Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

Pulmicort Turbohaler 200 micrograms Inhalation Powder

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each metered dose contains budesonide 200 micrograms

For full list of excipients, see section 6.1

3 PHARMACEUTICAL FORM

Inhalation powder
Product imported from the UK:

Breath-actuated, metered-dose, inhaler.

White to off white spherical granules which break into a fine powder on inhalation.

4 CLINICAL PARTICULARS

4.1 Therapeutic Indications

Pulmicort is recommended in patients with bronchial asthma.

Pulmicort is indicated for the treatment of chronic obstructive pulmonary disease (COPD). Treatment should be maintained where a beneficial response is obtained during the first 3-6 months of therapy.

4.2 Posology and method of administration

Pulmicort Turbohaler is for oral inhalation.

COPD
Adults (including the elderly): The recommended dose is 400 micrograms twice a day.

Bronchial asthma
When starting treatment, or during periods of severe asthma and whilst reducing or discontinuing the dosages of oral corticosteroids, the dosage should be adjusted to the individual needs of the patient.

Adults: Recommended dosage: 200-1600 micrograms daily.

In mild to moderate asthma, a dose of 200-800 micrograms daily, in single or divided doses, may be used.

In severe asthma, the daily dosage may be increased to a maximum of 1600 micrograms, in divided doses.

Children 5 years of age and above (as children under 5 years may not be able to handle the device properly):
Recommended dosage: 200-800 micrograms daily, in single or divided doses. In severe asthma, the daily dosage may be increased to a maximum of 800 micrograms, in divided doses.

Elderly: Dosage as for adults.
The maintenance dose should be the lowest possible. Administration once or twice daily (morning and evening) is usually sufficient.

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

Onset of effect
Improvement in asthma control following inhaled administration of Pulmicort Turbohaler can occur within 24 hours of initiation of treatment, although peak effect may not be achieved for 1 to 2 weeks or longer after starting treatment.

Patients maintained on oral glucocorticosteroids
Pulmicort Turbohaler may permit replacement or significant reduction in dosage of oral glucocorticosteroids with maintained or improved asthma control.

Initially, Pulmicort Turbohaler 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 a number of cases it has been possible to completely substitute the oral glucocorticosteroid with Pulmicort Turbohaler.

During withdrawal, some patients may experience symptoms of systemic corticosteroid withdrawal, e.g. joint and/or muscular pain, lassitude and depression, despite maintenance or even improvement in pulmonary function. Such patients should be encouraged to continue with Pulmicort Turbohaler but should be monitored for objective signs of adrenal insufficiency. If evidence of adrenal insufficiency occurs, the systemic corticosteroid doses should be increased temporarily and thereafter withdrawal should be continued more slowly. During periods of stress or during a severe asthma attack, patients transferred to inhaled steroids may require supplementary treatment with systemic corticosteroids.

Instruction for correct use of Pulmicort Inhaler
Pulmicort Turbohaler 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 is packed with each Turbohaler.
- 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 and spit it out, or to brush the teeth after inhaling the prescribed dose, to minimise the risk of oropharyngeal thrush.
- That they may not taste or feel any medication when using Pulmicort Turbohaler, due to the small amount of drug dispensed.

4.3 Contraindications

Hypersensitivity to budesonide.

4.4 Special warnings and precautions for use

Close observation and special care is needed in patients with both active and quiescent pulmonary tuberculosis. Patients with active pulmonary tuberculosis may use Pulmicort only if they are simultaneously treated with effective tuberculostatics. Similarly, patients with fungal, viral or other infections require close observation and may require anti-infective treatment.

Non steroid-dependent patients: A therapeutic effect is usually reached within 10 days. In patients with excessive mucus secretion in the bronchi, a short (about 2 weeks) additional oral corticosteroid regimen can be given initially.

Steroid-dependent patients: When transfer from oral steroids to Pulmicort Turbohaler is started, the patient should be in a relatively stable phase. A high dose of Pulmicort Turbohaler is then given in combination with the previously used oral steroid dose, for about 10 days. After that the oral steroid dose should be gradually reduced (by for example 2.5 mg prednisolone or the equivalent each month) to the lowest possible level. In many cases, it is possible to completely substitute Pulmicort in place of the oral steroid.

