SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT
FOREBEC 100 mcg/6 mcg Capsules with Inhalation Powder

2. QUALITATIVE AND QUANTITATIVE COMPOSITION
Each hard capsule contains:
Active substance(s):
Beclometasone dipropionate……100 micrograms
Formoterol fumarate dihydrate……6 micrograms
With each inhalation, the patient receives 81.9 mcg of beclometasone dipropionate and 5 mcg of formoterol fumarate dihydrate

Excipient(s):
Lactose monohydrate (Inhalac 250) (from bovine milk)…….11.9 mg
Lactose monohydrate (Inhalac 400) (from bovine milk)……2.9 mg
For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM
Powder for inhalation, hard capsules.
Transparent pink capsules containing white or almost white powder.

4. CLINICAL PARTICULARS
4.1 Therapeutic indications
This drug is indicated for the relief and control of asthma symptoms. It is given as of the third step in the stepwise management of asthma. In moderate to severe COPD cases, it reduces the symptoms and attack frequency.

4.2 Posology and method of administration
FOREBEC is for inhalation only.

Posology/frequency and duration of administration
Asthma
FOREBEC is not intended for the initial management of asthma.

The dosage of FOREBEC 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.

Because of its extra fine particle size distribution, dose adjustment is required when patients are transferred to FOREBEC from a formulation with a non-extrafine particle size distribution. When switching patients from previous treatments, it should be considered that the recommended total daily dose of beclometasone dipropionate for FOREBEC is lower than that for current beclometasone dipropionate-containing non-extrafine products and should be adjusted to the needs of the individual patient. However, patients who are transferred to FOREBEC dry powder inhaler from the combination of beclometasone dipropionate/formoterol pressurized metered inhaler do not need dose adjustment.

For adults 18 years and above
Maintenance therapy with FOREBEC: a rapid-acting rescue bronchodilator is used with FOREBEC which is used as regular maintenance therapy.

The need for a separate rapid-acting bronchodilator should always be considered and patients should be informed about this.

It is administered as 1 or 2 inhalations per day.

The maximum daily dose is 4 inhalations.

These patients should be reassessed and their maintenance therapy reconsidered.

Patients should be regularly reassessed by a doctor for the effectiveness of treatment. Thus, the dosage of FOREBEC remains optimal and is only changed on medical advice. The therapeutic 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-down could include the inhaled corticosteroid alone.

Patients should be advised to use the recommended dose of FOREBEC regularly, even when asymptomatic.

COPD
It is administered as 2 inhalations per day.

Method of administration
The inhaler must be used properly in order for the treatment to be successful. Patients should be advised to read the "Package Leaflet" carefully and follow the instructions for use.

When inhaling medication from the inhaler device, patients should stand in an upright body position if possible, or keep their back in an upright position when sitting.

In order to ensure the optimum dose reaches the lungs, a quick and deep breath should be taken from the mouthpiece. It should be recommended to hold the breath for 5-10 seconds or as long as the patient feels comfortable after inhaling the dose and then exhale slowly through the nose.

Patients should be warned not to exhale into the device prior to or after inhalation, as device performance can be affected.

Patients should be reminded to rinse their mouths with water or brush their teeth after inhalation (see section 4.4).

Instructions for Use of the Inhaler
Package Contents
This package contains the following:
- 120 capsules
- A mono-dose dry powder inhaler
- A package leaflet

If the contents of the package do not comply with those listed above, the inhaler should be returned to the supplier and a new one should be obtained.

General Warnings and Precautions

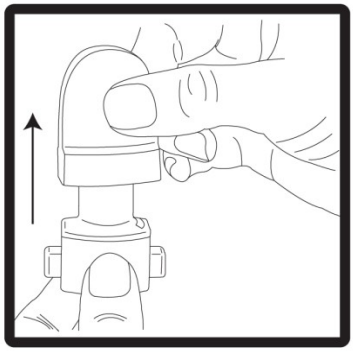
- The inhaler should only be used as directed.
- If the patients are not certain about dosing, they should wait until the next dose, which should be taken as scheduled. The patients should not take additional doses.
- The cap of the device should be kept closed until a dose from the inhaler is required.
- When not in use, the inhaler should be kept in a clean and dry place.
- For whatever reason, the inhaler should not be disassembled.

