SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT

Proxor 100/6 micrograms per actuation pressurised inhalation solution.

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each metered dose (ex-valve) contains:

100 micrograms of beclometasone dipropionate and 6 micrograms of formoterol fumarate dihydrate. This is equivalent to a delivered dose (ex-actuator) of 84.6 micrograms of beclometasone dipropionate and 5.0 micrograms of formoterol fumarate dihydrate.

Excipient with known effect:

This medicine contains 7 mg of alcohol (ethanol, anhydrous) per actuation (ex-valve)

For the full list of excipients see section 6.1.

3 PHARMACEUTICAL FORM

Pressurised inhalation solution.

Colourless to yellowish solution.

The canisters are fitted into a plastic actuator incorporating a mouthpiece and fitted with a dust cap.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

Asthma

Proxor is indicated in the regular treatment of asthma where use of a combination product (inhaled corticosteroid and long-acting $beta_2$-agonist) is appropriate:

- patients not adequately controlled with inhaled corticosteroids and 'as needed' inhaled rapid-acting $beta_2$-agonist or

- patients already adequately controlled on both inhaled corticosteroids and long-acting $beta_2$- agonists.

COPD

Symptomatic treatment of patients with severe COPD (FEV_1< 50% predicted normal) and a history of repeated exacerbations, who have significant symptoms despite regular therapy with long-acting bronchodilators.

4.2 Posology and method of administration

Proxor is for inhalation use.

Posology

Asthma

Proxor is not intended for the initial management of asthma. The dosage of the active substances of Proxor is individual and should be adjusted to the severity of the disease. This should be considered not only when treatment with combination products is initiated but also when the dose is adjusted. If an individual patient should require a combination of doses other than those available in the combination inhaler, appropriate doses of $beta_2$-agonists and/or corticosteroids by individual inhalers should be prescribed.

Beclometasone dipropionate in Proxor is characterised by an extrafine particle size distribution which results in a more potent effect than formulations of beclometasone dipropionate with a non-extra fine particle size distribution (100 micrograms of beclometasone dipropionate extrafine in Proxor are equivalent to 250 micrograms of beclometasone dipropionate in a non-extrafine formulation). Therefore, the total daily dose of beclometasone dipropionate administered in Proxor should be lower than the total daily dose of beclometasone dipropionate administered in a non-extrafine beclometasone dipropionate formulation.

This should be taken into consideration when a patient is transferred from a beclometasone dipropionate non-extrafine formulation to Proxor; the dose of beclometasone dipropionate should be lower and will need to be adjusted to the individual needs of the patients.

There are two treatment approaches:

A. Maintenance therapy: Proxor is taken as regular maintenance treatment with a separate as needed rapid-acting bronchodilator.

B. Maintenance and reliever therapy: Proxor is taken as regular maintenance treatment and as needed in response to asthma symptoms.

A. Maintenance therapy

Patients should be advised to have their separate rapid-acting bronchodilator available for rescue use at all times.

Dose recommendations for adults 18 years and above:

One or two inhalations twice daily.

The maximum daily dose is 4 inhalations.

B. Maintenance and reliever therapy

Patients take their daily maintenance dose of Proxor and in addition take Proxor as needed in response to asthma symptoms. Patients should be advised to always have Proxor available for rescue use.

Proxor maintenance and reliever therapy should especially be considered for patients with:

• not fully controlled asthma and in need of reliever medication

• asthma exacerbations in the past requiring medical intervention

Close monitoring for dose-related adverse effects is needed in patients who frequently take high numbers of Proxor as-needed inhalations.

Dose recommendations for adults 18 years and above:

The recommended maintenance dose is one inhalation twice daily (one inhalation in the morning and one inhalation in the evening).

Patients should take one additional inhalation as needed in response to symptoms. If symptoms persist after a few minutes, an additional inhalation should be taken.

The maximum daily dose is 8 inhalations.

Patients requiring frequent use of rescue inhalations daily should be strongly recommended to seek medical advice. Their asthma should be reassessed and their maintenance therapy should be reconsidered.

Dose recommendations for children and adolescents under 18 years:

The safety and efficacy of Proxor in children and adolescents under 18 years of age have not been established. Data available with beclometasone dipropionate/formoterol in children between 5 and 11 years of age and adolescents between 12 and 17 years of age are described in section 4.8, 5.1 and 5.2, but no recommendation on a posology can be made.

Patients should be regularly reassessed by a doctor, so that the dosage of Proxor remains optimal and is only changed on medical advice. The dose should be titrated to the lowest dose at which effective control of symptoms is maintained. When control of symptoms is maintained with the lowest recommended dosage, then the next step could include a test of inhaled corticosteroid alone.

Patients should be advised to take Proxor every day even when asymptomatic.

COPD

Dose recommendations for adults 18 years and above:

Two inhalations twice daily.

