

“פורמט עלון זה נקבע ע”י משרד הבריאות ותוכנו נבדק ואושר”. עלון אושר באוגוסט 2009  
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## 1. NAME OF THE MEDICINAL PRODUCT

Budicort<sup>®</sup> Inhaler

200 micrograms per actuation, pressurised inhalation suspension

## 2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each metered dose (ex-valve)/actuation contains budesonide 200 micrograms.

For excipients, see 6.1.

## 3. PHARMACEUTICAL FORM

Budicort Inhaler is a pressurised inhalation suspension. The suspension is delivered via a pressurised metered dose inhaler (pMDI).

Budicort Inhaler may also be administered via Nebuchamber<sup>®</sup>.

## 4. CLINICAL PARTICULARS

### 4.1 Therapeutic indications

Bronchial asthma.

### 4.2 Posology and method of administration

For inhalation use.

Adults, including the elderly: 200 micrograms twice daily, in the morning and in the evening. During periods of severe asthma, the daily dosage can be increased up to 1600 micrograms.

In patients whose asthma is well controlled, the daily dose may be reduced below 400 micrograms, but should not go below 200 micrograms.

The dose should be reduced to the minimum needed to maintain good asthma control.

Children 2 – 12 years of age: 200 to 800 micrograms daily.

**Budicort Inhaler is not recommended for use in children less than 2 years of age.**

The dose should be reduced to the minimum needed to maintain good asthma control.

### **Patients maintained on oral glucocorticosteroids**

Budicort Inhaler may permit replacement or significant reduction in the dosage of oral glucocorticosteroids while maintaining asthma control. For further information on the withdrawal of oral corticosteroids, see section 4.4 (*Special warnings and precautions for use*).

### **Method of Administration**

#### **Instructions for the correct use of Budicort Inhaler:**

Note: It is important to instruct the patient to:

Carefully read the detailed instructions for use and refer to the accompanying pictograms in the patient information leaflet that is packed with each inhaler.

Take his/her time when using the inhaler and not to rush through the individual steps.

To practise using the inhaler in front of the mirror. Advise the patient that if any mist is seen coming from the top of the inhaler or from the mouthpiece it may mean that he/she has not inhaled the medicine properly.

Shake the inhaler thoroughly for a few seconds to mix the contents of the inhaler properly.

Prime the inhaler by actuating it twice into the air when the inhaler is new, if it has been dropped, or when it has not been used for more than 7 days.

Place the mouthpiece in the mouth. While breathing in slowly and deeply, press the canister firmly to release the medication. Advise the patient that he/she may need to use both hands to operate the inhaler. Continue to breathe in and hold the breath for as long as is comfortable.

Remove the inhaler from the mouth before breathing out; the patient must be advised that he/she must not breathe out through the inhaler.

If a second or subsequent actuation is required the patient should be advised to wait for about half a minute and then replace the mouthpiece in the mouth and repeat the instructions at the preceding two bullet points, the sixth and seventh bullet points as listed.

Rinse the mouth out with water after inhaling the prescribed dose to minimise the risk of oropharyngeal thrush.

Clean the mouthpiece of the inhaler regularly, at least once a week. Remove the dust cap and the aerosol canister. Clean the plastic actuator and dust cap with a dry cloth or tissue. Refer to the detailed instructions for cleaning in the Patient Information Leaflet, which is packed with each inhaler. Advise the patient that the metal aerosol canister should **not** be put into water or be cleaned with water.

Always store Budicort Inhaler so that it stands upright on its brown plastic base (with the valve downwards).

The use of Budicort Inhaler with the NebuChamber™ spacer device is recommended to enable patients with difficulty in co-ordinating inhalation with actuation, such as infants, young children, the poorly co-operative or the elderly, to derive greater therapeutic benefit. The mouthpiece of Budicort Inhaler fits directly into the NebuChamber spacer device. Budicort Inhaler should only be used with the NebuChamber spacer device, it should NOT be used with any other spacer device as an alternative device may alter the pulmonary deposition of budesonide.

A spacer device should always be available together with a pressurised metered dose inhaler when a pressurised metered dose inhaler is prescribed for use by a child.

Instructions for the correct use of Budicort Inhaler with the NebuChamber Spacer device:

Note: It is important to instruct the patient to:

Carefully read the instructions for use in the patient information leaflet, which is packed with each inhaler.

Carefully read the instructions for use in the instruction leaflet, which is packed with each spacer device.

