SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT

Soprobec 250 micrograms per actuation pressurised inhalation solution

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each metered dose (the dose leaving the valve) contains 250 micrograms of beclometasone dipropionate

Excipients with known effect: 8.62 mg ethanol per actuation

For full list of excipients, see section 6.1

3 PHARMACEUTICAL FORM

Pressurised inhalation solution

The solution is clear and colourless.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

Soprobec is indicated for the maintenance treatment of asthma in adults, when the use of pressurised metered dose inhaler is appropriate.

4.2 Posology and method of administration

Posology

The starting dose of inhaled beclometasone dipropionate should be adjusted to the severity of the disease. The dose may then be adjusted until control is achieved and then should be titrated to the lowest dose at which effective control of asthma is maintained.

Adults (including the elderly): Usually 1000 micrograms daily, which may be increased to 2000 micrograms daily. This may then be reduced when the patient's

asthma has stabilised. The total daily dosage should be administered as two to four divided doses.

The Volumatic™ spacer device must always be used when Soprobec is administered to adults and adolescents 16 years of age and older taking total daily doses of 1000 micrograms or greater.

Children: Soprobec 250 is not recommended for children.

Patients with hepatic or renal impairment: No dosage adjustment is needed in patients with hepatic or renal impairment.

Method of Administration
Soprobec is for inhalation use.
To ensure proper administration of the medicinal product, the patient should be shown how to use the inhaler correctly by a physician or other health professional. Correct use of the pressurised metered dose inhaler is essential in order that treatment is successful. The patient should be advised to read the Package Leaflet carefully and follow the instructions for use as given in the Leaflet.

Testing the inhaler
Before using the inhaler for the first time or if the inhaler has not been used for 3 days or more, the patient should release one actuation into the air in order to ensure that the inhaler is working properly. Whenever possible patients should stand or sit in an upright position when inhaling from their inhaler.

Instructions for Use
1. Patients should remove the protective cap from the mouthpiece and check that the mouthpiece is clean and free from dust and dirt or any other foreign objects.
2. Patients should breathe out as slowly and deeply as possible.
3. Patients should hold the canister vertically with its body upwards and put the lips around the mouthpiece without biting the mouthpiece
4. At the same time, patients should breathe in slowly and deeply through the mouth. After starting to breathe in, they should press down on the top of the inhaler to release one puff.
5. Patients should hold the breath for about 5 to 10 seconds or as long as comfortable, and then breathe out slowly. If another dose is required, they should be advised to wait 30 seconds before repeating the procedure just described. Finally, they should remove the inhaler from the mouth and breathe out slowly. Patients should not breathe out into the inhaler.

IMPORTANT: patients should not perform steps 2 to 5 too quickly.

After use, patients should close the inhaler with protective cap.

If mist appears following inhalation, either from the inhaler or from the sides of the mouth, the procedure should be repeated from step 2.

For patients with weak hands it may be easier to hold the inhaler with both hands. Therefore, the index fingers should be placed on the top of the inhaler canister and both thumbs on the base of the inhaler.

Patients should rinse their mouth or gargle with water or brush the teeth after inhaling (see section 4.4).

Patients who find it difficult to co-ordinate actuation with inspiration of breath

should be told to use a Volumatic™ spacer device to ensure proper administration of the product.

The patient should be told of the importance of cleaning the inhaler at least weekly to prevent any blockage and to carefully follow the instructions on cleaning the inhaler printed on the Patient Information Leaflet. The inhaler must not be washed or put in water.
The patient should be told also to refer to the Patient Information Leaflet accompanying the Volumatic™ spacer device for the correct instructions on its use and cleaning.

4.3 Contra-indications

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

4.4 Special warnings and special 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. Patients should be reminded to take Soprobec daily as prescribed even when asymptomatic.

Soprobec should not be used for treatment of acute asthma attacks patients. For such cases patients should be advised to have their rapid-acting bronchodilator available at all times.

It is recommended that treatment with Soprobec should not be stopped abruptly. If patients find the treatment ineffective medical attention must be sought. Increasing use of rescue bronchodilators indicates a worsening of the underlying condition and warrants a reassessment of the asthma therapy. Sudden and progressive deterioration in control of asthma is potentially life- threatening and the patient should undergo urgent medical assessment.

Systemic effects of inhaled corticosteroids may occur, particularly when prescribed at high doses for prolonged 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 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 corticosteroids, if possible, to the lowest dose at which effective control of asthma is maintained. In addition, consideration should also be given to referring the patient to a paediatric respiratory specialist.