Special patient groups:

There is no need to adjust the dose in elderly patients. There are no data available for use of beclometasone dipropionate/formoterol in patients with hepatic or renal impairment (see section 5.2).

Method of administration

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 Patient Information Leaflet carefully and follow the instructions for use as given in the Leaflet.

Proxor inhaler is provided with a dose counter for the packs of 120 actuations and a dose indicator for the packs of 180 actuations both on the back of the actuator, which shows how many doses are left. For the 120 doses presentation each time the patient presses the canister, a puff of medicine is released and the counter counts down by one. For the 180 presentation, each time the patient presses the canister the counter rotates by a small amount and the number of puffs remaining is displayed in intervals of 20. Patients should be advised not to drop the inhaler as this may cause the counter to count down.

Testing the inhaler

Before using the inhaler for the first time or if the inhaler has not been used for 14 days or more, the patient should release one actuation into the air in order to ensure that the inhaler is working properly.

After testing the inhaler for the first time, the counter should read 120 or 180.

Whenever possible patients should stand or sit in an upright position when inhaling from their inhaler.

Use of the inhaler:

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 as long as possible and, finally, they should remove the inhaler from the mouth and breathe out slowly. Patients should not breathe out into the inhaler.

To inhale a further puff, patients should keep the inhaler in a vertical position for about half a minute and repeat steps 2 to 5.

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

After use, patients should close the inhaler with protective cap and check the dose counter or dose indicator.

Patients should be advised to get a new inhaler when the dose counter or indicator shows the number 20. They should stop using the inhaler when the counter shows 0 as any puffs left in the device may not be enough to release a full dose.

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).

Cleaning

Patients should be advised to read the Patient Information Leaflet carefully for cleaning instructions. For the regular cleaning of the inhaler, patients should remove the cap from the mouthpiece and wipe the outside and inside of the mouthpiece with a dry cloth. They should not remove the canister from the actuator and should not use water or other liquids to clean the mouthpiece.

Patients who find it difficult to synchronise aerosol actuation with inspiration of breath, may use the AeroChamber Plus® spacer device. They should be advised by their doctor, pharmacist or a nurse in the proper use and care of their inhaler and spacer and their technique checked to ensure optimum delivery of the inhaled medicinal product to the lungs. This may be obtained by the patients using the AeroChamber Plus® by one continuous slow and deep breath through the spacer, without any delay between actuation and inhalation.

4.3 Contraindications

Hypersensitivity to beclometasone dipropionate, formoterol fumarate dihydrate or to any of the excipients listed in section 6.1.

4.4 Special warnings and precautions for use

Proxor should be used with caution (which may include monitoring) in patients with cardiac arrhythmias, especially third degree atrioventricular block and tachyarrhythmias (accelerated and/or irregular heart beat), idiopathic subvalvular aortic stenosis, hypertrophic obstructive cardiomyopathy, severe heart disease, particularly acute myocardial infarction, ischaemic heart disease, congestive heart failure, occlusive vascular diseases, particularly arteriosclerosis, arterial hypertension and aneurysm.

Caution should also be observed when treating patients with known or suspected prolongation of the QTc interval, either congenital or drug induced (QTc > 0.44 seconds). Formoterol itself may induce prolongation of the QTc interval.

Caution is also required when Proxor is used by patients with thyrotoxicosis, diabetes mellitus, phaeochromocytoma and untreated hypokalaemia.

Potentially serious hypokalaemia may result from $beta_2$-agonist therapy. Particular caution is advised in severe asthma as this effect may be potentiated by hypoxia. Hypokalaemia may also be potentiated by concomitant treatment with other medicinal products which can induce hypokalaemia, such as xanthine derivatives, steroids and diuretics (see Section 4.5). Caution is also recommended in unstable asthma when a number of “rescue” bronchodilators may be used. It is recommended that serum potassium levels are monitored in such situations.

The inhalation of formoterol may cause a rise in blood glucose levels. Therefore, blood glucose should be closely monitored in patients with diabetes.

If anaesthesia with halogenated anaesthetics is planned, it should be ensured that Proxor is not administered for at least 12 hours before the start of anaesthesia as there is a risk of cardiac arrhythmias.

As with all inhaled medication containing corticosteroids, Proxor should be administered with caution in patients with active or quiescent pulmonary tuberculosis, fungal and viral infections in the airways.

It is recommended that treatment with Proxor 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 or COPD is potentially life- threatening and the patient should undergo urgent medical assessment. Consideration should be given to the need of increased treatment with corticosteroids, either inhaled or oral therapy, or antibiotic treatment if an infection is suspected.

Patients should not be initiated on Proxor during an exacerbation, or if they have significantly worsening or acutely deteriorating asthma. Serious asthma-related adverse events and exacerbations may occur during treatment with Proxor. Patients should be asked to continue treatment but to seek medical advice if asthma symptoms remain uncontrolled or worsen after initiation on Proxor.