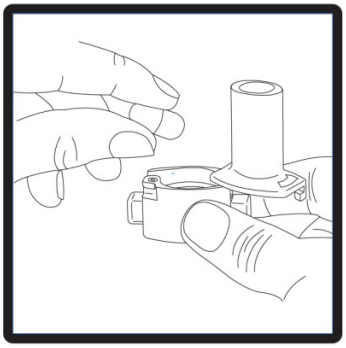
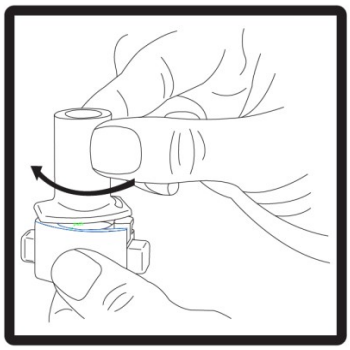
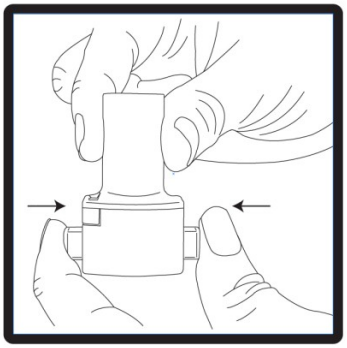
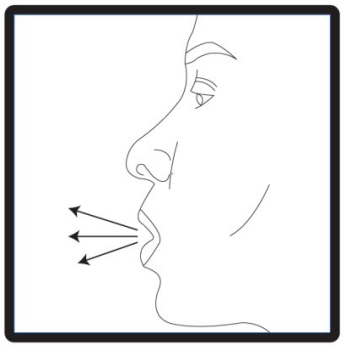
* The inhaler should not be used in the following situations:
  - After the expiry date of the drug
  - In case of any damage to the device

In these cases, the inhaler should be disposed of or returned to the provider and a replacement should be received.

Patients should be instructed to consult their pharmacists on how to dispose of inhalers when they are no longer needed.

Instructions for proper use

	1. The cap of the device should be pulled off.
	2. Holding the base of the inhaler firmly, the mouthpiece should be rotated in the arrow direction so that the capsule chamber can be opened.

	3. The capsule should be taken out of the blister right before use. It should be inserted into the capsule-shaped chamber at the base of the inhaler.
	4. The mouthpiece should be rotated back to reclose the capsule chamber.
	5. The device should be held in the upright position (with the mouthpiece facing upward) and the buttons on both edges should be pressed ONLY ONCE at the same time. After the capsule is pierced, the buttons should be left. Please note: The capsule might splinter at this step and small capsule fragments might get into the mouth or throat during inhalation. These fragments do not cause any harm if inhaled. Removing the capsule just before use and pressing the buttons only once to pierce it minimizes the risk of capsule rupture (see step 3).
	6. A vigorous exhalation should be performed.
	7. The mouthpiece should be placed in the mouth and the head should be tilted backwards slightly. The lips should be tightly closed around the mouthpiece and the patient should inhale as deeply and quickly as possible. As the powder disperses, a “whirring” will be heard since the capsule spins around in the chamber. If no such sound is heard, the capsule may be stuck in the chamber. If this is the case, the device should be opened and the capsule should be loosened by moving it in the chamber. The buttons MUST NOT be pressed more than once to loosen the capsule.

8. The breath should be held: While removing the inhaler from the mouth, the breath should be held for 5 to 10 seconds or as long as possible. Exhalation should then be performed. The inhaler should be opened to check for any powder remaining in the capsule. In case of any powder remaining in the capsule, the inhaler should be turned off and steps 6, 7 and 8 should be repeated. The majority of patients can empty the capsule in one or two inhalations. After inhalation, some patients may rarely experience a short-term cough. This should not cause any concern. An empty capsule indicates that the full dose of the medicine has been taken. In order to reduce the risk of candida infection, after each administration, it is recommended to rinse the mouth thoroughly with some water and subsequently spit out it out.
9. After use, the empty capsule should be discarded and the mouthpiece should be closed.

