Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

Budesitan 1.0mg/2ml Nebuliser Suspension.

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

One ml of suspension contains 0.5mg budesonide.
One ampoule of 2ml suspension contains 1.0mg budesonide.
For a full list of excipients, see section 6.1

3 PHARMACEUTICAL FORM

Nebuliser suspension
White to off-white suspension.

4 CLINICAL PARTICULARS

4.1 Therapeutic Indications

Treatment of persistent bronchial asthma in patients where use of a pressurised inhaler or dry powder formulation is unsatisfactory or inappropriate.

4.2 Posology and method of administration

Route of administration: For inhalation use only.

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

Adults (including the elderly) and children/adolescents over 12 years of age:
0.5 - 2 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 account of the severity of the disease and the 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 the symptoms.

Children aged 6 months and above:
0.25 - 1.0mg daily.

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

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 mg 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 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 Budesitan 1.0mg/2ml Nebuliser Suspension it is possible to replace or considerably reduce the dose of oral glucocorticosteroids and still maintain or improve the control of asthma.

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 replace the oral glucocorticosteroid entirely with inhaled budesonide.

When tapering off systemic corticosteroids some patients will experience steroid withdrawal symptoms, e.g. joint and/or muscle pain, lack of energy and depression or even a decreased lung function. Such patients must be advised to continue the 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 corticosteroid 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.

Dosage schedule:

Dosage in mg	**Volume of Budesonide Nebuliser Suspension**
0.25	-
0.5	-
0.75	-
1.0	2 ml
1.5	3 ml
2.0	4 ml

Division of the dose and miscibility:
The contents of the 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% sodium chloride solution. To ensure accurate dosing the use of a measuring syringe is recommended.

Budesitan 1.0mg/2ml Nebuliser Suspension may be mixed with 0.9% sodium chloride solution and with solutions for inhalation containing terbutaline, salbutamol, sodium cromoglycate or ipratropium.

Nebuliser:
Budesitan 1.0mg/2ml 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 (5-8 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 Budesitan 1.0mg/2ml Nebuliser Suspension and therefore cannot be recommended.

Instruction for use:
The spray container should be shaken before use.

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

To prevent irritation of the facial skin the face should be washed after using the nebuliser with a mask.

The nebuliser should be cleaned after each use.
Wash the nebuliser container and mouthpiece or face-mask in warm water using a mild detergent in accordance with the manufacturer's instructions. Rinse well and dry it by connecting the nebuliser container to the compressor or the air inlet.

4.3 Contraindications

Hypersensitivity to budesonide or any of the excipients.

4.4 Special warnings and precautions for use

Budesitan 1.0mg/2ml Nebuliser Suspension is not indicated 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 corticosteroids 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 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.

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.

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.

As with other inhalation therapies paradoxical bronchospasm may occur, manifested by an immediate increase in wheezing and shortness of breath after dosing. Paradoxical bronchospasm responds to a rapid-acting inhaled bronchodilator and should be treated straight away. Budesonide should be discontinued immediately, the patient should be assessed and, if necessary, alternative treatment instituted.
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 prolonged periods. These effects are much less likely to occur than with oral corticosteroids. Possible systemic effects include Cushing's syndrome, Cushingoid features, adrenal suppression, growth retardation in children and adolescents, decrease in bone mineral density, cataract, glaucoma and more rarely, a range of psychological or behavioural effects including

psychomotor hyperactivity, sleep disorders, anxiety, depression or aggression (particularly in children). It is important, therefore, that the dose of inhaled corticosteroid is titrated to the lowest dose at which effective control of asthma is maintained

It is recommended that the height of children receiving prolonged treatment with inhaled corticosteroids is regularly monitored. If growth is slowed, therapy should be reviewed with the aim of reducing the dose of inhaled corticosteroid, if possible, to the lowest dose at which effective control of asthma is maintained. In addition, consideration should be given to referring the patient to a paediatric respiratory specialist.

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.

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).

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 inhaled budesonide 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 care and adequate specific therapeutic control of patients with active and quiescent pulmonary tuberculosis is necessary before commencing treatment with inhaled budesonide. Similarly patients with fungal, viral or other infections of the airways require close observation and special care and should use budesonide only if they are also receiving adequate treatment for such infections.

