Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

Beclazone 200 micrograms CFC-Free Inhaler, Pressurised Inhalation Solution

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each metered dose contains 200 micrograms beclometasone dipropionate.

Excipient with known effect:
Each metered dose contains 5.13 mg alcohol (ethanol).

For a full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Pressurised Inhalation, Solution.

The product is a colourless solution which is to be administered by inhalation using an appropriate delivery device (metered dose inhaler) in which it is supplied.

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.

4.2 Posology and method of administration

Posology
The preparation is intended for oral inhalation 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 initial dose of inhaled beclometasone dipropionate should be appropriate to the severity of the disease.

The dose should be titrated to the lowest dose at which effective control of asthma is maintained.

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

Adults:
The dose range is from 50 mcg twice daily to 500 mcg twice daily (maximum daily dose 1000 mcg) depending on the patients' asthma severity.

The maintenance dose is normally 200-400mcg per day in divided doses. If necessary, higher doses of up to 1000 mcg in divided doses may be used.

Beclazone 200 and 250 micrograms CFC-Free Inhalers are not recommended for use in children due to insufficient data on safety and efficacy.

When asthma symptoms remain under satisfactory control the dose may be gradually reduced to the minimum effective dose to maintain symptom control.

The therapeutic effect occurs after a few days' treatment and reaches its maximum after 2-3 weeks.

When transferring a patient to Beclazone CFC-Free inhaler from other inhaler devices switch at same dose and titrate individually if necessary.

Special patient groups: There is no need to adjust the dose in older people or in those with hepatic or renal impairment.

Method of administration:

For inhalation use.

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 program, and patient response should be monitored clinically and by lung function tests.

Increasing use of bronchodilators, in particular short-acting inhaled β_2-agonists, to relieve 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.

Beclometasone dipropionate inhaler is not intended for the treatment of acute asthma attack 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.

Treatment with Beclazone CFC-Free inhaler should not be stopped abruptly.

Steroid-dependent patients: The transfer of steroid-dependent patients to beclometasone dipropionate inhaler, and their subsequent management, needs special care mainly because recovery from impaired adrenocortical function, caused by prolonged systemic steroid therapy, is slow. The patient should be in a reasonably stable state before being given beclometasone dipropionate inhaler in addition to his/her usual maintenance dose of systemic steroid. After about a week, gradual withdrawal of the systemic steroid is started by reducing the daily dose by 1mg prednisolone, or its equivalent of other corticosteroids, at not less than weekly intervals. Patients treated with systemic steroids for long periods of time or who have received high doses may have adrenocortical suppression. With these patients adrenocortical function should be monitored regularly and their dose of systemic steroid reduced cautiously. Some patients feel unwell (i.e. headache, nausea, articular or muscular discomfort) during the withdrawal phase despite maintenance or even improvement of respiratory function. They should be encouraged to persevere with the inhaler and withdrawal of systemic steroid continued unless there are objective signs of adrenal insufficiency. Spirometric and clinical assessment should be provided while reducing oral corticotherapy. Most

patients can be successfully transferred to beclometasone dipropionate inhaler with maintenance of good respiratory function, but special care is necessary for the first months after the transfer until the pituitary-adrenal system has sufficiently recovered to enable the patient to cope with emergencies such as trauma, surgery or infections.

Transferred patients whose adrenocortical function is impaired should carry a warning card indicating that they need supplementary systemic steroid during periods of stress or elective surgery.

They should also be given a supply of oral steroid to use in emergency, for example when the asthma worsens as a result of a chest infection. The dose of beclometasone dipropionate inhaler should be increased at this time and then reduced to the maintenance level after the systemic steroid has been discontinued.

Patients with high blood levels of Candida precipitins, indicating a previous infection, are more likely to develop candidiasis of the mouth and throat (thrush), (See section 4.8 "Undesirable Effects"). All patients may find it helpful to rinse their mouth with water after using the inhaler.

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. If such does appear, use should cease and alternative therapy introduced.

Replacement of systemic steroid treatment with beclometasone dipropionate inhaler 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.

Patients should be instructed in the proper use of the inhaler to ensure that the drug reaches the target areas within the lungs. Actuation of the aerosol should be synchronised with inspiration. They should also be made aware that beclometasone dipropionate inhaler has to be used regularly for optimum benefit even when they are asymptomatic. Patients being treated with Beclazone 50 or 100 micrograms CFC-Free Inhaler may be transferred directly to treatment with beclometasone dipropionate 200 micrograms CFC-Free Inhaler (at the same total daily dose up to a maximum of 1000 mcg). In the majority of patients no significant effects on plasma or urinary free cortisol occur until doses of 1,000 micrograms per day are exceeded. Some patients receiving 2,000 micrograms of beclometasone dipropionate CFC-Free Inhaler per day have shown reduced plasma or urinary free cortisol although short-term adrenal reserve remains intact. In any patients the risk of developing adrenal suppression should be balanced against the therapeutic advantages and precautions should be taken to provide systemic steroid cover in situations of prolonged stress.

