Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

Budesonide Teva 0.5 mg/2 ml Nebuliser Suspension

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each 2 ml ampoule contains 0.5 mg budesonide (0.25 mg/ml).
For the full list of excipients, see section 6.1

3 PHARMACEUTICAL FORM

Nebuliser Suspension.
A white to off white suspension.

4 CLINICAL PARTICULARS

4.1 Therapeutic Indications

Budesonide Nebuliser Suspension is indicated in adults, adolescents and in infants and children aged six months to 12 years.

Asthma
Budesonide Nebuliser Suspension is indicated for the use in asthma, in patients where use of a pressurised metered dose inhaler or dry powder device is unsatisfactory or inappropriate.

Pseudocroup
Very serious pseudocroup (laryngitis subglottica), in which hospitalisation is indicated.

4.2 Posology and method of administration

Posology

Paediatric population

The safety and efficacy of Budesonide Nebuliser Suspension in infants aged less than six months has not yet been established.

There is no relevant use of Budesonide Nebuliser Suspension in children aged less than six months in the indication.

Method of administration

For inhalation use.

Precautions to be taken before handling or administrating the medicinal product:

Do not use a partially used, opened or damaged ampoule.

Budesonide Nebuliser Suspension should be administered via a suitable nebuliser. The dose delivered to the patient varies depending on the nebulising equipment used. The nebulisation time and the dose delivered is dependent upon the flow rate, the volume of the nebulisation chamber and the fill volume. An air-flow of 6 – 8 litres per minute through the device should be employed. A suitable fill volume for most nebulisers is 2 – 4 ml.

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 NEBULISER SUSPENSION is:

Adults (including older people) and adolescents over 12 years of age: Usually 0.5 – 2.0 mg daily. In very severe cases the dosage may be further increased.

Children (6 months to 12 years): 0.25 – 1 mg daily. For patients in maintenance therapy with oral steroids, a higher dose of up to 2.0 mg daily could be considered.

Children should use BUDESONIDE NEBULISER SUSPENSION under supervision of an adult. The inhalation should be performed in an upright position.

Maintenance

The maintenance dose should be adjusted to the needs of the individual patient taking into account the severity of disease and the clinical response of the patient. When therapeutic effects are obtained, the maintenance dose should be reduced to the lowest dose, which maintains good asthma control.

Adults (including older people and adolescents): 0.5 – 2.0 mg daily. In very severe cases, the dose may be further increased.

Children (6 months to 12 years): 0.25 – 1.0 mg daily.

Once-daily administration:

Once-daily administration should be considered for children and adults with mild to moderate stable asthma. The maintenance dose should be between 0.25 mg and 1.0 mg Budesonide Nebuliser Suspension daily. Once-daily administration may be initiated in patients who are not receiving corticosteroid treatment and in well-controlled patients who are already taking inhaled steroids. The dose may be given in the morning or the evening. If the asthma symptoms worsen, the daily dose should be increased by administering the dose twice daily.

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 hours for a maximum of 36 hours or until clinical improvement.

Patients maintained on oral glucocorticosteroids

BUDESONIDE NEBULISER SUSPENSION may allow substitution or a reduction in the dose of oral glucocorticosteroids whilst maintaining asthma control. For further information on the withdrawal of oral corticosteroids, see section 4.4.

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

Recommended Dosage Table:

Dose (mg)	BUDESONIDE NEBULISER SUSPENSION 0.5 mg/2 ml (0.25 mg/ml) Volume (ml)
0.25	1*

0.5	2
0.75	3
1.0	4
1.5	6
2.0	8

*Should be mixed with 0.9% saline to a volume of 2 ml.

Dose division and Miscibility

BUDESONIDE NEBULISER SUSPENSION can be mixed with 0.9% saline solution and with nebuliser solutions such as terbutaline, salbutamol, sodium cromoglycate or ipratropium bromide.

The contents of the single-dose ampoule may be divided for adjustment of the dose. Half the ampoule contents should be placed in the Nebuliser cup and mixed with an equal volume of 0.9% saline. To ensure accurate dosing a 1 ml graduation is marked on the ampoule and a measuring syringe is recommended.

