

Budenocort

Budesonide 200 µg and 400 µg per actuation

Presentation

Budenocort 200 is a breath actuated metered dose dry powder inhaler. It consists of a white to off-white powder filled into a Miat-Haler® device which consists of a light grey body with a dark brown screw closure which when opened shows the light grey inhaler. Each actuation of the inhaler provides 200 µg of budesonide with each inhaler containing sufficient product to provide either 100 or 200 actuations.

Budenocort 400 is a breath actuated metered dose dry powder inhaler. It consists of a white to off-white powder filled into a Miat-Haler® device which consists of a light grey body with a dark brown screw closure which when opened shows the light grey inhaler. Each actuation of the inhaler provides 400 µg of budesonide with each inhaler containing sufficient product to provide either 100 or 200 actuations.

Uses

Actions

Budesonide is a glucocorticosteroid with a high local anti-inflammatory effect.

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. The intrinsic potency of budesonide, measured as the affinity to the glucocorticoid receptor, is approximately 15 times higher than that of prednisolone.

A clinical study in asthmatics comparing inhaled and oral budesonide showed statistically significant evidence of efficacy with inhaled budesonide when compared with placebo. The therapeutic effect of conventional doses of inhaled budesonide may therefore be explained by its direct action on the respiratory tract.

Budesonide has shown anti-anaphylactic and anti-inflammatory effects in provocation studies in animals and patients, manifested as decreased bronchial obstruction in the immediate, as well as the late allergic reaction.

Exacerbations 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

Therapy with inhaled budesonide, administered once or twice daily, has been effective when used for prevention of exercise-induced asthma.

Airway reactivity

Budesonide decreases airway reactivity to, direct and indirect challenge in hyper-reactive patients.

HPA axis function

Inhaled budesonide administered as a dry powder at the recommended doses, causes significantly less effect on the adrenal function than prednisone 10 mg, as shown by ACTH tests. No clinically important change in plasma cortisol levels and the response to ACTH stimulation was seen when budesonide was administered in doses up to 1600 mcg daily for 3 months to adults and up to 800 mcg daily to children. Long-term follow-up for up to 52 weeks confirmed the lack of suppression of the HPA-axis. Studies in healthy volunteers with budesonide have shown dose-related effects on plasma and urinary cortisol.

Growth

Asthma as well as inhaled glucocorticosteroids may affect growth.

Effects of inhaled budesonide on growth have been investigated in numerous studies. Several studies have shown a decrease in growth velocity of approximately 1 cm during the first year of corticosteroid treatment, however, carefully controlled epidemiological studies and long term studies have shown that children and adolescents treated with inhaled budesonide ultimately achieve their adult target height.

In a five-year study of children 5-11 years of age, treated with budesonide (200 µg twice daily), a 1.1 cm reduction in growth compared to placebo seen at the end of one year did not increase further during the trial. By the end of the five year study period, children treated with budesonide and children treated with placebo had similar growth velocities and the projected final height was identical in both groups. In another study, 142 children age 3-13 (mean 8.7 years of age) treated for 3-13 years (mean 9.2 years) with orally inhaled budesonide (mean 412 µg/day, range 110-877 µg/day) did achieve their predicted final height. These final heights were similar to a group of 51 healthy non-asthmatic siblings of the treatment group who were never treated with budesonide.

Pharmacokinetics

Absorption

Approximately 25-30% of the metered dose is deposited in the lungs after inhalation which is about twice that provided by pressured aerosols.

The maximal plasma concentration after oral inhalation of a single dose of 800 µg budesonide is about 4 nmol/L, occurring within 30 minutes. Systemic availability of budesonide via inhaler has been estimated as 38% of the metered dose, of which only about 1/6 was derived from swallowed budesonide .

Distribution

Budesonide has a volume of distribution of approximately 3 L/kg . Plasma protein binding averages 85-90%.

Biotransformation

Budesonide undergoes extensive first pass metabolism (approx. 90%) to metabolites of low glucocorticosteroid activity. The glucocorticosteroid activity of the major metabolites, 6β-hydroxybudesonide and 16 α-hydroxyprednisolone, is less than 1% of that of budesonide. The metabolism of budesonide is primarily mediated by cytochrome P450 CYP3A

Elimination

Budesonide metabolites and their conjugates are excreted mainly via the kidneys. No unchanged budesonide has been detected in the urine. Budesonide has a high systemic clearance (approximately 1.2 L/min) with the plasma half-life after IV dosing averaging 2-3 hours.

