BECLOMETASONE DIPROPIONATE INHALATION AEROSOL

NAME AND STRENGTH

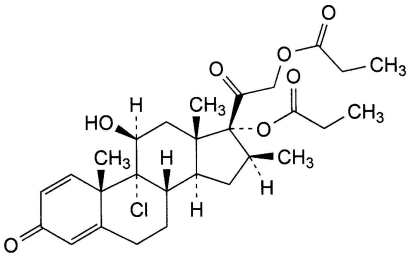
NAME: Beclometasone Dipropionate Inhalation Aerosol

STRENGTH: 50 mcg/dose × 200 doses

ACTIVE INGREDIENT

NAME: Anhydrous Beclometasone Dipropionate

CHEMICAL STRUCTURE:



FORMULA: $C_{28}H_{37}ClO_7$

MOLECULAR WEIGHT: 521.1

COMPOSITION

The active ingredient is Anhydrous Beclometasone Dipropionate, the other inactive ingredients are ethanol and 1,1,1,2-tetrafluoroethane.

CHARACTER

It is a clear and colourless to light yellow solution in a pressurised container equipped with a metered valve. The drug is sprayed out as a mist by actuation of the valve.

INDICATIONS It is indicated in the maintenance treatment of asthma as prophylactic therapy in patients 5 years of age and older. It is also indicated for asthma patients who require systemic corticosteroid administration, where adding this product may reduce or eliminate the need for the systemic corticosteroids.

Beclometasone dipropionate is NOT indicated for the relief of acute bronchospasm.

DOSAGE AND ADMINISTRATION

It is for inhalation use, the recommended dose is 100-800 mcg daily.

Mild asthma:	100 to 200 micrograms per day in two divided doses.
Moderate asthma:	200 to 400 micrograms per day in two divided doses.
Severe asthma:	400 to 800 micrograms per day in two divided doses.

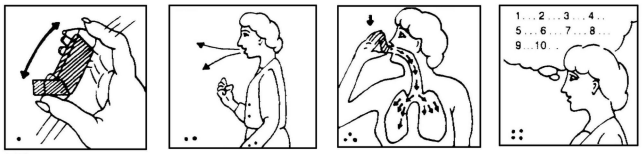
Physicians are advised to titrate the dose downward over time to the lowest level that maintains proper asthma control. The titration of the lowest dose should be conducted regularly.

For patients who have received systemic administration of glucocorticoid, it is important that

the asthma is well controlled before transferred to this product. Generally, start to reduce the dosage of systemic glucocorticoid after 7 days of the administration of this product, take oral Prednisone 10 mg/day as an example, gradually reduce in 1 mg at a interval of not less than 1 week to withdraw.

The use of this product should not be stopped abruptly, it should be gradually withdrawn.

Instructions for use:



1. Remove the cover from the mouthpiece and shake the inhaler well (See Figure 1).
2. Holding the inhaler as shown, breathe out gently (See Figure 2).
3. Place the mouthpiece in the mouth and close your lips around it. Start to breathe in slowly and deeply while press the inhaler firmly, to make the dry mist totally inhaled (See Figure 3).
4. Hold breath for 10 seconds before breathing out slowly, in order to make the drug exert its effectiveness fully (See Figure 4).
5. If you are to take a second inhalation, wait at least one minute before repeating steps 2, 3 and 4.

ADVERSE REACTIONS

Candidiasis of the mouth and throat occurs in some patients, patients may find it helpful to rinse their mouth thoroughly with water after inhalation and the infection can be treated with antifungal therapy. Hoarseness or throat irritation may occur occasionally and rash may occur in a few patients due to allergic reaction.

Drying and burning in the nose and pharynx, sneezing attacks and epistaxis may occur in a few patients.

Rare cases of increased intraocular pressure, nasal septum perforation, cataract and glaucoma may be related to the application of this product.

Foreign clinical trials find there are other adverse reactions such as: headache, pharyngitis, upper respiratory tract infection, rhinitis, increase in asthma symptom, sinusitis, pain, back pain, sick and dysphonia.