Additional information
Occasionally, small capsule particles may pass through the sieve into the mouth. The particles can then be felt on the tongue. Swallowing or inhaling these particles is not harmful. If the capsule is punctured multiple times (see Step 5), the probability of the capsule being ruptured increases.

Cleaning
- Normally, your inhaler does not need to be cleaned.
- If necessary, you can clean your inhaler after use with a dry cloth or tissue.
  - Do not clean your inhaler with water or other liquid. Keep it dry.

Storage
- The inhaler should be stored in a clean and dry place.
- The inhaler should not be exposed to heat or direct sunlight.
  - The inhaler should not be kept in damp or wet conditions.

* It should be kept out of the sight and reach of children.

Disposal
- Ask a pharmacist about disposing of medicines that you have finished or no longer need.
  - Medicines should not be disposed of together with common household waste.

Additional information on special populations
Renal/Hepatic impairment
No data are available on the use of beclometasone dipropionate/formoterol fumarate dihydrate in patients with renal or hepatic impairment (see section 5.2).

Pediatric population
FOREBEC should not be used in patients under 18 years of age.

The safety and efficacy of beclometasone dipropionate/formoterol fumarate dihydrate in children and patients younger than 18 years are currently under evaluation. No clinical data are available in children up to 11 years of age. The available data for adolescents 12-17 years of age are summarized in the sections 4.8 and 5.1; however, no recommendations can be made

regarding posology.
Geriatric population
No dosage adjustment is required in the elderly.

4.3 Contraindications
FOREBEC is contraindicated in case of known hypersensitivity to beclometasone dipropionate, formoterol fumarate dihydrate and/or any of its ingredients (see section 6.1).

4.4 Special warnings and precautions for use
It is recommended that the dose be tapered when the treatment is discontinued; treatment should not be stopped abruptly.

The management of asthma should normally follow a stepwise program, and patient response should be monitored clinically and by lung function tests at regular intervals.

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. Consideration should be given to the need for increased treatment with corticosteroids, either inhaled or oral therapy, or antibiotic treatment if an infection is suspected.

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

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

FOREBEC is not intended for the initial management of asthma.

For treatment of acute asthma attacks patients should be advised to have their short-acting bronchodilator available at all times.

Patients should be reminded to take FOREBEC regularly as prescribed even when asymptomatic.

Once asthma symptoms are controlled, the dose of FOREBEC should be gradually reduced.

Regular review of patients as treatment is stepped down is important. During this period, the lowest effective dose of FOREBEC should be used (see section 4.2).

Pneumonia in patients with COPD
An increase in the incidence of pneumonia, including pneumonia that requires hospitalization, 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 smoking, older age, low body mass index and severe COPD.

Systemic effects of inhaled corticosteroids may occur, particularly at high doses prescribed 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, glaucoma, and more rarely, a range of psychological or behavioral 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.

Prolonged treatment of patients with inhaled corticosteroids may result in adrenal suppression and acute adrenal crisis. Children and adolescents aged less than 16 years inhaling higher than recommended doses of beclometasone dipropionate may be at particular risk. Situations that 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, hypoglycemia, and seizures. Additional corticosteroids should be considered during periods of stress or elective surgery.

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.

FOREBEC should be administered with caution in patients with active or quiescent pulmonary tuberculosis, fungal and viral infections in the airways.

FOREBEC should be used with caution, which may include monitoring, in patients with cardiac arrhythmias, especially third degree atrioventricular block and tachyarrhythmias, idiopathic subvalvular aortic stenosis, hypertrophic obstructive cardiomyopathy, ischemic heart disease, severe heart failure, severe 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 FOREBEC is used by patients with thyrotoxicosis, diabetes mellitus, pheochromocytoma and untreated hypokalemia.

Potentially serious hypokalemia may result from beta$_2$-agonist therapy. Particular caution is advised in severe asthma as the severity of hypokalemia may be potentiated by hypoxia. Hypokalemia may also be potentiated by concomitant treatment with other drugs, which can induce hypokalemia, 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 of the patient be regularly 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 anesthesia with halogenated anesthetics is planned, it should be ensured that FOREBEC is not applied for at least 12 hours before the start of anesthesia, as there is a risk of cardiac arrhythmias.