Prolonged treatment of patients with high doses of inhaled corticosteroids may result in adrenal suppression and acute adrenal crisis. Situations which could potentially

trigger acute adrenal crisis, include trauma, surgery, infection or any rapid reduction in dosage. Presenting symptoms are typically vague and may include anorexia, abdominal pain, weight loss, tiredness, headache, nausea, vomiting, hypotension, decreased level of consciousness, hypoglycaemia, and seizures. Additional systemic corticosteroid cover should be considered during periods of stress or elective surgery. Care should be taken when transferring patients to Soprobec therapy, particularly if there is any reason to suppose that adrenal function is impaired from previous systemic steroid therapy.

Patients transferring from oral to inhaled corticosteroids may remain at risk of impaired adrenal reserve for a considerable time. Patients who have required high dose emergency corticosteroid therapy in the past or have received prolonged treatment with high doses of inhaled corticosteroids may also be at risk. This possibility of residual impairment should always be borne in mind in emergency and elective situations likely to produce stress, and appropriate corticosteroid treatment must be considered. The extent of the adrenal impairment may require specialist advice before elective procedures.

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.

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.

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 an immediate increase in wheezing, shortness of breath and cough after dosing. This should be treated immediately with a fast-acting inhaled bronchodilator. Soprobec should be discontinued immediately, the patient assessed and, if necessary, alternative therapy institute.

To reduce the risk of Candida infection, patients should be recommended to rinse their mouth properly after each drug administration.

Special care is necessary in patients with viral, bacterial and fungal infections of the eye, mouth or respiratory tract..

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.

This medicine contains 7.47 mg of alcohol (ethanol) in each actuation which is equivalent to 15% w/w. The amount of alcohol in each actuation is equivalent to less than 4 ml beer or 2 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

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

If used concomitantly with other systemic or intranasal steroids, a complementary suppressive effect of adrenal function occurs.

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.

4.6 Fertility, pregnancy and lactation

Fertility

In fertility study in rats, beclomethasone dipropionate caused decreased conception rates at an oral dose of 16 mg/kg/day. Impairment of fertility, as evidenced by inhibition of the estrous cycle in dogs, was observed at an oral dose of 0.5 mg/kg/day. No inhibition of the estrous cycle in dogs was seen following 12 months of exposure to beclomethasone dipropionate by the inhalation route at an estimated daily dose of 0.33 mg/kg/day.

Pregnancy

There is no experience of the use of this product in pregnancy and lactation in humans. It should not be used in pregnancy or lactation unless the expected benefits to the mother are thought to outweigh any potential risks to the fetus or neonate.

There is inadequate evidence of safety of beclometasone dipropionate in human pregnancy. Administration of corticosteroids to pregnant animals can cause abnormalities of fetal development including cleft palate and intra-uterine growth retardation. There may therefore, be a risk of such effects in the human fetus. It should be noted, however, that the fetal changes in animals occur after relatively high systemic 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.

Lactation

No specific studies examining the transfer 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.

There is no experience with or evidence of safety of propellant HFA-134a in human pregnancy or lactation. However, studies of the effect of HFA-134a on reproductive function and embryofetal development in animals have revealed no clinically relevant adverse effects.

4.7 Effects on ability to drive and use machines

Soprobec has no or negligible influence on the ability to drive and use machines.

4.8 Undesirable effects

Adverse events are listed below by system class and frequency. Frequencies are defined as: very common (≥1/10), common (≥1/100 and <1/10), uncommon (≥1/1,000 and <1/100), rare (≥1/10,000 and <1/1,000), very rare (≤1/10,000), unknown (frequency cannot be estimated from the available data).

System organ Class	**Adverse Reaction**	**Frequency**
Infections and Infestations	Oral candidiasis (of the mouth and throat)	Very Common
Immune System Disorders	Hypersensitivity reaction with the following	
	manifestations:	
	Rash, urticaria, pruritus, erythema	Uncommon
	Oedema of the eyes, face, lips and throat, anaphylactic / anaphylactoid reactions	Very Rare
Endocrine Disorders	Cushing's syndrome, cushingoid features, Adrenal suppression*, growth retardation* (in children and adolescents), bone density decreased*	Very Rare
Psychiatric Disorders (see section 4.4 Special warnings and precautions for use)	Psychomotor hyperactivity, sleep disorders, anxiety, depression, aggression, behavioural disorders (predominantly in children)	Unknown
Nervous System Disorders	Headache	Unknown
Eye Disorders	Cataract*, glaucoma*	Very Rare
	Vision, blurred*	Not known
Respiratory, Thoracic and Mediastinal Disorders	Hoarseness, throat irritation	Common
	Paradoxial bronchospasm **, wheezing, dyspnoea, cough	Very Rare
Gastrointestinal Disorders	Nausea	Unknown

*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).

