SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT
MAXAIR 0.5 mg/mL Nebuliser Suspension
Sterile

2. QUALITATIVE AND QUANTITATIVE COMPOSITION
Active ingredient:
Each 2 ml suspension for nebulization contains;
Budesonide…….1 mg (0.5 mg budesonide per 1 mL)

Excipient(s) with known effect:
For full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM
Vial containing sterile suspension for nebulization
Translucent, off-white, homogeneous suspension

4. CLINICAL PARTICULARS
4.1. Therapeutic indications
It is used as anti-inflammatory, bronchodilator, symptom controller in all steps of asthma and used to reduce the requirement for oral steroids. Not recommended for use alone in COPD.

MAXAIR is also recommended for use in infants and children with croup, in which hospitalization is indicated.

4.2. Posology and method of administration
Posology/frequency and duration of administration
The dose of MAXAIR varies according to the patient's condition and should be adjusted to the lowest maintenance dose after asthma control is achieved.

The administration can be once or twice a day. Once daily dosing is for 0.25-1 mg daily doses.

Recommended Starting Dose:
In Bronchial Asthma
Adults: The total daily dose is 1-2 mg.

Children 6 months and older: The total daily dose is 0.25-0.5 mg.
A higher starting dose in patients using oral glucocorticosteroids, e.g. a total of 1 mg per day may be considered.

Maintenance Treatment:
Once asthma control is achieved, it is important to adjust the dose to the lowest effective maintenance dose.

Maintenance dose - Dose range
Adults/elderly*:* The total daily dose is 0.5-4 mg. In very severe cases, the dose may be increased.
Children 6 months and older*:* The total daily dose is 0.25–2 mg.

Once-daily dosing
Once-daily dosing may be considered in both adult and pediatric patients with a maintenance dose of 0.25 to 1 mg daily. Once-daily dosing can be initiated in both noncorticosteroid-treated patients and patients well-controlled with inhaled glucocorticosteroids. The dose can be administered in the morning or evening. If worsening of asthma occurs, the dose should be increased and divided over the day as needed.

Onset of effect
After MAXAIR administration, an increase in asthma control may occur within 3 days of initiation of treatment, but the greatest benefit is achieved in 2-4 weeks.

Patients maintained on oral glucocorticosteroids
MAXAIR may permit significant reduction in dosage of oral glucocorticosteroids replacement of oral corticosteroids with inhaled glucocorticosteroids (MAXAIR) while maintaining asthma control or providing better control of asthma.

When transferal from oral steroids to MAXAIR is started, the patient should be in a relatively stable phase. Initially, a high dose of MAXAIR should be used at the same time as the usual maintenance dose of oral glucocorticosteroids. After one week, the oral steroid dose should be gradually reduced (by for example 2.5 milligrams prednisolone or the equivalent each month) to the lowest possible level. Slow discontinuation of the oral dose is strongly recommended. In many patients, it is possible to completely replace oral glucocorticosteroid with MAXAIR.

Despite maintenance or improvement in lung function upon discontinuation of the oral dose, some patients may experience symptoms of systemic corticosteroid deficiency; e.g. such as joint and/or muscle pain, fatigue and depression. Such patients should be advised to continue with MAXAIR, but should be carefully monitored for the occurrence of adrenal insufficiency. If adrenal insufficiency occurs, the systemic corticosteroid dose should be temporarily increased and oral dose discontinuation slowed further. In cases of stress or severe asthma attack, it may be necessary to add systemic corticosteroid therapy to transitional patients.

Dose division and miscibility
MAXAIR can be mixed with 0.9% sodium chloride (saline) and with solutions for nebulization of terbutaline, salbutamol, fenoterol, acetylcysteine, sodium cromoglycate or ipratropium. The admixture should be used within 30 minutes.

Dose adjustment can be made by dividing single-dose units. The single-dose vial is marked. This mark indicates the volume of 1 ml when the single-dose vial is held flat. If only 1 ml is to be used, empty the contents until the liquid reaches the surface mark. Keep the opened single-dose vial in the envelope, protected from light. Opened single-dose vials should be used within 12 hours. Please note that when only 1 ml is used, the remaining volume is not sterile.

