SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

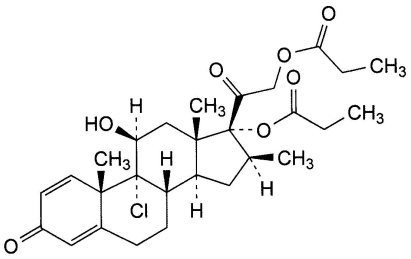
Beclometasone Dipropionate Inhalation

Strength: 100 mcg/dose × 200 doses

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

The active ingredient: Beclometasone Dipropionate

Chemical structure:



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

Molecular weight: 521.0

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Inhalation aerosol.

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

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

It is indicated for the prophylactic management of mild, moderate, or severe asthma.

4.2 Posology and method of administration

It is for inhalation use only.

Patients should be instructed in the proper use of their inhaler, including rinsing out their mouth with water after use.

The recommended dose should be the lowest dose. 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.

The use of this product should not be stopped abruptly, it should be gradually withdrawn.

Adult:

1-2 doses each time, 1-3 times a day or as directed by the physician.

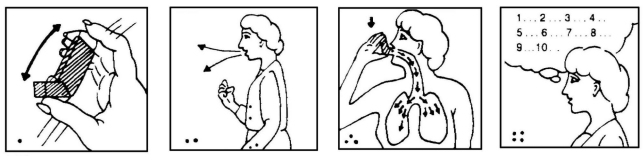
Paediatric Population:

There are no data to date on this product in children under 12 years of age, hence no definitive dosage recommendation can be made.

Special patient groups:

No special dosage recommendations are made for elderly or patients with hepatic or renal impairment.

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.

4.3 Contraindications

Hypersensitivity to beclometasone dipropionate or to any of the ingredients.

4.4 Special warnings and precautions for use

Patients should be properly instructed on the use of the inhaler to ensure that the drug reaches the target areas within the lungs. To be effective, this product must be used by patients on a regular basis, even when patients do not have asthma symptoms. When symptoms are controlled, maintenance this product therapy be reduced in a stepwise manner to the minimum effective dose. Inhaled steroid treatment should not be stopped abruptly.

Patients with asthma are at risk of acute attacks and should have regular assessments of their asthma control including pulmonary function tests.

This product is not indicated for the immediate relief of asthma attacks. Patients therefore need to have relief medication (inhaled short-acting bronchodilator) available for such circumstances.

Severe asthma requires regular medical assessment, including lung-function testing, as there is a risk of severe attacks and even death. Patients should be instructed to

seek medical attention if short-acting relief bronchodilator treatment becomes less effective, or more inhalations than usual are required as this may indicate deterioration of asthma control. If this occurs, patients should be assessed and the need for increased anti-inflammatory therapy considered (eg. higher doses of inhaled corticosteroid or a course of oral corticosteroid).

Severe asthma exacerbations should be managed in the usual way i.e. by increasing the dose of inhaled beclometasone dipropionate, giving a systemic steroid if necessary, and/or an appropriate antibiotic if there is an infection, together with β-agonist therapy.

Treatment with this product should not be stopped abruptly.

However systemic effects of inhaled corticosteroid may occur, particularly at high doses prescribed for prolonged periods. These effects are much less likely to occur than with oral corticosteroid. Possible systemic effects include Cushing's syndrome , Cushingoid features, adrenal suppression, growth retardation in children and adolescents, decrease in bone mineral density, cataract, glaucoma, blurred vision, and more rarely, a range of psychological behavioural effects including psychomotor hyperactivity, sleep disorders, anxiety, depression or aggression (particularly in children). It is important, therefore, that 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 is 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.

Prolonged treatment with high doses of inhaled corticosteroids, particularly higher than the recommended doses, may result in clinically significant adrenal suppression.

Additional systemic corticosteroid cover should be considered during periods of stress or elective surgery.

