Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

Becotide Evohaler 250 micrograms Pressurised Inhalation Solution.

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each metered dose contains 250 micrograms beclometasone dipropionate.

For a full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Pressurised Inhalation, Solution
Product imported from Italy:
Pressurised aluminium container closed with a metering valve containing a pressurised inhalation solution

4 CLINICAL PARTICULARS

4.1 Therapeutic Indications

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 instructions) 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.

Children:-

Any child who requires prophylactic asthma medication.

4.2 Posology and method of administration

Becotide Evohaler is for oral inhalation use only.
Patients should be made aware of the prophylactic nature of therapy with inhaled beclometasone dipropionate and that it should be taken regularly even when they are asymptomatic.
The dosage of beclometasone dipropionate 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 Evohaler.

The babyhaler spacer device is available for use in young children.

Adults and children over 12 years of age:-

Patients should be given a starting dose of inhaled beclometasone dipropionate, which is appropriate for the severity of their disease based on the following guidance:
Mild asthma: 200 to 600 micrograms per day in divided doses.
Moderate asthma: 600 to 1000 micrograms per day in divided doses.
Severe asthma: 1000 to 2000 micrograms per day in divided doses.
The dose may then be adjusted until control is achieved or reduced to the minimum effective dose according to the individual response.

Children over 4 years of age:-

Up to 400 micrograms per day in divided doses.
Children should be given a starting dose of inhaled beclometasone dipropionate, 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.

Testing the inhaler:

Before using for the first time or if the inhaler has not been used for three 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 the 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 you lips around 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 breathe, take the inhaler from your mouth and take your fingers from the top of the inhaler. Continue holding your breathe for as long as is comfortable.
8. If you are to take further puffs keep the inhaler upright and wait about half a minute 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. Practice 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 the inhaler

The inhaler should be cleaned at least once a week:
Pull the metal canister out of the plastic casing of the inhaler and remove the mouthpiece cover.
Wipe the plastic casing and mouthpiece with a damp cloth.
Leave to dry in a warm place. Avoid excessive heat.
Replace the canister and mouthpiece cover.
DO NOT PUT THE METAL CANISTER INTO WATER.

4.3 Contraindications

Becotide Evohaler is contra-indicated in patients with a history of hypersensitivity to any of its components.

4.4 Special warnings and precautions for use

The management of asthma should follow a stepwise programme, and patient response should be monitored clinically and by lung function tests.
Increasing use of short-acting inhaled beta-2-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.

Becotide Evohaler 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 beclometasone dipropionate and, if necessary, by giving a systemic steroid and/or an antibiotic if there is an infection.

Systemic effects of inhaled corticosteroid steroids may occur, 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, and more rarely, a range of psychological or 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 is maintained (see 4.8 Undesirable Effects).
It is recommended that the height of children receiving prolonged treatment with inhaled corticosteroid is regularly monitored.
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 beclometasone dipropionate therapy should be treated with special care, and adrenocortical function regularly monitored.

Following introduction of inhaled beclometasone dipropionate, 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 symptomatically treated with antihistamine and/or topical preparations, including topical steroids.

Treatment with Becotide Evohaler should not be stopped abruptly.
As with all inhaled corticosteroids, special care is necessary in patients with active or quiescent pulmonary tuberculosis.

Patients should be advised that this product contains small amounts of ethanol and glycerol. At the normal doses the amounts of ethanol and glycerol are negligible and do not pose a risk to patients.

4.5 Interaction with other medicinal products and other forms of interaction

Becotide Evohaler contains a small amount of ethanol. There is a theoretical potential for interaction in particularly sensitive patients taking disulfiram or metronizadole

4.6 Fertility, pregnancy and lactation

There is inadequate evidence of the safety of beclometasone dipropionate or Norflurane (HFA 134a or Tetrafluoroethane) propellant in human pregnancy.

In animal reproduction studies with beclometasone dipropionate, adverse effects typical of potent corticosteroids are only seen at high systemic exposure levels; direct inhaled application ensures minimal systemic exposure.

Studies of the effect of Norflurane (HFA 134a) on reproductive function and embryo-foetal development in animals have revealed no clinically relevant adverse events.
No clinically relevant adverse events have been associated with the administration of Norflurane (HFA 134a) propellant. Thus, it is unlikely that there will be any adverse effects in humans.

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 beclometasone dipropionate into the milk of lactating animals have been performed.

