Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

Pulmicort Respules 0.5 mg/2ml nebuliser suspension

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Budesonide, 250 micrograms/ml.

Each 2 ml Respule contains 500 micrograms (0.5mg) Budesonide.

For a full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Nebuliser suspension.

Product imported from the UK:
White to off-white sterile suspension in plastic single dose units.

4 CLINICAL PARTICULARS

4.1 Therapeutic Indications

Pulmicort Respules contain budesonide; a potent, non-halogenated corticosteroid for use in bronchial asthma patients, where use of a pressurised inhaler or dry powder formulation is unsatisfactory or inappropriate.

Pulmicort Respules are also recommended for use in infants and children with acute laryngotracheobronchitis (croup).

4.2 Posology and method of administration

Dosage schedules: Pulmicort Respules should be administered from suitable nebulisers. The dose delivered to the patient varies depending on the nebulising equipment used. The nebulisation time and the dose delivered is dependent on flow rate, volume of nebuliser chamber and fill volume. An air-flow rate of 6 - 8 litres per minute through the device should be employed.

A suitable fill volume for most nebulisers is 2 - 4 ml. The dosage of Pulmicort Respules should be adjusted to the need of the individual. The highest dose (2 mg per day) for children under 12 years should only be considered in children with severe asthma and during limited periods.

Bronchial asthma

Initiation of therapy
When treatment is started, during periods of severe asthma and while reducing or discontinuing oral glucocorticosteroids, the recommended dose of Pulmicort Respules is:

Adults (including elderly): Usually 1 - 2 mg twice daily. In very severe cases, the dosage may be further increased.

Children of 12 years and older: Dosage as for adults.

Children of 3 months to 12 years: 0.5 - 1 mg twice daily.

Maintenance dose
The maintenance dose should be the lowest dose which keeps the patient symptom-free.

Recommended doses are:

Adults (including elderly and children 12 years and older): 0.5 - 1 mg twice daily.

Children of 3 months to 12 years: 0.25 - 0.5 mg twice daily.

Onset of effect

Improvement in asthma control following inhaled administration of Pulmicort Respules can occur within 2-4 days of initiation of treatment, although peak effect may not be achieved for up to 3-6 weeks.

Patients maintained on oral glucocorticosteroids

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

Initially, Pulmicort Respules 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 Respules.

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 Respules 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.

Dose division and miscibility

Pulmicort Respules can be mixed with 0.9% saline and with solutions for nebulisation of terbutaline, salbutamol, fenoterol, acetylcysteine, sodium cromoglicate or ipratropium bromide. The admixture should be used within 30 minutes.

Recommended Dosage Table

Pulmicort Respules 0.5 mg (0.25 mg/ml)

Dose (mg)	Volume (ml)
0.25	1
0.5	2
0.75	3
1.0	4
1.5	6
2.0	8

Where an increased therapeutic effect is desired, especially in those situations without major mucus secretion in the airways, an increased dose of Pulmicort is recommended, rather than combined treatment with oral corticosteroids, because of the lower risk of systemic effects.

Acute laryngotracheobronchitis (croup)

In infants and children with croup, the usual dose is 2 mg of nebulised budesonide. This dose is given as a single administration, or as two 1 mg doses separated by 30 minutes.

Instructions for correct use of Pulmicort Respules

The Respule should be detached from the strip, shaken gently and opened by twisting off the wing tab. The open end of the Respule should be placed inside the nebuliser cup and the top of the nebuliser replaced.

Pulmicort Respules should be administered via a jet nebuliser equipped with a mouthpiece or suitable face mask. The nebuliser should be connected to an air compressor with an adequate air flow (6-8L/min), and the fill volume should be 2-4ml.

Note: It is important to instruct the patient

- to carefully read the instructions for use in the patient information leaflet which is packed together with each nebuliser
- that Ultrasonic nebulisers are not suitable for the administration of Pulmicort Respules and therefore are not recommended
- Pulmicort Respules can be mixed with 0.9% saline and with solutions for nebulisation of terbutaline, salbutamol, fenoterol, acetylcysteine, sodium cromoglycate and ipratropium bromide. The admixture should be used within 30 minutes.
- to rinse the mouth out with water after inhaling the prescribed dose to minimise the risk of oropharyngeal thrush
- to wash the facial skin with water after using the face mask to prevent irritation
- to adequately clean and maintain the nebuliser according to the manufacturer's instructions
- the dosage of Pulmicort Respules should be adjusted to the need of the individual.

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.

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. After the course of the oral drug, Pulmicort Respules alone should be sufficient therapy.

Steroid-dependent patients: When initiating the transfer from oral corticosteroid to treatment with Pulmicort, the patient should be in a relatively stable phase. Pulmicort is then given in combination with the previously used oral steroid dose, for about 10 days.

