Beclomethasone-dipropionate

QUALITATIVE AND QUANTITATIVE COMPOSITION

BECOTIDE 50 Inhaler is a metered dose aerosol which delivers 50 micrograms of beclomethasone dipropionate per actuation.

BECOTIDE 100 Inhaler is a metered dose aerosol which delivers 100 micrograms of beclomethasone dipropionate per actuation.

BECOTIDE 200 Inhaler is a metered dose aerosol which delivers 200 micrograms of beclomethasone dipropionate per actuation.

BECLOFORTE Inhaler is a metered dose aerosol which delivers 250 micrograms of beclomethasone dipropionate per actuation.

PHARMACEUTICAL FORM

Pressurised inhalation, suspension.

CLINICAL PARTICULARS

Indications

BECOTIDE/BECLOFORTE provides effective anti-inflammatory action in the lungs and offers preventative background treatment of asthma.

Severe asthma requires regular medical assessment as death may occur. Patients with severe asthma have constant symptoms and frequent exacerbations, with limited physical capacity, and PEF values below 60% predicted at baseline with greater than 30% variability, usually not returning entirely to normal after a bronchodilator. These patients will require high dose inhaled (see Dosage and Administration) or oral corticosteroid therapy. Sudden worsening of symptoms may require increased corticosteroid dosage which should be administered under urgent medical supervision.

Adults

Prophylactic management in:

Mild asthma (PEF values greater than 80% predicted at baseline with less than 20% variability): Patients requiring intermittent symptomatic bronchodilator asthma medication on more than an occasional basis.

Moderate asthma (PEF values 60 - 80% predicted at baseline with 20 - 30% variability):

Patients requiring regular asthma medication and patients with unstable or worsening asthma on other prophylactic therapy or bronchodilator alone.

Severe asthma (PEF values less than 60% predicted at baseline with greater than 30% variability):

Patients with severe chronic asthma. On transfer to high dose inhaled BECOTIDE/BECLOFORTE, many patients who are dependent on systemic corticosteroids for adequate control of symptoms may be able to reduce significantly or eliminate their requirement for oral corticosteroids.

Children

Any child who requires prophylactic asthma medication.

Dosage and Administration

BECOTIDE/BECLOFORTE Inhaler is administered by the inhaled route only.

Patients should be made aware of the prophylactic nature of therapy with inhaled BECOTIDE/BECLOFORTE and that it should be taken regularly even when they are asymptomatic.

The dosage of BECOTIDE/BECLOFORTE should be adjusted according to the individual response.

If patients find that short-acting relief bronchodilator treatment becomes less effective or they need more inhalations than usual, medical attention must be sought.

In patients who find co-ordination of a pressurised metered dose inhaler difficult a spacer may be used with BECOTIDE/BECLOFORTE Inhaler.

Adults and children over 12 years of age

Patients should be given a starting dose of inhaled beclomethasone dipropionate (BECOTIDE 50, 100, or
BECOTIDE/BECLOFORTE Inhaler is not for use in acute attacks, but for routine long-term management. Patients will require a fast- and short-acting inhaled bronchodilator to relieve acute asthmatic symptoms. Patients' inhaler technique should be checked to make sure that aerosol actuation is synchronised with inspiration of breath for optimum delivery of the drug to the lungs.

Lack of response or severe exacerbations of asthma should be treated by increasing the dose of inhaled BECOTIDE/BECLOFORTE and, if necessary, by giving a systemic steroid and/or an antibiotic if there is an infection.

Systemic effects may occur with any inhaled corticosteroid, particularly at high doses prescribed for long 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 dose of inhaled corticosteroid is titrated to the lowest dose at which effective control is maintained (see Adverse Reactions).

It is recommended that the height of children receiving prolonged treatment with inhaled corticosteroid is regularly monitored.

Contraindications
BECOTIDE/BECLOFORTE Inhaler is contraindicated in patients with a history of hypersensitivity to any of its components.

Warnings and Precautions
The management of asthma should follow a step-wise programme, and patient response should be monitored clinically and by lung function tests. Increasing use of short-acting inhaled β2 agonists to control symptoms indicates deterioration of asthma control. Under these conditions, the patient's therapy plan should be reassessed.

Sudden and progressive deterioration in asthma control is potentially life-threatening and consideration should be given to increasing corticosteroid dosage. In patients considered at risk, daily flow monitoring may be instituted.

Children over 4 years of age
Up to 400 micrograms per day in divided doses.

Children should be given a starting dose of inhaled BECOTIDE/BECLOFORTE which is appropriate for the severity of their disease.

The dose may then be adjusted until control is achieved or reduced to the minimum effective dose according to the individual response.

Special patient groups
There is no need to adjust the dose in elderly patients or in those with hepatic or renal impairment.

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Certain individuals can show greater susceptibility to the effects of inhaled corticosteroid than do most patients.