Linearity

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

Children

Budenoside has a systematic clearance of approximately 0.5 L/min in 4-6 year old asthmatic children. Per kg bodyweight children have a clearance which is approximately 50% greater than in adults. The terminal half-life of budesonide in asthmatic children is about the same as in healthy adults being approximately 2.3 hours.

Indications

Bronchial asthma requiring maintenance treatment with glucocorticosteroids for control of the underlying airways inflammation.

Dosage and Administration

The dosage of Budenocort should be individualised. The recommended starting dose and highest recommended dose of Budenocort, based on prior asthma therapy, are:

| | Previous Therapy | Recommended starting dose | Highest recommended dose |
|-----------------------------------|------------------------------|---------------------------|--------------------------|
| Adults and the elderly | Nonsteroid treatment | 200-400 µg once daily | 800 µg twice daily |
| | Inhaled glucocorticosteroids | 200-800 µg once daily | 800 µg twice daily |
| | Oral glucocorticosteroids | 400-800 µg once daily | 800 µg twice daily |
| Children 6 years and above | Nonsteroid treatment | 200-400 µg once daily | 400 µg twice daily |
| | Inhaled glucocorticosteroids | 200-400 µg once daily | 400 µg twice daily |
| | Oral glucocorticosteroids | 200-400 µg twice daily | 400 µg twice daily |

In severe asthma and during exacerbations some patients may benefit from dividing the daily dose into 3-4 administrations per day.

Maintenance

It is desirable to titrate to the lowest effective maintenance dose once asthma control is achieved.

Maintenance dose range: Adults and elderly: 200-1600 µg daily
Children: 200-800 µg daily

Once Daily Dosing

The daily dose is usually divided into 1-2 administrations. Once daily dosing may be considered in adult and paediatric patients (from six years of age) with mild to moderate asthma, requiring a maintenance dose of 200 to 400 µg budesonide per day. Once daily administration, can be initiated in both non steroid treated patients and patients well-controlled by inhaled glucocorticosteroids. A once daily regimen of up to 800 µg may be used by patients already controlled on inhaled steroids (e.g. budesonide or beclomethasone dipropionate) administered twice daily. The patient should be transferred to once daily dosing at the same equivalent total daily dose. The dose should subsequently be reduced to the minimum needed to maintain good asthma control. The dose can be administered either morning or evening. If deterioration of asthma occurs, the frequency of dosing and the daily dose should be increased.

Onset of effect

Improvement in asthma control following inhaled administration of Budenocort can occur within 24 hours of initiation of treatment, although maximum benefit may not be achieved for 1 to 2 weeks (or longer) after starting treatment.

Instructions for correct use of Budenocort

Budenocort is presented in a device called the Miat-Haler®, an inspiratory flow-driven device which when the patient activates the device and inhales through the mouthpiece, the budesonide will follow the inspired air into the airways.

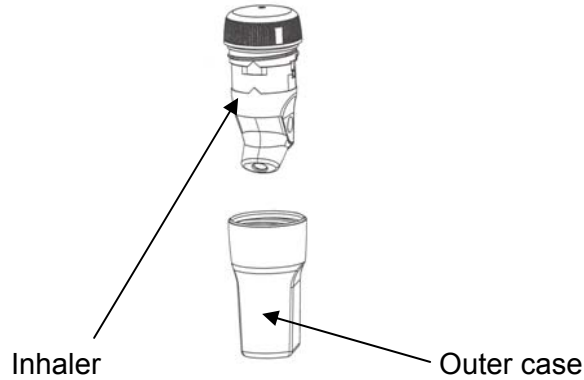
The inhaler is packed in an aluminium blister in the outer carton. The blister should not be opened or the inhaler removed from it until it is necessary to use the inhaler. The inhaler may rattle when shaken. This is not a cause for concern – it is part of the mechanism. The inhaler is easy to use when the instructions are followed.