As with other inhalation therapy paradoxical bronchospasm may occur with an immediate increase in wheezing and rapidness of breath after dosing. This should be treated immediately with a fast-acting inhaled bronchodilator. Proxor should be discontinued immediately, the patient assessed and alternative therapy instituted if necessary.

Proxor should not be used as the first treatment for asthma.

For treatment of acute asthma attacks patients should be advised to have their rapid-acting bronchodilator available at all times, either Proxor (for patients using Proxor as maintenance and reliever therapy) or a separate rapid-acting bronchodilator (for patients using Proxor as maintenance therapy only).

Patients should be reminded to take Proxor daily as prescribed even when asymptomatic. The reliever inhalations of Proxor should be taken in response to asthma symptoms but are not intended for regular prophylactic use, e.g. before exercise. For such use, a separate rapid-acting bronchodilator should be considered.

Once asthma symptoms are controlled, consideration may be given to gradually reducing the dose of Proxor. Regular review of patients as treatment is stepped down is important. The lowest effective dose of Proxor should be used (see also section 4.2).

Systemic effects may occur with any inhaled corticosteroid, particularly at high doses prescribed for long periods. These effects are much less likely to occur with inhaled than with oral corticosteroids. Possible systemic effects include: Cushing's syndrome, Cushingoid features, adrenal suppression, decrease in bone mineral density, growth retardation in children and adolescents, 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).

Therefore, it is important that the patient is reviewed regularly, and the dose of inhaled corticosteroid is reduced to the lowest dose at which effective control of asthma is maintained.

Single dose pharmacokinetic data (see section 5.2) have demonstrated that the use of beclometasone dipropionate/formoterol with Aerochamber Plus® spacer device in

comparison to the use of standard actuator, does not increase the total systemic exposure to formoterol and reduces the systemic exposure to beclometasone-17-monopropionate, while there is an increase for unchanged beclometasone dipropionate that reaches systemic circulation from the lung; however, since the total systemic exposure to beclometasone dipropionate plus its active metabolite does not change, there is no increased risk of systemic effects when using beclometasone dipropionate/formoterol with the named spacer device.

Prolonged treatment of patients with high doses of inhaled corticosteroids may result in adrenal suppression and acute adrenal crisis. Children aged less than 16 years taking/inhaling higher than recommended doses of beclometasone dipropionate may be at particular risk. 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 Proxor 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.

Pneumonia in patients with COPD

An increase in the incidence of pneumonia, including pneumonia requiring hospitalisation, has been observed in patients with COPD receiving inhaled corticosteroids. There is some evidence of an increased risk of pneumonia with increasing steroid dose but this has not been demonstrated conclusively across all studies. There is no conclusive clinical evidence for intra-class differences in the magnitude of the pneumonia risk among inhaled corticosteroid products. Physicians should remain vigilant for the possible development of pneumonia in patients with COPD as the clinical features of such infections overlap with the symptoms of COPD exacerbations. Risk factors for pneumonia in patients with COPD include current smoking, older age, low body mass index (BMI) and severe COPD.

Patients should be advised to rinse the mouth or gargle with water or brush the teeth after inhaling the prescribed dose to minimise the risk of oropharyngeal candida infection.

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.

Alcohol content

Proxor contains 7 mg of alcohol (ethanol) in each actuation which is equivalent to 0.19 mg/kg per dose of two actuations. The amount in 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

Pharmacokinetic interactions

Beclometasone dipropionate undergoes a very rapid metabolism via esterase enzymes.

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.

Pharmacodynamic interactions

Beta- blockers (including eye drops) should be avoided in asthmatic patients. If beta-blockers are administered for compelling reasons, the effect of formoterol will be reduced or abolished.

On the other hand, concomitant use of other beta-adrenergic drugs can have potentially additive effects, therefore caution is required when theophylline or other beta-adrenerigic drugs are prescribed concomitantly with formoterol.

Concomitant treatment with quinidine, disopyramide, procainamide, phenothiazines, antihistamines, monoamine oxidase inhibitors and tricyclic antidepressants can prolong the QTc-interval and increase the risk of ventricular arrhythmias.

In addition, L-dopa, L-thyroxine, oxytocin and alcohol can impair cardiac tolerance towards $beta_2$- sympathomimetics.

Concomitant treatment with monoamine oxidase inhibitors including agents with similar properties such as furazolidone and procarbazine may precipitate hypertensive reactions.

There is an elevated risk of arrhythmias in patients receiving concomitant anaesthesia with halogenated hydrocarbons.

Concomitant treatment with xanthine derivatives, steroids, or diuretics may potentiate a possible hypokalaemic effect of $beta_2$-agonists (see section 4.4.). Hypokalaemia may increase the disposition towards arrhythmias in patients who are treated with digitalis glycosides.

Proxor 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

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.

