Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

Budesonide Teva Pharma 1 mg/2 ml Nebuliser Suspension

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Budesonide Teva Pharma 1 mg/2 ml Nebuliser Suspension:
Each ampoule of 2 ml suspension contains 1 mg budesonide.

For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Nebuliser suspension.

A white to off white suspension in a single dose ampoule.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

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

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

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

Chronic obstructive pulmonary disease (COPD)
Exacerbations of chronic obstructive pulmonary disease (COPD) as an alternative to systemic corticosteroids.

4.2 Posology and method of administration

Posology

General
Budesonide Nebuliser Suspension are nebulised using a suitable nebuliser (jet nebuliser with mouthpiece and face mask). The amount of budesonide that reaches the patient when administered via a nebuliser varies and depends on the following factors, among others:
- nebulisation time
- the volume used;
- the properties of the nebuliser;
- the ratio of inspiratory and expiratory volume of the patient and the dead space;
- the use of face mask or mouthpiece.

Asthma

The dose should be given twice daily. Administration once daily may be considered in cases of mild to moderate stable asthma.

Initial dosage
The initial dose should be tailored to the severity of the disease and thereafter should be adjusted on an individual basis. The following doses are recommended but the minimum effective dose should always be sought.

Children aged 6 months and above

0.25 – 1.0 mg daily. For patients in maintenance therapy with oral steroids a higher initial dosage up to 2.0 mg daily should be considered.

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

Maintenance dose
The maintenance dose should be adjusted to meet the requirements of the individual patient taking into account the severity of the disease and clinical response of the patient. When the desired clinical effect has been obtained, the maintenance dose should be reduced to the minimum required for control of symptoms.

Children aged 6 months and above
0.25 – 1.0 mg daily.

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

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.

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

Exacerbations of COPD

Patients should be treated with a daily dose of 4 to 8 mg of Budesonide Nebuliser Suspension divided into 2 to 4 doses until clinical improvement, but not longer than 10 consecutive days.
An appropriate level of training in nebulised treatment must be provided for use in the home setting.

The use of Budesonide Nebuliser Suspension in COPD patients with pneumonia or requiring invasive mechanical ventilation has not been studied.

Method of administration
For inhalation use.

Asthma

Administration once daily
Administration once daily should be considered for children and adults with mild to moderate stable asthma and with a maintenance dose between 0.25 and 1 mg budesonide daily. Once-daily administration may be initiated both 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 a worsening of the asthma occurs, the daily dose should be increased by administering the dose twice daily.

Onset of effect
An improvement of the asthma following administration of budesonide may occur within 3 days after initiation of therapy. The maximum effect will only be obtained after 2 - 4 weeks of treatment.

Patients in maintenance therapy with oral glucocorticosteroids
With Budesonide Nebuliser Suspension it is possible to replace or considerably reduce the dose of oral glucocorticosteroids and still maintain or improve the control of asthma. When transferral from oral steroids to inhaled budesonide is started, the patient should be in a relatively stable phase.

Initially, a high dose of inhaled budesonide should be administered. It may be co-administered with the previously used oral glucocorticosteroid for approximately 10 days. The oral dose is then reduced (by for example 2.5 mg prednisolone or equivalent dose per month) to the lowest possible level. In many patients it is possible to completely replace the oral glucocorticosteroid entirely with inhaled budesonide.

When tapering off systemic corticosteroids some patients may experience steroid withdrawal symptom, e.g., muscle and/or joint pain, lack of energy and depression or even a decreased lung function. Such patients must be advised to continue inhaled budesonide therapy, but they should also be examined for any objective signs of adrenocortical insufficiency. If such signs are present, the dose of the systemic corticosteroids should be temporarily increased and then tapered off even more slowly. In periods of stress or severe asthma attacks, patients in the transition phase may require treatment with systemic corticosteroids. For further information on the withdrawal of corticosteroids, see section 4.4.