Patients who have received systemic steroids for long periods of time or at high doses, or both, need special care and subsequent management when being transferred to inhaled steroid therapy. Patients should have stable asthma before being given inhaled steroids in addition to the usual maintenance dose of systemic steroid. Withdrawal of system steroids should be gradual, starting about seven days after the introduction of this product the therapy. For daily oral doses of prednisolone of 10 mg or less, dose reduction in 1 mg steps, at intervals of not less than one week is recommended. For patients on daily maintenance doses of oral prednisolone greater than 10mg, larger weekly reductions in the dose might be acceptable. The dose reduction scheme should be chosen to correlate with the magnitude of the maintenance systemic steroid dose.

As recovery from impaired adrenocortical function, caused by prolonged systemic

steroid therapy is slow, adrenocortical function should be monitored regularly.

Patients should be advised that they may feel unwell in a non-specific way during systemic steroid withdrawal despite maintenance of, or even improved respiratory function. Patients should be advised to persevere with their inhaled product and to continue withdrawal of systemic steroid, even if feeling unwell, unless there is evidence of HPA axis suppression.

Patients weaned off oral steroids whose adrenocortical function is impaired should carry a steroid warning card indicating that they may need supplementary systemic steroids during periods of stress, eg. worsening asthma attacks, chest infections, major intercurrent illness, surgery, trauma, etc.

Discontinuation of systemic steroids may also cause exacerbation of allergic diseases such as atopic eczema and rhinitis. These should be treated as required with topical therapy, including corticosteroids and/or antihistamines.

Like other corticosteroids caution is necessary in patents with active or latent pulmonary tuberculosis.

Patients should be advised to seek medical attention for review of maintenance this product therapy if peak flow falls, symptoms worsen or if the short-acting bronchodilator becomes less effective and increased inhalations are required. This may indicate worsening asthma.

Most patient can be successfully transferred to inhaled steroids with maintenance of good respiratory function, but special care is necessary for the first few months after the transfer, until the hypothalamic-pituitary-adrenal (HPA) system has sufficiently recovered to enable the patent to cope with stressful emergencies such as trauma, surgery or serious infections. Patents should, therefore, carry a steroid warning card to indicate the possible need to re-instate systemic steroid therapy rapidly during periods of stress or where airways obstruction or mucus significantly compromises the inhaled route of administration. In addition, it may be advisable to provide such patients with a supply of corticosteroid tablets to use in these circumstances. The dose of inhaled steroids should be increased at this time and then gradually reduced to the maintenance level after the systemic steroid has been discontinued.

Beclometasone dipropionate, like other inhaled steroids, is absorbed into the systemic circulation from the lungs. Beclometasone dipropionate and its metabolites may exert detectable suppression of adrenal function. Within the dose range 100-800 micrograms daily, clinical studies have demonstrated mean values for adrenal function and responsiveness within the normal range.

Visual disturbance may be reported with systemic and topical corticosteroid use. If a patent 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. At the normal doses, the amounts of ethanol are negligible and do not pose a risk to patients (see section 4.5).

4.5 Interaction with other medicinal products and other forms of interaction

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

Beclometasone 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 (e.g. ritonavir cobicistat) cannot be excluded, and therefore caution and appropriate monitoring is advised with the use of such agents.

4.6 Fertility, pregnancy and lactation

The potential risk of this product for humans is unknown.

There is no experience of this product in pregnancy and lactation in humans, therefore the product should only be used if the expected benefits to the mother are thought to outweigh any potential risk to the foetus or neonate.

Beclometasone dipropionate

Pregnancy

There is inadequate evidence of safety in human pregnancy. Administration of corticosteroids to pregnant animals can cause abnormalities of foetal development including cleft palate and intra-uterine growth retardation. There may therefore, be a risk of such effects in the human foetus. It should be noted, however, that the foetal changes in animals occur after relatively high system exposure. Beclometasone dipropionate is delivered directly to the lungs by the inhaled route and so avoids the high level of exposure that occurs when corticosteroids are given by systemic routes.

The use of beclometasone dipropionate in pregnancy requires that the possible benefits of the drug be weighed against the possibles hazards. The drug has been in widespread use for many years without apparent ill consequence.

