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 a full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Inhalation Powder.

Product imported from Poland
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 while maintaining asthma control. When transferral 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 milligrams prednisolone or the equivalent each month) to the lowest possible level. In many cases, it is possible to completely substitute the oral steroid with Pulmicort Turbohaler. For further information on the withdrawal of corticosteroids, see section 4.4.

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/carer:
- To carefully read the instructions for use in the patient information leaflet which are packed together with each Turbohaler.
- To breath in forceafully and deeply through the mouthpiece, to ensure that an optimal dose is delivered to the lungs
- Never to breathe out through the mouthpiece.
- To minimise the risk of oropharyngeal candida infection, the patient should rinse their mouth out with water after inhaling
- 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

Special caution is necessary in patients with active or quiescent pulmonary tuberculosis and in patients with fungal or viral infections in the airways. Patients with active pulmonary tuberculosis may use Pulmicort Turbohaler only if they are simultaneously treated with effective tuberculostatics.

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 of impaired adrenal function. 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 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.

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.

Systemic effects may occur with any inhaled corticosteroid, particularly at high doses prescribed for long periods. These effects are much less likely to occur with inhalation treatment 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 important therefore, that the dose of inhaled corticosteroid is titrated to the lowest dose at which effective control of asthma is maintained.

Influence on Growth
It is recommended that the height of children receiving prolonged treatment with inhaled corticosteroids, is regularly monitored. If growth is slowed, therapy should be re-evaluated with the aim of reducing the dose of inhaled corticosteroid, if possible, to the lowest dose at which effective control of asthma is maintained. The benefits of the corticosteroid therapy and the possible risks of growth suppression must be carefully weighed. In addition, consideration should be given to referring the patient to a paediatric respiratory specialist.

Reduced liver function may affect the elimination of corticosteroids, causing lower elimination rate and higher systemic exposure. Be aware of possible systemic side effects. 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.

Concomitant use of ketoconazole, HIV protease inhibitors or other potent CYP3A4 inhibitors should be avoided. If this is not possible, the period between treatments should be as long as possible (see also section 4.5).

Oral candidiasis may occur during the therapy with inhaled corticosteroids. This infection may require treatment with appropriate antifungal therapy and in some patients discontinuation of treatment may be necessary (see also section 4.2).

As with other inhalation therapy paradoxical bronchospasm may occur with an immediate increase in wheezing after dosing. If this occurs, treatment with inhaled budesonide should be discontinued immediately, the patient assessed and alternative therapy instituted if necessary.

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. Inhibitors of this enzyme, e.g. ketoconazole and intraconazole can therefore increase systemic exposure to budesonide several times, see section 4.4. Since there is no data to support a dosage recommendation, the combination should be avoided. If this is not possible, the period between treatments should be as long as possible and a reduction of the budesonide dose could also be considered.

Limited data about this interaction for high-dose inhaled budesonide indicate that marked increases in plasma levels (on average four- fold) may occur if itraconazole, 200 mg once daily, is administered concomitantly with inhaled budesonide (single dose of 1000 μg).

Raised plasma concentrations of and enhanced effects of corticosteroids have been observed in women also treated with oestrogens and contraceptive steroids, but no effect has been observed with budesonide and concomitant intake of low dose combination oral contraceptives.

Because adrenal function may be suppressed, an ACTH stimulation test for diagnosing pituitary insufficiency might show false results (low values).

4.6 Fertility, pregnancy and lactation

Results from a large prospective epidemiological study and from world-wide post marketing experience indicate that, inhaled budesonide during pregnancy, has no adverse effects 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 are 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.

Maintenance treatment with inhaled budesonide (200 or 400 micrograms twice daily) in asthmatic nursing women results in negligible systemic exposure to budesonide in breast-fed infants.

In a pharmacokinetic study, the estimated daily infant dose was 0.3% of the daily maternal dose for both dose levels, and the average plasma concentration in infants was estimated to be 1/600th of the concentrations observed in maternal plasma, assuming complete infant oral bioavailability. Budesonide concentrations in infant plasma samples were all less than the limit of quantification.

Based on data from inhaled budesonide and the fact that budesonide exhibits linear PK properties within the therapeutic dosage intervals after nasal, inhaled, oral and rectal administrations, at therapeutic doses of budesonide, exposure to the breast-fed child is anticipated to be low.