Table 1. Dosage Table

Dose (mg)	Volume of MAXAIR	
	0,25 mg/mL	0,5 mg/mL
0.25	1 mL (*)	-
0.5	2 mL	-
0.75	3 mL	-
1	-	2 mL

1.5	-	3 mL
2	-	4 mL

(*) 0.9% sodium chloride (saline) solution should be added to reach a total volume of 2 mL.

Croup
In infants and children with croup, the usual dose is 2 mg of nebulized budesonide. This dose can be given as a single administration, or as two 1 mg doses separated by 30 minutes. Dosing can be repeated every 12 hour for a maximum of 36 hours or until clinical improvement.

Instruction for correct use of MAXAIR
MAXAIR should be administered via a jet nebulizer equipped with a mouthpiece or suitable face mask. The nebulizer should be connected to an air compressor with an adequate air flow (6-8 L/min), and the fill volume should be 2-4 mL.

Note: It is important to instruct the patient:
- to carefully read the instructions for use in the package leaflet which are packed together with each nebulizer
- that Ultrasonic nebulizers are not suitable for the administration of MAXAIR and therefore are not recommended
- MAXAIR can be mixed with 0.9% sodium chloride (saline) and with solutions for nebulization of terbutaline, salbutamol, fenoterol, acetylcysteine, sodium cromoglycate and ipratropium. The admixture should be used within 30 minutes.
- to minimize the risk of thrush, the patient should rinse their mouth out with water after inhaling.
- to wash the facial skin with water after using the face mask to prevent facial skin irritation
- to adequately clean and maintain the nebulizer according to the manufacturer's instructions

Additional information on special populations
Renal impairment:
No dosage adjustment is required in patients with renal impairment.

Hepatic impairment:
Decreased liver function may affect the elimination of corticosteroids. However, plasma clearance of intravenously administered budesonide is similar in patients with cirrhosis and in healthy subjects. In cases of reduced liver function, the systemic availability of orally administered budesonide is increased due to decreased first-pass metabolism. As no data are available for inhaled budesonide, its clinical relevance for treatment with MAXAIR is unknown; however, increased plasma levels and therefore an increased risk for systemic adverse effects can be expected.

Pediatric population:
It should be used in children aged 6 months and older at the indicated doses.

Geriatric population:
There are no special dose requirements in the elderly.

4.3. Contraindications
It should not be used in patients with hypersensitivity to budesonide or to any of its ingredients.

4.4. Special warning and precautions for use
Particular caution should be exercised in patients with active or latent pulmonary tuberculosis and in

patients with fungal or viral infections of the respiratory tract.
Nonsteroid-dependent patients: A therapeutic effect is usually reached within 10 days. In patients with excessive mucus secretion in the bronchi, a short (about 2 weeks) additional oral corticosteroid regimen can be given initially. After the course of the oral drug, budesonide alone should be sufficient therapy.

Steroid-dependent patients: When transfer from oral corticosteroid to treatment with budesonide is initiated, the patient should be in a relatively stable phase. Budesonide is then given, in combination with the previously used oral steroid dose, for about 10 days. After that, the oral steroid dose should be gradually reduced (by, for example, 2.5 mg prednisolone or the equivalent each month), to the lowest possible level. In many cases, it is possible to completely substitute budesonide for the oral corticosteroid.

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

A general insufficient glucocorticosteroid effect should be suspected if, in rare cases, symptoms such as tiredness, headache, nausea and vomiting should occur. In these cases, a temporary increase in the dose of oral glucocorticosteroids is sometimes necessary.

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

Patients, who have required high dose emergency corticosteroid therapy or prolonged treatment at the highest recommended dose of inhaled corticosteroids, may also be at risk of impaired adrenal function. These patients may exhibit signs and symptoms of adrenal insufficiency when exposed to severe stress. Additional systemic corticosteroid treatment should be considered during periods of stress or elective surgery.

Systemic effects may occur with any inhaled corticosteroids, particularly at high doses prescribed for long periods. These effects are much less likely to occur with inhalation treatment than with oral corticosteroids. Possible systemic effects include Cushing's syndrome, Cushingoid features, adrenal suppression, growth retardation in children and adolescents, decrease in bone mineral density, cataract, glaucoma and more rarely, a range of psychological or behavioral 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.

MAXAIR is not intended for rapid relief of acute episodes of asthma where an inhaled short-acting bronchodilator is required. If patients find short-acting bronchodilator treatment ineffective, or they need more inhalations than usual, medical attention must be sought. In this situation, consideration should be given to the need for or an increase in their regular therapy, e.g., higher doses of inhaled budesonide or the addition of a long-acting beta agonist, or for a course of oral glucocorticosteroid.