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.

Pulmicort Turbohaler is not intended for rapid relief 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.

Some patients feel unwell in a non-specific way during the withdrawal phase, e.g., pain in muscles and joints. A state of glucocorticoid deficiency 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 drug. These allergies should be symptomatically controlled with an antihistamine and/or topical preparations.

Exacerbations in COPD should be treated with a course of oral corticosteroids and/or an antibiotic.

Patients should be carefully instructed in the correct use of the Pulmicort Turbohaler and its care.

Prolonged or excessive administration may induce systemic corticosteroid effects, with reduction in plasma cortisol levels.

Prolonged use may increase the incidence of bacterial and fungal (including candidal) infections of the upper respiratory tract.

Systemic effects of inhaled corticosteroids may occur, particularly at high doses when prescribed for prolonged periods. These effects are much less likely to occur than with oral corticosteroids. Possible systemic effects include Cushing's syndrome, Cushingoid features, adrenal suppression, growth retardation in children and adolescents, decrease in bone mineral density, cataract, 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 of asthma is maintained.

It is recommended that the height of children receiving prolonged treatment with inhaled corticosteroids, is regularly monitored. 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.

Reduced liver function may affect the elimination of glucocorticosteroids. There is a relatively small, although significant difference between normal and cirrhotic subjects in intravenous pharmacokinetics including longer half life. 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 Turbohaler, as after inhalation the oral contribution to the systemic availability is relatively small.

In vivo studies have shown that oral administration of ketoconazole and itraconazole (known inhibitors of CYP3A4

activity in the liver and in the intestinal mucosa, see also Section 4.5) may cause an increase of the systemic exposure to budesonide. This is of limited clinical importance for short-term (1 - 2 weeks) treatment, but should be taken into consideration during long-term treatment.

4.5 Interaction with other medicinal products and other forms of interaction

When used in conjunction with other agents, such as systemic corticosteroids, any readjustment of dosage should be carried out with caution.

The metabolism of budesonide is primarily mediated by CYP3A4, one of the cytochrome P450 enzymes. Inhibitors of this enzyme, e.g. ketoconazole and intraconazole can therefore increase systemic exposure to budesonide, *see Section 4.4 Special Warnings and Special Precautions for Use.*

4.6 Fertility, pregnancy and lactation

Results from a large prospective epidemiological study and from world-wide post marketing experience indicate that, during pregnancy, there are no adverse effects of inhaled budesonide on the health of the foetus or new born child. As with other drugs, the administration of budesonide during pregnancy requires that the benefits for the mother be weighed against the risk for the foetus. If treatment with glucocorticosteroids during pregnancy is unavoidable, inhaled glucocorticosteroids should be preferred because of their lower systemic effect compared with equipotent anti-asthmatic doses of oral glucocorticosteroids.

Budesonide is excreted in breast milk. However, at therapeutic doses of Pulmicort Turbohaler no effects on the suckling child are anticipated. Pulmicort Turbohaler can be used during breast feeding.

4.7 Effects on ability to drive and use machines

Pulmicort Turbohaler 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 drug reactions may occur:

Common (>1/100, <1/10)	○ Mild irritation in the throat ○ Candida infection in the oropharynx ○ Hoarseness ○ Coughing
Rare (>1/10,000, <1/1,000)	○ Psychomotor hyperactivity, sleep disorders, anxiety, depression, aggression, behavioural changes (predominantly in children) ○ Immediate and delayed hypersensitivity reactions including rash, contact dermatitis, urticaria, angioedema, bronchospasm and anaphylactic reaction. ○ Skin bruising

Possible Candida infection in the oropharynx is due to drug deposition. Advising the patient to rinse the mouth out with water after each dosing, will minimise this risk.

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

In rare cases, signs or symptoms of systemic glucocorticosteroid effect, including hypofunction of the adrenal gland, decrease in bone mineral density, cataract, glaucoma and reduction of growth velocity, may occur with inhaled glucocorticosteroids, probably depending on dose, exposure time, concomitant and previous glucocorticosteroid

exposure and individual sensitivity.