On actuation of the aerosol, the dose is released into the inhalation chamber. The inhalation chamber is then emptied by two slow deep breaths. Young children may need to breathe 5 - 10 times through the mouthpiece. For further doses, the procedure is repeated. It is important to explain that when a small child is using the NebuChamber spacer device a parent or carer should hold and support the spacer device in the child's mouth to ensure that the child breathes through the spacer device properly. For young children who are unable to breathe through the mouthpiece, a face mask can be used. Compatible face masks are available separately and care should be taken to ensure a good fit is achieved.

### **4.3 Contraindications**

History of hypersensitivity to budesonide or any of the excipients.  
Active pulmonary tuberculosis.

Special care is needed in patients with quiescent pulmonary tuberculosis and with fungal and viral infections in the airways.

### **4.4 Special warnings and special precautions for use**

Patients not dependent on steroids: Treatment with the recommended doses of Budesonide usually gives a therapeutic benefit within 7 days. However, certain patients may have an excessive collection of mucus secretion in the bronchi. In these

cases, a short course of oral corticosteroids (usually 1 to 2 weeks) should be given in addition to the aerosol. After the course of the oral drug, the inhaler alone should be sufficient therapy.

Steroid-dependent patients: Transfer of patients on oral steroids to treatment with Budicort Inhaler demands special care, mainly due to the slow restitution of the disturbed hypothalamic-pituitary adrenocortical axis function, caused by extended treatment with oral corticosteroids. When the Budicort Inhaler treatment is initiated, the patient should be in a relatively stable phase. A high dose of budesonide, in combination with the previously used oral steroid dose, should be given for about 10 days.

The down titration dose should be selected at the discretion of the physician, based on the patient's disease and former steroid intake. For example, a down titration with 5 mg prednisolone per day, on a weekly basis; this reduction will mean that a daily dose of 20 mg per day would be reduced to 15 mg per day in the first week, 10 mg per day in the second week etc. The oral dose is thus reduced to the lowest level that, in combination with budesonide, provides maintained or improved asthma control.

In many cases it may be possible to completely substitute the oral steroid with inhaled budesonide; however some patients may have to be maintained on a low dose of oral steroid together with inhaled budesonide.

During the withdrawal of oral steroids some patients may experience uneasiness and may feel generally unwell in a non-specific way even though respiratory function is maintained or improved. Patients should be encouraged to continue with inhaled budesonide whilst withdrawing the oral steroid unless there are clinical signs to indicate the contrary.

Patients who have previously been dependent on oral steroids may, as a result of prolonged systemic steroid therapy, experience the effects of impaired adrenal function. Recovery may take a considerable amount of time after cessation of oral steroid therapy and hence oral steroid-dependent patients transferred to inhaled budesonide may remain at risk from impaired adrenal function for some considerable time. In such circumstances HPA axis function should be monitored regularly. These patients should be instructed to carry a steroid warning card indicating their needs.

Prolonged treatment with high doses of inhaled corticosteroids, particularly higher than recommended doses, may also result in clinically significant adrenal suppression. Therefore additional systemic corticosteroid cover should be considered during periods of stress such as severe infections or elective surgery. Such patients should be instructed to carry a steroid warning card indicating their needs (See also Section 4.8. *Undesirable effects*). Rapid reduction in the dose of steroids can induce acute adrenal crisis. Symptoms and signs which might be seen in acute adrenal crisis may be somewhat vague but may include anorexia, abdominal pain, weight loss, tiredness, headache, nausea, vomiting, decreased level of consciousness, seizures, hypotension and hypoglycaemia.

Treatment with supplementary systemic steroids or inhaled budesonide should not be stopped abruptly.

During transfer from oral therapy to Budicort Inhaler, a generally lower systemic steroid 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.

Exacerbations of asthma caused by bacterial infections are usually controlled by appropriate antibiotic treatment and possibly increasing the budesonide dosage or, if necessary, by giving systemic steroids.

As with other inhalation therapy paradoxical bronchospasm may occur with an immediate increase in wheezing and shortness of breath after dosing. Paradoxical bronchospasm responds to a rapid-acting inhaled bronchodilator and should be treated straightaway. Budicort Inhaler should be discontinued immediately, the patient should be assessed and an alternative therapy instituted if necessary.

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 and glaucoma. It is important, therefore, that the patient is reviewed regularly and 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 be 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.

Budicort Inhaler is not intended for rapid relief of acute episodes of asthma or symptoms of asthma. In these situations an inhaled short-acting bronchodilator is required. Patients should be advised to have such 'rescue' medication with them at all times.

If patients find short-acting bronchodilator treatment ineffective, or they need more inhalations than usual and respiratory symptoms persist, 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, the addition of a long-acting beta agonist or a course of oral glucocorticosteroids.

