SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT

Pulmicort® Respules® 1 mg, nebuliser suspension

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Budesonide 0.5 mg/ml. Each 2 ml Respule contains 1 mg budesonide.

For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Sterile nebuliser suspension. White to off-white suspension in plastic single dose units.

4. CLINICAL PARTICULARS

4.1. Therapeutic indications

Pulmicort Respules contain the potent, non-halogenated, corticosteroid, budesonide, for use in bronchial asthma, in 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 croup (acute viral upper respiratory tract infection also known as viral laryngotracheobronchitis or laryngitis subglottica), in which hospitalisation is indicated.

4.2 Posology and method of administration

Posology
The dosage of Pulmicort Respules should be adjusted to the need of the individual.

Dosage schedules: 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 dose should be reduced to the minimum needed to maintain good asthma control. 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 the elderly): Usually 1 – 2 mg twice daily. In very severe cases the dosage may be further increased.

Paediatric population
Children 12 years and older: Dosage as for adults.

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

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

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

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

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

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

Recommended Dosage Table

Pulmicort Respules 1 mg (0.5 mg/ml)

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

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

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. Dosing can be repeated every 12 hour for a maximum of 36 hours or until clinical improvement.

Method of administration
Pulmicort Respules should be administered from suitable nebulisers.

Instruction 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 contents of the Respule should be gently squeezed into the nebuliser cup. The empty Respule should be thrown away and the top of the nebuliser cup 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 (6-8 L/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 are 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 minimise the risk of oropharyngeal candida infection, the patient should rinse their mouth out with water after inhaling.

- to wash the facial skin with water after using the face mask to prevent facial skin irritation

- to adequately clean and maintain the nebuliser according to the manufacturer's instructions

4.3 Contraindications

Hypersensitivity to the active substance or to any of the excipients listed in section 6.1.

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.

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 transfer from oral corticosteroid to treatment with Pulmicort Respules is initiated, the patient should be in a relatively stable phase. Pulmicort Respules 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 Respules for the oral corticosteroid.

During transfer from oral therapy to Pulmicort Respules, a generally lower systemic corticosteroid action will be experienced, which may result in the appearance of allergic or arthritic symptoms such as rhinitis, eczema and muscle and joint pain. Specific treatment should be initiated for these conditions. A general insufficient glucocorticosteroid effect 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.

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

Systemic effects may occur with any inhaled corticosteroids, 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. Pulmicort Respules 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 or an increase in their regular therapy, e.g., higher doses of inhaled budesonide or the addition of a long-acting beta agonist, or for a course of oral glucocorticosteroid.

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

The plasma clearance following an intravenous dose of budesonide however was similar in cirrhotic patients and in healthy subjects. After oral ingestion systemic availability of budesonide was increased by compromised liver function due to decreased first pass metabolism. The clinical relevance of this to treatment with Pulmicort Respules is unknown as no data exist for inhaled budesonide, but increases in plasma levels and hence an increased risk of systemic adverse effects could be expected.

Co-treatment with CYP3A inhibitors, e.g. itraconazole, ketoconazole, HIV protease inhibitors and cobicistat-containing products is expected to increase the risk of systemic corticosteroid side effects. Therefore, the combination should be avoided unless the benefit outweighs this increased risk, in which case patients should be monitored for systemic corticosteroid side effects. This is of limited clinical importance for short-term (1-2 weeks) treatment with itraconazole or ketoconazole or other potent CYP3A inhibitors, but should be taken into consideration during long-term

treatment. A reduction in the dose of budesonide should also be considered (see section 4.5).

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

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).

Pneumonia in patients with COPD
An increase in the incidence of pneumonia, including pneumonia requiring hospitalisation, has been observed in patients with COPD receiving inhaled corticosteroids. There is some evidence of an increased risk of pneumonia with increasing steroid dose but this has not been demonstrated conclusively across all studies.

There is no conclusive clinical evidence for intra-class differences in the magnitude of the pneumonia risk among inhaled corticosteroid products.

Physicians should remain vigilant for the possible development of pneumonia in patients with COPD as the clinical features of such infections overlap with the symptoms of COPD exacerbations.