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

In patients with severe hepatic dysfunction, treatment with inhaled budesonide can result in a reduced elimination rate and hence enhanced systemic availability. Possible systemic effects may then result and therefore HPA axis function in these patients should be monitored at regular intervals.

Concomitant treatment with ketoconazole, HIV protease inhibitors or other potent CYP3A4 inhibitors should be avoided (see section 4.5). If this is not possible the time interval between administration of the two drugs should be as long as possible.

Recent epidemiological studies show that there is an increased incidence of pneumonia in patients with Chronic Obstructive Pulmonary Disease (COPD) treated with inhaled corticosteroids, with an adjusted odds ratio of 1.7 (Reference). Care should be exercised in prescribing budesonide for those patients whose respiratory disease might have a component of COPD.

Budesitan 1.0mg/2ml Nebuliser Suspension should be used with a jet nebuliser device. An ultrasonic nebuliser should not be used as this is not appropriate for nebuliser suspensions.

4.5 Interaction with other medicinal products and other forms of interaction

Budesitan 1.0mg/2ml Nebuliser Suspension can increase the efficacy of inhaled beta-2-sympathomimetics**.**

The metabolism of budesonide is primarily mediated by CYP3A4. Inhibitors of this enzyme, e.g., ketoconazole and itraconazole, can therefore increase systemic exposure to budesonide several times, see section 4.4. Since there are no data to support dosage recommendations, 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. 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).

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

Cimetidine had a weak but clinically insignificant inhibiting effect on hepatic metabolism 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.

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 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 suckling child is anticipated to be low.

4.7 Effects on ability to drive and use machines

Inhaled budesonide has no or negligible influence on the ability to drive and use machines.

4.8 Undesirable effects

Tabulated list of adverse reactions
The following definitions apply to the incidence of undesirable effects: Very common (≥1/10); common (≥1/100, <1/10); uncommon (≥1/1,000, <1/100); rare (≥1/10,000, <1/1,000); very rare (<1/10,000), not known (cannot be estimated from the available data).

Infections and infestations	Common	Oropharyngeal candidiasis
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**
Eye disorders	Not known	Cataracts, glaucoma
Psychiatric disorders	Rare	Restlessness, nervousness, depression, behavioural changes (predominantly in children)
	Not known	Sleep disorders, anxiety, psychomotor activity, aggression,
Respiratory, thoracic and mediastinal disorders	Common	Hoarseness, cough, throat irritation
	Rare	Bronchospasm
Gastrointestinal disorders	Common	Oral mucosal irritation, difficulty in swallowing
Skin and subcutaneous disorders	Rare	Bruising, skin reactions, pruritus, erythema
Musculoskeletal and connective tissue disorders	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 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 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 beta-2 agonist (e.g. terbutaline) 5-10 minutes before administration of Budesitan 1.0mg/2ml 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.

4.9 Overdose

Symptoms:
Acute overdose with budesonide usually does not constitute a clinical problem. 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 overdosage: There is no need for acute measures. The treatment with budesonide should be continued with the lowest possible effective maintenance dose, and the adrenocortical function will repair itself automatically within 1-2 days.

Chronic overdosage: The patient should be treated as a steroid dependent and be transferred to a suitable maintenance dose with a systemic steroid, for example prednisolone. When the condition is stabilized, the patient should continue the treatment with the inhalation of budesonide at the recommended dose.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Other drugs for obstructive airways diseases, inhalant, Glucocorticoids
ATC code: R03 BA 02

Budesonide is a glucocorticosteroid with a powerful local anti-inflammatory action.

The precise mechanism of action of glucocorticosteroids in the treatment of asthma is not fully understood. Anti-inflammatory effects (including T-cells, eosinophilic cells and mast cells) such as inhibition of the release of inflammatory mediators and inhibition of cytokine-mediated immune response, are probably important. The strength of budesonide, measured as affinity for glucocorticoid receptors, is approximately 15 times stronger than that of prednisolone.

A clinical trial with asthma patients in which inhaled and oral budesonide was compared with placebo, showed statistically significant effects of inhaled budesonide, but not of oral budesonide. The therapeutic effect of normally used doses of inhaled budesonide may therefore chiefly be explained by a direct effect on the airways.

Budesonide has demonstrated an 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 the later 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.