Method of administration
Asthma

Administration once daily:
Administration once daily should be considered for children and adults with mild to moderate stable asthma and with a maintenance dose between 0.25 and 1 mg budesonide daily. Once-daily administration may be initiated both 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 a worsening of the asthma occurs, the daily dose should be increased by administering the dose twice daily.

Onset of effect:
An improvement of the asthma following administration of budesonide may occur within 3 days after initiation of therapy. The maximum effect will only be obtained after 2 - 4 weeks of treatment.

Patients in maintenance therapy with oral glucocorticosteroids:
With Budesonide Nebuliser Suspension it is possible to replace or considerably reduce the dose of oral glucocorticosteroids and still maintain or improve the control of asthma. When transferral from oral steroids to inhaled budesonide is started, the patient should be in a relatively stable phase.

Initially, a high dose of inhaled budesonide should be administered. It may be co-administered with the previously used oral glucocorticosteroid for approximately 10 days. The oral dose is then reduced (by for example 2.5 mg prednisolone or equivalent dose per month) to the lowest possible level. In many patients it is possible to completely replace the oral glucocorticosteroid entirely with inhaled budesonide.

When tapering off systemic corticosteroids some patients may experience steroid withdrawal symptom, e.g., muscle and/or joint pain, lack of energy and depression or even a decreased lung function. Such patients must be advised to continue inhaled budesonide therapy, but they should also be examined for any objective signs of adrenocortical insufficiency. If such signs are present, the dose of the systemic corticosteroids should be temporarily increased and then tapered off even more slowly. In periods of stress or severe asthma attacks, patients in the transition phase may require treatment with systemic corticosteroids. For further information on the withdrawal of corticosteroids, see section 4.4.

Dosage schedule:
The following schedule should be followed:

Dosage in mg	**Volume of Budesonide Nebuliser Suspension**				
	0.25 mg/2 ml		**0.5 mg/2 ml**		**1 mg/2 ml**
0.25	2 ml				
0.5	4 ml	or	2 ml		
0.75***	2 ml	plus	2 ml		
1*			4 ml	or	2 ml
1.5**			2 ml	plus	2 ml
2					4 ml

* either 2 ampoules of Budesonide Nebuliser Suspension 0.5 mg/2 ml or one ampoule of Budesonide Nebuliser Suspension 1 mg/2 ml

** One ampoule of Budesonide Nebuliser Suspension 0.5 mg/2 ml plus one ampoule of Budesonide Nebuliser Suspension 1 mg/2 ml.

*** One ampoule of Budesonide Nebuliser Suspension 0.25 mg/2 ml plus one ampoule of Budesonide Nebuliser Suspension 0.5 mg/2 ml.

Division of the dose and miscibility:
Budesonide Nebuliser Suspension may be mixed with 0.9% sodium chloride solution and with solutions for inhalation containing terbutaline, salbutamol, sodium cromoglycate or ipratropium.

Nebuliser:
Budesonide Nebuliser Suspension must be administered with a jet nebuliser supplied with a mouthpiece or mask. The nebuliser should be connected to an air compressor with adequate air flow (6-8 l/min), and the filling volume should be 2-4 ml.

There can be variation in the performance (dose delivered) between nebulisers, even those of the same make and model

Note! Ultrasound nebulisers are not suitable for nebulisation of Budesonide Nebuliser Suspension and therefore cannot be recommended.

Instructions for use:

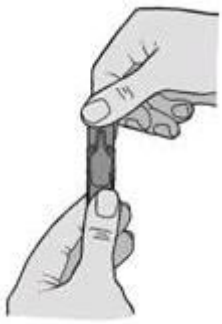
To minimise the risk of oropharyngeal candida infection, the patient should rinse their mouth out with water after inhaling.

- Prepare the nebuliser for use according to the manufacturer's instructions.

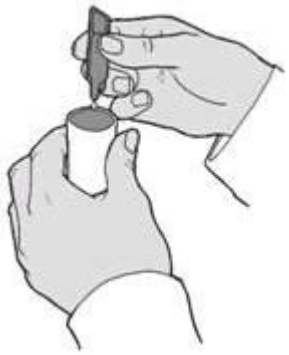
- Open the foil envelope and take out the strip of ampoules. Remove an ampoule from the strip by twisting and pulling (Figure 1).