Instructions for Use of BUDESONIDE NEBULISER SUSPENSION

BUDESONIDE NEBULISER SUSPENSION should be administered from suitable nebulisers, such as jet nebulisers, of which the Pari LC Jet Plus is an example with a Pari Master compressor. Ultrasonic nebulisers are not suitable..

BUDESONIDE NEBULISER SUSPENSION 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. **Patients should be instructed on the proper use of BUDESONIDE NEBULISER SUSPENSION. Children and their caregivers should be encouraged and trained to use the mouthpiece rather than the face mask.**

Instruction for use:

- Prepare the nebuliser for use according to the manufacturer’s instructions;
- Remove an ampoule from the labelled strip by twisting and pulling;
- Shake the ampoule gently;
- Hold the ampoule upright and twist off the cap;
- Squeeze the contents into the reservoir of the nebuliser;
- BUDESONIDE NEBULISER SUSPENSION is a single-use ampoule. Therefore after each administration any unused medication should be discarded and the nebuliser chamber should be washed and cleaned. Wash the nebuliser chamber and mouthpiece or face mask in warm water or mild detergent. Rinse well and dry by connecting the nebuliser chamber to the compressed air inlet of compressor.
- Patients should be instructed to rinse their mouth out with water after inhaling the prescribed dose to minimise the risk of oropharyngeal thrush.
- Patients should be instructed to wash the facial skin with water after using the face mask to prevent facial skin irritation.

4.3 Contraindications

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

4.4 Special warnings and precautions for use

Budesonide Nebuliser Suspension is not indicated for the treatment of acute dyspnoea or status asthmaticus. These conditions should be treated with short-acting β-adrenoceptor agonists and other bronchodilators.

Non steroid-dependent patients:

Usually a therapeutic effect can be reached within 10 days. A short (about 2 weeks) additional oral corticosteroid

treatment can be given initially, in patients with excessive mucus secretion in the bronchi. After the course of the oral drug, BUDESONIDE NEBULISER SUSPENSION alone should be sufficient therapy.

Steroid-dependent patients:

The transfer of patients treated with oral corticosteroids to the inhaled corticosteroid and their subsequent management requires special care. The patient should be in a relatively stable phase before transfer from oral corticosteroid to treatment with BUDESONIDE NEBULISER SUSPENSION is initiated. BUDESONIDE NEBULISER SUSPENSION 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 BUDESONIDE NEBULISER SUSPENSION for the oral corticosteroid.

Transferred patients whose adrenal function is impaired may require supplementary systemic corticosteroids during periods of stress e.g., surgery, infection or worsening asthma attacks. This also applies to patients who have received prolonged treatment with high doses of inhaled corticosteroids. They may also have impaired adrenocortical function that may result in clinically significant adrenal suppression and may need systemic corticosteroid therapy during periods of stress.

A generally lower systemic corticosteroid action will be experienced during transfer from oral therapy to BUDESONIDE NEBULISER SUSPENSION, which may result in the appearance of allergic or arthritic symptoms such as rhinitis, eczema, muscle and joint pain. Specific treatment should be instigated for these conditions. A general deficiency of 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 a severe reaction occurs, treatment should be reassessed and an alternative therapy established if necessary.

When an acute episode of dyspnoea occurs, despite a well-monitored treatment, a fast-acting inhaled bronchodilator should be used and medical reassessment should be considered. If asthma symptoms are not adequately controlled, despite maximum doses of inhaled corticosteroids, patients may require systemic corticosteroids for a short period of time. In such cases, it is necessary to maintain the inhaled corticosteroid therapy in conjunction with systemic treatment.

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.

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 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 side effects.

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) cause an increase in systemic exposure to budesonide. Concomitant

treatment with ketoconazole, HIV protease inhibitors or other potent CYP3A4 inhibitors should be avoided (see section 4.5 Interactions). If this is not possible, the time interval between administrations of the interacting drugs should be as long as possible. A reduction in the dose of budesonide should also be considered.

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

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.