4.7 Effects on ability to drive and use machines

Pulmicort Turbohaler has no influence on the ability to drive and use machines.

4.8 Undesirable effects

Tabulated list of adverse reactions
The following definitions apply to the incidence of undesirable effects: Frequencies are defined as: very common (≥1/10); common (≥1/100 to <1/10); uncommon (≥1/1,000 to <1/100); rare (≥1/10,000 to <1/1,000); very rare (<1/10,000).
Table 1 Adverse Drug Reactions (ADR) by System Organ Class (SOC) and Frequency

SOC	Frequency	Adverse Drug Reaction
Infections and infestations	common	Oropharyngeal candidiasis
immune system disorders	Rare	Immediate and delayed hypersensitivity reactions including rash, contact dermatitis, urticaria, angioedema and anaphylactic reaction
Endocrine disorders	Rare	Signs and symptoms of systemic corticosteroid effects, including adrenal suppression and growth retardation*
Eye disorder	Unknown	Glaucoma
		cataract
Psychiatric disorders	Rare	Psychomotor hyperactivity
		Sleep disorders
		Anxiety
		Depression
		Aggression
		Behavioural changes (predominantly in children)
Respiratory, thoracic and mediastinal disorders	Common	Cough
		Hoarseness
		Throat irritation
	rare	Bronchospasm
		Dysphonia
		Hoarseness**
Skin and subcutaneous tissue disorders	Rare	Bruising

*refer to paediatric population, below
** rare in children

Description of selected adverse reactions
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.

There is an increased risk of pneumonia in patients with newly diagnosed COPD starting treatment with inhaled corticosteroids. However a weighted assessment of 8 pooled clinical trials involving 4643 COPD patients treated with budesonide and 3643 patients randomised to non-ICS treatments did not demonstrate an increased risk for pneumonia. The results from the first 7 of these 8 trials have been published as a meta-analysis.

Paediatric population
Due to the risk of growth retardation in the paediatric population, growth should be monitored as described in section 4.4.

4.9 Overdose

Acute overdosage with Pulmicort Turbohaler, even in excessive doses, is not expected to be a clinical problem. 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 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 Pulmicort Turbohaler 400 micrograms, slowed the accelerated annual decline in FEV1 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.

Paediatric population
Slit lamp examinations were performed in 157 children (5-16 years old), treated with an average daily dose of 504 μg for 3-6 years. Findings were compared with 111 age-matched asthmatic children. Inhaled budesonide was not associated with an increased occurrence of posterior subcapsular cataract.

Influence on plasma cortisol concentration
Studies in healthy volunteers with Pulmicort Turbohaler have shown dose-related effects on plasma and urinary 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
Following oral inhalation via Pulmicort Turbohaler, peak plasma concentrations of budesonide (4.0 nmol/L after a dose of 800 μg) occur within 30 minutes. Maximum plasma concentration and area under the plasma concentration time profile increase linearly with dose, but are slightly (20-30%) higher following repeated doses (3 weeks treatment) than after a single dose. Lung deposition in healthy subjects was estimated to 34% ±10% of the metered dose (arithmetic mean ± SD), while 22% was retained in the mouthpiece and the rest (approximately 45% of the metered dose) was swallowed.

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 on first passage 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 CYP 3A4, 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 terminal half-life of budesonide after i.v. dosing averages 2-3 hours.

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

Paediatric population
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.

In asthmatic children treated with Pulmicort Turbohaler (800 μg single dose), plasma concentration reached Cmax (4.85 nmol/L) at 13.8 minutes after inhalation, and then decreased rapidly; AUC was 10.3 nmol·h/L. The value for AUC is generally comparable to that observed in adults at the same dose, however, the Cmax value tends to be higher in children.

Lung deposition in children (31% of the nominal dose) is similar to that measured in healthy adults (34% of nominal dose).

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 carton 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

IMED Healthcare Ltd.
Unit 625 Kilshane Avenue,
Northwest Business Park,
Ballycoolin,
Dublin 15,
Ireland

8 PARALLEL PRODUCT AUTHORISATION NUMBER

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9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 4th May 2012

10 DATE OF REVISION OF THE TEXT

January 2014