SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

Pulmicort 0.125 mg/ml suspension for nebulisator
Pulmicort 0.25 mg/ml suspension for nebulisator
Pulmicort 0.5 mg/ml suspension for nebulisator

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

1 single-dose unit à 2 ml contains: 0.25 mg or 0.5 mg or 1 mg budesonide.

For excipients see 6.1.

3. PHARMACEUTICAL FORM

Suspension for nebulisator.

Whitish suspension in single-dose unit made of plastic.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

- Bronchial asthma.
- Very serious pseudocroup (laryngitis subglottica) in which hospitalisation is indicated.

This pharmaceutical form is indicated for patients who cannot use the inhalation spray or Turbuhaler for administration of the medical product.

4.2 Posology and method of administration

Dosage
The dosage of Pulmicort is individual. In the case of daily doses up to 1 mg the whole dose may be given in one administration. In the case of higher daily doses the dose is divided into two administrations per day. For children, the highest dose (2 mg per day) should only be administered in case of severe asthma and during a limited period of time.

Initially the dosage should be:
Children from 6 months: 0.25-0.5 mg per day. If necessary, the dose may be increased to 1 mg per day.

Adults: 1-2 mg per day.

For maintenance treatment:
Children from 6 months: 0.25-2 mg per day.

Adults: 0.5 – 4 mg per day. In very severe cases the dose may be increased further.

Dosage table

Dose (mg)	Volume of Pulmicort suspension for nebulisator		
	0.125 mg/ml	0.25 mg/ml	0.5 mg/ml
0.25	2 ml	1 ml*	-
0.5	4 ml	2 ml	-
0.75	-	3 ml	-
1	-	4 ml	2 ml
1.5	-	-	3 ml
2	-	-	4 ml

** should be diluted to 2 ml with 0.9% saline or solution for nebulisator, see 6.6.*

Following a single dose an effect may be expected after a few hours. The full therapeutic effect is achieved only after several weeks of treatment. Treatment with Pulmicort is prophylactic therapy with no demonstrated effect on acute disorders.

In patients in whom an increased therapeutic effect is desired, in general an increase of the Pulmicort dose is to be recommended in preference to combination treatment with oral corticosteroids on account of the lower risk of systemic side effects.

The maintenance dose should be the lowest possible.

Asthma
Pulmicort may permit replacement or significant reduction in dosage of oral glucocorticosteroids while maintaining asthma control. ***When transferral from oral steroids to Pulmicort is started, the patient should be in a relatively stable phase. A high dose of Pulmicort 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. For further information on the withdrawal of corticosteroids, see section 4.4.

Since budesonide given as Pulmicort suspension for nebulisator is deposited in the lungs with the aid of inspiration, it is important that the patient inhales calmly and with even breaths through the mouthpiece of the nebulisator.

Hepatic or renal impairment
There is no experience of treatment of patients with impaired hepatic or renal function. Since budesonide is predominantly eliminated through hepatic metabolism, increased exposure may be expected in patients with severe cirrhosis of the liver.

Pseudocroup
In infants and children with pseudocroup, the commonly used dose is 2 mg of nebulised budesonide. This is given as a single administration, or as two 1 mg doses separated by 30 minutes. Dosing can be repeated every 12 hour for a maximum of 36 hours or until clinical improvement.

A face-mask can be used for children who cannot breathe in through the mouthpiece.

Method of administration
Instruction for correct use of Pulmicort suspension for nebulisator:
Pulmicort suspension for nebulisator is inhaled with the aid of a jet nebuliser fitted with a mouthpiece or suitable face-mask.

To minimise the risk of oropharyngeal candida infection, the patient should rinse their mouth out with water after inhaling.

NOTE! It is important to instruct the patient/carer to wash the facial skin with water after using the face-mask to prevent facial skin irritation.

Ultrasonic nebulisers must not be used, as they deliver too low a dose of budesonide to the patient.
The nebuliser and compressor (propeller unit) must be adjusted so that the majority of the delivered drops of liquid are in the range of 3 to 5 micrometres.

An *in-vitro* study has shown that nebulisers of the types Pari Inhalierboy, Pari Master and Aiolos deliver comparable doses of budesonide.
The amount of budesonide delivered to a patient varies between 11 and 22 % of the amount administered in the nebuliser, and depends on factors such as

- nebulisation time
- volume fill
- technical performance of the compressor (propeller unit) and the nebulisator
- patient's tidal volume
- use of face-mask or mouthpiece.