Pregnancy

There are no relevant clinical data on the use of Proxor in pregnant women. Animal studies using beclometasone dipropionate and formoterol combination showed evidence of toxicity to reproduction after high systemic exposure (see 5.3 Preclinical safety data). Because of the tocolytic actions of $beta_2$- sympathomimetic agents particular care should be exercised in the run up to delivery. Formoterol should not be recommended for use during pregnancy and particularly at the end of pregnancy or during labour unless there is no other (safer) established alternative.

Proxor should only be used during pregnancy if the expected benefits outweigh the potential risks.

Breast-feeding

There are no relevant clinical data on the use of Proxor in lactation in humans.

Although no data from animal experiments are available, it is reasonable to assume that beclometasone dipropionate is secreted in milk, like other corticosteroids.

While it is not known whether formoterol passes into human breast milk, it has been detected in the milk of lactating animals.

Administration of Proxor to women who are breast-feeding should only be considered if the expected benefits outweigh the potential risks.

Fertility

There are no data in humans. In animal studies in rats, the presence of beclometasone dipropionate at high doses in the combination was associated with reduced female fertility and embryotoxicity (see section 5.3).

4.7 Effects on ability to drive and use machines

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

4.8 Undesirable effects

As Proxor contains beclometasone dipropionate and formoterol fumarate dihydrate, the type and severity of adverse reactions associated with each of the compounds may be expected. There is no incidence of additional adverse events following concurrent administration of the two compounds.

Undesirable effects which have been associated with beclometasone dipropionate and formoterol administered as a fixed combination (Proxor) and as single agents are given below, listed by system organ class. Frequencies are defined as: very common (≥1/10), common (≥1/100 to <1/10), uncommon (≥1/1,000 to <1/100), rare

(≥1/10,000 < 1/1,000) and very rare (≤1/10,000), not known (cannot be estimated from the available data.

Common and uncommon ADRs were derived from clinical trials in asthmatic and COPD patients.

System Organ Class	Adverse Reaction	Frequency
Infections and Infestations	Pharyngitis, oral candidiasis, pneumonia* (in COPD patients)	Common
	Influenza, oral fungal infection, oropharyngeal candidiasis, oesophageal candidiasis, vulvovaginal candidiasis, gastroenteritis, sinusitis, rhinitis,	Uncommon
Blood and lymphatic system disorders	Granulocytopenia	Uncommon
	Thrombocytopenia	Very rare
Immune system disorders	Dermatitis allergic	Uncommon
	Hypersensitivity reactions, including erythema, lips, face, eye and pharyngeal oedema	Very rare
Endocrine disorders	Adrenal suppression	Very rare
Metabolism and nutrition disorders	Hypokalaemia, hyperglycaemia	Uncommon
Psychiatric disorders	Restlessness	Uncommon
	Psychomotor hyperactivity, sleep disorders, anxiety, depression, aggression, behavioural changes (predominantly in children)	Not known
Nervous system disorders	Headache	Common
	Tremor, dizziness	Uncommon
Eye disorders	Glaucoma, cataract	Very rare
	Vision, blurred (see also section 4.4)	Not known

Ear and labyrinth disorders	Otosalpingitis	Uncommon
Cardiac disorders	Palpitations, electrocardiogram QT corrected interval prolonged, electrocardiogram change, tachycardia, tachyarrhythmia, atrial fibrillation*,	Uncommon
	Ventricular extrasystoles, angina pectoris	Rare
Vascular disorders	Hyperaemia, flushing	Uncommon
Respiratory, thoracic and mediastinal disorders	Dysphonia	Common
	Cough, productive cough, throat irritation, asthmatic crisis	Uncommon
	Bronchospasm paradoxical	Rare
	Dyspnoea, exacerbation of asthma	Very rare
Gastrointestinal disorders	Diarrhoea, dry mouth, dyspepsia, dysphagia, burning sensation of the lips, nausea, dysgeusia	Uncommon
Skin and subcutaneous tissue disorders	Pruritus, rash, hyperhidrosis, urticaria	Uncommon
	Angioedema	Rare
Musculoskeletal and connective tissue disorders	Muscle spasms, myalgia	Uncommon
	Growth retardation in children and adolescents	Very rare
Renal and urinary disorders	Nephritis	Rare
General disorders and administration site conditions	Oedema peripheral	Very rare
Investigations	C-reactive protein increased, platelet count increased, free fatty acids increased, blood insulin increased, blood ketone body increased, blood cortisol decrease*	Uncommon
	Blood pressure increased, blood pressure decreased	Rare
	Bone density decreased	Very rare

* One related non serious case of pneumonia was reported by one patient treated with beclometasone dipropionate/formoterol in a pivotal clinical trial in COPD patients. Other adverse reactions observed with beclometasone dipropionate/formoterol in COPD clinical trials were: reduction of blood cortisol and atrial fibrillation.

As with other inhalation therapy, paradoxical bronchospasm may occur (see 4.4 'Special Warnings and Precautions for Use').

Among the observed adverse reactions those typically associated with formoterol are:

hypokalemia, headache, tremor, palpitations, cough, muscle spasms and prolongation of QTc interval.