CONTRAINDICATIONS

Hypersensitivity to beclometasone dipropionate or to any of the ingredients.

WARNINGS AND PRECAUTIONS

1. It is not indicated for the immediate relief of asthma attacks. Patients therefore need to have relief medication available for such circumstances.

2. It is desirable to titrate to the lower dosage and stop once asthma is well controlled, usually, lower and stop of the dosage after 4-5 days treatment.

3. Do not use if the character changed.

4. Use with caution in patients with active or quiescent pulmonary tuberculosis.

5. For patients who have received oral administration of glucocorticoid, if there is already an adrenocortical function impair, the fully recovery of hypothalamic-pituitary-adrenal system is needed before transferred to this product

6. For patients who have received this product over the recommended dosage, who hypersensitive to this product and who receive oral administration of glucocorticoid, a systemic reaction may occur.

7. Before first use of the inhaler, or if the inhaler has not been used for one week or more, prime the inhaler by releasing several puffs into the air; if it could not be sprayed out, check if it is correctly used or the orifice is unobstructed.

8. The canister is pressurised. Keep away from sunlight and heat. Do not puncture, break or burn even when apparently empty.

9. Keep out of reach of children.

10. [WARNINGS] Particular care is needed in patients who are transferred from systemically active corticosteroids to this product because deaths due to adrenal insufficiency have occurred in asthmatic patients during and after transfer from systemic corticosteroids to inhaled corticosteroids. After withdrawal from systemic corticosteroids, a number of months are required for recovery of hypothalamic-pituitary-adrenal (HPA) function.

Patients who have been previously maintained on 20 mg or more per day of prednisone (or its equivalent) may be most susceptible, particularly when their systemic corticosteroids have been almost completely withdrawn. During this period of HPA suppression, patients may exhibit signs and symptoms of adrenal insufficiency when exposed to trauma, surgery, or infections (particularly gastroenteritis) or other conditions with severe electrolyte loss. Although this product may provide control of asthmatic symptoms during these episodes, in recommended doses it supplies less than normal physiological amounts of glucocorticoid systemically and does NOT provide the mineralocorticoid that is necessary for coping with these emergencies. During periods of stress or a severe asthmatic attack, patients who have been withdrawn from systemic corticosteroids should be instructed to resume oral corticosteroids (in large doses) immediately and to contact their physician for further instruction. These patients should also be instructed to carry a warning card indicating that they may need supplementary systemic steroids during periods of stress or a severe asthma attack.

Transfer of patients from systemic steroid therapy to this product may unmask allergic conditions previously suppressed by the systemic steroid therapy, e.g., rhinitis, conjunctivitis and eczema.

Persons who are on drugs which suppress the immune system are more susceptible to infections than healthy individuals. Chickenpox and measles, for example, can have a more serious or even fatal course in non-immune children or adults on corticosteroids. In such children or adults who have not had these diseases or been properly immunized, particular care should be taken to avoid exposure. It is not known how the dose, route and duration of corticosteroid administration affects the risk of developing a disseminated infection. Nor is the contribution of the underlying disease and/or prior corticosteroid treatment known. If exposed to chickenpox, prophylaxis with varicella-zoster immune globulin (VZIG) may be indicated. If exposed to measles, prophylaxis with pooled intramuscular immunoglobulin (IG) may be indicated. If chickenpox develops, treatment with antiviral agents may be considered.

This product is not a bronchodilator and is not indicated for rapid relief of bronchospasm. As with other inhaled asthma medications, bronchospasm, with an immediate increase in wheezing, may occur after dosing. If bronchospasm occurs following dosing with this product, it should be treated immediately with a short-acting inhaled bronchodilator. Treatment with this product should be discontinued and alternate therapy instituted. Patients should be instructed to contact their physician immediately when episodes of asthma, which are not responsive to bronchodilators, occur during the course of treatment with this product. During such episodes, patients may require therapy with oral corticosteroids.