Patients should be reminded of the importance of taking prophylactic therapy regularly, even when they are asymptomatic. Patients should also be reminded of the risk of oropharyngeal Candida infection, due to drug deposition in the oropharynx. Advising the patient to rinse the mouth out with water after each dose will minimise the risk. Oropharyngeal Candida infection usually responds to topical anti-fungal treatment without the need to discontinue the inhaled corticosteroid.

Patients should be instructed in the proper use of their inhaler and their technique should be checked to ensure that the patient can synchronise aerosol actuation with inspiration of breath to obtain optimum delivery of the inhaled drug to the lungs.

Reduced liver function may affect the elimination of glucocorticosteroids. 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 Budicort 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.

In vivo studies have shown that oral administration of ketoconazole and itraconazole (known inhibitors of CYP3A4 activity in the liver and in the intestinal mucosa) causes an increase in the systemic exposure to budesonide. Concomitant treatment with ketoconazole and itraconazole or other potent CYP3A4 inhibitors should be avoided (see section 4.5 Interactions). If this is not possible, the time interval between administration of the interacting drugs should be as long as possible. A reduction in the dose of budesonide should also be considered.

#### **4.5 Interactions with other medicinal products and other forms of interaction**

The metabolism of budesonide is primarily mediated by CYP3A4, one of the cytochrome p450 enzymes. Inhibitors of this enzyme, e.g. ketoconazole and itraconazole, can therefore increase systemic exposure to budesonide, (see Section 4.4 Special Warnings and Special Precautions for Use and Section 5.2 Pharmacokinetic Properties). Other potent inhibitors of CYP3A4 are also likely to markedly increase plasma levels of budesonide.

#### **4.6 Pregnancy and lactation**

There is no experience with or evidence of safety of propellant HFA 134a in human pregnancy or lactation. However studies of the effect of HFA 134a on reproductive function and embryofetal development in animals have revealed no clinically relevant adverse effects.

##### **Pregnancy**

Results from a large prospective epidemiological study and from worldwide post marketing experience indicate no adverse effects of inhaled budesonide during pregnancy on the health of the fetus / newborn child. Animal studies have shown

reproductive toxicity (see Section 5.3 *Preclinical safety data*). The potential risk for humans is unknown.

There are no relevant clinical data on the use of Budicort Inhaler in human pregnancy.

Administration of Budicort Inhaler during pregnancy requires that the benefits for the mother be weighed against the risks for the fetus. Budicort Inhaler should only be used during pregnancy if the expected benefits outweigh the potential risks.

### **Lactation**

There is no information regarding the passage of budesonide into breast milk.

There are no relevant clinical data on the use of Budicort Inhaler during lactation in humans. Administration of Budicort Inhaler to women who are breast-feeding requires careful consideration. As it is not known whether budesonide has any harmful effects on the neonate the use of budesonide formulated with propellant HFA 134a (as Budicort Inhaler) should only be considered in situations where it is felt that the expected benefits to the mother will outweigh any potential risks to the neonate.

#### 4.7 Effects on ability to drive and use machines

Budicort Inhaler has no or negligible influence on the ability to drive and use machines.

#### 4.8 Undesirable effects

Clinical trials, literature reports and post-marketing experience of orally inhaled budesonide suggest that the following adverse drug reactions may occur:

Common

(>1/100, <1/10)

- Mild irritation in the throat
- Candida infection in the oropharynx
- Hoarseness
- Coughing

Rare

(>1/10 000, <1/1 000)

- Nervousness, restlessness, depression, behavioural disturbances
- Immediate and delayed hypersensitivity reactions including rash, contact dermatitis, urticaria, angioedema and bronchospasm and anaphylactic reaction.
- Skin bruising

Candida infection in the oropharynx is due to drug deposition. Advising the patient to rinse the mouth out with water after each dosing will minimise the risk. The incidence should be less with the NebuChamber<sup>®</sup> spacer device since this reduces oral deposition.

As with other inhalation therapy, paradoxical bronchospasm may occur, with an immediate increase in wheezing and shortness of breath after dosing. Paradoxical bronchospasm responds to a rapid-acting inhaled bronchodilator and should be treated straightaway. Budicort Inhaler should be discontinued immediately, the patient should be assessed and an alternative therapy instituted if necessary.

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 and glaucoma. Increased

susceptibility to infections and impairment of the ability to adapt to stress may also occur. Effects is probably dependent on dose, exposure time, concomitant and previous steroid exposure, and individual sensitivity.