To reduce the risk of oral candidiasis and hoarseness, patients should be advised to:

- Rinse their mouth with water after each inhalation to minimise the risk of oropharyngeal thrush;
- Wash their face after the use of the face mask to prevent skin irritation;

Oral candidiasis can be rapidly controlled by local antimycotic treatment without the need to discontinue treatment with Budesonide Nebuliser suspension (see also section 4.2).

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 reviewed, 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 e.g., ritanovir and saquinavir, can therefore increase systemic exposure to budesonide several times, see section 4.4 and section 5.2. Since there is 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. Other potent inhibitors of CYP3A4 such as erythromycin and clarithromycin are also likely to markedly increase plasma levels of budesonide. Simultaneous administration with cimetidine can cause a slight increase in plasma budesonide concentration, which is generally not of clinical significance.

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.

The suppressive effect on adrenal function is additive if used concomitantly with systemic or intranasal steroids. 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 a large prospective epidemiological study and from world-wide post marketing experience indicate that inhaled budesonide during pregnancy has no adverse effects on the health of the foetus/new born child. As with other drugs, the administration of budesonide during pregnancy requires that the benefits for the mother are weighed against the risks for the foetus.

Breastfeeding
Budesonide is excreted in breast milk. However, at therapeutic doses of budesonide no effects on the suckling child are anticipated. Budesonide 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 concentration observed in maternal plasma, assuming complete infant 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 suckling child is expected to be low.

4.7 Effects on ability to drive and use machines

BUDESONIDE NEBULISER SUSPENSION has no or negligible influence on the ability to drive and use machines.

4.8 Undesirable effects

Adverse events are listed below by system organ class, symptoms and frequency. Frequencies are defined as: very common (≥1/10), common (≥1/100 to <1/10), uncommon (≥1/1000 to <1/100), rare (≥1/10,000 to <1/1000) and very rare (<1/10,000), not known (cannot be estimated from the available data).

System Organ Class	Symptoms	Frequency
Infections and infestations	Candida infection in the oropharynx	Common
Immune system disorders	Immediate and delayed hypersensitivity reactions* including rash, contact dermatitis, urticaria, angioedema and anaphylactic reaction	Rare
Endocrine disorders	Signs and symptoms of systemic corticosteroid effects including adrenal suppression and growth retardation**	Rare
Psychiatric disorders	Restlessness, Nervousness, Depression, Behavioural changes (predominantly in children) Sleep disorders, Anxiety, Psychomotor hyperactivity, Aggression	Rare Not known
Eye disorders	Cataract, Glaucoma	Not known
Respiratory, thoracic and mediastinal disorders	Cough, Throat irritation Bronchospasm, Dysphonia, Hoarseness	Common Rare
Skin and subcutaneous tissue disorders	Bruising	Rare

* refer to Description of selected adverse reactions; facial skin irritation below.
** refer to Paediatric population, below

Description of selected adverse reactions

The Candida infection in the oropharynx is due to drug deposition. Advising the patient to use their Budesonide Nebuliser Suspension before meals and to rinse the mouth out with water after each dosing will minimise the risk. Candidiasis responds to topical antifungal therapy without the need to discontinue inhaled Budesonide.

Coughing can be prevented by inhaling a β_2-adrenoceptor agonist 5 – 10 minutes before administering Budesonide Nebuliser Suspension.

The ability to adapt to stress may be impaired (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.

There is an increased risk of pneumonia in patients with newly diagnosed COPD starting treatment with inhaled corticosteroids. However a weighted assessment of 8 pooled clinical trials involving 4643 COPD patients treated with budesonide and 3643 patients randomized to non-ICS treatments did not demonstrate an increased risk for pneumonia. The results from the first 7 of these 8 trials have been published as a metaanalysis.

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, Earlsfort Terrace, IRL - Dublin 2; Tel: +353 1 6764971; Fax: +353 1 6762517. Website: www.hpra.ie; E-mail: medsafety@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..

Treatment
Acute overdosage: There is no need to take acute measures; treatment with Budesonide should continue with the lowest possible effective maintenance dose. The impaired adrenocortical function will repair automatically within a few days.