11. [CAUTION] General: During withdrawal from oral corticosteroids, some patients may experience symptoms of systemically active corticosteroid withdrawal, e.g., joint and/or muscular pain, lassitude and depression, despite maintenance or even improvement of respiratory function. Although suppression of HPA function below the clinical normal range did not occur with doses of this product up to and including 640 mcg/day, a dose-dependent reduction of adrenal cortisol production was observed. Since inhaled Beclometasone dipropionate is absorbed into the circulation and can be systemically active, HPA-axis suppression by this product could occur when recommended doses are exceeded or in particularly sensitive individuals. Since individual sensitivity to effects on cortisol production exist, physicians should consider this information when prescribing this product. Because of the possibility of systemic absorption of inhaled corticosteroids, patients treated with these drugs should be observed carefully for any evidence of systemic corticosteroid effect. Particular care should be taken in observing patients postoperatively or during periods of stress

for evidence of inadequate adrenal response.

It is possible that systemic corticosteroid effects, such as hypercorticism and adrenal suppression, may appear in a small number of patients, particularly at higher doses. If such changes occur, this product should be reduced slowly, consistent with accepted procedures for management of asthma symptoms and for tapering of systemic steroids.

The long-term and systemic effects of this product in humans are still not fully known. In particular, the effects resulting from chronic use of the agent on developmental or immunologic processes in the mouth, pharynx, trachea, and lung are unknown.

Inhaled corticosteroids should be used with caution, if at all, in patients with active or quiescent tuberculosis infection of the respiratory tract; untreated systemic fungal, bacterial, parasitic or viral infections; or ocular herpes simplex.

Rare instances of glaucoma, increased intraocular pressure, and cataracts have been reported following the inhaled administration of corticosteroids.

12. [INFORMATION FOR THE PATIENTS] Patients being treated with this product should receive the following information and instructions. This information is intended to aid them in the safe and effective use of this medication. It is not a disclosure of all possible adverse or intended effects.

Persons who are on immunosuppressant doses of corticosteroids should be warned to avoid exposure to chickenpox or measles. Patients should also be advised that if they are exposed to these diseases, medical advice should be sought without delay.

Patients should use this product at regular intervals as directed. Results of clinical trials indicated significant improvements may occur within the first 24 hours of treatment in some patients; however, the full benefit may not be achieved until treatment has been administered for 1 to 2 weeks, or longer. The patient should not increase the prescribed dosage but should contact their physician if symptoms do not improve or if the condition worsens.

Patients should be advised that this product is not intended for use in the treatment of acute asthma. The patient should be instructed to contact their physician immediately if there is any deterioration of their asthma.

Patients should be instructed on the proper use of their inhaler. Patients may wish to rinse their mouth after this product use. The patient should also be advised that this product may have a different taste and inhalation sensation than that of an inhaler containing CFC propellant.

Use of this product should not be stopped abruptly. The patient should contact their physician immediately if use of this product is discontinued.

For the proper use of this product, the patient should read and carefully follow the

accompanying Patient's Instructions.

Pregnancy and Lactation

This product should be used with caution in pregnancy and lactation.

Because of the potential for serious adverse reactions in nursing infants from this product, a decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother.

There are no adequate and well-controlled studies in pregnant women. Beclometasone dipropionate should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Non-teratogenic Effects: Findings of drug-related adrenal toxicity in fetuses following administration of Beclometasone dipropionate to rats suggest that infants born of mothers receiving substantial doses of this product during pregnancy should be observed for adrenal suppression.

Pediatric Use

The safety and effectiveness of this product in children below 5 years of age have not been established.

Geriatric Use

Use as advised by the doctor

DRUG INTERACTION

It may affect the uptake, removal and conversion of thyroid with iodine; insulin may generate antagonism with this product, the diabetic patients should adjust the dose.

OVERDOSAGE

When used at excessive doses (>0.8 mg/day), systemic corticosteroid effects may appear.