Risk factors for pneumonia in patients with COPD include current smoking, older age, low body mass index (BMI) and severe COPD.

Visual disturbance
Visual disturbance may be reported with systemic and topical corticosteroid use. If a patient presents with symptoms such as blurred vision or other visual disturbances, the patient should be considered for referral to an ophthalmologist for evaluation of possible causes which may include cataract, glaucoma or rate diseases such as central serous chorioretinopathy (CSCR) which have been reported after use of systemic and topical corticosteroids.

Paediatric population
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.

4.5 Interaction with other medicinal products and other forms of interaction

The metabolism of budesonide is primarily mediated by CYP3A4. Co-treatment with CYP3A inhibitors, e.g. itraconazole, ketoconazole, HIV protease inhibitors and cobicistat-containing products, are expected to increase the risk of systemic side effects (see Section 4.4 and Section 5.2).

The combination of Pulmicort with potent CYP3A inhibitors should be avoided unless the benefit outweighs the increased risk of systemic corticosteroid side effects, in which case patients should be monitored for systemic corticosteroid side effects. If Pulmicort is co-administered with anti-fungals (such as itraconazole and ketoconazole), the period between treatments should be as long as possible. A reduction of the budesonide dose could 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).

Paediatric population
Interaction studies have only been performed in adults.

4.6 Fertility, pregnancy and lactation

Pregnancy
Most results from prospective epidemiological studies and world-wide post-marketing data have not been able to detect an increased risk for adverse effects for the foetus and newborn child from the use of inhaled budesonide during pregnancy.

In animal studies, glucocorticosteroids have been shown to induce malformations (see section 5.3). This is not likely to be relevant for humans given recommended doses, but therapy with inhaled budesonide should be regularly reviewed and maintained at the lowest effective dose. It is important for both foetus and mother to maintain an adequate asthma treatment during pregnancy. As with other drugs administered during pregnancy, the benefit of the administration of budesonide for the mother should be weighed against the risks to the foetus.

Inhaled glucocorticosteroids should be considered in preference to oral glucocorticosteroids because of the lower systemic effects at the doses required to achieve similar pulmonary responses.

Breast-feeding
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.

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 Respules has no or negligible 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 Pneumonia (in COPD patients)
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**
Psychiatric disorders	Uncommon	Anxiety Depression
	Rare	Psychomotor hyperactivity
		Sleep disorders
		Aggression
		Behavioural changes (predominantly in children)
Nervous system disorders	Uncommon	Tremor***
Eye disorders	Uncommon	Cataract
		Vision, blurred (see also section 4.4)
	Unknown	Glaucoma
Respiratory, thoracic and mediastinal disorders	Common	Cough
		Hoarseness
		Throat irritation
	Rare	Bronchospasm
		Dysphonia
		Hoarseness****
Skin and subcutaneous tissue disorders	Rare	Bruising
Musculoskeletal and connective tissue disorders	Uncommon	Muscle spasm

* refer to Description of selected adverse reactions; facial skin irritation below
** refer to Paediatric population, below
*** based on frequency reported in clinical trials
**** rare in children

Occasionally, signs or symptoms of systemic glucocorticosteroid-side effects may occur with inhaled glucocorticosteroids, probably depending on dose, exposure time, concomitant and previous corticosteroid exposure, and individual sensitivity (see section 4.4).

Description of selected adverse reactions
The 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 the risk.

As with other inhalation therapy, paradoxical bronchospasm may occur in very rare cases (see Section 4.4).

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

In placebo-controlled studies, cataract was also uncommonly reported in the placebo group.

Clinical trials with 13119 patients on inhaled budesonide and 7278 patients on placebo have been pooled. The frequency of anxiety was 0.52% on inhaled budesonide and 0.63% on placebo; that of depression was 0.67% on inhaled budesonide and 1.15% on placebo.

Paediatric population
Due to the risk of growth retardation in the paediatric population, growth should be monitored 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 via the Yellow Card Scheme. Website: www.mhra.gov.uk/yellowcard.