In recommended doses Budesonide Nebuliser Suspension has a significantly smaller influence on the adrenal function than 10 mg prednisone, shown by the ACTH test. No clinically relevant changes in the plasma cortisol values or response to ACTH stimulation were observed when budesonide was given in doses up to 1600 µg daily for 3 months to adults and up to 800 µg daily to children. Long-term monitoring for up to 52 weeks confirmed that the HPA axis was not suppressed.

Both asthma and inhaled glucocorticosteroids may affect the growth in length. The effect of Budesonide Nebuliser Suspension on the growth in length was studied in 519 children (from 8 months to 9 years) in three prospective, randomised, open, non-blinded studies. The studies did not show any significant difference in the growth in length of children treated either with Budesonide Nebuliser Suspension or with conventional asthma therapy. Two studies (N = 239 and 72 patients, respectively) showed 7 mm and 8 mm greater growth after one year of treatment with Budesonide Nebuliser Suspension compared with traditional asthma therapy (not statistically significant), while one study (N = 208) showed a growth in length that after one year was 8 mm smaller in the Budesonide Nebuliser Suspension group

than in the group of conventional asthma treatment (statistically significant difference).

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 declared dose and 40-70 % of the dose delivered to the patient. A small part of the systemically available dose comes from inhalation suspension that is swallowed. The peak plasma concentration following administration of a single dose of 2 mg is achieved 10-30 minutes after the beginning of inhalation and is approximately 4 nmol/l. In children (4-6 years), the systemic bioavailability of budesonide after administration of Budesonide Nebuliser Suspension via a jet nebuliser is approximately 6 % of the declared dose and 26 % of the dose administered to the patient. The peak plasma concentration following administration of a single dose of 1 mg is reached approximately 20 minutes after the beginning of inhalation and is approximately 2.4 nmol/l.

Distribution:
The volume of distribution in adults is approximately 3 l/kg. Plasma protein binding is approximately 85-90 %.

Metabolism:
Budesonide undergoes extensive (~ 90%) first pass biotransformation in the liver via CYP 3A4 to metabolites with a low glucocorticosteroid activity. The in-vitro activity of the main metabolites, 6-β-hydroxybudesonide and 16-α-hydroxyprednisolone, is less than 1% of that of budesonide.

Excretion:
The metabolites are excreted in unchanged or conjugated form predominantly via the kidneys. No unchanged budesonide is found in the urine. Budesonide has a high systemic clearance (approximately 1.2 litres/min) in healthy adults, and the elimination half-life following intravenous administration is approximately 2-3 hours. Budesonide has a systemic clearance of approximately 0.5 l/min in 4 to 6-year-old asthmatic children. Children have an approximately 50 % higher clearance per kg bodyweight than adults. The half-life of budesonide following inhalation is about 2.3 hours in asthmatic children, which is roughly the same as in healthy adults.

5.3 Preclinical safety data

Preclinical data revealed no special hazard for humans in the therapeutic dose range based on studies of chronic toxicity, genotoxicity and carcinogenicity.

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

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Disodium edetate
Sodium chloride
Polysorbate 80
Citric acid
Sodium citrate
Water for injection

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

3 years.

After first opening of the foil sachet, the ampoule may be stored unopened for three months.
Use ampoule within 12 hours of opening.

6.4 Special precautions for storage

Store in the original package in order to protect from light and moisture.

6.5 Nature and contents of container

Low density polyethylene ampoule containing 2ml nebuliser suspension.
Pack sizes: Tri-laminate foil sachets containing 5, 20, 24, 40 (2 x 20) and 60 ampoules (in strips of 4, 5, 8, 10 or 12 ampoules).

Not all pack sizes may be marketed.

6.6 Special precautions for disposal of a used medicinal product or waste materials derived from such medicinal product and other handling of the product

Budesonide nebuliser suspension can be mixed with 0.9% saline and with solutions of terbutaline, salbutamol, sodium chromoglycate, or ipratropium bromide.

For single use only. Any unused solution should be discarded.

7 MARKETING AUTHORISATION HOLDER

Breath Limited
Whiddon Valley,
Barnstaple,
Devon
EX32 8NS
United Kingdom

8 MARKETING AUTHORISATION NUMBER

PA 1831/001/002

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 21 October 2005

Date of last renewal: 24 February 2009

10 DATE OF REVISION OF THE TEXT

November 2013