- Shake the ampoule gently for about 10 seconds or until no sediment is seen.

- Hold the ampoule in the upright position and twist off the upper tab (Figure 2).



- Turn the ampoule upside down and squeeze the contents into the reservoir (chamber) of the nebuliser (Figure 3).



- The ampoule is for single use. Therefore after each administration any unused medication should be discarded and the nebuliser chamber 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 the 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 also wash their face 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 suitable for the treatment of acute dyspnoea or status asthmaticus. These conditions should be treated with short acting β-sympathomimetics and other bronchodilators.

The transfer of patients treated with oral corticosteroid to the inhaled corticosteroid and their subsequent management requires special care. The patients should be in a reasonably stable state before initiating a high dose of inhaled corticosteroid in addition to their usual maintenance dose of systemic corticosteroid. After about 10 days, withdrawal of the systemic corticosteroid is started by reducing the daily dose gradually (by for example 2.5 milligrams prednisolone or the equivalent each month) to the lowest possible level. It may be possible to completely replace the oral corticosteroid with inhaled corticosteroid. Transferred patients whose adrenocortical function is impaired may need supplementary systemic corticosteroid during periods of stress e.g. surgery, infection or worsening asthma attacks.

Patients who have required high dose emergency corticosteroid therapy or prolonged treatment at the highest recommended dosage 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.

During transfer from oral therapy to inhaled budesonide, symptoms may appear that had previously been suppressed by systemic treatment with glucocorticosteroids, for example symptoms of allergic rhinitis, eczema, muscle and joint pain. Specific treatment should be co-administered to treat these conditions.

Patients who have previously been dependent on oral corticosteroids may, as a result of prolonged systemic corticosteroid therapy, experience effects of impaired adrenal function. Recovery may take a considerable amount of time after cessation of oral corticosteroid therapy and hence oral steroid-dependent patients transferred to budesonide may remain at risk from impaired adrenocortical function for some considerable time. In such circumstances hypothalamic pituitary adrenocortical (HPA) axis function should be monitored regularly.

Some patients may feel unwell in a non-specific way during the withdrawal of systemic corticosteroids despite maintenance or even improvement in respiratory function. Such patients should be encouraged to continue treatment with inhaled budesonide and withdrawal of oral corticosteroid unless there are clinical signs to indicate the contrary, for example signs which might indicate adrenal insufficiency. In these cases, a temporary increase in the dose of the oral glucocorticosteroid is sometimes necessary.

The elimination of corticosteroids may be affected by liver function disorders. The elimination rate is reduced and systemic exposure is increased. Possible side effects must be expected. However, the pharmacokinetics of budesonide after intravenous administration was similar in cirrhotic patients and in healthy volunteers. However, oral budesonide administration had an effect on pharmacokinetics in patients with hepatic impairment: systemic availability increased. This may be clinically relevant in patients with severe hepatic impairment.

As with other inhalation therapy, paradoxical bronchospasm may occur with an immediate increase in wheezing after dosing. If this occurs, treatment with inhaled budesonide must be immediately discontinued. The patient must be assessed and an alternative treatment be initiated, if needed.

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

Systemic effects of inhaled corticosteroids may occur, 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.

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.

Exacerbation of clinical symptoms of asthma may be due to acute respiratory tract bacterial infections and treatment with appropriate antibiotics may be required. Such patients may need to increase the dose of Budesonide Nebuliser Suspension and a short course of oral corticosteroids may be required. A rapid-acting inhaled bronchodilator should be used as 'rescue' medication to relieve acute asthma symptoms.

Special caution is needed in patients with active or quiescent pulmonary tuberculosis, and in patients with fungal or viral infections of the respiratory tract. This should be taken into account with the treatment of asthma in patients who also have a respiratory tract infection; both the asthma and the respiratory tract infection should be treated adequately.

In patients with excessive mucous secretion in the respiratory tract, short term therapy with oral corticosteroids may be necessary.