Breast-feeding

No Specific studies examining the transfer of beclometasone dipropionate into the milk of lactating animals have been performed. It is probable that beclometasone dipropionate is excreted in milk. However, given the relatively low doses used by the inhalation route, the levels are likely to be low. In mothers breast feeding their baby the therapeutic benefits of the drug should be weighed against the potential hazards to mother and baby.

There is no experience with or evidence of safety of propellant 134a in human pregnancy or lactation. However, studies on the effect of 134a on reproductive

function and embryofoetal development in animals have revealed no clinically relevant adverse effects.

4.7 Effects on ability to drive and use machines

Not relevant.

4.8 Undesirable effects

A serous hypersensitivity reaction including oedema of the eye, face, lips and throat (angioedema) has been reported rarely.

As with other inhaled therapy, paradoxical bronchospasm may occur after dosing. Immediate treatment with a short-acting bronchodilator treatment should be initiated, this product should be discontinued immediately and an alternate prophylactic treatment introduced.

Systemic effects of inhaled corticosteroids may occur, particularly with high doses prescribed for prolonged periods. These include adrenal suppression, growth retardation in children, decrease in bone mineral density and the occurrence of cataract and glaucoma.

Commonly, when taking this product, hoarseness and candidiasis of the throat and mouth may occur. To reduce the risk of hoarseness and candida infection , patients are advised to rinse their mouth after using their inhaler.

Based on the MedDra system organ class and frequencies, adverse events are listed in the table below according to the following frequency estimate: 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); not known (cannot be estimated from the available data).

MedDra – system organ class	**Frequency and Symptom**
Infections and infestations	*Common*: Candidiasis in mouth and throat
Immune system disorders	*Rare*: Allergic reactions, angioedema in eyes, throat, lips and face
Endocrine disorders	*Very rare*: Adrenal suppression*, growth retardation * (in children and adolescents), bone density decreased*
Nervous system disorders	*Uncommon:* Headache, vertigo, tremor
Eye disorders	*Uncommon:* Vision, blurred (see also section 4.4) *Very rare*: Cataract*, glaucoma* *Not known:* Central serous retinopathy,
Respiratory, thoracic and mediastinal disorders	*Common*: Hoarseness, pharyngitis

	Uncommon: Cough, increased asthma symptoms *Rare*: Paradoxical bronchospasm
Gastrointestinal disorders	*Common*: Taste disturbances *Uncommon*: Nausea
Skin and subcutaneous tissue disorders	*Uncommon*: Urticaria, rash, pruritus, erythema, purpura
Musculoskeletal and connective tissue disorders	*Very rare*: Decrease bone mineral density
Psychiatric Disorders	*Unknown*: Psychomotor hyperactivity, sleep disorders, anxiety, depression, aggression, behavioural changes (predominantly in children)

*Systemic reactions are a possible response to inhaled corticosteroids, especially when a high dose is prescribed for a prolonged time (see section 4.4 Special warnings and precautions for use).

4.9 Overdose

Acute overdosage is unlikely to cause problems. The only harmful effect that follows inhalation of large amounts of the drug over a short time period is suppression of HPA function. Specific emergency action need not be taken. Treatment with this product should be continued at the recommended dose to control the asthma: HPA function recovers in a day or two.

If excessive doses of beclometasone dipropionate were taken over a prolonged period a degree of atrophy of the adrenal cortex could occur in addition to HPA suppression. In this event the patient should be treated as steroid dependent and transferred to a suitable maintenance dose of a systemic steroid such as prednisolone. Once the condition is stabilised, the patient should be returned to this product by the method described above in Section 4.4.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Glucocorticoids, ATC code : R03BA01.

It contains beclometasone dipropionate in solution in propellant 134a resulting in an extra fine aerosol. The aerosol droplets are on average much smaller than the beclometasone dipropionate particles delivered by CFC-suspension formulations or dry powder formulations of beclometasone dipropionate. The extra fine particle fraction will be 60% to 20% of the drug particles ≤3.3 microns per shot, ex-actuator.