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

The plasma clearance following an intravenous dose of budesonide however was similar in cirrhotic

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

Co-treatment with CYP3A inhibitors (e.g. itraconazole, ketoconazole, HIV protease inhibitors and cobicistat-containing products) is expected to increase the risk of systemic corticosteroid side effects. Therefore, the combination should be avoided unless the benefit outweighs this increased risk, in which case patients should be monitored for systemic corticosteroid side effects. This is of limited clinical importance for short-term (1-2 weeks) treatment with itraconazole or ketoconazole or other potent CYP3A inhibitors, but should be taken into consideration during long-term treatment. A reduction in the dose of budesonide should also be considered (see section 4.5).

The nebulizer chamber should be cleaned after every administration. The nebulizer chamber and mouthpiece or face-mask should be washed in hot water using a mild detergent. It should be rinsed well and dried, by connecting the nebulizer chamber to the compressor or air inlet.

Oral candidiasis may occur during the therapy with inhaled corticosteroids. This infection may require treatment with appropriate antifungal therapy and in some patients discontinuation of treatment may be necessary (see also section 4.2).

The risk of pneumonia may increase in elderly patients with COPD in whom inhaled steroids are combined.

Pneumonia in patients with COPD
An increase in the incidence of pneumonia, including pneumonia requiring hospitalization, 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 and severe COPD.

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

Pediatric population
Influence on growth
It is recommended that the height of children receiving prolonged treatment with inhaled

corticosteroids is regularly monitored. If growth is slowed, therapy should be re-evaluated with the aim of reducing the dose of inhaled corticosteroid, if possible, to the lowest dose at which effective control of asthma is maintained. The benefits of the corticosteroid therapy and the possible risks of growth suppression must be carefully weighed. In addition, consideration should be given to referring the patient to a pediatric respiratory specialist.

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

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

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

Raised plasma concentrations of and enhanced effects of corticosteroids have been observed in women also treated with estrogens and contraceptive steroids, but no effect has been observed with budesonide and concomitant intake of low dose combination oral contraceptives.

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

Additional information on special populations:
No interaction studies specific to special populations have been conducted.

Pediatric population
Interaction studies have only been performed in adults.

Geriatric population:
No data available.

4.6. Fertility, pregnancy and lactation
General recommendation
Pregnancy category: B

Women of child-bearing potential / Birth control (Contraception)
High plasma concentrations and enhanced effects of corticosteroids are observed in women using contraceptive steroids or estrogens, but no effects have been observed with concomitant administration of budesonide and low-dose combination oral contraceptives.

Pregnancy
Animal studies of inhaled budesonide are insufficient for effects on pregnancy/and-or/embryonic/ fetal development/and-or/parturition/and-or postnatal development (see section 5.3).

The potential risk for humans is unknown.

Caution should be exercised when administered to pregnant women.

Most results from prospective epidemiological studies and worldwide postmarketing data have not been able to detect an increased risk for adverse effects for the fetus and newborn child from the use of inhaled budesonide during pregnancy. In animal studies, glucocorticosteroids have been shown to induce malformations (see section 5.3).

This is not likely to be relevant for humans given recommended doses, but therapy with inhaled budesonide should be regularly reviewed and maintained at the lowest effective dose. It is important for both fetus 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 fetus.

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

Breast-feeding
Budesonide is excreted in breast milk. However, at therapeutic doses of MAXAIR no effects on the breast-fed child are anticipated. MAXAIR 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 pharmacokinetic properties within the therapeutic dosage intervals after nasal, inhaled, oral and rectal administrations, at therapeutic doses of budesonide, exposure to the breast-fed child is anticipated to be low.

4.7. Effects on ability to drive and use machines
MAXAIR does not affect the ability to drive and use machines.

4.8. Undesirable effects
Based on clinical trials, literature records, and post-marketing experience, the following side effects may occur:

Undesirable effects are grouped by frequency using the following classification:
Very common (≥1/10); common (≥1/100 to <1/10); uncommon (≥1/1,000 to < 1/100); rare (≥1/10,000 to <1/1,000), very rare (< 1/10,000), not known (cannot be estimated from the available data).

