Budesonide Pressurised Inhalation

1. Name of the Product

Budesonide Pressurised Inhalation

2. Qualitative and quantitative composition

Each metered actuation contains 200 micrograms of budesonide from the valve and delivers 165 mcg of budesonide from the actuator, and each canister provides 200 deliveries

3. Pharmaceutical form

Pressurised inhalation.

4. Clinical particulars

4.1 Therapeutic indications

Treatment of mild, moderate, and severe persistent asthma.

4.2 Dosage and administration

Posology should be adjusted according to the single patient and relating to severity of asthma and therapy phase.

When transferring a patient to this product from other inhalation devices, the treatment should be individualised.

The previous active substance, dose regimen, and method of delivery should be considered.

Adults and adolescents: in case of severe asthma, at the start of therapy with inhaled corticoids or when reducing or discontinuing oral corticosteroid therapy, the recommended dosage is 200 micrograms (1 puff) 2-4 times daily. During the periods of severe asthma, the daily posology can be increased up to a maximum of 1600 micrograms. The maintenance dose is individual, and should be the minimum dose allowing suppression of symptoms: 200 micrograms (1 puff) per day are generally sufficient.

Children from 6 to 12 years of age: generally 200 micrograms (1 puff) daily. If necessary, dosage can be increased up to 400 mcg daily. The age limit depends on the possibility of properly using the product. The dose should be reduced to the minimum needed to maintain good asthma control.

Patients not treated with corticosteroids: the therapeutic effect of budesonide generally occurs within 10 days of therapy start: however, for patients with abundant bronchial secretion, such as to hinder mucosal absorption of the active ingredient, short-term concomitant treatment (about two weeks) with oral corticosteroids is recommended. This should be started at full dosage and reduced gradually until maintenance with this product only is achieved. Asthma exacerbations due to bacterial infections should be treated with antibiotics while increasing this product.

Patients treated with corticosteroids: switch from oral corticosteroidal therapy to treatment with this product requires special attention, due to the slow reactivation of those hypothalamic functions impaired by the prolonged oral corticosteroidal therapy. Introducing this product into therapy should occur when the patient is relatively stabilised. This product will have to be administered concomitantly with oral corticosteroids for about 10 days; then this should be gradually reduced, down to the minimum dose that, combined with this product, ensures a stable response. In many cases it is possible to completely withdraw the oral therapy, whilst in some patients it will be necessary to continue treatment with a minimum oral corticosteroids dose. Nevertheless, in some cases when switching from oral therapy to this product, the systemic steroidal effect may decrease, with occurrence of rhinitis,

eczema, headache, muscular and articular pain, and, rarely, of nausea and vomiting. Should these events occur, the physician shall evaluate the opportunity to maintain the patient on inhalation therapy. It might take a long time to recover the physiological production of natural corticosteroids, and in some conditions, such as physical stress due to severe infections, injuries or surgery, it may be necessary to combine this product with oral corticosteroidal therapy; also in case of asthma exacerbations, especially when associated with increased viscosity and formation of mucus plugs, a short-term concomitant treatment with oral steroids may be necessary. It is of utmost importance that the patient follows the instructions for use.

4.3 Contraindications

Hypersensitivity to budesonide or any of the excipients.

4.4 Special warnings and precautions

It is not intended for rapid relief of acute episodes of asthma where an inhaled short-acting bronchodilator is required.

Patients should be instructed about the correct use of the inhaler.

It provides a prophylactic therapy of the asthmatic disease: therefore, it should be administered regularly at the prescribed doses as long as directed by the physician and should not be stopped abruptly. In case of gastrointestinal ulcer, strict medical surveillance is advisable throughout therapy duration.

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 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.

During transfer from oral therapy to inhaled budesonide symptoms may appear that had previously been suppressed by systemic treatment with glucocorticosteroids, with occurrence of rhinitis, eczema, headache, muscular and articular pain, and, rarely, of nausea and vomiting. 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.

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.

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

When despite a well monitored treatment, an acute episode of dyspnoea occurs, 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.