Because of the possibility of impaired adrenal response, patients transferring from oral steroid therapy to inhaled BECOTIDE/BECLOFORTE therapy should be treated with special care, and adrenocortical function regularly monitored.

Following introduction of inhaled BECOTIDE/BECLOFORTE, withdrawal of systemic therapy should be gradual and patients encouraged to carry a steroid warning card indicating the possible need for additional therapy in times of stress. Similarly replacement of systemic steroid treatment with inhaled therapy sometimes unmasks allergies such as allergic rhinitis or eczema previously controlled...
by the systemic drug. These allergies should be symp-
tomatically treated with antihistamine and/or topical
preparations, including topical steroids.
Treatment with BECOTIDE/BECLOFORTE Inhaler
should not be stopped abruptly.
As with all inhaled corticosteroids, special care is
necessary in patients with active or quiescent pul-
monary tuberculosis.

Interactions
There are no proven drug interactions.

Pregnancy and Lactation
There is inadequate evidence of safety of BECO-
TIDE/BECLOFORTE in human pregnancy. In animal
reproduction studies adverse effects typical of potent
corticosteroids are only seen at high systemic expo-
sure levels; direct inhaled application ensures minimal
systemic exposure.
Administration of drugs during pregnancy should only
be considered if the expected benefit to the mother is
greater than any possible risk to the foetus.
No specific studies examining the transference of
beclomethasone dipropionate into the milk of lactat-
ing animals have been performed.
It is reasonable to assume that beclomethasone
dipropionate is secreted in milk but at the dos-
ages used for direct inhalation, there is low poten-
tial for significant levels in breast milk. The use of
BECOTIDE/BECLOFORTE in mothers breast feed-
ing their babies requires that the therapeutic bene-
fits of the drug be weighed against the potential haz-
ards to the mother and baby.

Effects on Ability to Drive and Use Machines
BECOTIDE/BECLOFORTE is unlikely to produce an
effect.

Adverse Reactions
Adverse events are listed below by system organ
class and frequency. Frequencies are defined as:
very rare: <1/10,000 including isolated
reports.

Very common, common and uncommon events
were generally determined from clinical trial data.
The incidence in placebo and comparator group has
not been taken into account in estimation of these
frequencies. Rare and very rare events were gener-
ally determined from spontaneous data.

Infections and infestations
Very common: Candidiasis of the mouth and throat.
Candidiasis of the mouth and throat (thrush) occurs in some patients, the incidence of which is
increased with doses greater than 400 µg beclo-
methasone dipropionate per day.

Patients with high blood levels of Candida precipi-
tins, indicating a previous infection, are most likely
to develop this complication. Patients may find it
helpful to rinse out their mouth with water after using
the inhaler. Symptomatic candidiasis can be treated
with topical anti-fungal therapy whilst still continuing
with the BECOTIDE/BECLOFORTE Inhaler.

Immune system disorders
Hypersensitivity reactions with the following mani-
festations have been reported:

Uncommon: Rashes, urticaria, pruritus, erythema

Very rare: Oedema of the eyes, face, lips and throat,
respiratory symptoms (dyspnoea and/or broncho-
spasm), anaphylactoid/anaphylactic reactions.

Endocrine disorders
Possible systemic effects include (see Warnings and
Precautions):

Very rare: Cushing’s syndrome, Cushingoid fea-
tures, adrenal suppression, growth retardation in
children and adolescents, decrease in bone mineral
density, cataract, glaucoma.

Psychiatric disorders
Very rare: Anxiety, sleep disorders and behavioural
changes, including hyperactivity and irritability (pre-
dominantly in children).

Respiratory, thoracic and mediastinal disorders
Common: Hoarseness, throat irritation.
In some patients inhaled BECOTIDE/BECLOFORTE may cause hoarseness or throat irritation. It may be helpful to rinse out the mouth with water immediately after inhalation. The use of a large volume ‘spacer’ device may be considered. Very rare: Paradoxical bronchospasm.

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 inhaled bronchodilator. BECOTIDE/BECLOFORTE Inhaler should be discontinued immediately, the patient assessed, and if necessary alternative therapy instituted.

**Overdose**

Acute inhalation of BECOTIDE/BECLOFORTE doses in excess of those recommended may lead to temporary suppression of adrenal function. This does not need emergency action as adrenal function is recovered in a few days, as verified by plasma cortisol measurements. However if higher than recommended dosage is continued over prolonged periods, some degree of adrenal suppression may result. Monitoring of adrenal reserve may be necessary. In cases of BECOTIDE/BECLOFORTE overdose, therapy may still be continued at a suitable dosage for symptom control.

**PHARMACOLOGICAL PROPERTIES**

**Pharmacodynamics**

Beclomethasone Dipropionate (BDP) is a pro-drug with weak glucocorticoid receptor binding affinity. It is hydrolysed via esterase enzymes to the active metabolite beclomethasone-17-monopropionate (B-17-MP), which has high topical anti-inflammatory activity.