It is important to:

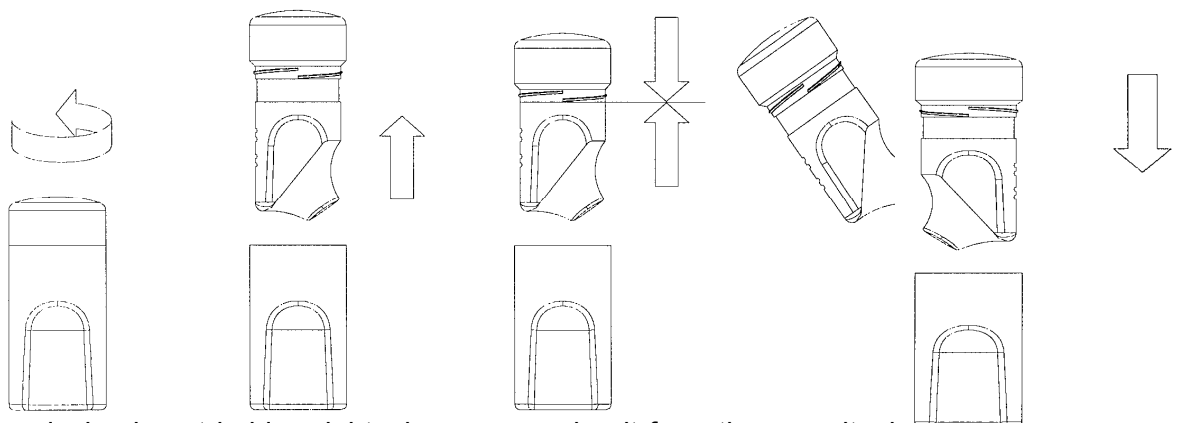
- carefully read the instructions contained in the patient information leaflet supplied with each inhaler
- breathe in as deeply and hard as possible through the mouthpiece to ensure that an optimal dose is delivered to the lungs. never to breathe out through the mouthpiece

- rinse their mouth out with water after inhaling the prescribed dose to minimise the risk of oropharyngeal thrush
- replace the inhaler in the outer case after use. This will make it ready for the next dose.

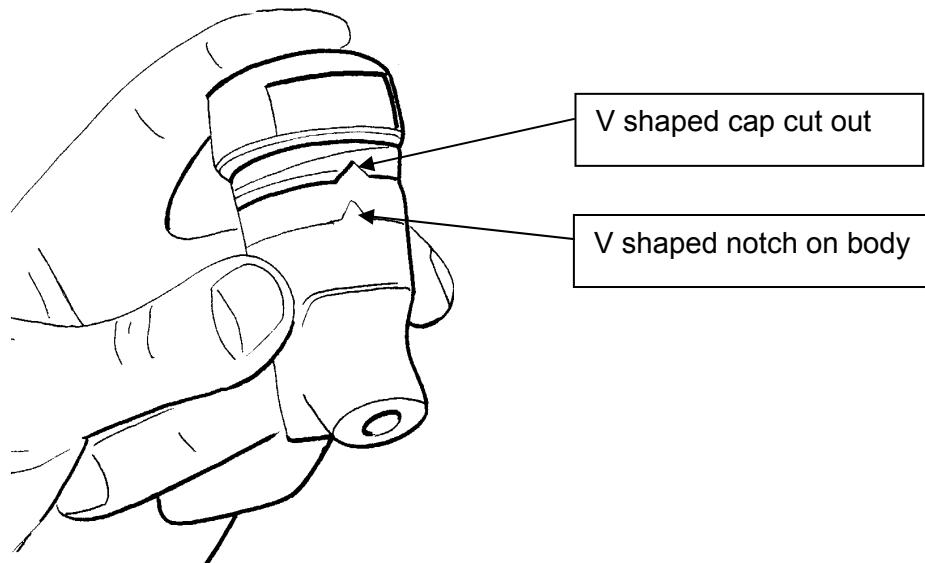
The Miat-Haler consists of two pieces as shown below. It is light grey except for the cap which is dark brown.