Prolonged treatment with high doses of inhaled corticosteroids, particularly higher than recommended doses, may also result in clinically significant adrenal suppression. Therefore additional systemic corticosteroid cover should be considered during periods of stress, such as severe infections or elective surgery. Such patients should be instructed to carry a steroid warning card indicating their needs. (See also Section 4.4 *Special warnings and precautions for use*)

#### **4.9 Overdose**

The only harmful effect that follows inhalation of large amounts of the drug over a short period is suppression of hypothalamic-pituitary-adrenal (HPA) axis function. No special emergency action needs to be taken. Treatment with Budicort Inhaler should be continued at the recommended dose to control the asthma.

### **5. PHARMACOLOGICAL PROPERTIES**

#### **5.1 Pharmacodynamic properties**

Budesonide is a glucocorticosteroid which possesses a high local anti-inflammatory action, with a lower incidence and severity of adverse effects than those seen with oral corticosteroids.

Pharmacotherapeutic group: Other drugs for obstructive airway diseases, inhalants, glucocorticoids. ATC Code: R03B A02.

#### **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, improvement in lung function has been shown to occur within 2 days of initiation of treatment, although maximum benefit may not be achieved for up to 4 weeks.

### **Airway reactivity**

Budesonide has also been shown to decrease airway reactivity to histamine and methacholine in hyper-reactive patients.

### **Exercise-induced asthma**

Therapy with inhaled budesonide has effectively been used for prevention of exercise-induced asthma.

### **Growth**

Limited data from long term studies suggest that most children and adolescents treated with inhaled budesonide ultimately achieve their adult target height. However, an initial small but transient reduction in growth (approximately 1 cm) has been observed. This generally occurs within the first year of treatment (see section 4.4).

### **HPA axis function**

Studies in healthy volunteers with inhaled budesonide (administered as a dry powder via Turbohaler) have shown dose-related effects on plasma and urinary cortisol. At recommended doses, Budicort Turbohaler, causes less effect on the adrenal function than prednisolone 10mg, as shown by ACTH tests.

## **5.2 Pharmacokinetic properties**

After inhalation of budesonide via pressurised metered dose inhaler, approximately 10% to 15% of the metered dose is deposited in the lungs.

The maximal plasma concentration after oral inhalation of a single dose of 800 or 1600 micrograms budesonide was 1.32 and 2.41 nmol/L respectively, and was reached after about 40 minutes.

Budesonide undergoes an extensive degree (approximately 90%) of biotransformation in the liver, to metabolites of low glucocorticosteroid activity.

The glucocorticosteroid activity of the major metabolites, 6 $\beta$ -hydroxybudesonide and 16 $\alpha$ -hydroxyprednisolone, is less than 1% of that of budesonide. The metabolism of budesonide is primarily mediated by CYP3A4, one of the cytochrome p450 enzymes.

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.

### **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 glucocorticoids studied (beclomethasone dipropionate, flucinolone 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 the 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 no indication 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 behaviour at exposures below the teratogenic dose range.

The safe use of norflurane has been fully evaluated in preclinical studies. It is well accepted and used in several pressurised metered dose inhalers, and is essentially non-toxic. Magnesium stearate has a history of safe use in man for many years, which supports the view that magnesium stearate is essentially biologically inert. The safe use of magnesium stearate for inhalation has been fully evaluated in preclinical studies. Inhalation toxicity studies conducted with magnesium stearate in rats (26 weeks) and dogs (4 weeks) did not show signs of toxicity up to doses about 490 and 11000 times

higher, respectively, than the maximum exposure achievable during the daily treatment with the new formulation. Furthermore, toxicity studies carried out using Budicort pressurised metered dose inhaler have shown no evidence of any local or systemic toxicity or irritation attributable to the excipients.

## **6. PHARMACEUTICAL PARTICULARS**

### **6.1 List of excipients**

Norflurane (HFA 134a) - a CFC-free propellant  
Magnesium stearate.

### **6.2 Incompatibilities**

None known.

### **6.3 Special precautions for storage**

Do not store above 30°C.  
Always store Budicort Inhaler so that it stands upright on its brown plastic base (with the valve downwards).

The canister contains a pressurised liquid. Do not expose to temperatures higher than 50°C. Do not pierce the canister.

### **6.4 Nature and contents of container**

The immediate container is an aluminium can which is sealed with a metering valve.

The container is assembled with an actuator containing a mouthpiece. The actuator and the mouthpiece are made of polypropylene.

Each inhaler delivers 120 metered doses/actuations after initial priming.

### **6.5 Special precautions for disposal**

The canister should not be broken, punctured or burnt, even when apparently empty.

## **7. MANUFACTURER**

AstraZeneca AB, Sweden

Registration Holder and Importer - AstraZeneca Israel Ltd POB 4070, Raanana 43000