The air-flow rate through the nebulisator is also important. In order to obtain the maximum available dose of budesonide a flow rate of 5-8 l/min is required. The fill volume should be 2-4 ml.
The available dose for small children is maximised by the use of a closely fitting face- mask.

The single-dose unit must be shaken carefully before being opened.

The nebulisator chamber must be cleaned after every administration. Wash the chamber and mouthpiece or face-mask with warm tap water and use a mild detergent.
Rinse thoroughly and dry the chamber by connecting it to the compressor or air inlet.
See also the nebulisator manufacturer's instructions.

4.3 Contraindications

Hypersensitivity to budesonide or any of the excipients.

4.4 Special warnings and precautions for use

Budesonide is not intended for rapid relief of acute episodes of asthma where an inhaled short-acting bronchodilator is required.

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 treatment should be considered during periods of stress or elective surgery.

Systemic effects of inhaled corticosteroids may occur, particularly at high doses 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.

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

Concomitant use of ketoconazole, itraconazole, 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).

Special caution is necessary in patients with active or quiescent pulmonary tuberculosis, and in patients with fungal or viral infections in the airways.

Oral candidiasis may occur during the therapy with inhaled corticosteroids. This infection may require treatment with appropriate antifungal treatment 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.

Patients must be instructed to contact their physician if the effect of the treatment generally diminishes, as repeated inhalations for severe asthma attacks must not delay the initiation of other important therapy. In the event of acute deterioration the treatment should be supplemented with a course of oral steroid for a short period.

During transfer from oral steroid therapy to Pulmicort, patients may experience previous symptoms such as muscle and joint pain. In these cases a temporary increase of the oral steroid dose may be necessary. If, in isolated cases, fatigue, headache, nausea, vomiting or similar symptoms occur, a generally inadequate steroid effect should be suspected.

Replacement of systemic steroid treatment by Pulmicort sometimes reveals allergies, e.g. rhinitis and eczema that were previously controlled by the systemic treatment.

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. 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.

4.5 Interaction with other medicinal products and other forms of interaction

The metabolism of budesonide is primarily mediated by CYP3A4. Inhibitors of this enzyme, e.g. ketoconazole, itraconazole and HIV-protease inhibitors can therefore increase systemic exposure to budesonide several times (see section 4.4). Since there are 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 1,000 μg).

Raised plasma concentrations of and increased 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

Pregnancy
Results from approximately 2,000 pregnancies have not revealed any increased risk of malformations as a result of treatment with budesonide. Animal studies have shown that glucocorticosteroids can induce malformations (see 5.3), but this is judged not to be relevant for humans with the recommended dosage.

Animal studies have also identified an involvement of excess prenatal glucocorticoids in increased risks for intrauterine growth retardation, adult cardiovascular disease and permanent changes in glucocorticoid receptor density, neurotransmitter turnover and behaviour at exposures below the teratogenic dose range.

During pregnancy the aim must be the lowest effective dose of budesonide while taking account of the risk of a worsening of the asthma.

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

4.7 Effects on ability to drive and use machines

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

4.8 Undesirable effects

Frequencies are defined as: very common (≥1/10); common (≥1/100, <1/10); uncommon (≥1/1,000, <1/100); rare (≥1/10,000, <1/1,000); very rare (<1/10,000).

Table 1 Undesirable drug effects by organ system and frequency

Organ system	Frequency	Undesirable drug effect
Infections and infestations	Common	Candida infections in the oral cavity and throat
Immune system disorders	Rare	Immediate and delayed hypersensitivity reactions* including rash, contact dermatitis, urticaria, angioedema and anaphylactic reaction
Endocrine system disorders	Rare	Signs and symptoms of systemic corticosteroid effects, including adrenal suppression and growth retardation**
Eye disorders	Unknown	Glaucoma Cataract
Psychiatric disorders	Rare	Restlessness Nervousness Depression Behavioural changes (predominantly in children)
	Unknown	Sleep disorders Anxiety Psychomotor hyperactivity Aggression
Respiratory, thoracic and mediastinal disorders	Common	Cough Throat irritation
	Rare	Bronchospasm Dysphonia Hoarseness
Skin and subcutaneous tissue disorders	Rare	Bruising

* facial skin irritation, see below
** "Paediatric population", see below

On account of the risk of candida infections in the oral cavity and throat the patient must rinse the mouth with water after every dose.

* Facial skin irritation, as an example of a hypersensitivity reaction, has occurred in some cases when a nebulisator with a face-mask has been used. To prevent irritation, the facial skin should be washed with water after use of the face-mask.