It is reasonable to assume that beclometasone dipropionate is secreted in milk but at the dosages used for direct inhalation, there is low potential for significant levels in breast milk. The use of beclometasone dipropionate in mothers breast-feeding their babies requires that the therapeutic benefits of the drug be weighed against the potential hazards to the mother and baby.

4.7 Effects on ability to drive and use machines

Becotide Evohaler is unlikely to produce an effect.

4.8 Undesirable effects

Adverse events are listed below by system organ class and frequency. Frequencies are defined as: very common (≥ 1/10), common (≥1/100 and <1/10), uncommon (≥1/1000 and <1/100), rare (≥1/10,000 and <1/1000) and 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 generally 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 micrograms beclometasone dipropionate per day. Patients with high blood levels of Candida

precipitins, 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 Evohaler.

Immune system disorders
Hypersensitivity reactions with the following manifestations have been reported:
Uncommon: Rashes, urticaria, pruritus, erythema.
Very rare: Oedema of the eyes, face, lips and throat, respiratory symptoms (dyspnoea and/or bronchospasm) and anaphylactoid/anaphylactic reactions.

Endocrine disorders
Possible systemic effects include (see 4.4 Special Warnings and Precautions for Use):
Very rare: Cushing's syndrome, Cushingoid features, adrenal suppression, growth retardation in children and adolescents, decrease in bone mineral density, cataract, and glaucoma.

Psychiatric disorders
Very rare: Anxiety, sleep disorders and behavioural changes, including hyperactivity and irritability (predominantly in children).
Unknown: Psychomotor hyperactivity, sleep disorders, anxiety, depression, aggression, behavioural changes (predominantly in children)

Respiratory, thoracic and mediastinal disorders
Common: Hoarseness, throat irritation.
In some patients inhaled beclometasone dipropionate 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 Evohaler should be discontinued immediately, the patient assessed, and if necessary alternative therapy instituted.

4.9 Overdose

Acute inhalation of beclometasone dipropionate 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 beclometasone dipropionate overdose, therapy may still be continued at a suitable dosage for symptom control.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

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

5.2 Pharmacokinetic properties

Absorption

When administered via inhalation (via metered dose inhaler), systemic absorption of unchanged beclometasone dipropionate (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 and oral absorption of the swallowed dose. The absolute bioavailability following inhalation is approximately 60% of the nominal dose forB-17-MP. BDP is absorbed rapidly with peak plasma concentrations first being observed (t_{max}) at 0.3h. B-17-MP appears more slowly with a t_{max} 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 approximately 40% of the dose being absorbed as B-17-MP.

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%).

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, beclometasone-21-monopropionate (B-21-MP) and beclometasone (BOH) are also formed but these contribute little to the systemic exposure.

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 0.5h 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.

5.3 Preclinical safety data

Preclinical safety studies indicate that beclometasone dipropionate shows negligible systemic toxicity when administered by the inhaled route.
The non-CFC propellant, Norflurane (HFA134a), has been shown to have no toxic effect at very high vapour concentrations, far in excess of those likely to be experienced by patients, in a wide range of animal species exposed daily for periods of two years.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Norflurane (Hydrofluoroalkane (HFA) 134a)
Ethanol Anhydrous
Glycerol

6.2 Incompatibilities

Not applicable.

6.3 Shelf Life

The shelf-life expiry date of this product shall be the date shown on the container and outer package of the product on the market in the country of origin.

6.4 Special precautions for storage

The canister contains a pressurised liquid. Do not expose to temperatures higher than 50°C. Do not pierce the canister.
Do not store above 30ºC.
Do not refrigerate or freeze.

As with most inhaled medications in pressurised canisters, the therapeutic effect of this medication may decrease when the canister is cold.

6.5 Nature and contents of container

The inhaler comprises an aluminium can fitted with a metering valve, plastic actuator and dust cap. Each canister contains 200 metered doses.

6.6 Special precautions for disposal of a used medicinal product or waste materials derived from such medicinal product and other handling of the product

Patients should be carefully monitored in the proper use of their inhaler.

7 PARALLEL PRODUCT AUTHORISATION HOLDER

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United Kingdom

8 PARALLEL PRODUCT AUTHORISATION NUMBER

PPA 1328/77/1

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of First Authorisation: 11th January 2008

10 DATE OF REVISION OF THE TEXT

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