

NEW ZEALAND DATA SHEET

1. PRODUCT NAME

PULMICORT TURBUHALER 100 µg, inhalation powder
PULMICORT TURBUHALER 200 µg, inhalation powder
PULMICORT TURBUHALER 400 µg, inhalation powder

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

PULMICORT TURBUHALER 100 µg: budesonide 100 micrograms/inhalation
PULMICORT TURBUHALER 200 µg: budesonide 200 micrograms/inhalation
PULMICORT TURBUHALER 400 µg: budesonide 400 micrograms/inhalation

For a full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Inhalation powder

PULMICORT TURBUHALER 100 µg/inhalation– Inspiratory flow driven multidose, dry powder inhaler. White to off-white rounded granules, which disintegrate to a fine powder upon slight pressure, filled into a specially designed inhaler made of plastic materials. The colour of the turning grip is light brown. On the bottom of the turning grip, Budesonide 100, is embossed. 100 µg/actuation, 200 actuations.

PULMICORT TURBUHALER 200 µg/inhalation– Inspiratory flow driven multidose, dry powder inhaler. White to off-white rounded granules, which disintegrate to a fine powder upon slight pressure, filled into a specially designed inhaler made of plastic materials. The colour of the turning grip is brown. On the bottom of the turning grip, budesonide 200, is embossed. 200 µg/actuation, 200 actuations.

PULMICORT TURBUHALER 400 µg/inhalation– Inspiratory flow driven multidose, dry powder inhaler. White to off-white rounded granules, which disintegrate to a fine powder upon slight pressure, filled into a specially designed inhaler made of plastic materials. The colour of the turning grip is dark brown. On the bottom of the turning grip, budesonide 400, is embossed. 400 µg/actuation, 200 actuations.

4. CLINICAL PARTICULARS

4.1 THERAPEUTIC INDICATIONS

Bronchial asthma requiring maintenance treatment with glucocorticosteroids for control of the underlying airways inflammation.

4.2 DOSE AND METHOD OF ADMINISTRATION

The dosage of PULMICORT TURBUHALER is individual.

The recommended starting dose and 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	200-400 µg once daily <i>or</i> 100-400 µg twice daily	800 µg twice daily
	Inhaled glucocorticosteroids	200-800 µg once daily <i>or</i> 100-400 µg twice daily	800 µg twice daily
	Oral glucocorticosteroids	400-800 µg twice daily	800 µg twice daily
Children, 6 years and above	Nonsteroid Treatment	200-400 µg once daily <i>or</i> 100-200 µg twice daily	400 µg twice daily
	Inhaled glucocorticosteroids	200-400 µg once daily <i>or</i> 100-200 µg twice daily	400 µg twice daily
	Oral glucocorticosteroids	200-400 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

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

Once Daily Dosing

The daily dose is usually divided into 1-2 administrations. Once daily dosing may be considered both in adult and in paediatric patients with mild to moderate asthma, from six years of age, who require a maintenance dose of 100 to 400 µg budesonide per day. Once daily administration can be initiated both in non steroid treated patients and in patients well-controlled by inhaled glucocorticosteroids. A once daily regimen of up to 800 µg may be used by patients already controlled on inhaled steroids (e.g. budesonide or beclomethasone dipropionate) administered twice daily. The patient should be transferred to once daily dosing at the same equivalent total daily dose. The dose should subsequently be reduced to the minimum needed to maintain good asthma control. The dose can be administered either in the morning or in the evening. If deterioration of asthma occurs, the frequency of dosing and the daily dose should be increased.

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 above. 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 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 to as much as half the pMDI dose.

Also a dose reduction for PULMICORT TURBUHALER may be considered for patients transferred from other inhaled glucocorticosteroids. The patient should initially be given a similar dose to that of the other glucocorticosteroid, it may be possible to reduce the dose to as much as half.

Patients maintained on oral glucocorticosteroids

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

Initially, PULMICORT 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.

During withdrawal some patients may experience symptoms of systemic glucocorticosteroid withdrawal, e.g. joint and/or muscle pain, lassitude and depression, despite maintenance or even improvement in pulmonary function. Such patients should be encouraged to continue with PULMICORT but should be monitored for objective signs of adrenal insufficiency. If evidence of adrenal insufficiency occurs, the systemic glucocorticosteroid doses should be temporarily increased and thereafter withdrawal should continue more slowly. Supplementary treatment with systemic glucocorticosteroid may be required during periods of stress or severe asthma attack.

