Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

Budesonide Azure 1 mg/2 ml Nebuliser Suspension

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each ampoule of 2 ml suspension contains 1 mg budesonide (500 micrograms/ml).

For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Nebuliser suspension.
A white to off-white sterile suspension in a single-dose ampoule.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

Asthma
Budesonide Azure is indicated for use in bronchial asthma, in patients where use of a pressurised inhaler or dry powder formulation is unsatisfactory or inappropriate.

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

Paediatric population
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 the elderly and children 12 years and older): 0.5 - 1 mg twice daily.

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

Initially, budesonide nebuliser suspension 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 budesonide nebuliser suspension.

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 budesonide nebuliser suspension 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
Budesonide nebuliser suspension 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

Dose (mg)	Volume of budesonide nebuliser suspension (ml)	
	0.5 mg/2 ml (0.25 mg/ml)	1 mg/2 ml (0.5 mg/ml)
0.25	1	-
0.5	2	1
0.75	3	-
1.0	4	2
1.5	6	3
2.0	8	4

Where an increased therapeutic effect is desired, especially in those situations without major mucus secretion in the airways, an increased dose of budesonide 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 hours for a maximum of 36 hours or until clinical improvement.

Method of administration
For inhalation use.

Instructions for correct use of budesonide nebuliser suspension
An inhalation system including the nebuliser with compressor is required to inhale Budesonide nebuliser suspension. Budesonide nebuliser suspension should be administered via a jet nebuliser (e.g. PARI LC PLUS) and compressor (e.g. PARI Boy SX), equipped with a mouthpiece or suitable face mask (e.g., PARI Baby mask with PARI Baby bend).

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. The nebulisation time and the dose delivered are dependent on breathing pattern and fill volume.

Aerosol characteristic data for Budesonide Azure administered by PARI LC PLUS [1]

Performance parameter	**Budesonide Azure 0.25 mg/mL nebuliser suspension**		**Budesonide Azure 0.5 mg/mL nebuliser suspension**
	Infant	**Child**	**Adult**
Total drug delivered [µg]	56.8	84.5	307.2
Drug delivery rate [µg/min]	4.6	8.1	31.8
Fine particle mass < 5 µm [mg]	82.9		162.2
Droplet size distribution [µm]	Dv10: 1.9 Dv50: 4.5 Dv90: 9.8		Dv10: 1.9 Dv50: 4.5 Dv90: 9.5

[1] connected with the compressor PARI Boy SX

The ampoule should be detached from the strip, shaken gently for 30 seconds and opened by twisting off the wing tab. The open end of the ampoule should be placed inside the nebuliser cup and the top of the nebuliser replaced.

There is no information available in respect of pulmonary inhalation and deposition patterns across nebuliser systems that have not been studied in the development programme; the use of an alternative untested nebuliser system may alter the pulmonary deposition of the active substance, this in turn may alter the efficacy and safety of the product and dose adjustment may then become necessary.

For instructions on dilution of the medicinal product before administration, see section 6.6.

The patient should be instructed in the correct use of the Budesonide Azure. Children should use Budesonide Azure only under adult supervision.

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 budesonide nebuliser suspension and therefore are not recommended
- budesonide nebuliser suspension 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(s) 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 and quiescent pulmonary tuberculosis and in patients with fungal or viral infections in the airways. Patients with active pulmonary tuberculosis may use budesonide only if they are simultaneously treated with effective tuberculostatics.

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, budesonide nebuliser suspension alone should be sufficient therapy.

Steroid-dependent patients
When initiating the transfer from oral corticosteroid to treatment with budesonide, the patient should be in a relatively stable phase. budesonide nebuliser suspension 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 budesonide nebuliser suspension 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 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.

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

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 budesonide nebuliser suspension, as after inhalation the oral contribution to the systemic availability is relatively small.

Budesonide nebuliser suspension 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 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 may occur with any inhaled corticosteroid, 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.

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.

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).

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.

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 rare 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 CYP3A enzymes. Inhibitors of these enzymes, e.g., ketoconazole, itraconazole, HIV protease inhibitors or cobicistat can therefore increase systemic exposure to budesonide several times, see section 4.4.

