom / effect	Talk with your doctor or pharmacist		Stop taking drug and immediately seek emergency medical attention
	Only if severe	In all cases	
Rare Bronchospasm: shortness of breath, chest tightness which causes wheezing			X
Severe Allergic Reactions: swelling of the face, lips, tongue, and/or throat (which may cause difficulty in breathing or swallowing), hives, rash and itching			X

SIDE EFFECTS AND WHAT TO DO ABOUT THEM

This is not a complete list of side effects. For any

unexpected effects while taking PULMICORT TURBUHLAER, contact your doctor or pharmacist.

HOW TO STORE IT

Keep PULMICORT TURBUHALER out of the reach and sight of children.

Always replace the cover after using PULMICORT TURBUHALER. Store the inhaler at room temperature (15-30°C).

REPORTING SIDE EFFECTS

You can report any suspected side effects associated with the use of health products to Health Canada by:

- Visiting the Web page on Adverse Reaction Reporting (<https://www.canada.ca/en/health-canada/services/drugs-health-products/medeffect-canada/adverse-reaction-reporting.html>) for information on how to report online, by mail or by fax; or
- Calling toll-free at 1-866-234-2345.

NOTE: Contact your health professional if you need information about how to manage your side effects. The Canada Vigilance Program does not provide medical advice.

MORE INFORMATION

NOTE: This CONSUMER INFORMATION leaflet provides you with the most current information at the time of printing.

The Consumer Information Leaflet plus the full Product Monograph, prepared for health professionals can be found at:

www.astrazeneca.ca,
or by contacting the sponsor, AstraZeneca Canada Inc. at:
1-800-668-6000.

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Last revised: November 8, 2017