Adverse reactions typically associated with the administration of beclomethasone dipropionate are:

oral fungal infections, oral candidiasis, dysphonia, throat irritation.

Dysphonia and candidiasis may be relieved by gargling or rinsing the mouth with water or brushing the teeth after using the product. Symptomatic candidiasis can be treated with topical anti-fungal therapy whilst continuing the treatment with Proxor.

Systemic effects of inhaled corticosteroids (e.g. beclometasone dipropionate) may occur particularly when administered at high doses prescribed for prolonged periods, these may include adrenal suppression, decrease in bone mineral density, growth retardation in children and adolescents, cataract and glaucoma (see also 4.4).

Hypersensitivity reactions including rash, urticaria pruritus, erythema and oedema of the eyes, face, lips and throat may also occur.

Paediatric Population

In a 12-week study in adolescent asthma patients, the safety profile of a medicinal containing beclometasone dipropionate and formoterol was not different to that of beclomethasone dipropionate monotherapy.

Beclometasone/Formoterol paediatric experimental formulation of beclometasone dipropionate and formoterol fumarate 50/6 micrograms per actuation administered to asthmatic children aged 5-11 years over 12 weeks tratement period, showed a safety profile similar to the approved marketed formoterol and beclometasone dipropionate single agents.

However, the same paediatric formulation of Beclometasone/Formoterol 50/6 micrograms administered to asthmatic children aged 5-11 years over 2 weeks did not demonstrate non-inferiority to the free combination of marketed formoterol and beclometasone dipropionate single agents in terms of lower leg growth rate.

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

4.9 Overdose

Inhaled doses of beclometasone dipropionate/formoterol up to twelve cumulative actuations (total beclometasone dipropionate 1200 micrograms, formoterol 72 micrograms) have been studied in asthmatic patients. The cumulative treatments did not cause abnormal effect on vital signs and neither serious nor severe adverse events were observed.

Excessive doses of formoterol may lead to effects that are typical of $beta_2$-adrenergic agonists: nausea, vomiting, headache, tremor, somnolence, palpitations, tachycardia, ventricular arrhythmias, prolongation of QTc interval, metabolic acidosis, hypokalaemia, hyperglycaemia.

In case of overdose of formoterol, supportive and symptomatic treatment is indicated. Serious cases should be hospitalised. Use of cardio selective beta-adrenergic blockers may be considered, but only subject to extreme caution since the use of beta-adrenergic blocker medication may provoke bronchospasm. Serum potassium should be monitored.

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 recovers in a few days, as verified by plasma cortisol measurements. In these patients treatment should be continued at a dose sufficient to control asthma.

Chronic overdose of inhaled beclometasone dipropionate: risk of adrenal suppression (see section 4.4.). Monitoring of adrenal reserve may be necessary. Treatment should be continued at a dose sufficient to control asthma.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Drugs for obstructive airway diseases; Adrenergics, inhalants

ATC-code: R03 AK08.

Mechanisms of action and pharmacodynamic effects

Proxor contains beclometasone dipropionate and formoterol. These two actives have different modes of action. In common with other inhaled corticosteroids and $beta_2$-agonist combinations, additive effects are seen in respect of reduction in asthma exacerbations.

Beclometasone dipropionate

Beclometasone dipropionate given by inhalation at recommended doses has a glucocorticoid anti-inflammatory action within the lungs, resulting in reduced symptoms and exacerbations of asthma with less adverse effects than when corticosteroids are administered systemically.

Formoterol

Formoterol is a selective beta$_2$-adrenergic agonist that produces relaxation of bronchial smooth muscle in patients with reversible airways obstruction. The broncho dilating effect sets in rapidly, within 1-3 minutes after inhalation, and has a duration of 12 hours after a single dose.

ASTHMA

Clinical efficacy for beclometasone dipropionate/formoterol maintenance therapy

In clinical trials in adults, the addition of formoterol to beclometasone dipropionate improved asthma symptoms and lung function and reduced exacerbations.

In a 24-week study the effect on lung function of a medicinal product containing beclomethasone and formoterol 100/6 HFA was at least equal to that of the free combination of beclometasone dipropionate and formoterol, and exceeded that of beclometasone dipropionate alone.

Clinical efficacy for beclometasone dipropionate/formoterol maintenance and reliever therapy

In a 48-week parallel group study involving 1701 asthma patients, the efficacy of beclometasone dipropionate/formoterol administered as maintenance (1 inhalation BID) and reliever therapy (up to a total of 8 puffs per day) was compared to beclometasone dipropionate/formoterol administered as maintenance therapy (1 inhalation BID) plus as needed salbutamol, in adult patients with un-controlled moderate to severe asthma. The results demonstrated that beclometasone dipropionate/formoterol used as maintenance and reliever therapy significantly prolonged the time to first severe exacerbation (*) when compared with the fixed combination beclomethasone dipropionate and formoterol used as maintenance plus as needed salbutamol ($p< 0.001$ for both ITT and PP population). The rate of severe asthma exacerbations per patients/year, was significantly reduced in the maintenance and reliever therapy group compared to salbutamol group: 0,1476 vs 0,2239 respectively (statistically significant reduction: $p<0.001$). Patients in the beclometasone dipropionate/formoterol maintenance and reliever group achieved a clinically meaningful improvement in asthma control. The mean number of inhalations/day of reliever medication and the proportion of patients using reliever medication decreased similarly in both groups.