Oral candidiasis can occur during treatment with inhaled corticosteroids. In such cases, treatment with an appropriate antimycotic agent may be necessary and in some patients discontinuation of the corticosteroid may be necessary (see section 4.2).

It is recommended to inhale the nebulised corticosteroid via a mouthpiece rather than a face mask in order to prevent local skin irritations of the face. When a face mask is used, the face should be washed with water after completion of the nebulisation.

The nebuliser chamber and the mouth piece (or face mask) should be cleaned with hot water and mild detergent after every administration. They should then be rinsed well with water and dried by connecting the nebuliser chamber to the compressor.

Concomitant use of ketoconazole, HIV protease inhibitors or other potent CYP3A4 inhibitors should be avoided. If this is not possible, the period between treatments should be as long as possible (see section 4.5).

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.

Paediatric population

There is insufficient data available regarding the possible growth-inhibiting effect of budesonide in children aged from six months to four years of age.

Influence on growth
It is recommended that the height of children receiving prolonged treatment with inhaled corticosteroids is regularly monitored. If growth is slowed, therapy should be re-evaluated with the aim of reducing the dose of inhaled corticosteroid. The benefits of the corticosteroid therapy and the possible risks of growth suppression must be carefully weighed. In addition, consideration should be given to referring the patient to a paediatric respiratory specialist.

4.5 Interaction with other medicinal products and other forms of interaction

The metabolism of budesonide is primarily mediated by CYP 3A4. Inhibitors of this enzyme such as ketoconazole, itraconazole and HIV protease inhibitors (ritanovir and saquinavir) can, therefore, increase systemic exposure to budesonide several fold (see section 4.4). Because there are no data to support a dosage recommendation, the combination should be avoided. If this is not possible, the period between treatments should be as long as possible and a reduction of the budesonide dose could also be considered.

Co-treatment with CYP3A inhibitors, including cobicistat-containing products, is expected to increase the risk of systemic side-effects. The combination 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.

Because adrenal function may be suppressed, an ACTH stimulation test for diagnosing pituitary insufficiency might show false results (low values).

Limited data about this interaction for high-dosed inhaled budesonide indicate that marked increases in plasma levels (on average four-fold) can occur if itraconozole, 200 mg once daily, is administered concomitantly with inhaled budesonide (single dose of 1000 µg).

Other potent CYP3A4 inhibitors such as erythromycin and clarithromycin are also likely to markedly increase plasma concentrations of budesonide.

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.

Concomitant administration of cimetidine can cause a slight increase in the plasma concentration of budesonide, which is generally not clinically relevant.

The suppressive effect on adrenal function is additive, if used with systemic or intranasal steroids.

No interactions have been observed between budesonide and other medicines used in the treatment of asthma.

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.

Breast-feeding

Budesonide is excreted into breast milk. However, at therapeutic doses of budesonide no effects on the suckling child are anticipated. Budesonide can be used during breastfeeding.

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 the data from inhaled budesonide and the fact that budesonide exhibits linear pharmacokinetic properties within the therapeutic dosage intervals after nasal, inhaled, oral and rectal adminstrations, at therapeutic doses of budesonide, exposure to the suckling child is anticipated 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

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

List of adverse reactions
The frequencies of adverse events are ranked according to the following: very common (≥1/10), common (≥1/100 to <1/10), uncommon (≥1/1000 to <1/100), rare (≥1/10000 to < 1/1000), very rare (<1/10000) and not known (cannot be estimated from the available data).

System Organ Class	Frequency	Undesirable effect
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 Rare	Anxiety, depression Sleep disorders, psychomotor hyperactivity, aggression Restlessness, nervousness, behavioural changes (predominantly in children)
Nervous system disorders	Uncommon	Tremor
Eye disorders	Uncommon Not known	Cataracts, vision, blurred (see also section 4.4) Glaucoma
Respiratory, thoracic and mediastinal disorders	Common Rare	Cough, hoarseness, throat irritation Bronchospasm, dysphonia
Gastrointestinal disorders	Common	Oral mucosal irritation, difficulty in swallowing

Skin and subcutaneous disorders	Rare	Bruising, skin reactions, pruritus, erythema
Musculoskeletal and connective tissue disorders	Uncommon	Muscle spasm
	Rare	Growth retardation
Investigations	Very rare	Bone density decreased

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

Description of selected adverse reactions
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 using 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 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.