| | | | |
|--|----------------------|-----------|---|
| 1. Unscrew inhaler and remove from case keeping in an upright position | 2. Depress brown cap | 3. Inhale | 4. Replace inhaler in case and screw closed |
|--|----------------------|-----------|---|



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1. If the device is not held upright when unscrewing it from the case it will make a clicking sound to remind you. Unscrew the brown cap (anticlockwise) and remove from the case. Unscrewing the brown cap actuates the device.
 2. The brown cap must be pressed to prepare the dose of medicine for use. The V shaped notch on the body must be aligned with the V shape on the cap or the device will not operate. The inhaler should be held correctly thus:



3. Breathe out gently (not into the inhaler), then place the inhaler in the mouth. Breathe in as deeply and hard as possible. Remove inhaler from mouth and hold breath for 10 seconds or as long as is comfortable.
4. Clean the outside of the mouthpiece with a dry tissue after use. Never use water or any other liquid. Replace inhaler in the outer case and screw closed (clockwise). If it is not held upright it will make a clicking noise.
5. If 2 inhalations are required repeat steps 1-4.
6. After taking wash mouth out with water and/or clean teeth. This will reduce the risk of oropharyngeal thrush.

Patients not receiving glucocorticosteroids

Patients who require maintenance therapy of their asthma may benefit from treatment with Budenocort at the doses recommended above. For patients who do not respond adequately to the starting dose, higher doses may provide additional asthma control.

Patients maintained on oral glucocorticosteroids

Budenocort may permit replacement or significant reduction in the dosage of oral glucocorticosteroids with maintained or improved asthma control.

Initially, Budenocort should be used concurrently with the patient's usual maintenance dose of oral glucocorticosteroid. After approximately one week the oral dose is gradually reduced to the lowest possible level. A slow rate of withdrawal is strongly recommended. In many cases it is possible to completely substitute the oral glucocorticosteroid with Budenocort.

During withdrawal some patients may experience symptoms of systemic glucocorticosteroid withdrawal, e.g. joint and/or muscle pain, lassitude and depression, despite maintenance or even improvement in pulmonary function. Such patients should be encouraged to continue with Budenocort but should be monitored for objective signs of adrenal insufficiency. If evidence of adrenal insufficiency occurs, the systemic glucocorticosteroid doses should be temporarily increased and thereafter withdrawal should continue more slowly. Supplementary treatment with systemic glucocorticosteroid may be required during periods of stress or severe asthma attack.

Patients maintained on inhaled glucocorticosteroids

When patients treated with a pressured aerosol are transferred to Budenocort and asthma control is good, it may be possible to reduce the dose significantly (possibly as low as approximately half the pressured aerosol dose).

Contraindications

Hypersensitivity to budesonide and/or lactose.

Warnings and Precautions

Budenocort 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 increased anti-inflammatory therapy, e.g. higher doses of inhaled budesonide or a course of oral glucocorticosteroid.

Particular care is needed in patients who are being transferred from systemic to inhaled glucocorticosteroids. During this period of HPA suppression, patients may exhibit signs and symptoms of adrenal insufficiency when exposed to trauma, surgery, or infection (particularly gastroenteritis) or other conditions associated with severe electrolyte loss. Although Budenocort may provide control of asthma symptoms during these episodes, in recommended doses it supplies less than normal physiological amounts of glucocorticosteroid systemically and does NOT provide the mineralocorticosteroid activity that is necessary for coping with these emergencies.

Some patients may feel unwell in a non-specific way during the withdrawal phase, e.g. pain in muscles and joints. A general insufficient glucocorticosteroid effect should be suspected if symptoms such as tiredness, headache, nausea and vomiting should occur. In these cases a temporary increase in the dose of oral glucocorticosteroids may be necessary.

Replacement of systemic glucocorticosteroid treatment with inhaled therapy sometimes unmasks allergies, e.g. rhinitis and eczema, which were previously controlled by the systemic agent. These allergies should be symptomatically controlled with an antihistamine and/or topical preparations.

Reduced liver function may affect the elimination of corticosteroids. The intravenous pharmacokinetics of budesonide are similar in cirrhotic patients and healthy subjects. The pharmacokinetics after oral ingestion of budesonide are affected by compromised liver function as evidenced by increased systemic availability. This is of limited clinical importance for Budenocort, as after inhalation the oral contribution to the systemic availability is relatively small.