Instruction 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 in the patient information leaflet which are packaged together with each inhaler
- 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
- replace the cover of the PULMICORT TURBUHALER after use
- rinse the mouth out with water after inhaling the prescribed dose to minimise the risk of oropharyngeal thrush

The TURBUHALER is a breath-activated metered dose inhaler which does not require a co-ordinated inhalation technique. It contains only the active ingredient budesonide i.e. there are no propellants, carrier substances or preservatives. Patients, especially those accustomed to aerosol inhalation devices, may not taste or feel any medication when inhaling from TURBUHALER. This lack of sensation should not be taken to mean that the patient has failed to receive the correct dose or the full benefit from PULMICORT TURBUHALER.

4.3 CONTRAINDICATIONS

Hypersensitivity to budesonide.

4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE

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 glucocorticosteroid.

Systemic effects may occur with any inhaled corticosteroid, particularly at high doses prescribed for long periods; these effects are much less likely to occur than with oral corticosteroids (see section 4.9). Possible systemic effects include Cushing's syndrome, Cushingoid features, adrenal suppression, growth retardation in children and adolescents, decrease in bone mineral density, cataract and glaucoma and more rarely a range of psychological or behavioural effects including psychomotor hyperactivity, sleep disorders, anxiety, depression or aggression (particularly in children). It is important, therefore, that the dose of inhaled corticosteroid is titrated to the lowest dose at which effective control is maintained.

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 corticosteroid, 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.

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, in rare cases, 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 agent. These allergies should be symptomatically controlled with an antihistamine and/or topical preparations.

Reduced liver function may affect the elimination of corticosteroids. The intravenous pharmacokinetics of budesonide 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 clinical importance for PULMICORT TURBUHALER, as after inhalation the oral contribution to the systemic availability is relatively small.

In vivo studies have shown that oral administration of ketoconazole or itraconazole (known inhibitors of CYP3A activity in the liver and in the intestinal mucosa, also see section 4.5) may cause an increase of the systemic exposure to budesonide, and consequently lead to systemic adverse reactions, such as Cushing's Syndrome. This is of limited importance for short-term (1-2 weeks) treatment, but should be taken into consideration during long-term treatment.

The long term local and systemic effects of PULMICORT in man are not completely known. The dose should be titrated to the lowest effective maintenance dose once control of asthma is achieved.

Long term studies show that children and adolescents treated with inhaled budesonide ultimately achieve their adult target height. However an initial small but transient reduction in growth velocity (approx 1 cm) has been observed. This generally occurs within the first year of treatment.

Rare individuals may be exceptionally sensitive to inhaled corticosteroids. Physicians should monitor the growth of children and adolescents taking corticosteroids by any route to identify patients with increased sensitivity. The clinical benefit of inhaled corticosteroids should be weighed against any potential growth effects of prolonged treatment.

High doses of glucocorticosteroids may mask some signs of existing infection and new infections may appear during their use. Special care is needed in patients with active or quiescent pulmonary tuberculosis or fungal, bacterial or viral infections of the respiratory system.

Clinical studies and meta-analyses indicate that treatment of COPD with inhaled corticosteroids may lead to an increased risk of pneumonia. However, the absolute risk for budesonide is small. A meta-analysis of 11 COPD double blind trials including 10,570 patients did not demonstrate a statistically significant increased risk of pneumonia in patients treated with budesonide (with or without eformoterol) compared to non-budesonide containing treatments (placebo or eformoterol). The incidence rate of pneumonia reported as a serious adverse event was 1.9% per year on budesonide containing treatments and 1.5% per year on non-budesonide containing treatments. The pooled hazard ratio comparing all budesonide-containing versus non-budesonide containing treatments was 1.15 (95% CI: 0.83, 1.57). The pooled hazard ratio comparing budesonide alone versus placebo was 1.57 (95% CI: 0.90, 2.74). A causal relationship with budesonide-containing products has not been established.

4.5 INTERACTION WITH OTHER MEDICINES AND OTHER FORMS OF INTERACTION

Budesonide has not been observed to interact with any agent 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 and itraconazole, can therefore increase systemic exposure to budesonide (see section 4.4).