Systemic effects of inhaled corticosteroid may occur, particularly at high doses prescribed for prolonged periods. These effects are much less likely to occur with inhaled 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 and glaucoma and more rarely, a range of psycological or behavioural effects including psychomotor hyperactivity, sleep disorders, anxiety, depression or aggression (particularly in children).

Therefore, it is important that the patient is reviewed regularly, and the dose of inhaled corticosteroid is reduced to the lowest dose at which effective control of asthma is maintained.

Very rare cases of acute adrenal crises occurred in young patients exposed to doses higher than those recommended (about 1000 mcg/day) for prolonged periods (several months or years). Adrenal insufficiency symptoms are initially aspecific and include anorexia, abdominal pain, weight loss, tiredness, headache, nausea, vomiting; specific symptoms occurring with inhaled corticosteroids also include hypoglycemia with impaired consciousness and/or seizures. Situations that might potentially determine an adrenal crisis are: traumas, surgery, infections and rapid reduction of dosage.

Patients receiving high doses should be strictly monitored and their dose gradually reduced. Monitoring the adrenal reserve may also be necessary.

It is recommended that the height of children receiving prolonged treatment with inhaled corticosteroids is regularly monitored. In case of growth retardation, therapy should be reviewed in order to reduce the glucocorticoid dosage to the lowest possible 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).To reduce the risk of oral candidiasis and hoarseness patients should be advised to rinse out the mouth properly or brush the teeth after each administration of inhaled corticosteroid.

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

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

Reduced liver function affects the elimination of corticosteroids, causing lower elimination rate and higher systemic exposure. Be aware of possible systemic side effects. HPA axis function in these patients should be monitored at regular intervals.

Concomitant treatment with ketoconazole and itraconazole 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).

This product contains small amounts of ethanol (less than 10 mg per dose) and glycerol. These amounts are negligible and do not represent any risk for the patient at usual therapeutic doses.

4.5 Interactions

In patients undergoing treatment with oral corticosteroids, switching to the use of only budesonide by inhalation should occur gradually. After stabilising the patient, budesonide is combined to the therapy and oral corticosteroid dose is progressively reduced, while regularly assessing the patient's general conditions. This is necessary due to the slow reactivation of adrenal function, compromised by prolonged use of oral corticosteroids.

The metabolism of budesonide is primarily mediated by CYP3A4. Inhibitors of this enzyme, eg, ketoconazole and itraconazole, can therefore increase systemic exposure to budesonide several times. Since there is no data to support a dosage recommendation, the combination should be avoided. If this is not possible, the period between treatments should be as long as possible and a reduction of the budesonide dose could also be considered.

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

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

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

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.

In animal studies glucocorticosteroids have been shown to induce malformations. This is not likely to be relevant for humans given recommended dose.

The lowest effective dose of budesonide needed to maintain adequate asthma control should be used.

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 microg 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

No effects on ability to drive and use machines have been observed.

4.8 Undesirable effects

Infections and infestations: Oropharyngeal candidiasis

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

Psychiatric disorders: Psychotic disorder, restlessness nervousness, depression and behavioural changes (predominantly in children)

Nervous system disorders: Dysgeusia

Respiratory, Thoracic & Mediastinal Disorders: Cough, hoarseness, throat irritation

Gastrointestinal disorders: Dysphagia, Nausea, glossodynia, stomatitis, dry mouth

Skin and subcutaneous tissue disorders: Skin atrophy, pruritus, erythema, bruising,

Musculoskeletal and connective tissue disorders: Back pain

General disorders and administration site conditions: Irritability

Investigations: Bone density decreased

4.9 Overdosage

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

Symptoms of overdose

The acute toxicity of budesonide is low. Chronic use in excessive doses can result in systemic glucocorticosteroid effects, such as increased susceptibility to infection, hypercorticism and adrenal suppression. Atrophy of the adrenal cortex can occur and the ability to adapt to stress can be impaired.