In vivo studies have shown that oral administration of ketoconazole (a known inhibitor of CYP3A activity in the liver and in the internal mucosa, also see Interactions) may cause an increase of the systemic exposure to budesonide. This is of limited clinical importance for short-term (1-2 weeks) treatment with ketoconazole, but should be taken into consideration during long-term treatment.

The long term local and systemic effects of budesonide in man are not completely known. The dose should be titrated to the lowest effective maintenance dose once control of asthma is achieved.

Long term studies show that children and adolescents treated with inhaled budesonide ultimately achieve their adult target height. However an initial small but transient reduction in growth velocity (approx 1 cm) has been observed. This generally occurs within the first year of treatment.

Rare individuals may be exceptionally sensitive to inhaled corticosteroids. Physicians should monitor the growth of children and adolescents taking corticosteroids to identify patients with increased sensitivity. The clinical benefit of inhaled corticosteroids should be weighed against any potential growth effects of prolonged treatment.

High doses of glucocorticosteroids may mask some signs of existing infection and new infections may appear during their use. Special care is needed in patients with active or quiescent pulmonary tuberculosis or fungal, bacterial or viral infections of the respiratory system.

Use during Pregnancy and Lactation

Category A

Results from a epidemiological study and post marketing experience indicate no adverse effects from use of inhaled budesonide during pregnancy on the health of the foetus / newborn child. As with other medicines the benefits for the mother should be weighed against the potential risks for the foetus. Inhaled glucocorticosteroids should be considered for use during pregnancy because of the lower systemic effects when compared with oral glucocorticosteroid doses required to achieve similar pulmonary responses.

In pregnant animals, administration of budesonide, like other glucocorticosteroids, is associated with abnormalities of foetal development. The relevance of these findings to man has not been established.

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

Effects on ability to drive and use machines

Budenocort does not affect the ability to drive and use machines.

Adverse Effects

Clinical trials, literature reports and post-marketing experience suggest that the following adverse reactions may occur:

- Mild irritation in the throat, irritation of the tongue, mouth or larynx, coughing and hoarseness, dry mouth, bad taste, thirst.
- Candida infection in the oropharynx.
- Immediate and delayed hypersensitivity reactions, including rash, contact dermatitis, urticaria, angioedema, and bronchospasm.
- Headache, light-headedness, diarrhoea, nausea, weight gain, tiredness.
- Psychiatric symptoms such as nervousness, restlessness, and depression, as well as behavioural disturbances.

Rare reports of skin bruising following treatment with inhaled glucocorticosteroids have occurred.

In rare cases, medicines for inhalation may cause bronchospasm.

In rare cases signs or symptoms of a systemic glucocorticosteroid effect may occur with inhaled glucocorticosteroids. Possible systemic effects include hypofunction of the adrenal gland and a reduction in growth velocity in children and adolescents. These systemic effects are probably dependent on dose, exposure time, concomitant and previous glucocorticosteroid exposure, and individual sensitivity.

Studies with inhaled budesonide indicate that the reduction in growth velocity is transient and that adult target height may ultimately be achieved (see Warnings and Precautions).

Interactions

Budesonide has not been observed to interact with any agent used for the treatment of asthma.

The metabolism of budesonide is primarily mediated by cytochrom P450 CYP3A P450. Inhibitors of this enzyme, e.g. ketoconazole and itraconazole, may increase systemic exposure to budesonide.

At recommended doses, cimetidine has a slight but clinically insignificant effect while omeprazole has no effect on the pharmacokinetics of oral budesonide.

Overdosage

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

Pharmaceutical Precautions

Store below 25°C.

Keep container tightly closed. On order to protect from moisture always replace the inhaler in the outer case and screw closed immediately after every use. The case contains a desiccant which is marked that it is not for ingestion – this should not be removed.

Medicines Classification

Prescription Medicine

Package Quantities

Budenocort inhalers contain sufficient product to provide 100 or 200 actuations. Budenocort is available in packs of 1 or 3 inhalers.

Further Information

The product also contains lactose.

Instructions for use and cleaning of the inhaler are provided with each inhaler

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