At recommended doses, cimetidine has a slight but clinically insignificant effect and omeprazole has no effect on the pharmacokinetics of oral budesonide.

4.6 FERTILITY, PREGNANCY AND LACTATION

Pregnancy

Results from a large prospective epidemiological study and from world-wide post marketing experience indicate no adverse effects of inhaled budesonide during pregnancy on the health of the foetus / newborn child. As with other medicines the administration of budesonide during pregnancy requires that the benefits for the mother be weighed against the risks for the foetus. Inhaled glucocorticosteroids should be considered because of the lower systemic effects compared with oral glucocorticosteroid doses required to achieve similar pulmonary responses.

In pregnant animals, administration of budesonide, like other glucocorticosteroids, is associated with abnormalities of foetal development. The relevance of these findings to man has not been established. As with other medicines the administration of budesonide during pregnancy requires that the expected benefits for the mother outweigh the risks for the foetus.

Breast-feeding

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 breast feeding.

4.7 EFFECTS ON ABILITY TO DRIVE AND USE MACHINES

PULMICORT does not affect the ability to drive and use machines.

4.8 UNDESIRABLE EFFECTS

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

- Mild irritation in the throat, irritation of the tongue, mouth or larynx, coughing and hoarseness, dry mouth, bad taste, thirst.
- Candida infection in the oropharynx.
- Immediate and delayed hypersensitivity reactions, including rash, contact dermatitis, urticaria, angioedema, bronchospasm and anaphylactic reaction.
- Headache, light-headedness, diarrhoea, nausea, weight gain, tiredness.
- Psychiatric symptoms such as nervousness, restlessness, and depression, as well as behavioural changes (predominantly in children), sleep disorders, anxiety, psychomotor hyperactivity and aggression.

Rare reports of skin bruising following treatment with inhaled glucocorticosteroids have occurred.

In rare cases, through unknown mechanisms, medicines for inhalation may cause bronchospasm.

In rare cases signs or symptoms of a systemic glucocorticosteroid effect may occur with inhaled glucocorticosteroids. Possible systemic effects include hypofunction of the adrenal gland and a reduction in growth velocity in children and adolescents. These systemic effects are probably dependent on dose, exposure time, concomitant and previous glucocorticosteroid exposure, and individual sensitivity.

Studies with inhaled budesonide indicate that the reduction in growth velocity is transient and that adult target height may ultimately be achieved (see section 4.4).

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicine is important. It allows continued monitoring of the benefit/risk balance of the medicine. Healthcare professionals are asked to report any suspected adverse reactions via <https://nzphvc.otago.ac.nz/reporting/>.

4.9 OVERDOSE

Acute overdosage with PULMICORT, even in excessive doses, is not expected to be a clinical problem.

For advice on the management of overdose please contact the National Poisons Centre on 0800 POISON (0800 764 766).

5. PHARMACOLOGICAL PROPERTIES

5.1 PHARMACODYNAMIC PROPERTIES

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

Topical anti-inflammatory effect

The exact mechanism 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. The intrinsic potency of budesonide, measured as the affinity to the glucocorticoid receptor, is about 15 times higher than that of prednisolone.

A clinical study in asthmatics comparing inhaled and oral budesonide demonstrated statistically significant evidence of efficacy with inhaled but not oral budesonide compared with placebo. Thus, the therapeutic effect of conventional doses of inhaled budesonide may be largely explained by its direct action on the respiratory tract.

Budesonide has shown anti-anaphylactic and anti-inflammatory effects in provocation studies in animals and patients, manifested as decreased bronchial obstruction in the immediate, as well as the late allergic reaction.

Exacerbations of asthma

Inhaled budesonide, administered once or twice daily, has been shown to effectively prevent exacerbations of asthma in both children and adults.

Exercise-induced asthma

Therapy with inhaled budesonide, administered either as once or twice daily, has been effective when used for prevention of exercise-induced asthma.

Airway reactivity

Budesonide has also been shown to decrease airway reactivity to, both direct and indirect challenge in hyper-reactive patients.

CLINICAL EFFICACY AND SAFETY

HPA axis function

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.

Growth

Asthma as well as inhaled glucocorticosteroids may affect growth.