Patients should be advised to rinse the mouth or gargle with water or brush the teeth after inhaler use to minimize the risk of oropharyngeal fungal infections and dysphonia.

Serious and sometimes fatal asthma-related respiratory problems may occur, although rarely, due to long-acting beta$_2$-agonist preparations.

Long-acting beta$_2$-agonists should be used for the shortest period of time that provides asthma symptom control, and their use should be discontinued when asthma control is achieved, if possible. Afterwards, patients should be maintained with a regular controller therapy.

In adolescent patients using long-acting beta$_2$-agonists in addition to inhaled corticosteroids, it is recommended to use a combination preparation containing both an inhaled corticosteroid and a long-acting beta-agonist to ensure compliance with both drugs.

Treatment with long-acting beta$_2$-agonists should not be initiated if patients are in exacerbations, or if they have significant or acutely worsening asthma.

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.

FOREBEC contains lactose. Patients with rare hereditary problems of galactose intolerance, Lapp lactase insufficiency or glucose-galactose malabsorption should not use this medicine.

4.5 Interactions with other medicinal products and other forms of interaction
Pharmacokinetic interactions
Beclometasone dipropionate is rapidly metabolized to its active metabolite, beclometasone monopropionate, via esterase enzymes without the contribution of the cytochrome P-450 system.

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.

The use of other beta-adrenergic drugs may have potentially additive effects; therefore, caution is required when theophylline or other beta-adrenergic drugs are prescribed concomitantly with formoterol.

Concomitant treatment with quinidine, disopyramide, procainamide, phenothiazines, certain antihistamines (e.g. terfenadine), 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 (MAOIs), 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 anesthesia with halogenated hydrocarbons.

Concomitant treatment with xanthine derivatives, steroids, or diuretics may potentiate a possible hypokalemic effect of beta$_2$-agonists (see section 4.4). Hypokalemia may increase the disposition towards arrhythmias in patients who are treated with digitalis glycosides.

Additional information on special populations
There are no interaction studies with beclometasone dipropionate/formoterol fumarate dihydrate in renal/hepatic insufficiency.

Pediatric population
There are no interaction studies with beclometasone dipropionate/formoterol fumarate dihydrate in asthma and COPD patients under 18 years of age.

4.6 Fertility, pregnancy and lactation
General principles
Pregnancy category is C.

Women of childbearing potential/Contraception
There are no adequate data on the use of beclometasone dipropionate/formoterol fumarate dihydrate in women of childbearing potential and for contraception.

Pregnancy
There are no adequate data on the use of beclometasone dipropionate/formoterol fumarate dihydrate in pregnant women. Animal studies showed evidence of toxicity to reproduction (see section 5.3). The potential risk to humans is unknown.

High doses of corticosteroids administered to pregnant animals are known to cause abnormalities of fetal development including cleft palate and intra-uterine growth retardation. 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 labor unless there is no other and safer established alternative.

Administration of FOREBEC during pregnancy should only be considered if the expected benefits outweigh the potential risks.

Lactation
There are no relevant clinical data on the use of beclometasone dipropionate/formoterol fumarate dihydrate during 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 FOREBEC to women who are breast-feeding should be considered only if the expected benefits outweigh the potential risks. A decision must be made whether to discontinue breast-feeding or to discontinue FOREBEC therapy, taking into account the benefit of breast-feeding for the child and the benefit of therapy for the woman.

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

4.8. Undesirable effects
The most common adverse reaction is tremor. In a 12-week clinical trial with beclometasone dipropionate/formoterol fumarate dihydrate, tremor was seen only with the highest dose regimen (2 inhalations bid), appeared most frequently at the beginning of treatment and was mild in intensity. No patient was withdrawn from the trial as a result of tremor.

<u>Clinical Trials Experience in asthma patients</u>
The safety of beclometasone dipropionate/formoterol fumarate dihydrate was assessed in active- and placebo-controlled clinical trials in which 719 patients aged 12 and older with asthma of varying severity were exposed to the drug. The incidence of adverse reactions given below is relevant to asthmatic patients aged 12 years and older and is based upon the safety findings of two pivotal clinical trials where beclometasone dipropionate/formoterol fumarate dihydrate was administered at recommended doses for a period of 8-12 weeks.