**Pharmacokinetics**

**Absorption**

When administered via inhalation (via metered dose inhaler), systemic absorption of unchanged BDP occurs through the lungs with negligible oral absorption of the swallowed dose. There is extensive conversion of BDP to its active metabolite B-17-MP within the lung prior to absorption. The systemic absorption of B-17-MP arises from both lung deposition (36%) and oral absorption of the swallowed dose (26%). The absolute bioavailability following inhalation is approximately 2% and 62% of the nominal dose for unchanged BDP and B-17-MP respectively. BDP is absorbed rapidly with peak plasma concentrations first being observed (tmax) at 0.3 h. B-17-MP appears more slowly with a tmax of 1 h. There is an approximately linear increase in systemic exposure with increasing inhaled dose. When administered orally the bioavailability of BDP is negligible but pre-systemic conversion to B-17-MP results in 41% of the dose being absorbed as B-17-MP.

**Metabolism**

BDP is cleared very rapidly from the systemic circulation, by metabolism mediated via esterase enzymes that are found in most tissues. The main product of metabolism is the active metabolite (B-17-MP). Minor inactive metabolites, beclomethasone-21-monopropionate (B-21-MP) and beclomethasone (BOH), are also formed but these contribute little to the systemic exposure.

**Distribution**

The tissue distribution at steady-state for BDP is moderate (20 l) but more extensive for B-17-MP (424 l). Plasma protein binding is moderately high (87%).

**Elimination**

The elimination of BDP and B-17-MP are characterised by high plasma clearance (150 and 120 l/h) with corresponding terminal elimination half-lives of 0.5 h and 2.7 h. Following oral administration of tritiated BDP, approximately 60% of the dose was excreted in the faeces within 96 hours mainly as free and conjugated polar metabolites. Approximately 12% of the dose was excreted as free and conjugated polar metabolites in the urine. The renal clearance of BDP and its metabolites is negligible.

**Pre-clinical Safety Data**

Preclinical safety studies indicate that beclomethasone
dipropionate shows negligible systemic toxicity when administered by the inhaled route.

PHARMACEUTICAL PARTICULARS

List of Excipients
Oleic acid,
Trichlorofluoromethane,
Dichlorofluoromethane.

Incompatibilities
None reported.

Shelf Life
The expiry date is indicated on the packaging.

Special Precautions for Storage
Replace the mouthpiece cover firmly and snap it into position.
Do not store above 30°C.
Protect from frost and direct sunlight.

Nature and Contents of Container
Aluminium canister with valve and actuator.
As with most inhaled medications in aerosol canisters, the therapeutic effect of this medication may decrease when the canister is cold.
The canister should not be punctured, broken or burnt even when apparently empty.

Instructions for Use/Handling
Testing your inhaler:
Before using for the first time or if your inhaler has not been used for 3 days or more remove the mouthpiece cover by gently squeezing the sides of the cover, shake the inhaler well, and release one puff into the air to make sure that it works.

Using your inhaler:
1. Remove the mouthpiece cover by gently squeezing the sides of the cover.
2. Check inside and outside of the inhaler including the mouthpiece for the presence of loose objects.
3. Shake the inhaler well to ensure that any loose objects are removed and that the contents of the inhaler are evenly mixed.
4. Hold the inhaler upright between fingers and thumb with your thumb on the base, below the mouthpiece.
5. Breathe out as far as is comfortable and then place the mouthpiece in your mouth between your teeth and close your lips around it but do not bite it.
6. Just after starting to breathe in through your mouth press down on the top of the inhaler to release beclometasone dipropionate while still breathing in steadily and deeply.
7. While holding your breath, take the inhaler from your mouth and take your finger from the top of the inhaler. Continue holding your breath for as long as is comfortable.
8. If you are to take further puffs keep the inhaler upright and wait about half a min before repeating steps 3 to 7.
9. Replace the mouthpiece cover by firmly pushing and snapping the cap into position.

IMPORTANT:
Do not rush stages 5, 6 and 7. It is important that you start to breathe in as slowly as possible just before operating your inhaler. Practise in front of a mirror for the first few times. If you see “mist” coming from the top of your inhaler or the sides of your mouth you should start again from stage 2.
If your doctor has given you different instructions for using your inhaler, please follow them carefully. Tell your doctor if you have any difficulties.

Cleaning:
It should not normally be necessary to clean the inhaler. If cleaning is needed, instructions are given below:
1. Pull the metal canister out of the plastic casing of the inhaler and remove the mouthpiece cover.
2. Wipe the plastic casing and mouthpiece with a damp cloth.
3. Leave to dry in a warm place. Avoid excessive heat.
4. Replace the canister and mouthpiece cover.
DO NOT PUT THE METAL CANISTER INTO WATER.
(For detailed instructions for use refer to the Patient Information Leaflet.)
Not all presentations are available in every country.

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