BECLOTEN® INHALER 100mcg

Beclometasone dipropionate
pressurised metered-dose inhaler/solution

Description
A pressurised metered-dose inhaler containing not less than 200 actuations of *beclometasone dipropionate* clear solution filled in a 19 ml aluminium canister fitted with a 50-microliter plastic and elastomeric metering valve with a white polypropylene actuator and a light brown polypropylene dust cap and packed into individual printed carton. Each actuation delivers 100 microgram *beclometasone dipropionate.*

Pharmacodynamics
Beclometasone dipropionate is a pro-drug with weak glucocorticoid receptor binding affinity. It is hydrolyzed via esterase enzymes to an active metabolite *beclometasone-17-monopropionate* which has higher topical anti-inflammatory activity compared with *beclometasone dipropionate*. The *in vitro* study shows that, *beclometasone 17-monopropionate* exhibits affinity for the human glucocorticoid receptor is 13 times that of *dexamethasone*, 6 times that of *triamcinolone acetonite*, 1.5 times that of *budesonide*, and 25 times that of parent compound.

Inflammation is an important component in the pathogenesis of asthma. The wide range of inhibitory activities against multiple cell types (mast cells, eosinophils, neutrophils, macrophages and lymphocytes) and mediators (histamine, eicosanoids, leukotrienes and cytokines) involved in allergic and non-allergic-mediated inflammation may contribute to their efficacy in asthma.

Pharmacokinetics
Absorption:
Following inhalation, systemic absorption of *beclomethasone dipropionate* occurs through the lung with negligible oral absorption of the swallowed dose. Prior to absorption within the lung, there is an extensive conversion of *beclometasone propionate*, to its active metabolite, *beclometasone 17-monopropionate.* The systemic absorption of *beclometasone 17-monopropionate* arises from lung deposition and oral absorption is 36 and 26% respectively. Following inhalation of the nominal dose, the absolute bioavailability of the unchanged *beclometasone dipropionate* and *beclometasone 17-monopropionate* is approximately 2 and 26% respectively. *Beclometasone dipropionate* is absorbed more rapidly compared with *beclometasone 17-monopropionate* with t_{max} of 0.3h and 1.0h respectively. It exhibits an approximately linear increase in systemic exposure with increasing inhaled dose.

The bioavailability of *beclometasone dipropionate* is negligible following oral administration, but pre-systemic conversion to *beclometasone 17-propionate* results in 41% of the dose being absorbed as *beclometasone 17-monopropionate.*

Distribution:
Tissue distribution, at steady state is 20L and 424L for *beclometasone propionate* and *beclometasone 17-monopropionate*, respectively. Plasma protein binding is 87%. There is no evidence of tissue storage of *beclometasone propionate* or its metabolites.

Metabolism:
Beclometasone propionate is cleared very rapidly from the systemic circulation, by metabolism mediated via esterase enzymes that are found in most tissues, to its active *beclometasone 17-monopropionate* and its inactive metabolites, *beclometasone 21-monopropionate* and *beclometasone.* These inactive metabolites contribute little to the systemic exposure.

Excretion:
Beclometasone dipropionate is mainly (60%) excreted in the feces within 96 hours as free and conjugated polar metabolites. Less than 12% of the dose are excreted in the urine. The renal clearance of *beclometasone propionate* and its metabolites is negligible.
Excretion of *beclometasone propionate* and *beclometasone 17-monopropionate* are characterized by high plasma clearance (150 and 120L/h) with corresponding $t_{1/2}$ of 0.5 and 2.7h.

Indication
Becloten® Inhaler 100mcg is indicated for the prophylactic management of mild, moderate, or severe asthma in adults or children:

Mild asthma: Patients requiring intermittent symptomatic bronchodilator asthma medication on a regular basis.

Moderate asthma: Patients with unstable or worsening asthma despite prophylactic therapy or bronchodilator alone.

Severe asthma: Patients with severe chronic asthma and those who are dependent on systemic corticosteroids for adequate control of symptoms.

Recommended Dose
Becloten® Inhaler 100mcg is for inhalation use only. The spacer device may be used by patients who have difficulty synchronising aerosol actuation with inspiration of breath.

The starting dose of inhaled *beclometasone dipropionate* should be adjusted to the severity of the disease. The dose may then be adjusted until control is achieved and then should be titrated to the lowest dose at which effective control of asthma is maintained.

Adults (including the elderly): The usual starting dose is 200 micrograms twice daily. In severe cases this may be increased to 600 to 800 micrograms daily. This may then be reduced when the patient's asthma has stabilised. The total daily dosage should be administered as two to four divided doses.