4.9 Overdose

The only harmful effect that follows inhalation of large amounts of the drug over a short period, is suppression of hypothalamic-pituitary-adrenal (HPA) function. No special emergency action needs to be taken. Treatment with Pulmicort Turbohaler should be continued at the recommended dose to control the asthma or COPD symptoms.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

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

Pharmacotherapeutic group: Other drugs for obstructive airway diseases, inhalants, glucocorticoids. ATC Code: RO3B A02.

Topical anti-inflammatory effect
The exact mechanism of action of glucocorticosteroids in the treatment of asthma and COPD are not fully understood. Anti-inflammatroy actions involving T-cells, eosinophils and mastcells, such as inhibition of inflammatory mediator release and inhibition of cytokine-mediated immune response are probably important.

A clinical study in asthmatics comparing inhaled and oral budesonide at similar plasma concentrations 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 patients, manifested as decreased bronchial obstruction in the immediate, as well as the late, allergic reaction.

After a single dose, improvement of the lung function is achieved within a few hours. However, the full effect of budesonide, as for other glucocorticosteroids, is not achieved until after a couple of days.

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

Exercise-induced asthma
Therapy with inhaled budesonide has effectively been used for prevention of exercise induced asthma.

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

COPD
In patients with mild to moderate COPD, twice daily treatment with Pulicort Turbohaler 400 micrograms, slowed the accelerated annual decline in FEV_1 compared with placebo.

Growth
Some long term studies have shown that children and adolescents treated with inhaled budesonide (400mg) ultimately achieve their target height. However, an initial small but transient reduction in growth (approximately 1 cm) has been observed. This generally occurs within the first year of treatment.

HPA axis function
Studies in healthy volunteers with inhaled budesonide (administered as a dry powder via Turbohaler) have shown dose-related effects on plasma cortisol. At recommended doses, Pulmicort Turbohaler, causes significantly less effect on the

adrenal function than prednisolone 10mg, as shown by ACTH tests.

5.2 Pharmacokinetic properties

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

The maximal plasma concentration after repeated oral inhalation of a dose of 800 micrograms budesonide given twice daily, is approximately 4nmol/L, occurring within 30 minutes. Systemic availability of budesonide via Turbohaler has been estimated to 38% of the metered dose, of which only about 1-6 was derived from swallowed drug.

Of the fraction which is swallowed, approximately 90% is inactivated by first pass metabolism in the liver.

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

Biotransformation
Budesonide undergoes an extensive degree (approximately 90%) of biotransformation in 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 CYP 3A4, one of the cytochrome p450 enzymes.

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 i.v. dosing averages 2-3 hours.

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

5.3 Preclinical safety data

The acute toxicity of budesonide is low and of the same order of magnitude and type as that of the reference glucocorticosteroids studied (beclometasone dipropionate, fluocinolone acetonide). Results from subacute and chronic toxicity studies show that the systemic effects of budesonide are less severe than, or similar to, those observed after administration of the other glucocorticosteroids, e.g. decreased body-weight gain and atrophy of lymphoid tissues and adrenal cortex.

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 on 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 the reference glucocorticosteroids. These effects are most probably related to a receptor effect and thus represent a class effect.

Available clinical experience shows no indication that budesonide, or other glucocorticosteroids, induce brain gliomas or primary hepatocellular neoplasms in man. Budesonide has been used successfully for the treatment of asthma for many years.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

None.

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

The shelf life expiry date of this product is the date shown on the container and outer package of the product on the market in the country of origin.

6.4 Special precautions for storage

Do not store above 30°C. Replace the cover properly after use

6.5 Nature and contents of container

The outer protecting parts of the container consist of a tubular cover screwed onto a bottom plate. These parts are made of polyethylene. Inside this is the inhaler with its main parts, a mouthpiece, a dosing mechanism and a substance store.

Each inhaler contains 100 metered doses.

6.6 Special precautions for disposal of a used medicinal product or waste materials derived from such medicinal product and other handling of the product

See section 4.2

7 PARALLEL PRODUCT AUTHORISATION HOLDER

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8 PARALLEL PRODUCT AUTHORISATION NUMBER

PPA1596/11/2

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 26th November 2010

10 DATE OF REVISION OF THE TEXT

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