Infections and infestations
Common: Oropharyngeal candida infection, pneumonia (in COPD patients)

Immune system disorders
Rare: Immediate and delayed hypersensitivity reactions* including rash, contact dermatitis, urticaria, angioedema and anaphylactic reaction

Endocrine disorders
Rare: Signs and symptoms of systemic corticosteroid effects, including adrenal suppression and growth retardation **

Psychiatric disorders
Uncommon: Anxiety, depression
Rare: Psychomotor hyperactivity, sleep disorders, aggression, behavioral changes (predominantly in children)

Nervous system disorders
Uncommon: Tremor***

Eye disorders
Uncommon: Cataract, blurred vision (see section 4.4)
Not known: Glaucoma

Respiratory, thoracic and mediastinal disorders
Common: Cough, hoarseness, throat irritation
Rare: Bronchospasm, dysphonia, hoarseness****

Skin and subcutaneous tissue disorders
Rare: Bruising

Musculoskeletal and connective tissue disorders
Uncommon: Muscle spasm

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

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

Description of selected adverse reactions
The candida infection in the oropharynx is due to drug deposition. Advising the patient to rinse the mouth out with water after each dosing will minimize the risk.

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

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

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

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

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

Reporting of suspected adverse reactions
Reporting suspected adverse reactions after authorization 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 in accordance with local requirements.

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

5. PHARMACOLOGICAL PROPERTIES

5.1. Pharmacodynamic properties

Pharmacotherapeutic group: Other drugs for obstructive airway diseases (inhalants)
ATC Code: RO3BA02

Budesonide is a glucocorticosteroid which possesses a strong local anti-inflammatory action.

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

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

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

Onset of effect
After a single dose of orally inhaled budesonide, delivered via dry powder inhaler, improvement of the lung function is achieved within a few hours. After therapeutic use of orally inhaled budesonide delivered via dry powder inhaler, maximum benefit may be achieved for up to 4 weeks, while improvement in lung function has been shown to occur within 2 days of initiation of therapy.

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

Exacerbation of asthma
Inhaled budesonide administered once or twice daily has been shown to effectively prevent

exacerbations of asthma in both children and adults.

Exercise-induced asthma
Budesonide treatment, administered once or twice daily via inhalation, has been effective in preventing exercise-induced bronchoconstriction.

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

Influence on plasma cortisol concentration
Studies with budesonide in healthy volunteers have shown a dose-proportional effect on plasma and urinary cortisol levels. At recommended doses, budesonide has a significantly less effect on adrenal function than 10 mg of prednisolone, as demonstrated by the budesonide test.

Pediatric population
Clinical – asthma
The efficacy of budesonide has been evaluated in a large number of studies, and it has been shown that budesonide is effective both in adults and children as once- or twice-daily medication for prophylactic treatment of persistent asthma. Some examples of representative studies are given below.

Clinical – croup
A number of studies in children with croup have compared budesonide with placebo. Examples of representative studies evaluating the use of budesonide for the treatment of children with croup are given below.

Efficacy in children with mild to moderate croup
A randomized, double-blind placebo-controlled trial in 87 children (aged 7 months to 9 years), admitted to hospital with a clinical diagnosis of croup, was conducted to determine whether budesonide improves croup symptom scores or shortens the duration of stay in hospital. An initial dose of budesonide (2 mg) or placebo was given followed by either 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 symptom score above 3. There was also a 33% reduction in the length of stay.

Efficacy in children with moderate to severe croup
A randomized, double-blind, placebo-controlled study compared the efficacy of budesonide and placebo in the treatment of croup in 83 infants and children (aged 6 months to 8 years) admitted to hospital for croup. Patients received either budesonide 2 mg or placebo every 12 h for a maximum of 36 h or until discharge from hospital. The total croup symptom score was assessed at 0, 2, 6, 12, 24, 36 and 48 hours after the initial dose. At 2 hours, both the budesonide and placebo groups showed a similar improvement in croup symptom score, with no statistically significant difference between the groups. By 6 hours, the croup symptom score in the budesonide 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

General properties

Absorption:

In adults the systemic availability of budesonide following administration of budesonide via a jet nebulizer is approximately 15% of the nominal dose and 40% to 70% of the dose delivered to the patients. A minor fraction of the systemically available drug comes from swallowed drug.

The maximal plasma concentration, occurring about 10 to 30 min after start of nebulization is approximately 4 nmol/L after a single dose of 2 mg.