Note*: severe exacerbations were defined as deterioration in asthma resulting in hospitalisation or emergency room treatment, or resulting in the need for systemic steroids for more than 3 days.

In another clinical study, a single dose of the fixed combination beclomethasone dipropionate and formoterol 100/6 micrograms provided a quick bronchodilation effect and a rapid relief from dyspnea symptoms similar to that of salbutamol 200 micrograms/dose in asthmatic patients when metacholine challenge is used to induce bronchoconstriction.

Paediatric population

In a 12-week study in adolescent asthma patients beclometasone dipropionate/formoterol 100/6 micrograms was not superior to beclomethasone dipropionate monotherapy, neither in terms of pulmonary function parameters (primary variable: change from baseline in pre-dose morning PEF), secondary efficacy variables, nor clinical outcome measures.

COPD

In two 48-weeks studies, the effects on lung function and the rate of exacerbation (defined as courses of oral steroids and/or course of antibiotics and/or hospitalizations) in patients with severe COPD (30% <FEV_1%<50%) was evaluated.

One pivotal trial showed a significant improvement in lung function (primary endpoint change in pre-dose FEV_1) compared to formoterol after 12 weeks of treatment (adjusted mean difference between the fixed combination and formoterol: 69 ml) as well as at each clinic visit during the whole treatment period (48 weeks). The study demonstrated that the mean number of exacerbations per patient/year (exacerbation rate, co-primary endpoint) was statistically significantly reduced with the fixed combination as compared with formoterol treatment (adjusted mean rate 0.80 compared with 1.12 in the formoterol group, adjusted ratio 0.72, $p<0.001$) over 48 weeks treatment period in a total of 1199 patients with severe COPD. In addition, the fixed combination beclomethasone dipropionate and formoterol statistically significantly prolonged the time to first exacerbation compared to formoterol. The superiority of the originator medicine beclomethasone dipropionate and formoterol versus formoterol was also confirmed in terms of exacerbation rate in subgroups of patients taking (around 50% in each treatment arm) or not Tiotropium Bromide as concomitant medication.

The other pivotal study, which was a three arm, randomized, parallel group study in 718 patients, confirmed the superiority of the fixed combination beclomethasone dipropionate and formoterol versus formoterol treatment in terms of change in pre-dose FEV_1 at the end of treatment (48weeks) and demonstrated the non-inferiority of the fixed combination beclomethasone dipropionate and formoterol compared to budesonide/formoterol fixed dose combination on the same parameter.

All the studies described in this section are the outcome of literature search.

5.2 Pharmacokinetic properties

The systemic exposure to the active substances beclometasone dipropionate and formoterol in the fixed combination have been compared to the single components.

In a pharmacokinetic study conducted in healthy subjects treated with a single dose of beclometasone dipropionate/formoterol fixed combination (4 puffs of 100/6 micrograms) or a single dose of beclometasone dipropionate CFC (4 puffs of 250 micrograms) and formoterol HFA (4 puffs of 6 micrograms), the Area Under the Curve (AUC) of beclometasone dipropionate main active metabolite (beclometasone-17-monopropionate) and its maximal plasma concentration were, respectively, 35% and 19% lower with the fixed combination than with non-extrafine beclometasone dipropionate CFC formulation, in contrast, the rate of absorption was more rapid (0.5 vs 2h) with the fixed combination compared to non-extrafine beclometasone dipropionate CFC formulation alone.

For formoterol, maximal plasma concentration was similar after administration of the fixed or the extemporary combination and the systemic exposure was slightly higher after administration of beclometasone dipropionate/formoterol than with the extemporary combination.

There was no evidence of pharmacokinetic or pharmacodynamic (systemic) interactions between beclometasone dipropionate and formoterol.

The use of Aerochamber Plus® spacer increased the lung delivery of beclometasone dipropionate active metabolite beclometasone 17-monopropionate and formoterol by

41% and 45% respectively, in comparison to the use of standard actuator in a study conducted in healthy volunteers. The total systemic exposure was unchanged for formoterol, reduced by 10% for beclometasone 17-monopropionate and increased for unchanged beclometasone dipropionate.

A lung deposition study conducted in stable COPD patients, healthy volunteers and asthmatic patients, demonstrated that on average 33% of the nominal dose is deposited into the lung of COPD patients compared to 34% in healthy subjects and 31% in asthmatic patients. Beclometasone 17-monopropionate and formoterol plasma exposures were comparable across the three groups during the 24 hours following the inhalation. The total exposure of beclometasone dipropionate was higher in COPD patients compared to the exposure in asthmatic patients and healthy volunteers.