Radiolabelled deposition studies in adults with mild asthma have demonstrated that the majority of drug (>55 % ex-actuator) is deposited in the lung and a small amount (<35% ex-actuator) is deposited in the oropharynx. These studies were performed with Aerosol.

Inhaled beclometasone dipropionate is now well established in the management of asthma. It is a synthetic glucocorticoid and exerts a topical, anti-inflammatory effect on the lungs, with fewer systemic effects than oral corticosteroids.

Comparative clinical studies have demonstrated that asthma patients achieve equivalent pulmonary function and control of symptoms with aerosol at lower total daily doses than CFC containing beclometasone dipropionate aerosol inhalers.

Pharmacodynamic studies in patients with mild asthma given aerosol for 14 days, have shown that there is a linear correlation among urinary free cortisol suppression, dose administered, and serum total-beclometasone levels obtained. At a daily dose of 800 micrograms, suppression of urinary free cortisol was comparable with that observed with the same daily dose of CFC containing beclometasone dipropionate, indicating a wider safety margin, as this product is administered at lower doses than the CFC product.

5.2 Pharmacokinetic properties

The pharmacokinetic shows that the peak serum concentration for total -beclometasone dipropionate (BOH) (total of any beclometasone OH and beclometasone dipropionate or monopropionate hydrolysed to beclometasone OH) or after single and multiple doses is achieved after 30 minutes.

The value at the peak is approximately 2 nanogram/mL after a total daily dose of 800 micrograms and the serum levels after 100, 200 and 400 micrograms are proportioal. The principal route of elimination of beclometasone dipropionate and its several metabolites is in the faeces. Between 10 % and 15% of an orally administered dose is excreted in the urine, as both conjugated and free metabolites of the drug.

In both single dose and multiple dose pharmacokinetic studies, a dose of 200 micrograms of the product achieved comparable total-BOH levels, as a dose of 400 micrograms of CFC containing beclometasone dipropionate aerosol inhalers. This provided the scientific rationale for investigating lower total daily doses of the product to achieve the same clinical effect.

Pharmacokinetic studies has not been carried out in any special populations

5.3 Preclinical safety data

In animal studies, propellant 134a has been shown to have no significant pharmacological effects other than at very high exposure concentrations, then narcosis and a relatively weak cardiac sensitising effect were found . The potency of the cardiac sensitisation was less than that of CFC-11 (trichlorofluoromethane).

In studies to detect toxicity, repeated high dose levels of propellant 134a indicated that safety margins based on systemic exposure would be of the order 2200, 1314 and 381 for mouse, rat and dog with respect to humans.

There are no reasons to consider propellant 134a as a potential mutagen , clastogen or carcinogen judged from *in vitro* and *in vivo* studies including long-term administration by inhalation in rodents.

Studies of propellant 134a administered to pregnant and lactating rats and rabbits have not revealed any special hazard.

In animals, systemic administration of relatively high doses can cause abnormalities of foetal development including growth retardation and cleft palate. There may therefore be a very small risk of such effects in the human foetus. However , inhalation of beclometasone dipropionate into the lungs avoids the high level of exposure that occurs with administration by systemic routes.

Safety studies with aerosol (an equivalent inhaler) in rat and dog showed few, if any , adverse effects other than those normally associated with general steroid exposure including lymphoid tissue alterations such as reduction in thymus, adrenal and spleen weights. An inhalation reproductive study with aerosol (an equivalent inhaler) in rats did not exhibit any teratogenic effects.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Ethanol

Propylene glycol

Norflurane

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

36 months

6.4 Special precautions for storage

Do not store above 30°C. Protect from frost and direct sunlight.

6.5 Nature and contents of container

200 metered doses per canister, each dose contains 100 mcg of Beclometasone Dipropionate from the valve, 82 mcg of Beclometasone Dipropionate from the actuator.

6.6 Special precautions for disposal and other handling

Not applicable.

7. MANUFACTURER

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