Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

Pulmicort CFC-Free Inhaler 200 micrograms per metered dose, pressurised inhalation suspension

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

Pressurised inhalation, suspension.

Pulmicort CFC-free Inhaler may be administered via a NebuChamber spacer device.

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: 100 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 CFC-Free Inhaler may permit replacement or significant reduction in the dosage of oral glucocorticosteroids with maintained or improved asthma control.
Initially, Pulmicort CFC-Free 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 CFC-Free 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 CFC-Free 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 continue more slowly. During periods of stress or a severe asthma attack, patients transferred to inhaled steroids may require supplementary treatment with systemic corticosteroids.

Instruction for correct use of Pulmicort CFC-Free Inhaler
On actuation of Pulmicort CFC-Free 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 is packed with each inhaler.
- shake the inhaler thoroughly for a few seconds to mix the contents of the inhaler properly.
- prime the inhaler by actuating it twice into the air when the inhaler is new and also when it has not been used for more than 7 days.
- place the mouthpiece in the mouth. While breathing in slowly and deeply, press the canister firmly to release the medication. Continue to breathe in and hold the breath for as long as is comfortable.
- rinse the mouth out with water after inhaling the prescribed dose to minimise the risk of oropharyngeal thrush.
- clean the mouthpiece of the inhaler regularly, at least once a week.

The use of Pulmicort CFC-Free Inhaler with a spacer device is recommended to enable patients with difficulty in co-ordinating inhalation with actuation, such as infants, young children, the poorly co-operative or the elderly, to derive greater therapeutic benefit.
The use of the a spacer device obviates the need to co-ordinate breathing and actuation, whilst also reducing oropharyngeal absorption of budesonide.

Instructions for the correct use of Pulmicort CFC-Free Inhaler with a spacer device

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 inhaler.
- carefully read the instructions for use in the instruction leaflet which is packed with each spacer device.

On actuation of the aerosol, the dose is released into the inhalation chamber. The inhalation chamber is then emptied by two slow deep breaths. Young children may need to breathe 5–10 times through the mouthpiece. For further doses, the procedure is repeated. For young children who are unable to breathe through the mouthpiece, a face mask can be used. Compatible face masks are available separately and care should be taken to ensure a good fit is achieved.

4.3 Contraindications

History of hypersensitivity to budesonide or any of the excipients.

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.

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.

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 glucocorticosteroid 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 of 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 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, 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 *Interaction with other medicinal products and other forms of interaction*) 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 itraconazole, 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 newborn 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.
Budesonide is excreted in breast milk. However at therapeutic doses of Pulmicort CFC-Free Inhaler, no effects on the suckling child are anticipated . Pulmicort CFC-Free Inhaler can be used during breast feeding.

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, 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. The incidence should be less with a spacer device since this reduces 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.
Inhaled budesonide possesses a local anti-inflammatory action in the lungs, without giving rise to systemic corticosteroid effects.

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 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.

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.

Growth
Some long term studies have shown that children and adolescents treated with inhaled budesonide (400 mg) 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 CFC-Free 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 2 nmol/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 3 L/Kg. Plasma protein binding averages 85–90%.

Biotransformation
Budesonide undergoes an extensive degree (~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 CYP3A4, 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.

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 (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 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.

The safe use of norflurane has been fully evaluated in preclinical studies. It is well accepted and used in several pressurised metered dose inhalers, and is essentially non-toxic. Magnesium stearate has a history of safe use in man for many years, which supports the view that magnesium stearate is essentially biologically inert.

The safe use of magnesium stearate for inhalation has been fully evaluated in preclinical studies. Inhalation toxicity studies conducted with magnesium stearate in rats (26 weeks) and dogs (4 weeks) did not show signs of toxicity up to doses about 490 and 11000 times higher, respectively, than the maximum exposure achievable during the daily treatment with the new formulation. Furthermore, toxicity studies carried out using Pulmicort pMDI have shown no evidence of any local or systemic toxicity or irritation attributable to the excipients.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Norflurane (HFA 134a)
Magnesium stearate.

6.2 Incompatibilities

Not applicable.

6.3 Shelf Life

2 years

6.4 Special precautions for storage

Do not store above 30°C.

Store with the valve downwards.The canister contains a pressurised liquid. Do not expose to temperatures higher than 50°C. Do not pierce the canister.

6.5 Nature and contents of container

A pressurised container, comprising aluminium can, sealed with a metering valve and fitted into a plastic actuator for oral inhalation. The actuator is brown with a white mouthpiece, protected by a grey dust cap. Each inhaler delivers 120 doses after initial priming.

6.6 Special precautions for disposal and other handling

The canister should not be broken, punctured or burnt, even when apparently empty.

7 MARKETING AUTHORISATION HOLDER

AstraZeneca UK Ltd.,
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LU1 3LU, UK.

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