Effects of inhaled budesonide on growth have been investigated in numerous short and long term studies. Several studies have shown a decrease in growth velocity of approximately 1 cm during the first year of corticosteroid treatment. However, carefully controlled epidemiological studies and long term studies have shown that despite this initial small but transient reduction in growth velocity, children and adolescents treated with inhaled budesonide ultimately achieve their adult target height.

In a five-year study of children 5-11 years of age, treated with budesonide (200 µg BID), a 1.1 cm reduction in growth compared to placebo seen at the end of one year did not increase further during the trial. By the end of the five year study period, children treated with budesonide and children treated with placebo had similar growth velocities and the projected final height was identical in both groups. Additionally, in another study, 142 children age 3-13 (mean 8.7 years of age) treated for 3-13 years (mean 9.2 years) with orally inhaled budesonide (mean 412 µg/day, range 110-877 µg/day) did achieve their predicted final height. These final heights were similar to a group of 51 healthy non-asthmatic siblings of the treatment group who were never treated with budesonide.

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 section 4.4 about titration to the lowest effective dose and about monitoring the growth in children.

5.2 PHARMACOKINETIC PROPERTIES

Absorption

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

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

Distribution

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

Biotransformation

Budesonide undergoes an extensive degree (approx. 90%) of biotransformation on first pass through the liver to metabolites of low glucocorticosteroid activity. The glucocorticosteroid activity of the major metabolites, 6β-hydroxybudesonide and 16α-hydroxyprednisolone, is less

than 1% of that of budesonide. The metabolism of budesonide is primarily mediated by CYP3A, a subfamily of cytochrome p450.

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

Linearity

The kinetics of budesonide are dose-proportional at clinically relevant doses.

Children

Budesonide has a systemic clearance of approximately 0.5 L/min in 4-6 years old asthmatic children. Per kg body weight, children have a clearance which is approximately 50% greater than in adults. The terminal half-life of budesonide after inhalation is approximately 2.3 hours in asthmatic children. This is about the same as in healthy adults.

5.3 PRECLINICAL SAFETY DATA

Results from acute, subacute and chronic toxicity studies show that the systemic effects of budesonide, e.g. decreased body weight gain and atrophy of lymphoid tissues and adrenal cortex, are less severe or similar to those observed after administration of other glucocorticosteroids.

The mutagenic potential of budesonide was evaluated in 6 different test systems. No mutagenic or clastogenic properties of budesonide were found.

An increased incidence of brain gliomas in male rats in a carcinogenicity study could not be verified in a repeat study, in which the incidence of gliomas did not differ between any of the groups with active treatment (budesonide, prednisolone, triamcinolone acetonide) and the control groups.

Liver changes (primary hepatocellular neoplasms) found in male rats in the original carcinogenicity study were noted again in the repeat study with budesonide as well as with reference glucocorticosteroids. These effects were most probably related to a receptor effect and thus represent a class effect.

Available clinical experience shows that there are no indications that budesonide or other glucocorticosteroids induce brain gliomas or primary hepatocellular neoplasms in man.

6. PHARMACEUTICAL PARTICULARS

6.1 LIST OF EXCIPIENTS

PULMICORT TURBUHALER contains only active drug, budesonide. There are no propellants, lubricants, preservatives, carrier substances or other additives.

6.2 INCOMPATIBILITIES

Not applicable

6.3 SHELF-LIFE

24 months.

6.4 SPECIAL PRECAUTIONS FOR STORAGE

PULMICORT TURBUHALER should be stored at temperatures not exceeding 30°C, with the cover tightened.

6.5 NATURE AND CONTENTS OF CONTAINER

PULMICORT TURBUHALER is a multidose, inspiratory flow driven dry powder inhaler. The inhaler is made of plastic parts. One inhaler contains 200 doses.

6.6 SPECIAL PRECAUTIONS FOR DISPOSAL

Return unused and expired medicines to your local pharmacy for disposal.

7. MEDICINE SCHEDULE

Prescription Medicine.

8. SPONSOR

AstraZeneca Limited
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9. DATE OF FIRST APPROVAL

10 November 1988

10. DATE OF REVISION OF THE TEXT

2 May 2018

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SUMMARY TABLE OF CHANGES

Section changed	Summary of new information
Various	SPC style format changes.
5.2	Pharmacokinetic information in children specific to Pulmicort Respules is deleted.