Distribution:

It 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 CYP3A4, 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 intravenous dosing averages 2 - 3 hours.

Linearity / Non-linearity

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

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

Characteristics in patients

Renal impairment:

No dosage adjustment is required in patients with renal impairment.

Hepatic impairment:

Decreased liver function may affect the elimination of corticosteroids. However, plasma clearance of intravenously administered budesonide is similar in patients with cirrhosis and in healthy subjects. In cases of reduced liver function, the systemic availability of orally administered budesonide is increased due to decreased first-pass metabolism. As no data are available for inhaled budesonide, its clinical relevance for treatment with budesonide is unknown; however, increased plasma levels and therefore an increased risk for systemic adverse effects can be expected.

Children:

In 4-6 years old asthmatic children, the systemic availability of budesonide, following administration of budesonide via a jet nebulizer (Pari LC Jet Plus with Pari Master compressor) is approximately 6% of the nominal dose and 26% of the dose delivered to the patients. The systemic availability in children is about half of that in healthy adults. The maximal plasma concentration, occurring approximately 20 min after start of nebulization is approximately 2.4 nmol/L in 4-6 years old asthmatic children after a 1 mg dose.

Budesonide has a systemic clearance of approximately 0.5 L/min in 4-6 years old asthmatic children. Per kg body weight children have a clearance which is approximately 50% greater than in adults. The terminal half-life of budesonide after inhalation is approximately 2.3 hours in asthmatic children. This is about the same as in healthy adults.

The exposure (C_{max} and AUC) of budesonide following administration of a single 1 mg dose by nebulization to 4 - 6 year old children is comparable to that in healthy adults given the same delivered dose by the same nebulizer system.

5.3. Preclinical safety data

The acute toxicity of budesonide is low and of the same order of magnitude and type as that of the reference glucocorticosteroids studied (beclomethasone dipropionate, fluocinolone acetonide).

Results from subacute and chronic toxicity studies show that the systemic effects of budesonide are less severe than, or similar to, those observed after administration of other glucocorticosteroids, e.g. decreased body-weight gain and atrophy of lymphoid tissues and adrenal cortex.

An increased incidence of brain gliomas in male rats, in a carcinogenicity study, could not be verified in a repeat study in which the incidence of gliomas did not differ between any of the groups on active treatment (budesonide, prednisolone, triamcinolone acetonide) and the control groups.

Liver changes (primary hepatocellular neoplasms) found in male rats in the original carcinogenicity study were noted again in the repeat study with budesonide, as well as with the reference glucocorticosteroids. These effects are most probably related to a receptor effect and thus represent a class effect.

Available clinical experience shows that there are no indications that budesonide, or other glucocorticosteroids, induce brain gliomas or primary hepatocellular neoplasms in man.

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

Animal studies have also identified an involvement of excess prenatal glucocorticosteroids, in increased risk for intrauterine growth retardation, adult cardiovascular disease and permanent changes in glucocorticoid receptor density, neurotransmitter turnover and behavior at exposures below the teratogenic dose range.

6. PHARMACEUTICAL PARTICULARS

6.1. List of excipients

Sodium chloride
Disodium edetate
Sodium citrate dihydrate

Polysorbate 80
Citric acid monohydrate
Water for injections

6.2. Incompatibilities
There is no known incompatibility. The products with proven compatibility are presented in the section "4.2 Posology and method of administration".

6.3. Shelf life
24 months.

6.4. Special precautions for storage
Store at room temperature below 25°C. The product should be stored in sachets in an upright position and protected from light.
After opening the sachets, the nebules in it should be used within 3 months.
Vials are for single-use only. Any unused portion should be discarded within 12 hours. Please note that if only 1 ml is used, the remaining contents will not remain sterile.

6.5. Nature and contents of container
Available in 2 mL, transparent, low-density polyethylene, single-use vials and sachets.
Each box contains 4 sachets and each sachet contains 5 single-use vials.

6.6. Special precautions for disposal and other handling
Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

7. MARKETING AUTHORIZATION HOLDER
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8. MARKETING AUTHORIZATION NUMBER
2018/517

9. DATE OF FIRST AUTHORIZATION / RENEWAL OF THE AUTHORIZATION
Date of first authorization: 21.09.2018
Date of renewal:

10. DATE OF REVISION OF THE TEXT