After that, the oral 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 corticosteroid.

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.

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.

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 Respules, as after inhalation the oral contribution to the systemic availability is relatively small.

Pulmicort Respules are not intended for rapid relief episodes of asthma where an inhaled short-acting bronchodilator is required. If patients find shortacting 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.

The nebuliser chamber should be cleaned after every administration. Wash the nebuliser chamber and mouthpiece (or facemask) in hot water using a mild detergent. Rinse well and dry by connecting the nebuliser chamber to the compressor or air inlet.

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 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.

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

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 the equipotent anti-asthmatic doses of oral glucocorticosteroids.

Budesonide is excreted in breast milk. However, at therapeutic doses of Pulmicort Respules no effects on the suckling child are anticipated, Pulmicort Respules 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 machinery.

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, <1/1000)	▪ 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.

Facial skin irritation has occurred in some cases, when a nebuliser with a facemask has been used. To prevent irritation, the facial skin should be washed with water after use of the face mask.

4.9 Overdose

Pulmicort Respules contain 0.1mg/ml disodium edetate which has been shown to cause bronchoconstriction at levels above 1.2mg/ml. Acute overdose with Pulmicort should not present a clinical problem.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Budesonide is a gluococorticosteroid with a 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 is 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 animals and patients, manifested as decreased bronchial obstruction in the immediate, as well as the late, allergic reaction.

After a single dose of orally inhaled budesonide, delivered via dry powder inhaler, improvement of the lung function is achieved within a few hours. However, after therapeutic use of orally inhaled budesonide, several weeks may pass before the full effect is obtained.

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

Asthma as well as inhaled glucocorticosteroids may affect growth. The benefits of treatment with inhaled glucocorticoids and the danger/risks of not treating should be considered in any discussion of their possible effects on growth.

Effects of Pulmicort Respules on growth have been studied in 519 children (age 8 months to 9 years) in three prospective randomised open label 12 month studies.

Two studies (n=239 and 72 respectively) showed a 7mm and 8mm greater growth after one year’s treatment with Pulmicort Respules compared to the control group, conventional asthma therapy including inhaled glucocorticosteroids (not statistically significant). In one study (n=208) the growth during one year was 8mm lower in the Pulmicort Respules group than in the control group, conventional asthma therapy without inhaled glucocorticosteroids (statistically significant difference).

5.2 Pharmacokinetic properties

Absorption

In adults the lung deposition and systemic availability of budesonide following administration of Pulmicort Respules via a jet nebuliser is approximately 15% of the nominal dose and 40-70% 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 10-30 min after start of nebulisation is approximately 4nmol/L after a single dose of 2mg.

Distribution

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

Biotransformation

Budesonide undergoes an extensive biotransformation in the liver to metabolites of low glucocorticosteroid activity. The glucocorticosteroid activity of the major metabolites, 6ß-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 high systemic clearance (approximately 1.2 L/Min) in healthy adults, 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.

Children

In 4-6 year old asthmatic children, the systemic availability of budesonide following administration of Pulmicort Respules via a jet nebuliser is approximately 6% of the nominal dose and 26% of the dose delivered to the patients. The systemic availability in children is about half that in healthy adults. The maximum plasma concentration, occurring approximately 20min after start of nebulisation is approximately 2.4nmol/L in 4-6 year old asthmatic children after a 1mg dose.

Budesonide has a systemic clearance of approximately 0.5L/min in 4-6 year 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.

The exposure (Cmax and AUC) of budesonide following administration of a single 1mg dose by nebulisation to 4-6 year old children is comparable to that in healthy adults given the same delivered dose by the same nebuliser system.

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 carcinogeniticity 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 that there are no indications that budesonide, or other glucocorticosteroids, induce brain gliomas or primary hepatocellular neoplasms in man.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Disodium edetate
Sodium chloride
Polysorbate 80
Citric acid anhydrous
Sodium citrate
Water for injections

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

The shelf-life expiry date of this product shall be the date shown on the container and outer packaging of the product on the market in the country of origin.
Use within 3 months of opening the foil envelope.
If only 1 ml of suspension is used, the remaining suspension is not sterile and should be discarded.

6.4 Special precautions for storage

Do not store above 30°C.
Do not freeze.
Store in an upright position.
Store in the original package in order to protect from light.

6.5 Nature and contents of container

Single dose units of 2ml each, in sealed envelopes of 5 units packed into cartons of 20 units.

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

No special requirements (See section 4.2, Posology administration).

7 PARALLEL PRODUCT AUTHORISATION HOLDER

Clear Pharmacy
157-173 Roden Street
Belfast BT12 5QA
United Kingdom

8 PARALLEL PRODUCT AUTHORISATION NUMBER

PPA 1596/062/001

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 24th February 2012

10 DATE OF REVISION OF THE TEXT