Therapeutic management of overdose

For acute overdosage, no special emergency action needs to be taken. The treatment with inhaled budesonide should be continued at the recommended dose to control asthma. HPA axis function recovers in a few days.ism and adrenal suppression, may appear.

5. Pharmacological properties

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Other drugs for obstructive airway diseases, inhalants Glucocorticoids. ATC code: R03B A02

Budesonide is a synthetic, non-halogenated corticosteroid for topic inhalation use only, endowed with potent antiinflammatory activity and, at the recommended doses, devoid of systemic effects or of activity inhibiting the adrenocortical function.

Improvement in asthma control following inhalation of budesonide can occur within 24 hours

of commencing the treatment although maximum benefit is achieved after a few weeks of continuous treatment.

Mechanism of action

The precise mechanism of corticosteroid actions on inflammation in asthma is not known. Budesonide has been shown to have a wide range of inhibitory effects against several cell types (e.g., eosinophils, macrophages, mast cells, lymphocytes, and neutrophils) and mediators (e.g., cytokines, leukotrienes, eicosanoids, and histamine) involved in allergic and non-allergic respiratory inflammation. These actions of budesonide may contribute to its efficacy in asthma resulting in a reduction of hypersecretion, hyperreactivity and inhibiting the occurrence of bronchospasm. In patients with hyperreactivity the administration of budesonide reduces airway reactivity after stimulation with histamine or methacholine.

5.2 Pharmacokinetic properties

Budesonide is provided as a mixture of two epimers (22R and 22S). In glucocorticoid receptor affinity studies, the 22R form is twice as active as the 22S epimer. These two forms of budesonide do not interconvert.

Absorption and distribution

Budesonide is a moderately lipophilic drug with high affinity for the glucocorticoid receptors that is rapidly absorbed by the airway mucosa.

Approximately 20 minutes after administration by inhalation budesonide forms esters with the intracellular fatty acids via a reversible conjugation process that is able to prolong the local antiinflammatory activity at pulmonary level.

The quantity absorbed into circulation, partly through the lungs and partly swallowed by oral route, varies between 10 and 30% and is rapidly and widely metabolised at the hepatic level to yield poorly active metabolites. Bonding to plasma proteins is 88% and the distribution volume is high.

Biotransformation

Budesonide is mainly eliminated by metabolism. Budesonide is rapidly and extensively metabolised in liver via cytochrome P4503A4 to two major metabolites. The in vitro glucocorticoid activity of these metabolites is less than 1% of that of the parent compound. Negligible metabolic inactivation has been observed in human lung and serum preparations.

Elimination

Budesonide is excreted in urine and faeces as conjugated and non-conjugated metabolites.

The elimination half-life after inhalation is approximately 3 hours.

Special patient populations

The exposure to budesonide may be increased in patients with liver disease. In children the elimination half-life from plasma is markedly lower than in adults.

5.3 Preclinical safety data

The toxicity observed in animal studies with budesonide was associated with exaggerated pharmacological activity.

No genotoxic effects of budesonide have been observed in conventional genotoxicity tests.

In animal reproduction studies, corticosteroids such as budesonide have been shown to induce malformations (cleft palate, skeletal malformations). Similar effects are considered unlikely to occur in humans at therapeutic doses.

Specific tolerability studies by inhalation proved the good local tolerability of this budesonide formulation propelled with HFA 134a.

The HFA 134a propellant did not show any toxic effects, even at concentrations far higher than those recommended for human use, when administered by daily nebulisation to different animal species for up to two years.

Studies on the effects of the propellant HFA 134a on reproductive function and embryofoetal development in animals failed to detect any clinically important adverse events. It is therefore unlikely that adverse events can occur in humans.

6. Pharmaceutical particulars

6.1 list of excipients

Norflurane (HFA-134a)

6.2 Incompatibilites

Not applicable.

6.3 Shelf life

24 months.

6.4 Special precautions for storage

Store below 30 °C. Keep in airtight container.

6.5 Nature and contents of container

The product is packaged in a pressurized aluminium canister fitted with a metering dose valve.

6.6 Special precautions for disposal and other handling

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