There is an increased risk of pneumonia in patients with newly diagnosed COPD starting treatment with inhaled corticosteroids. However, a weighted analysis of 8 pooled clinical trials involving 4,643 COPD patients treated with budesonide and 3,643 patients randomised to non-inhaled corticosteroid treatments did not demonstrate an increased risk of pneumonia. The results from the first 7 of these 8 trials have been published as a meta-analysis.

<u>** Paediatric population</u>
Due to the risk of growth retardation in the paediatric population, growth should be monitored regularly, as described in section 4.4.

Reporting of suspected adverse reactions
Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions to (see details below):

Läkemedelverket
Box 26
751 03 Uppsala
www.lakemedelsverket.se

4.9 Overdose

Acute overdosage with Pulmicort suspension for nebulisator, even in excessive doses, is not expected to be a clinical problem. If it is used chronically in high doses, systemic effects of glucocorticosteroids such as hypercortisolism and adrenal suppression may occur.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Inhalation drugs for obstructive airway diseases.
ATC code: R03B A02

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

The precise mechanism of action of glucocorticosteroids in the treatment of asthma is not fully understood. Anti-inflammatory effects such as inhibited release of inflammatory mediators and inhibition of cytokine-mediated immune response are probably important. The activity of budesonide, measured as affinity for glucocorticosteroid receptors is approximately 15 times higher than that of prednisolone.

Clinical efficacy
Budesonide has shown anti-inflammatory effects such as reduced bronchial obstruction during both the early and the late phase of an allergic reaction. Budesonide reduces histamine and metacholine activity in the airways in hyper-reactive patients.

Studies have shown that the earlier the treatment with budesonide is initiated after the onset of asthma, the better is the lung function that can be expected.

Clinical safety
Influence on plasma cortisol concentration:
Dose-related suppression of plasma and urinary cortisol have been observed in studies in healthy volunteers treated with Pulmicort Turbuhaler. At recommended doses, Pulmicort Turbuhaler causes a significantly lower effect on the adrenal function than prednisolone 10 mg, as shown by ACTH tests.

Paediatric population
Clinical efficacy - asthma
The efficacy of Pulmicort suspension for nebulisator has been evaluated in a large number of studies, and it has been shown that Pulmicort suspension for nebulisator is effective both in adults and children as once- or twice-daily medication for prophylactic treatment of persistent asthma. Some examples of representative studies are given below.

In children over the age of 3 years no systemic effects have been detected with doses up to 400 micrograms/day. In the dose range 400-800 micrograms/day biochemical signs of a systemic effect may occur, while such signs are common with daily doses in excess of 800 micrograms. This information relates to Pulmicort administrated as inhalation spray and inhalation powder.

Asthma, like inhaled corticosteroids, can retard growth. Limited data from long-term studies suggest that most children and adolescents treated with inhaled budesonide will ultimately achieve their adult 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.

Inhalation therapy with budesonide is effective in preventing effort-induced asthma.

Clinical – croup
A number of studies in children with croup have compared Pulmicort Respules with placebo. Examples of representative studies evaluating the use of Pulmicort Respules for the treatment of children with croup are given below.

Efficacy of in children with mild to moderate croup
A randomized, double-blind placebo-controlled trial in 87 children (aged 7 months to 9 years), admitted to hospital with a clinical diagnosis of croup, was conducted to determine whether Pulmicort Respules improves croup symptom scores or shortens the duration of stay in hospital. An initial dose of Pulmicort Respules (2 mg) or placebo was given followed by either Pulmicort Respules 1 mg or placebo every 12 hours. Pulmicort Respules statistically significantly improved croup score at 12 and 24 hours and at 2 hours in patients with an initial croup symptom score above 3. There was also a 33% reduction in the length of stay.

Efficacy of in children with moderate to severe croup
A randomized, double-blind, placebo-controlled study compared the efficacy of Pulmicort Respules and placebo in the treatment of croup in 83 infants and children (aged 6 months to 8 years) admitted to hospital for croup. Patients received either Pulmicort Respules 2 mg or placebo every 12 h for a maximum of 36 h or until discharge from hospital. The total croup symptom score was assessed at 0, 2, 6, 12, 24, 36 and 48 hours after the initial dose. At 2 hours, both the Pulmicort Respules and placebo groups showed a similar improvement in croup symptom score, with no statistically significant difference between the groups. By 6 hours, the croup symptom score in the Pulmicort Respules group was statistically significantly improved compared with the placebo group, and this improvement versus placebo was similarly evident at 12 and 24 hours.

