Part II

Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

Pulmicort LS 50 micrograms Inhaler

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each metered dose contains budesonide 50 micrograms.

For excipients, see Section 6.1.

3 PHARMACEUTICAL FORM

Pressurised inhalation, suspension

Metered dose aerosol consisting of a 10 ml aluminium vial and a 50 microlitre metering value, available with standard adapter or spacer adapter.

May also be administered via Nebuhaler®.

4 CLINICAL PARTICULARS

4.1 Therapeutic Indications

In the management of bronchial asthma, not previously well controlled on bronchodilators and/or anti-allergic agents.

4.2 Posology and method of administration

Adults and children 12 years and over: 200 micrograms twice daily, in the morning and in the evening. During periods of severe asthma, the daily dose can be increased up to 1600 micrograms.

In patients whose asthma is well controlled, the daily dose may be reduced below 400 micrograms, but should not go below 200 micrograms.

Budesonide should not be relied upon to control an acute asthmatic attack.

Children under 12 years: 50 to 400 micrograms to be given twice daily, i.e. maximum dosage 800 micrograms/day.

Elderly: Dosage as for adults.

The dose should be reduced to the minimum needed to maintain good asthma control.

Onset of effect

Improvement in asthma control following inhaled administration of Pulmicort pMDI 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 Inhaler may permit replacement or significant reduction in dosage of oral glucocorticosteroids with maintained or improved asthma control.

Initially, Pulmicort Inhaler 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 Inhaler.

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 Inhaler 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

On actuation of Pulmicort inhaler, a suspension of the substance is pumped out of the canister at a high velocity.

When the patient inhales through the mouthpiece at the same time as releasing a dose, the substance will follow the inspired air into airways.

Note: It is important to instruct the patient:

- To carefully read the instructions for use in the patient information leaflet which are packed together with each inhaler.
- To shake the inhaler thoroughly to mix the contents of the inhaler properly.
- To breath in slowly and deeply through the mouthpiece and to release the dose whilst continuing to breathe in.
- To rinse the mouth out with water after inhaling the prescribed dose to minimise the risk of oropharyngeal thrush.

4.3 Contraindications

History of hypersensitivity to budesonide or any of the excipients. Use in the presence of untreated local airways infections of bacterial, fungal or viral origin, or in cases of pulmonary tuberculosis.

4.4 Special warnings and precautions for use

Patients should be carefully instructed in the correct use of the aerosol and its care. Prolonged or excessive administration may induce systemic corticosteroid effects, with reduction of plasma cortisol levels. Prolonged use may increase the incidence of bacterial and fungal (including Candidal) infection of the upper respiratory tract.

Particular caution is required in patients with a history of tuberculosis.

Patients not dependent on steroids: Treatment with the recommended doses of Pulmicort usually produces therapeutic benefit within 7 days. However, certain patients may have an excessive collection of mucus in the bronchi, which reduces penetration of the active substance in the airways. In these cases, a short course of oral corticosteroids (usually 1 to 2 weeks) should be given in addition to the aerosol. After the course of the oral drug, the inhaler alone should provide sufficient therapy. Exacerbations of asthma caused by bacterial infections, can usually be controlled by appropriate antibiotic treatment and possibly increasing the Pulmicort dosage or, if necessary, by giving systemic steroids.

Steroid-dependent patients: Transfer of patients dependent upon oral steroids to treatment with Pulmicort demands special care, mainly due to the slow restoration of the disturbed hypothalamic pituitary function, following extended treatment with oral corticosteroids. When Pulmicort treatment is initiated, patients should be in a relatively stable phase. Pulmicort should then be given in combination with the previously used oral steroid dose, for about 10 days. After this period of time, the reduction of the oral corticosteroids can be started, with a dose reduction corresponding to about 1 mg prednisolone per day per week. The oral dose can thus be reduced to the lowest level which, in combination with Pulmicort, gives a stable respiratory capacity.

In many cases, it may eventually be possible to withdraw the oral steroid completely, but other cases may have to be maintained on a low oral steroid dosage with Pulmicort treatment.

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 glucocorticosteroids treatment with inhaled therapy sometimes unmasks allergies e.g. rhinitis and eczema, which are previously controlled by the systemic drug. These allergies should be symptomatically controlled with an antihistamine and/or topical preparations.

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 if inhaled budesonide or a course of oral glucocorticosteroid.

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.

Systemic effects of inhaled corticosteroids may occur, particularly when prescribed at high doses for prolonged periods. These effects are much less likely to occur than with oral corticosteroids. Possible systemic effects include adrenal suppression and growth retardation in children and adolescents, decrease in bone density, cataract and glaucoma. 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 junction 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 was affected by compromised liver junction as evidenced by increased systemic availability. This is however of limited clinical importance for Pulmicort, 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 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 the equipotent anti-asthmatic doses of oral glucocorticosteroids.
There is no information regarding the passage of budesonide into breast milk. Budesonide is not recommended for use in women who are breast-feeding infants.

4.7 Effects on ability to drive and use machines

Pulmicort does not affect the ability to drive or 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)	▪ Nervousness, restlessness, depression, behavioural disturbances. ▪ Immediate and delayed hypersensitivity reactions including rash, contact dermatitis, urticaria, angioedema and bronchospasm. ▪ 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. The incidence should be less with the spacer adaptor or Nebuhaler, as these reduce-oral deposition.

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 the hypothalamic-pituitary-adrenal (HPA) function. No special emergency action needs to be taken. Treatment with Pulmicort should be continued at the recommended dose to control the asthma.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pulmicort contains the potent, non-halogenated corticosteroid, budesonide.

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 is not fully understood. Anti-

inflammatory actions involving T-cells, eosinophils and mast cells, 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.

Exercise-induced asthma

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

Airway reactivity

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

Exacerbations of asthma

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

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 adrenocorticotropic hormone (ACTH) tests.

5.2 Pharmacokinetic properties

Absorption

After inhalation via Pulmicort inhaler approximately 10-15% of the metered dose is deposited in the lungs.

The maximal plasma concentration after oral inhalation of a single dose of 1 mg budesonide is about 2nmol/L and is reached after about 30 minutes. Systemic availability of budesonide via inhaler has been estimated to 26% of the metered dose, with about 2/5 being derived from swallowed drug.

Distribution

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

Biotransformation

Budesonide undergoes an extensive degree (^90%) biotransformation on first passage through the liver to metabolites of low glucocorticosteroid activity. The glucocorticosteroid activity of the major metabolites, 6 beta-hydroxybudesonide and 16 alpha-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 high systemic clearance (approximately 1.2 L/Min) in healthy adults, and the plasma half-life of budesonide after i.v. dosing averages 2-3 hours.

Linearity

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

Children

After oral inhalation, using NebuChamber™, the systemic exposure (AUC and T1/2) in children (2-6 years old) was similar to that in adults given the same 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 (beclomethasone 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 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.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Sodium trioleate
Trichlorofluoromethane
Dichlorotetrafluoroethane
Dichlorodifluoromethane

6.2 Incompatibilities

Not applicable.

6.3 Shelf Life

2 years.

6.4 Special precautions for storage

Do not store above 30ºC.
The canister contains pressurised liquid. Do not expose to temperatures higher than 50ºC. Do not pierce the canister.

6.5 Nature and contents of container

Aerosol canister, containing 200 metered doses, complete with standard and spacer adapter delivery systems.

Aerosol canister containing 200 metered doses together with Nebuhaler®.

Refill canister.

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 MARKETING AUTHORISATION HOLDER

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PA 970/50/2

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