The spacer device must always be used when Becloten® Inhaler 100mcg is administered to adults and adolescents 16 years of age and older taking total daily doses of 1000 micrograms or greater.

Children: The usual starting dose is 100 micrograms twice daily. Depending on the severity of asthma, the daily dose may be increased up to 400 micrograms administered in two to four divided doses.

Becloten® Inhaler 100mcg must always be used with the Volumatic™ spacer device when administered to children and adolescents 15 years of age and under, whatever dose has been prescribed.

Patients with hepatic or renal impairment: No dosage adjustment is needed in patients with hepatic or renal impairment.

Patients Not Receiving Systemic Corticosteroids:
For patients who are inadequately controlled with bronchodilators and who are not receiving systemic corticosteroids, it is recommended that they continue to use a bronchodilator when treatment with Becloten® Inhaler commences. Any improvement in respiratory function is usually apparent in 1 to 4 weeks. Some of the patients who do not respond during this period may have excessive mucus in their bronchi so that the drug is unable to penetrate to its site of action. A short course of systemic steroid in relatively high dosage should be given to eliminate mucus and other inflammatory changes in the lungs. Continuation of treatment with Becloten® Inhaler usually maintains the improvement achieved with the oral steroid while it is being withdrawn gradually. Exacerbation of asthma caused by infection is usually controlled by appropriate antibiotic treatment and, if necessary, by increasing the dose of Becloten® Inhaler. However, it is necessary to give a short, intensive course of systemic steroids to tide over the duration of the stress.

Mode of Administration
Respiratory (Inhalation) only.

Contraindication
Becloten® Inhaler is contraindicated in primary treatment of status asthmaticus, other episodes of asthma where intensive measures are required and history of hypersensitivity to any of the drug product components.

Warnings and Precautions
Patients should be advised on the need to take the medication regularly even when they are asymptomatic. Becloten® Inhaler is not for use in acute attacks, but for long-term management. Patients will require a fast and short-acting inhaled bronchodilator to relieve acute asthmatic symptoms.

The management of asthma should be followed a step-wise program, and patient response should be monitored clinically and by lung function tests.

Increasing use of short-acting beta2-agonist to control symptoms indicates deterioration of asthma control. Under these conditions, the patient's therapy plan should be reassessed. If patients find short-acting bronchodilator treatment ineffective or they need more inhalations than usual. In this situation consideration should be given to the need for or an increase in their regular therapy, e.g., higher doses of inhaled corticosteroid or the addition of a long-acting beta2-agonist, or for a course of oral corticosteroid.

Sudden and progressive deterioration or severe exacerbations in asthma control is potentially life-threatening and consideration should be given to increasing the dose of Becloten® Inhaler and if necessary, by giving a systemic steroid and/or an antibiotic if there is an infection. In patients considered at risk, daily flow monitoring may be instituted.

In patients with high dose prescribed for long periods, systemic effects may occur with any corticosteroid; 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 to titrate the dose to the lowest dose at which effective control is maintained. Physician should closely monitor the height of children receiving prolonged treatment with inhaled corticosteroid and weigh the benefit of corticosteroid therapy and asthma control against the possibility of growth retardation.

As with other inhalation therapy, paradoxical bronchospasm may occur, with an immediate increase in wheezing after dosing. This should be treated immediately with a fast-acting bronchodilator. Becloten® Inhaler should be discontinued immediately, the patient assessed, and if necessary alternative therapy instituted.

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.

Patients should be advised that this product contains small amounts of ethanol (approximately 0.00305g per actuation). At normal doses, the amounts of ethanol are negligible and do not pose a risk to patients.

Treatment with Becloten® Inhaler should not be stopped abruptly.

Transferring Patients from Systemic Corticosteroid Therapy:
Particular care must be given to patients who are transferred from systemic to inhaled corticosteroid, because death may occur due to adrenal insufficiency. Several months are required for the hypothalamic-pituitary-adrenal (HPA)-axis function to recover, after withdrawal of systemic corticosteroid. In such circumstances, HPA axis functions should be monitored regularly.
When transferring from oral to inhaled corticosteroid, the patient should be in a relatively stable phase. A high dose of inhaled corticosteroid should be given in combination with the previously used oral corticosteroid dose for about 10 days. After that, the oral corticosteroid dose should be gradually reduced (by for example 2.5 milligrams prednisolone or the equivalent each month) to the lowest possible level. In many cases, it is possible to completely substitute inhaled corticosteroid for oral corticosteroid.