The combination of budesonide 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. A reduction of the budesonide dose could be considered. If budesonide is co-administered with anti-fungals (such as itraconazole and ketoconazole), the period between treatments should be as long as possible.

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. 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.

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.

Breast-feeding
Budesonide is excreted in breast milk. However, at therapeutic doses of budesonide nebuliser suspension no effects on the suckling child are anticipated. Budesonide nebuliser suspension 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

Budesonide has no or negligible influence on the ability to drive or 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 the 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
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.

Facial skin irritation, as an example of a hypersensitivity reaction, 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.

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 HPRA Pharmacovigilance. Website: www.hpra.ie.

4.9 Overdose

Budesonide nebuliser suspension contains 0.1 mg/ml disodium edetate which has been shown to cause bronchoconstriction at levels above 1.2 mg/ml. Acute overdosage with budesonide, 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: R03BA02

Budesonide is a gluococorticosteroid with a high local anti-inflammatory effect.

Topical anti-inflammatory effect
The exact mechanism of action of glucocorticosteroids in the treatment of asthma is not fully understood. Anti-inflammatory actions involving T-cells, eosinophils and mast cells, such as inhibition of inflammatory mediator release and inhibition of cytokine-mediated immune response are probably important.

A clinical study in asthmatics comparing inhaled and oral budesonide at similar plasma concentrations demonstrated statistically significant evidence of efficacy with inhaled but not oral budesonide compared with placebo. Thus, the therapeutic effect of conventional doses of inhaled budesonide may be largely explained by its direct action on the respiratory tract.

Budesonide has shown anti-anaphylactic and anti-inflammatory effects in provocation studies in 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 budesonide nebuliser suspension 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 budesonide nebuliser suspension 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 budesonide nebuliser suspension group than in the control group, conventional asthma therapy without inhaled glucocorticosteroids (statistically significant difference).

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

Paediatric population

Clinical – asthma
The efficacy of budesonide nebuliser suspension has been evaluated in a large number of studies, and it has been shown that budesonide nebuliser suspension 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 budesonide nebuliser suspension with placebo. Examples of representative studies evaluating the use of budesonide nebuliser suspension 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 budesonide nebuliser suspension improves croup symptom scores or shortens the duration of stay in hospital. An initial dose of budesonide nebuliser suspension (2 mg) or placebo was given followed by either budesonide nebuliser suspension 1 mg or placebo every 12 hours. Budesonide nebuliser suspension 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 budesonide nebuliser suspension 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 budesonide nebuliser suspension 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 budesonide nebuliser suspension 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 budesonide nebuliser suspension 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 budesonide nebuliser suspension 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 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 i.v. dosing averages 2-3 hours.

Linearity

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

Paediatric population

Budesonide has a systemic clearance of approximately 0.5 L/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. In 4-6 years old asthmatic children, the systemic availability of budesonide following administration of budesonide 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 that in healthy adults. The maximum plasma concentration, occurring approximately 20 min after start of nebulisation is approximately 2.4 nmol/L in 4-6 year 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 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 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.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Disodium edetate
Sodium chloride
Polysorbate 80
Citric acid
Sodium citrate
Hydrochloric acid or Sodium hydroxide (for pH-adjustment)
Water for injections

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

Unopened: 24 months.
After first opening the foil sachet: 3 months.

Do not refrigerate.

6.4 Special precautions for storage

Store in the original package and foil sachet in order to protect from light.
Units should be stored in an upright position and should be protected from freezing.

For storage conditions after first opening of the medicinal product, see section 6.3.

6.5 Nature and contents of container

Single-dose ampoule made of low-density polyethylene. Each ampoule contains 2 ml of suspension. Strips of five ampoule units are packed into a foil sachet and sachets are packed into an outer carton.

Pack sizes: 20 ampoules for single-use only.

6.6 Special precautions for disposal and other handling

Budesonide nebuliser suspension 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 (see section 4.2).

Ultrasonic nebulisers are not suitable for the administration of budesonide nebuliser suspension and therefore are not recommended.

Each ampoule is for single-use only. Discard any unused suspension.

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

7 MARKETING AUTHORISATION HOLDER

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The Rock Road
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8 MARKETING AUTHORISATION NUMBER

PA22871/035/002

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

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10 DATE OF REVISION OF THE TEXT