** See section 4.4

Candidiasis of the mouth and throat occurs in some patients, the incidence

increasing 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 their mouth thoroughly with water after inhalation. Symptomatic oral candidiasis can be treated with topical antifungal therapy while continuing with Soprobec.

Hoarseness or throat irritation may occur in some patients. These patients should be advised to rinse the mouth out with water immediately after inhalation. Use of the Volumatic™ spacer device may be considered.

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 the Yellow Card Scheme at www.mhra.gov.co.uk/yellowcard or search for MHRA Yellow Card in the Google Play or Apple App Store.

4.9 Overdose

There is no specific treatment for beclometasone dipropionate overdose. In case of overdose, the patient must receive the necessary support treatment and appropriate follow-up.

Acute: Inhalation of doses in excess of those recommended may lead to temporary suppression of adrenal function. This does not require emergency action. In these patients treatment should be continued at a dose sufficient to control asthma; adrenal function recovers in a few days and can be verified by measuring plasma cortisol.

Chronic: Use of inhaled beclometasone dipropionate in daily doses in excess of 1,500 micrograms over prolonged periods may lead to adrenal suppression. Monitoring of adrenal reserve may be indicated. Treatment should be continued at a dose sufficient to control asthma.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic Group:

Glucocorticoid ATC Code: R03B A01

Beclometasone dipropionate given by inhalation at recommended doses has a glucocorticoid anti-inflammatory action within the lungs.

5.2 Pharmacokinetic properties

Beclometasone dipropionate is a pro-drug with weak glucocorticoid receptor binding affinity that is hydrolysed via esterase enzymes to an active metabolite beclometasone-17-monopropionate which has a more potent topical anti-

inflammatory activity compared with the pro-drug beclometasone dipropionate.

Absorption when administered via inhalation by a MDI

Systemic absorption of unchanged beclometasone dipropionate (BDP) occurs through the lungs. There is negligible oral absorption of the swallowed dose of unchanged BDP. Prior to absorption there is extensive conversion of BDP to its active metabolite B-17-MP. 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 observed (tmax) at 0.3 hours. B-17-MP appears more slowly with a tmax of 1 hour. 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.

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 %).

Biotransformation

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 L/hour and 120 L/hour) with corresponding terminal elimination half-lives of
0.5 hours and 2.7 hours. 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.

Special populations

The pharmacokinetics of beclometasone dipropionate in patients with renal or hepatic impairment has not been studied; however, as beclometasone dipropionate undergoes a very rapid metabolism via esterase enzymes present in intestinal fluid, serum, lungs and liver, to originate the more polar products beclometasone-21-monopropionate, beclometasone-17-monopropionate and beclometasone, hepatic impairment is not expected to modify the pharmacokinetics and safety profile of beclometasone dipropionate.
As beclometasone dipropionate or its metabolites were not traced in the urine, an increase in systemic exposure is not envisaged in patients with renal impairment.

5.3 Preclinical safety data

Preclinical safety studies indicate that beclometasone dipropionate shows negligible systemic toxicity when administered by inhalation.
The non-CFC propellant HFA-134a 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 up to two years.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Norflurane (HFA-134a)
Ethanol anhydrous
Glycerol

6.2 Incompatibilities

Not applicable

6.3 Shelf life

2 years

6.4 Special precautions for storage

As with most inhaled medicines in aerosol canisters, the therapeutic effect may decrease when the canister is cold.
Do not freeze.
Store in the original package in order to protect from the light.
The canister contains a pressurised liquid. Do not expose to temperatures higher than 50 °C. Do not pierce the canister, even when it´s empty.

6.5 Nature and contents of container

250mcg:
Soprobec is supplied in an aluminium canister fitted with a metering valve, maroon coloured actuator and grey colour dust cap.
Each pack contains either a single inhaler, or two inhalers.

Each inhaler delivers 200 actuations.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal

Not applicable

7 MARKETING AUTHORISATION HOLDER

Glenmark Pharmaceuticals Europe Limited
Laxmi House, 2B Draycott Avenue

Kenton, Middlesex, HA3 0BU
United Kingdom.

8 MARKETING AUTHORISATION NUMBER(S)

PL 25258/0281

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