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

Treatment with inhaled budesonide may result in candida infection in the oropharynx. Experience has shown that candida infection occurs less often when inhalation is performed before meals and/or when the mouth is rinsed after inhalation. In most cases this condition responds to topical anti-fungal therapy without discontinuing treatment with inhaled budesonide.

Coughing can usually be prevented by inhaling a β_2-adrenoceptor agonist (e.g. terbutaline) 5 – 10 minutes before administration of Budesonide Nebuliser Suspension.

Systemic effects of inhaled corticosteroids may occur, particularly at high doses prescribed for prolonged periods. These may include adrenal suppression, growth retardation in children and adolescents, decrease in bone mineral density, cataract and glaucoma, and susceptibility to infections. The ability to adapt to stress may be impaired. The systemic effects described, however, are much less likely to occur with inhaled budesonide than with oral corticosteroids.

Paediatric population
Due to the risk of growth retardation in the paediatric population, growth should be monitored as described in section 4.4.

There are limited data available on the safety and efficacy of Budesonide Nebuliser Suspension in overweight or obese children, however, weight loss is a key target that must be considered.

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

Acute overdosage with budesonide, even in excessive doses, is not expected to be a clinical problem.

Symptoms
The only harmful effect after a large amount of sprays during a short period is a suppression of the cortex function. If it is a matter of chronic use of very high doses, effects such as a degree of cortex atrophy in addition to adrenocortical suppression may occur.

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

Chronic overdose: Systemic glucocorticosteroid effects, such as hypercorticism and adrenal suppression, may occur in patients using chronically excessive doses of budesonide (see section 4.4). Patients receiving higher than approved doses should be closely monitored and the dosage should be gradually reduced. The patient should be treated as 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: Glucocorticoids, ATC code: R03B A02

Mechanism of action
Budesonide is a halogen-free glucocorticosteroid, which possesses a high local anti-inflammatory action with few systemic effects. This is because budesonide is rapidly inactivated in the liver after absorption (see also section 5.2). The exact mechanism of action of glucocorticoids in the treatment of asthma is not fully understood. Anti-inflammatory actions (including T-cells, eosinophilic cells and mast cells) such as inhibition of inflammatory mediator release and inhibition of cytokine-mediated immune response are considered important.

Following a single dose of orally inhaled budesonide administered via Turbuhaler, improvement in pulmonary function can be demonstrated within hours. However, a therapeutic effect of orally inhaled budesonide is only maximised after several weeks.

Pharmacodynamic effects
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 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 demonstrated anti-anaphylactic and anti-inflammatory effect in challenge tests in experimental animals and in patients. This effect has manifested itself as reduced bronchial obstruction in both the immediate and late allergic reaction.

It was also demonstrated that budesonide reduces the airways' reactivity to histamine and metacholine in hyperreactive patients. Treatment with inhaled budesonide has been used to effectively prevent exercise-induced asthma.

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

In clinical trials, budesonide has been shown to have good efficacy in bronchial asthma and side effects with maintenance therapy are usually mild.

Exacerbations of COPD
Several studies have shown that nebulised budesonide, 4 to 8 mg daily, effectively treats exacerbations of COPD.

In a double-blind randomised placebo-controlled study of 199 patients with acute COPD exacerbations, patients were treated with nebulised budesonide 8 mg daily (2 mg four times daily (n=71)) or with oral prednisolone, 30 mg every 12 hours (n=62) or with placebo (n=66), for 3 days. Improvement in FEV1 after airway dilation compared to placebo was 0.10 l with budesonide and 0.16 l with prednisolone; the difference between the two active treatments was not statistically significant. The proportion of patients with a clinical improvement of at least 0.15 l in FEV1 after airway dilation was greater in the budesonide nebulised group (34%) and in the prednisolone group (48%) than in the placebo group (18%). The differences were statistically significant for both active treatments versus placebo ($p<0.05$) but not between active treatments.

