Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

Becotide Evohaler 250 micrograms, Pressurised Inhalation Solution

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

One metered dose contains 250 micrograms Beclometasone Dipropionate

Excipient with known effect:
One metered dose contains 8.93 mg of ethanol.

For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Pressurised Inhalation, Solution
Clear and colourless solution in an aluminium canister with a valve.

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 section 4.2) 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:

Children who require 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 older people 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 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 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. 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 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

Hypersensitivity to the active substance or to any of the excipients listed in Section 6.1.

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 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, 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 section 4.8).

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.

As with other inhalation therapy, paradoxical bronchospasm may occur with animmediate 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.

Visual disturbance
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 which have been reported after use of systemic and topical corticosteroids

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

Patients should be advised that this medicine contains 8.93 mg of ethanol in each dose which is equivalent to 15.12% w/w. The amount in one dose of this medicine is equivalent to less than 1 ml beer or 1 ml wine.
The small amount of alcohol in this medicine will not have any noticeable effects.

4.5 Interaction with other medicinal products and other forms of interaction

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

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

4.6 Fertility, pregnancy and lactation

Pregnancy
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.

Breast-feeding
The excretion of beclometasone dipropionate in milk has not been studied in animals. It is reasonable to assume that beclometasone dipropionate is secreted in milk but at the dosage used for direct inhalation, there is low potential for significant levels in breast milk. Beclometasone dipropionate should only be used in a nursing mother if the expected benefit justifies the risk to the newborn/infant.

4.7 Effects on ability to drive and use machines

Becotide Evohaler has no or negligible influence on the ability to drive and used machines.

4.8 Undesirable effects

Adverse reactions 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), very rare (<1/10,000) including isolated reports and not known (cannot be estimated from the available data). Very common, common and uncommon reactions 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 reactions were generally determined from spontaneous data.

Infections and infestations
Very common: Candidiasis of the mouth and throat.

Immune system disorders
Hypersensitivity reactions with the following manifestations have been reported:

Uncommon: Rash, urticaria, pruritus, erythema.
Very rare: Angioedema, respiratory symptoms (dyspnoea and/or bronchospasm) and anaphylactoid/anaphylactic reactions.

Endocrine disorders
Possible systemic effects include (see section 4.4):
Very rare: Cushing's syndrome, Cushingoid features, 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 (predominantly in children).
Unknown: Depression, aggression (predominantly in children).

Respiratory, thoracic and mediastinal disorders
Common: Hoarseness, throat irritation.
The use of a large volume 'spacer' device may be considered.
Very rare: Paradoxical bronchospasm (see section 4.4)

Eye disorder
Not known: Vision, blurred (see section 4.4)

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.

Reporting of suspected adverse reactions
Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via HPRA Pharmacovigilance, Website: www.hpra.ie.

4.9 Overdose

Further management should be as clinically indicated or as recommended by the national poisons centre, where available.

There is no specific treatment for an overdose of beclometasone dipropionate. If overdose occurs, the patient should be treated supportively with appropriate monitoring as necessary.

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 clinically appropriate dosage (within the approved range) for symptom control.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group, ATC code: not yet assigned

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 for B-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.

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.

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 0.5h 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

2 years

6.4 Special precautions for storage

Do not store above 30°C.

Protect from frost and direct sunlight. Do not refrigerate or freeze.

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

The canister contains a pressurised liquid. Do not expose to temperatures higher than 50°C. The canister should not be punctured, broken or burnt, even when apparently empty.

6.5 Nature and contents of container

The inhaler comprises an aluminium can fitted with a 50 microlitre metering valve, plastic actuator and dust cap.
Each canister contains 200 metered doses.

6.6 Special precautions for disposal

Any used medicinal product or waste material should be disposed of in accordance with local requirements.

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

7 MARKETING AUTHORISATION HOLDER

GlaxoSmithKline (Ireland) Limited
12 Riverwalk
Citywest Business Campus
Dublin 24
Ireland

8 MARKETING AUTHORISATION NUMBER

PA1077/042/009

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

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Date of last renewal: 07 January 2010

10 DATE OF REVISION OF THE TEXT

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