Chronic overdosage: The patient should be treated as a steroid dependent and be transferred to a suitable maintenance dose with a systemic steroid e.g., prednisolone. When the condition is stabilised, the patient should continue treatment with inhaled Budesonide at the recommended dose.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: other drugs for obstructive airway diseases, inhalants, glucocorticoids

ATC code: RO3 BA02

Budesonide is a glucocorticoid, 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 glucocorticoids 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 considered important.

A clinical study in patients with asthma 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. 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 showed decreased bronchial constriction in immediate as well as late asthmatic reactions.

Onset of effect

After a single dose of orally inhaled budesonide, delivered via a dry powder inhaler, improvement of the lung function is achieved within a few hours. After therapeutic use of orally inhaled budesonide delivered via a 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 until 4 weeks.

Airway reactivity

Budesonide has 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

Limited data from long-term studies suggest that most children and adolescents treated with inhaled budesonide 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 (see section 4.4).

Influence on plasma cortisol concentration

Studies in healthy volunteers have shown a dose-related effect on plasma and urinary cortisol. At recommended doses, budesonide causes significantly less effect on adrenal function than prednisolone 10 mg as shown by the ACTH test.

Paediatric population

Clinical –asthma

The efficacy of Budesonide Nebuliser Suspension has been evaluated in a large number of studies. It has been shown that budesonide is effective in both adults and children as once- or twice-daily medication for prophylactic treatment of persistent asthma.

Clinical – croup

A number of studies in children with croup have compared Budesonide Nebuliser Suspension with placebo. Examples of representative studies are given below.

Efficacy in children with mild to moderate croup

A randomised, double-blind placebo-controlled study in 87 children (aged 7 months to 9 years), admitted to hospital with 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 (2 mg) or placebo followed either by budesonide 1 mg or placebo every 12 hours. Budesonide statistically significantly improved croup score at 12 and 24 hours and at 2 hours in patients with an initial croup score above 3. There was also a 33% reduction in the length of hospital 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 eight years) admitted to hospital for croup. Patients received either budesonide 2 mg or placebo every 12 hours for a maximum of 36 hours or until discharge for 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 active and placebo groups showed a similar improvement in croup symptom score, with no statistically significant difference between the groups. By six hours, the croup symptom score in the budesonide 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% 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 minutes 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 averaged 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 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 year old asthmatic children. Based on per kg body weight, children have a clearance that 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 year 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 of that in healthy adults.

The maximal plasma concentration, occurring approximately 20 minutes after the 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 asthmatic 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 other glucocorticosteroids including beclomethasone dipropionate and 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 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 indicates that there are no suggestions 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.

Results from 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 E433
Citric Acid Monohydrate E330
Sodium Citrate E331
Water for Injections

6.2 Incompatibilities

This medicinal product must not be mixed with other medicinal products except those mentioned in section 4.2 and 6.6.

6.3 Shelf life

2 years
After first opening the foil sachet: 3 months.
For single use only. Any unused solution should be discarded.

6.4 Special precautions for storage

Store in the upright position.
Do not store above 25°C. Store the ampoule in the original package in order to protect from light.
For storage conditions of the opened product see section 6.3.
The product is sterile until opened.

6.5 Nature and contents of container

Single dose ampoule made of low density polyethylene. Each ampoule contains 2 ml of suspension. Strips of 5 units are packed into a foil sachet. Sachets are packed into a carton.

Pack sizes:

5, 10, 15, 20, 25, 30, 40, 50 or 60 ampoules for single use only.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal and other handling

Budesonide Nebuliser Suspension can be mixed with 0.9% saline and with solutions of terbutaline, salbutamol, sodium cromoglycate or ipratropium bromide. The admixture should be used within 30 minutes.

An ampoule should not be used if the contents are discoloured or cloudy, which does not disappear after shaking.

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

7 MARKETING AUTHORISATION HOLDER

Teva Pharma B.V.
Computerweg 10
3542 DR Utrecht
The Netherlands

8 MARKETING AUTHORISATION NUMBER

PA0749/141/001

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 11th March 2011
Date of last renewal: 28th January 2014

10 DATE OF REVISION OF THE TEXT

November 2014