During period of HPA-axis suppression, patients may exhibit signs and symptoms of adrenal insufficiency when exposed to trauma, injury or infection (particularly gastroenteritis) or conditions related to severe electrolyte loss. During this period of stress or severe asthma attacks, patients who have been transferred from systemic to inhaled corticosteroid must immediately resume large doses of oral corticosteroid temporarily and thereafter withdrawal should continue more slowly. Replacement of systemic corticosteroid treatment with inhaled therapy sometimes unmask allergies such as allergic rhinitis or eczema previously controlled by the systemic drug. These allergies should be treated with antihistamine and/or topical preparation, including topical steroids.

Pregnancy and Lactation
In animal reproduction studies, adverse effects of potent corticosteroid are seen only at high systemic exposure levels; direct inhaled application ensures minimal systemic exposure. There are no adequate and well controlled studies in pregnant women. Administration of Becloten® Inhaler during pregnancy should only be considered if the expected benefit to the mother is greater than any possible risk to the fetus.

Corticosteroids are secreted in human breast milk and it is reasonable to assume that inhaled *beclometasone dipropionate* is secreted at a low potential for significant levels in breast milk. Because of the potential of serious reaction in nursing infants from Becloten® Inhaler, a decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to mother.

Interactions with Other Medications
Beclomethasone is less dependent on CYP3A metabolism than some other corticosteroids, and in general interactions are unlikely; however, the possibility of systemic effects with concomitant use of strong CYP3A inhibitors (eg. *cobicistat*) cannot be excluded, and therefore caution and appropriate monitoring is advised with the use of such agents.

No clinically significant drug interactions have been associated with *beclomethasone dipropionate* at therapeutic doses.

Becloten® Inhaler contains a small amount of ethanol. There is a theoretical potential for interaction in particularly sensitive patients taking disulfiram or metronidazole.

Effects on ability to drive and use machines

Becloten® Inhaler has no influence on the ability to drive and use machines.

Becloten® Inhaler contains alcohol. THIS MEDICINE CONTAINS 0.00305g of alcohol (ethanol) in each inhalation. The small amount of alcohol contained in this medicine does not produce any noticeable effect.

Side Effect

The following definitions apply to the incidence of undesirable effects: Frequencies are defined as: 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).

Adverse Drug Reactions (ADR) by System Organ Class (SOC) and Frequency

SOC	Frequency & Adverse Drug Reaction
Infections and infestations	Very Common: Candidiasis of the mouth and throat.
Immune system disorders	Hypersensitivity reactions with the following manifestations; Uncommon: rashes, urticaria, pruritis, erythema and bruising. Very Rare: Oedema of the eyes, face, lips and throat.
Endocrine disorders	Very Rare: Cushing's syndrome, Cushingoid features, adrenal suppression, growth retardation in children and adolescents and decrease in bone mineral density.
Eye disorder	Very Rare: Glaucoma and cataract
Psychiatric disorders	Unknown: Psychomotor hyperactivity, sleep disorders, anxiety, depression, aggression and behavioral changes including hyperactivity and irritability (predominantly in children).
Respiratory, thoracic and mediastinal disorders	Common: Hoarseness or throat irritation. Very Rare: Dyspnoea and/or paradoxical bronchospasm.

Becloten® Inhaler may cause throat irritation and hoarseness, which may be useful to rinse out the mouth with water immediately after inhalation.

Symptoms and Treatment of Overdose

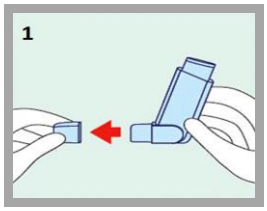
Acute inhalation of Becloten® Inhaler in doses higher than the those recommended, may lead to temporary suppression of adrenal function but it does not require emergency action as adrenal function recovery is in a few days, as verified by plasma cortisol measurements. However, if excessive dose is given over a long period, some degree of adrenal suppression may result. In cases of overdose, Becloten® Inhaler may still be continued at a suitable dosage for symptom control.

Instructions How to Use Your Inhaler

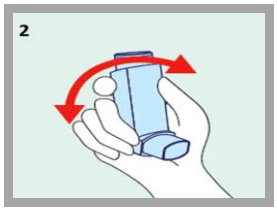
Testing Your Inhaler:

Before using the first time or if your inhaler has not been used for a week or more, remove the mouthpiece cover by gently pressing and pulling it away from the inhaler. Shake the inhaler well and prime the inhaler by releasing 2 puffs into the air to ensure that it works.

Using Your Inhaler For Adults:



1) Remove dust cap from the inhaler by gently pressing and pulling it away from the inhaler.
Check inside and outside of the inhaler including the mouthpiece for the presence of loose objects.



2) Shake the inhaler to ensure that any loose objects are removed and the contents of the inhaler are evenly mixed.