Paediatric population

Beclometasone dipropionate/formoterol was not bioequivalent to a free combination of extrafine beclometasone dipropionate and formoterol if administered to asthmatic adolescents aged 12 to 17 years in a single dose pharmacokinetic study (4 actuations of 100/6 micrograms). This result was independent of whether a spacer (Aerochamber Plus®) was used or not.

If a spacer was not used, available data point towards a lower peak plasma concentration of inhaled corticosteroid component from beclometasone dipropionate/formoterol in comparison with the free combination (point estimate of the ratios of adjusted geometric means for Cmax of beclometasone 17-monopropionate [B17MP] 84.38 %, 90%CI 70.22; 101.38).

When beclometasone dipropionate/formoterol was used with the spacer, the peak plasma concentration of formoterol was increased by about 68% in comparison with the free combination (point estimate of the ratios of adjusted geometric means for Cmax 168.41, 90%CI 138.2; 205.2). The clinical significance of these differences in case of chronic use is unknown.

Total systemic exposure to formoterol (AUC_{0-t}) was equivalent to that of the free combination, irrespective of whether the spacer was used or not. For beclometasone 17-monopropionate, equivalence was demonstrated only when spacer was not used, while 90% CI of AUC_{0-t} was slightly outside the equivalence interval when spacer was used (point estimate of the ratios of adjusted geometric means 89.63%, CI 79.93; 100.50).

Beclometasone dipropionate/formoterol used without spacer in adolescents produced lower beclometasone 17-monopropionate or equivalent formoteroltotal systemic exposure (AUC_{0-t}) as compared to that observed in adults. Moreover, average peak plasma concentrations (C_{max}) for both substances were lower in adolescents than in adults.

In a single dose pharmacokinetic study beclometasone dipropionate/formoterol paediatric experimental formulation 50/6 micrograms per actuation administered with Aerochamber Plus® was not bioequivalent to a free combination of beclometasone dipropionate and formoterol administered to asthmatic children aged 5 to 11 years. Study results indicate a lower AUC_{0-t} and peak plasma concentration of inhaled corticosteroid component from beclometasone dipropionate/formoterol 50/6 in comparison with the free combination (point estimate of the ratios of adjusted geometric means for beclometasone 17-monopropionate AUC_{0-t}: 81%, 90%CI 69.7;94.8; Cmax: 82 %, 90%CI 70.1; 94.7). Total systemic exposure to formoterol (AUC_{0-t}) was equivalent to that of the free combination, while Cmax was slightly lower for beclometasone dipropionate /formoterol combination 50/6 in comparison with the free combination (point estimate of the ratios of adjusted geometric means 92%, 90%CI 78;108).

Beclometasone dipropionate

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, distribution and biotransformation

Inhaled beclometasone dipropionate is rapidly absorbed through the lungs; prior to absorption there is extensive conversion to its active metabolite beclometasone-17-monopropionate via esterase enzymes that are found in most tissues. The systemic availability of the active metabolite arises from lung (36 %) and from gastrointestinal absorption of the swallowed dose. The bioavailability of swallowed beclometasone dipropionate is negligible however, pre-systemic conversion to beclometasone-17-monopropionate results in 41% of the dose being absorbed as the active metabolite.

There is an approximately linear increase in systemic exposure with increasing inhaled dose.

The absolute bioavailability following inhalation is approximately 2% and 62% of the nominal dose for unchanged beclometasone dipropionate and beclometasone-17-monopropionate respectively.

Following intravenous dosing, the disposition of beclometasone dipropionate and its active metabolite are characterised by high plasma clearance (150 and 120L/h respectively), with a small volume of distribution at steady state for beclometasone dipropionate (20L) and larger tissue distribution for its active metabolite (424L).

Plasma protein binding is moderately high.

Elimination

Faecal excretion is the major route of beclometasone dipropionate elimination mainly as polar metabolites. The renal excretion of beclometasone dipropionate and its metabolites is negligible. The terminal elimination half-lives are 0.5 h and 2.7 h for beclometasone dipropionate and beclometasone- 17-monopropionate respectively.

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.

Formoterol

Absorption and distribution

Following inhalation, formoterol is absorbed both from the lung and from the gastrointestinal tract. The fraction of an inhaled dose that is swallowed after administration with a metered dose inhaler (MDI) may range between 60% and 90%. At least 65% of the fraction that is swallowed is absorbed from the gastrointestinal tract. Peak plasma concentrations of unchanged drug occur within 0.5 to 1 hours after oral administration. Plasma protein binding of formoterol is 61-64% with 34% bound

to albumin. There was no saturation of binding in the concentration range attained with therapeutic doses. The elimination half-life determined after oral administration is 2-3 hours. Absorption of formoterol is linear following inhalation of 12 to 96 μg of formoterol fumarate.