PHARMACOLOGY AND TOXICOLOGY

Pharmacology

Beclometasone dipropionate, the diester of Beclometasone, is a synthetic potent corticosteroid, it exerts anti-inflammatory, anti-allergic and relieve itching reaction etc., and can

Beclometasone dipropionate is a potent synthetic adrenal corticosteroid, it is the diester of beclometasone, it has anti-inflammatory, anti-allergic and anti-itching reaction, etc. and can inhibit bronchial exudate, eliminate swelling of the bronchial mucosa and relieve bronchospasm. The local contraction reaction of microvascular is 5000 times of hydrocortisone, and the local anti-inflammatory effect is 5 times of hydrogen fluoride triamcinolone; its effect on sodium retention is weak, and no male, female hormones and anabolic hormones-like effect, so topical application generally does not inhibit human adrenal cortex, and usually does not

cause dysfunction of the adrenal cortex to produce adverse reactions.

Carcinogenesis

The carcinogenicity of Beclometasone dipropionate was evaluated in rats which were exposed for a total of 95 weeks, 13 weeks at inhalation doses up to 0.4 mg/kg/day and the remaining 82 weeks at combined oral and inhalation doses up to 2.4 mg/kg/day. There was no evidence of carcinogenicity in this study at the highest dose, which is approximately 30 and 55 times the maximum recommended daily inhalation dose in adults and children, respectively, on a mg/m^2 basis.

Mutagenesis

Beclometasone dipropionate did not induce gene mutation in the bacterial cells or mammalian Chinese Hamster ovary (CHO) cells *in vitro*. No significant clastogenic effect was seen in cultured CHO cells *in vitro* or in the mouse micronucleus test *in vivo*.

In rats, Beclometasone dipropionate caused decreased conception rates at an oral dose of 16 mg/kg/day (approximately 200 times the maximum recommended daily inhalation dose in adults on a mg/m^2 basis). Impairment of fertility, as evidence by inhibition of the estrous cycle in dogs, was observed following treatment by the oral route at a dose of 0.5 mg/kg/day (approximately 20 times the maximum recommended daily inhalation dose in adults on a mg/m^2 basis). No inhibition of the estrous cycle in dogs was seen following 12 months of exposure to Beclometasone dipropionate by the inhalation route at an estimated daily dose of 0.33 mg/kg (approximately 15 times the maximum recommended daily inhalation dose in adults on a mg/m^2 basis).

Teratogenic Effects

Pregnancy Category C: Like other corticosteroids, parenteral (subcutaneous) Beclometasone dipropionate was teratogenic and embryocidal in the mouse and rabbit when given at a dose of 0.1 mg/kg/day in mice or at a dose of 0.025 mg/kg/day in rabbits. These doses in mice and rabbits were approximately one-half the maximum recommended daily inhalation dose in adults on a mg/m^2 basis. No teratogenicity or embryocidal effects were seen in rats when exposed to an inhalation dose of 15 mg/kg/day (approximately 190 times the maximum recommended daily inhalation dose in adults on a mg/m^2 basis).

PHARMACOKINETICS

It is inhaled by the lung rapidly after inhalation, the bioavailability is 10%-25%. A part of the drug may remain in the mouth, 75% of which will be swallowed down and absorbed by the gastrointestinal. After absorption, the drug is distributed rapidly in the bronchus and lung to show potent anti-inflammatory and antiallergic reaction; the drug distributed in the nasal cavity

shows anti allergic rhinitis reaction; it may also be distributed in the tissue such as liver (as majority) and placental etc. The apparent volume of distribution (V_d) is 0.3 L/kg. The swallowed drug is deactivated by the lung, part of which is hydrolyzed by the esterase. The half life is 15 h, it may be longer when there is a liver disease. 70% of the metabolism is excreted in bile while 10%-15% is excreted in the urine.

STORAGE

Do not store above 25°C. Protect from frost and direct sunlight.

PACKAGE

Aluminum bottle, 1 bottle per box.

SHELF LIFE

36 months.