3) Hold the inhaler upright between index finger and thumb, with your thumb on the base of the mouthpiece. Gently breathe in and out through your mouth several times.



4) Breathe out as far as is comfortable and then place the mouthpiece in your mouth between your teeth and close your lips around it. Do not bite it.



5) Start to breathe in slowly through your mouth. Just after starting to breathe in, press down the canister using your index finger to release the medication while still breathing in steadily and deeply.



6) While holding your breath, remove the inhaler from your mouth. Continue holding your breath for 10 seconds or for as long as is comfortable. Then breathe out through your mouth slowly.

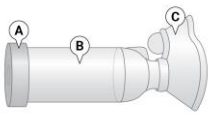
7) If you are to take another puff, keep the inhaler upright and wait for 30 to 60 seconds before repeating step 2 to 6.

8) Afterward, rinse your mouth with water and spit it out.

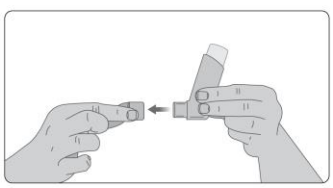
9) Replace the mouthpiece cover by firmly pushing and snapping it into position.

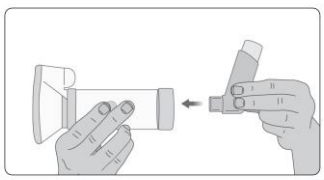
Important:
Do not rush step 4,5 and 6.
It is important that you start to breathe in as slowly as possible just before releasing the medication. Practice in front of a mirror for the first few times.
If you see "mist" coming from the top of the inhaler or the sides of your mouth, you should start again from step 2. This escaping mist indicates failure of technique.
If your doctor has given you different instruction for using your inhaler, please follow the instruction carefully. Please inform or consult your doctor/pharmacist if you have any difficulties.

Using Inhaler with Mask Spacer for Children:

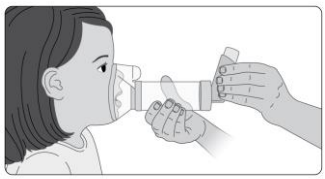


Mask Spacer:
A- Adapter
B- Chamber
C- Face Mask

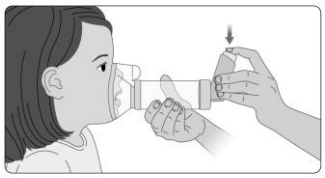




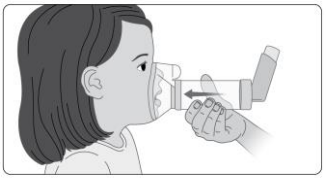
1) Remove dust cap from the inhaler by gently pressing and pulling it away from the inhaler. Shake the inhaler well. Hold the inhaler upright with the mouthpiece at the bottom, and insert the mouthpiece into the spacer adapter.

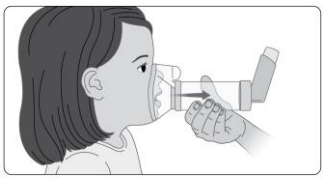


2) Place the mask securely over the child's face and ensure effective seal over mouth and nose.



3) Breathe out gently, into the spacer. Press the canister once at the beginning of a slow inhalation.





4) Keep the spacer in place and have the child breathe in and out normally for 5 breaths. This is the time taken to breathe in all the medicine*.

5) Remove the mask spacer (with the inhaler) from the mouth and breathe out gently. If the child needs another puff, wait for another 30 to 60 seconds and repeat step 2 to 5.

6) Remove the inhaler from the spacer and replace the dust cap by firmly pushing and snapping it into position.

**Varies from product to product. Refer to manufacturer's recommendations.*

Inform or consult your doctor/pharmacist if you have any difficulties.

Cleaning your inhaler:

Your inhaler should be cleaned at least once a week.

1) Remove the metal canister and mouthpiece cover from the actuator (plastic casing).
2) Rinse the actuator and mouthpiece cover thoroughly using warm water.
3) Dry the actuator and mouthpiece cover inside and out.
4) Replace the metal canister and the mouthpiece cover.
5) Do not put the metal canister into water.

Storage Condition
Store below 30°C. Protect from direct sunlight. Do not freeze. Keep out of reach of children.
As with most inhaled medications in aerosol canisters, the therapeutic effect of this medication may decrease when the canister is cold.
Pressurised can, do not puncture, break or burn, even when apparently empty.

Shelf Life
The expiry date is indicated on the packaging.

Dosage Form & Packaging Available
Pressurised Metered-Dose Inhaler. Each canister contains 200 actuations of *beclomethasone dipropionate*.

Product Registration Holder and Manufacturer
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