Biotransformation

Formoterol is widely metabolised and the prominent pathway involves direct conjugation at the phenolic hydroxyl group. Glucuronide acid conjugate is inactive. The second major pathway involves O-demethylation followed by conjugation at the phenolic 2'-hydroxyl group. Cytochrome P450 isoenzymes CYP2D6, CYP2C19 and CYP2C9 are involved in the O-demethylation of formoterol. Liver appears to be the primary site of metabolism. Formoterol does not inhibit CYP450 enzymes at therapeutically relevant concentrations.

Elimination

The cumulative urinary excretion of formoterol after single inhalation from a dry powder inhaler increased linearly in the 12 – 96 μg dose range. On average, 8% and 25% of the dose was excreted as unchanged and total formoterol, respectively. Based on plasma concentrations measured following inhalation of a single 120 μg dose by 12 healthy subjects, the mean terminal elimination half-life was determined to be 10 hours. The (R,R)- and (S,S)-enantiomers represented about 40% and 60% of unchanged drug excreted in the urine, respectively. The relative proportion of the two enantiomers remained constant over the dose range studied and there was no evidence of relative accumulation of one enantiomer over the other after repeated dosing.

After oral administration (40 to 80 μg), 6% to 10% of the dose was recovered in urine as unchanged drug in healthy subjects; up to 8% of the dose was recovered as the glucuronide.

A total 67% of an oral dose of formoterol is excreted in urine (mainly as metabolites) and the remainder in the faeces. The renal clearance of formoterol is 150 ml/min.

Special populations

Hepatic/Renal impairment: the pharmacokinetics of formoterol has not been studied in patients with hepatic or renal impairment; however, as formoterol is primarily eliminated via hepatic metabolism, an increased exposure can be expected in patients with severe liver cirrhosis.

All the studies described in this section are the outcome of literature search.

5.3 Preclinical safety data

The toxicity observed in animal studies with beclometasone dipropionate and formoterol, given in combination or separately, consisted mainly of effects associated with exaggerated pharmacological activity. They are related to the immuno-suppressive activity of beclometasone dipropionate and to the known cardiovascular effects of formoterol evident mainly in dogs. Neither increase in toxicity nor occurrence of unexpected findings were observed upon administration of the combination.

Reproduction studies in rats showed dose-dependent effects. The combination was associated with reduced female fertility and embryofetal toxicity. High doses of corticosteroids to pregnant animals are known to cause abnormalities of fetal

development including cleft palate and intra-uterine growth retardation, and it is likely that the effects seen with the beclometasone dipropionate /formoterol combination were due to beclometasone dipropionate. These effects were noted only with high systemic exposure to the active metabolite beclometasone-17-monopropionate (200 fold the expected plasma levels in patients). Additionally, increased duration of gestation and parturition, an effect attributable to the known tocolytic effects of $beta_2$-sympathomimetics, was seen in animal studies.

These effects were already noted for maternal plasma formoterol levels below the levels expected in patients treated with beclometasone dipropionate/formoterol .

Genotoxicity studies performed with a beclometasone dipropionate/formoterol combination do not indicate mutagenic potential. No carcinogenicity studies have been performed with the proposed combination. However animal data reported for the individual constituents do not suggest any potential risk of carcinogenicity in man.

Pre-clinical data on the CFC-free propellant HFA-134a reveal no special hazard for humans based on conventional studies of safety pharmacology, repeated dose toxicity, genotoxicity, carcinogenic potential and toxicity to reproduction.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Norflurane

Ethanol anhydrous

Hydrochloric acid, concentrated

See leaflet for further information.

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

21 months.

6.4 Special precautions for storage

Before use:

Store in a refrigerator (2-8°C)

After use: Do not store above 25°C for a maximum of 3 months.

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

The inhalation solution is contained in a pressurised aluminium container sealed with a metering valve and fitted into a white polypropylene plastic actuator which incorporates a dose-counter (120 doses pack) or a dose indicator (180 doses pack) and a mouthpiece is provided with a pink plastic protective cap.

Each pack contains:

1 pressurised container which provides 120 actuations or

2 pressurised containers which provide 120 actuations each or

3 pressurised containers which provide 120 actuations each or

1 pressurised container which provides 180 actuations

Not all pack sizes may be marketed.

6.6 Special precautions for disposal

For pharmacies:

Enter the date of dispensing to the patient on the pack.

Ensure that there is a period of at least 3 months between the date of dispensing and the expiry date printed on the pack.

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

7 MARKETING AUTHORISATION HOLDER

Genus Pharmaceuticals Ltd. (trading as ‘STADA’),

Linthwaite,

Huddersfield,

HD7 5QH,

UK

8 MARKETING AUTHORISATION NUMBER(S)

PL 06831/0391

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

06/11/2024

10 DATE OF REVISION OF THE TEXT

06/11/2024