Particular care should be taken to minimise the use of topical corticosteroids in patients with immunosuppression.

As with all inhaled corticosteroids, special care is necessary in patients with active or quiescent pulmonary tuberculosis.

Special care is needed in patients with viral, bacterial, and fungal infections of the eye or the mouth or respiratory tract. In the case of bacterial infection of the respiratory tract an adequate antibiotic co-medication may be required.

Systemic effects of inhaled corticosteroids may occur, particularly at high doses prescribed for prolonged periods. The 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, glaucoma, blurred vision, 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 of asthma is maintained (see section 4.8).

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 ofasthma is maintained. In addition, consideration should be given to referring the patient to a paediatric respiratory specialist.

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

Prolonged treatment with high doses of inhaled corticosteroids, particularly higher than the recommended dose, may result in clinically significant adrenal suppression. Additional systemic corticosteroid cover should be considered during periods of stress or elective surgery.

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 (CSCR) which have been reported after use of systemic and topical corticosteroids.

Excipient(s)
Ethanol
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

Concurrent administration of barbiturates, phenytoin or rifampicin may enhance the metabolism and reduce the effects of oral corticosteroids. Response to anti-coagulants may be reduced and, on some occasions enhanced, by oral corticosteroids. Concurrent administration of oral corticosteroids or potassium-depleting diuretics such as thiazides or frusemide may cause excessive potassium loss. No known interactions have been reported for inhaled beclometasone dipropionate.

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.

Beclazone CFC-Free Inhaler 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

Beclazone 200 micrograms CFC-Free Inhaler has no or negligible influence on the ability to drive and use machinery.

4.8 Undesirable effects

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)

Infections and infestations Very common	Candidiasis in mouth and throat

Immune system disorders Very rare	Angioedema, respiratory symptoms (dyspnoea and/or bronchospasm) and anaphylactoid/anaphylactic reactions
Endocrine disorders Very rare	Possible systemic effects include (see section 4.4): Cushing's syndrome, Cushingoid features, Adrenal suppression , Growth retardation in children and adolescents
Eye disorders Uncommon Very rare Not known	 Blurred vision (see section 4.4) Cataract, glaucoma (systemic effect) Central serous retinopathy
Respiratory, thoracic and mediastinal disorders Common Very rare	 Hoarseness and throat irritation Paradoxical bronchospasm (see section 4.4)
Skin and subcutaneous tissue disorders Uncommon	 Urticaria, rash, pruritus, erythema
Musculoskeletal and connective tissue disorders Very rare	 Decreased bone mineral density
Psychiatric disorders Very rare Not known	 Anxiety, sleep disorders and behavioural changes, including hyperactivity and irritability (predominantly in children) Depression, aggression, (predominantly in children)

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. Beclazone CFC-Free Inhaler 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: Anti-asthmatics, Inhalants Glucocorticoids
ATC Code: R03B A01

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 (tmax) at 0.3h. 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 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

Ethanol anhydrous 99.5%
Norflurane 134a (HFA-134a)

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

3 years.

6.4 Special precautions for storage

Do not store above 25°C. Do not refrigerate or freeze.
The canister contains a pressurised liquid. Do not expose to temperatures higher than 50°C. Do not pierce the canister.

6.5 Nature and contents of container

Pressurised container fitted with a metering valve.

The can is of 19 ml nominal capacity manufactured from aluminium with either a debossed or a plain base. The can opening is configured to accept 20 mm valves. Each pack contains a single inhaler which supplies a minimum of 200 actuations.

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 properly instructed in the correct use of the inhaler. Instructions for use are included on the Patient Information Leaflet supplied with each inhaler.

The canister is pressurised; it must not be burnt, punctured or broken even when apparently empty.

Medicines no longer required should not be disposed of via wastewater or the municipal sewage system. Return them to your pharmacy or ask your pharmacist how to dispose of them in accordance with the national regulations. These measures will help to protect the environment.

7 MARKETING AUTHORISATION HOLDER

Norton Waterford
T/A IVAX Pharmaceuticals Ireland
Unit 301
IDA Industrial Park
Cork Road, Waterford
Ireland

8 MARKETING AUTHORISATION NUMBER

PA0436/021/011

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