Paediatric population
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).

Clinical – asthma

The efficacy of budesonide nebuliser suspension has been evaluated in a large number of studies and 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 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 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 was given 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 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 bioavailability 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 patient. Only a small quantity of the systemically available dose originates from the swallowed portion of the medicine. The maximum plasma concentration, which is reached 10 to 30 minutes after the start of the nebulisation, is approximately 4 nmol/l after a single dose of 2 mg.

Distribution
Budesonide has a Volume of Distribution in adults of approximately 3.0 l/kg and plasma protein binding is on average 85 to 90%.

Biotransformation
Approximately 90% of budesonide is converted by first-pass biotransformation in the liver via CYP3A4 into metabolites with a low glucocorticosteroid activity. The glucocorticosteroid activity of the most important metabolites, 6-β-hydroxy budesonide and 16-alpha-hydroxy prednisolone, is less than 1% of the activity of budesonide.

Elimination
The metabolites are excreted unchanged or conjugated primarily via the kidneys. No unchanged budesonide was recovered in the urine. In healthy adults, budesonide has a high systemic clearance (approximately 1.2 l/min) and an average elimination half life of 2 – 3 hours after intravenous administration.

Linearity
In clinically relevant doses, the pharmacokinetics for budesonide is dose proportional.

Paediatric population
Budesonide has a systemic clearance of approximately 0.5 l/ml in children (4 – 6 years of age) with asthma. On a per kilogram basis, the budesonide clearance in children is 50% higher than that in adults. In children with asthma, the elimination half life of budesonide after inhalation is about 2.3 hours; this is about the same as that in healthy adults. In children aged 4 – 6 years of age with asthma, the systemic bioavailability of budesonide after administration of nebulised budesonide via a jet nebuliser (Pari LC Jet Plus® with Pari Master® compressor) is approximately 6% of the nominal dose and 26% of the dose that is administered to the patient. The systemic availability in children is approximately half of that in healthy adults.

The maximum plasma concentration that occurs 20 minutes after the start of a 1 mg budesonide nebulisation is approximately 2.4 nmol/l in children aged 4 – 6 years with asthma. The exposure (C_{max} and AUC) of budesonide after a single dose of 1 mg via nebulisation in 4 – 6 year old children is comparable to that of healthy adults, who were given the same dose of budesonide using the same nebulisation 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.

Results from subacute and chronic toxicity, as well as genotoxicity and carcinogenicity studies did not pose any special risk to humans when budesonide was given in therapeutic doses.

Although there was an increased incidence of brain gliomas in male rats, this could not be verified in a repeat study. Available clinical experience indicates there are no suggestions that budesonide induces brain gliomas or other primary neoplasms in man.

Glucocorticosteroids, including budesonide, have produced teratogenic effects in animal studies, including cleft palate and skeletal abnormalities. Similar effects are considered unlikely to occur in humans at the recommended dose levels.

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 glucocorticosteroid 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 6.6.

6.3 Shelf life

Unopened: 2 years
After first opening the foil sachet: 3 months
Opened ampoule: use immediately. Discard any unused portion.

6.4 Special precautions for storage

Do not freeze.

Store in the upright position. Store the ampoule in the opened sachet. The opened sachet should be stored in the outer carton to protect from light and should not be frozen. For shelf life of the opened sachet 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 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 cromoglicate or ipratropium bromide. The admixture should be used within 30 minutes.

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

The product is sterile until opened.

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

7 MARKETING AUTHORISATION HOLDER

Teva Pharma B.V.
Swansweg 5
2031GA Haarlem
Netherlands

8 MARKETING AUTHORISATION NUMBER

PA0749/207/003

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 7th March 2014
Date of last renewal: 4th July 2023

10 DATE OF REVISION OF THE TEXT

October 2022