4.9 Overdose

Pulmicort Respules contains 0.1 mg/ml disodium edetate which has been shown to cause bronchoconstriction at levels above 1.2 mg/ml. Acute overdosage with Pulmicort Respules, even in excessive doses, is not expected to be a clinical problem.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Other drugs for obstructive airway diseases, inhalants, glucocorticoids. ATC Code: RO3B A02.

Budesonide is a glucocorticosteroid which possesses a high local anti-inflammatory action, with a lower incidence and severity of adverse effects than those seen with oral corticosteroids.

Topical anti-inflammatory effect
The exact mechanism of action of glucocorticosteroids in the treatment of asthma is not fully understood. Anti-inflammatory 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 doses calculated to achieve similar systemic bioavailability 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.

In a provocation study pre-treatment with budesonide for four weeks has shown decreased bronchial constriction in immediate as well as late asthmatic reactions.

Onset of effect
After a single dose of orally inhaled budesonide, delivered via dry powder inhaler, improvement of the lung function is achieved within a few hours. After therapeutic use of orally inhaled budesonide delivered via dry powder inhaler, improvement in lung function has been shown to occur within 2 days of initiation of treatment although maximum benefit may not be achieved for up to 4 weeks.

Airway reactivity
Budesonide has also been shown to decrease airway reactivity to histamine and methacholine in hyperreactive patients.

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

Growth
In short term studies a small and generally transient reduction in growth has been observed, which usually occurs within the first year of treatment. Long-term observational studies suggest that children and adolescents treated with inhaled corticosteroids on average achieve their adult target height. However, in one study children who had been treated with high dose inhaled budesonide via a dry powder inhaler (400 micrograms daily) for up to 6 years without titration to the lowest effective dose were found on average to be 1.2 cm shorter as adults than those treated with placebo over the same period. See section 4.4 about titration to the lowest effective dose and about monitoring the growth in children.

Influence on plasma cortisol concentration
Studies in healthy volunteers with Pulmicort Turbohaler have shown dose-related effect on plasma and urinary cortisol. At recommended doses, Pulmicort Turbohaler causes significantly less effect on adrenal function than prednisone 10 mg, as shown by ACTH test.

Paediatric population
Clinical – asthma
The efficacy of Pulmicort Respules has been evaluated in a large number of studies, and it has been shown that Pulmicort Respules 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.

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 in children with mild to moderate croup
A randomised, 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 in children with moderate to severe croup
A randomised, 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 Nebuliser Suspension 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.

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

In a study, 100 mg ketoconazole taken twice daily, increased plasma levels of concomitantly administered oral budesonide (single dose of 10 mg) on average, by 7.8-fold. Information about this interaction is lacking for inhaled budesonide, but marked increases in plasma levels could be expected.

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 Nebuliser Suspension via a jet nebuliser (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 (Cmax 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 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 (beclomethasone dipropionate, fluocinolone acetonide).

Results from subacute and chronic toxicity studies show that the systemic effects of budesonide are less severe 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 that there are no indications that budesonide or other glucocorticosteroids induce brain gliomas or primary hepatocellular neoplasms in man.

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

Animal studies have also identified an involvement of excess prenatal glucocorticosteroids in increased risk 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.

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

None applicable.

6.3 Shelf life

24 months
Use within 3 months of opening the foil envelope.
If only 1ml of suspension is used, the remaining suspension is not sterile and should be discarded immediately.

See section 6.4

6.4 Special precautions for storage

Do not store above 30°C. Store the Respules in the foil envelope to protect them from light.

Units should be stored in an upright position and should be protected from freezing

6.5. Nature and Content of Container

Single dose unit made of LD-polyethylene. Each single dose unit contains 2 ml of suspension. Sheets of 5 units are packed in a heat sealed envelope of foil laminate. 4 heat sealed envelopes are packed into a carton.

6.6 Special precautions for disposal

No special requirements for disposal.

See section 4.2

7 MARKETING AUTHORISATION HOLDER

AstraZeneca UK Limited,
1 Francis Crick Avenue,
Cambridge,
CB2 0AA,
UK.

8. MARKETING AUTHORISATION NUMBER(S)

PL 17901/0161

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 18th April 1991

Date of latest renewal: 11th June 2002

10 DATE OF REVISION OF THE TEXT

22/03/2023