5.2 Pharmacokinetic properties

Absorption
In adults the systemic availability of budesonide following administration of Pulmicort suspension for nebulisator via a jet nebuliser is approximately 15% of the nominal dose and 40% to 70% of the dose delivered to the patients. A minor fraction of the systemically available drug comes from swallowed drug. The maximal plasma concentration, occurring about 10 to 30 min after start of nebulisation is approximately 4 nmol/L after a single dose of 2 mg.

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 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 high systemic clearance (approximately 1.2 L/min) in healthy adults, and the terminal half-life of budesonide after iv dosing averages 2-3 hours. The pharmacokinetics of budesonide are proportional to the dose at clinically relevant doses.

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

Pharmacokinetic/pharmacodynamic relationship(s)
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 4-6 years old asthmatic children, the systemic availability of budesonide following administration of Pulmicort suspension for nebulisator via a jet nebulisator (Pari LC Jet Plus® with Pari Master® compressor) is approximately 6% of the nominal dose and 26% of the dose delivered to the patients. The systemic availability in children is about half of that in healthy adults. The maximal plasma concentration, occurring approximately 20 min after start of nebulisation is approximately 2.4 nmol/L in 4-6 years old asthmatic children after a 1 mg dose.
The exposure (C_{max} and AUC) of budesonide following administration of a single 1 mg dose by nebulisation to 4-6 year old children is comparable to that in healthy adults given the same delivered dose by the same nebulisator system.

The pharmacokinetics of budesonide in patients with impaired renal function are unknown. Exposure to budesonide may be increased in patients with hepatic disease.

5.3 Preclinical safety data

In toxicity studies budesonide caused only the expected glucocorticoid effects.
Budesonide has not exhibited any genotoxic effects.

In animal reproduction studies, corticosteroids such as budesonide have been shown to induce malformations (cleft palate, skeletal malformations) in various species. However, these animal experimental results do not seem to be relevant in humans at the recommended doses.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Disodium edetate dihydrate
Sodium chloride
Polysorbate 80
Anhydrous citric acid
Sodium citrate
Water for injections

6.2 Incompatibilities

Pulmicort suspension for nebulisator should not be mixed with other drugs than those mentioned under 6.6.

6.3 Shelf-life

2 years from manufacture if the single-dose units are stored in the unopened foil envelope. Single-dose units that are stored in an opened envelope must be used within 3 months. The contents of an opened single-dose unit must be used within 12 hours. Observe that if only 1 ml has been used the remaining volume is not sterile.

6.4 Special precautions for storage

Do not store above 30°C. Do not freeze.
The single-dose units should be stored in an upright position, to protect the suspension from sedimentation.
After an envelope has been opened the single-dose units must be stored in a sealed envelope.
Sensitive to light.

6.5 Nature and content of container

20 single-dose units made of LD-polyethylene (4 x 5 x 2 ml):
The single-dose units are packed in fives in an aluminium foil envelope. One package contains 4 aluminium foil envelopes. Each single-dose unit contains 2 ml suspension.

21 single-dose units made of LD-polyethylene (3 x 7 x 2 ml):
The single-dose units are packed in sevens in an aluminium foil envelope. One package contains 3 aluminium foil envelopes. Each single-dose unit contains 2 ml suspension.

For the strengths 0.25 and 0.5 mg/ml there is a line indicating 1 ml when the single-dose units are held upside down.

Not all pack sizes may be marketed.

6.6 Instructions for use and handling

Pulmicort suspension for nebulisator can be mixed with sodium chloride solution 9 mg/ml (0.9 %) and/or with solution for nebulisator containing terbutaline, salbutamol, fenoterol, acetylcysteine, sodium cromoglicate or ipratropium bromide. The mixture should be used within 30 minutes.

Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

7. MARKETING AUTHORISATION HOLDER

AstraZeneca AB
151 85 Södertälje

8. MARKETING AUTHORISATION NUMBERS

Pulmicort suspension for nebulisator 0.125 mg/ml	12351
Pulmicort suspension for nebulisator 0.25 mg/ml	12352
Pulmicort suspension for nebulisator 0.5 mg/ml	12353

9. DATE OF FIRST AUTHORISATION / RENEWAL OF THE AUTHORISATION

22.05.1995/01.07.2008

10. DATE OF REVISION OF THE TEXT

17.12.2014