No psychiatric disorders were observed in the clinical trials with beclometasone dipropionate/formoterol fumarate dihydrate but they are included as a potential class-effect of inhaled corticosteroids.

The incidence of adverse effects obtained from clinical trials is classified according to the MedDRA system; 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 (frequency cannot be estimated from the available data).

Placebo incidences were not taken into account.

Infections and infestations
Common: Pneumonia (in COPD patients)
Uncommon: Nasopharyngitis, oral candidiasis

Metabolic and nutrition disorders
Uncommon: Hypertriglyceridemia

Psychiatric disorders
Not known: Psychomotor hyperactivity, sleep disorders, anxiety, depression, aggression, behavioral changes (predominantly in children)

Nervous system disorders
Common: Tremor
Uncommon: Headache

Eye disorders
Not known: Blurred vision (see section 4.4)

Cardiac disorders
Uncommon: Tachycardia, sinus bradycardia, angina pectoris, myocardial ischemia

Respiratory, thoracic and mediastinal disorders
Uncommon: Throat irritation, asthma exacerbation, dyspnea, oropharyngeal pain, dysphonia, cough

Gastrointestinal disorders
Uncommon: Nausea

General disorders and administration site conditions
Uncommon: Fatigue, irritability

Investigations
Uncommon: Electrocardiogram QT prolonged, cortisol free urine decreased, blood cortisol decreased, blood potassium increased, blood glucose increased, electrocardiogram poor r-wave progression

Among the observed adverse reactions those typically associated with formoterol are: tremor, headache, tachycardia, sinus bradycardia, angina pectoris, myocardial ischemia, QT prolongation.

Among the observed adverse reactions those typically associated with beclometasone dipropionate are: nasopharyngitis, oral candidiasis, dysphonia, throat irritation, irritability, cortisol free urine decreased, blood cortisol decreased, blood glucose increased.

Additional adverse reactions not observed in the clinical experience with beclometasone dipropionate/formoterol fumarate dihydrate but typically associated with the inhaled administration of beclometasone dipropionate are other oral fungal infections and pneumonia. Taste disturbances have occasionally been reported during inhaled corticosteroid therapy.

See section 4.4 for measures to minimize the occurrence of oral fungal infections, oral candidiasis and dysphonia.

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

Additional adverse reactions not observed in the clinical experience with therapeutic doses of beclometasone dipropionate/formoterol fumarate dihydrate but typically associated with the administration of long-acting beta$_2$-agonist such as formoterol are palpitations, atrial fibrillation, ventricular extrasystoles, tachyarrhythmia, potentially serious hypokalemia and increase/decrease of blood pressure. Insomnia, dizziness, restlessness, and anxiety have occasionally been reported during inhaled formoterol therapy. Formoterol may also induce muscle cramps, myalgia.

Hypersensitivity reactions including rashes, urticaria, pruritus and erythema, and edema of the eye, face, lips and throat (angioedema) have been reported.

As with other inhalation therapy, paradoxical bronchospasm with an immediate increase in wheezing, cough and shortness of breath may occur after dosing (see also section 4.4).

Additional information regarding special populations:

Pediatric population:

No information is available regarding the safety of beclometasone dipropionate/formoterol fumarate dihydrate in children up to 11 years of age. There is limited information only in adolescents 12-17 years of age. In a 12-week randomized clinical trial in adults and adolescents, 162 adolescents aged 12-17 years with moderate to severe asthma received beclometasone dipropionate/formoterol fumarate dihydrate dry powder inhaler or pressurized metered-dose inhaler formulation of the corresponding combination, 1 or 2 inhalations twice a day. The frequency, type and severity of adverse drug reactions were not different in adolescents compared to adults.

Reporting of suspected adverse reactions:
Reporting suspected adverse reactions after authorization 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 national reporting system.

4.9 Overdose and treatment

The highest recommended dose of FOREBEC in a single administration is 2 inhalations. Inhaled doses of up to 4 cumulative actuations of FOREBEC (total beclometasone dipropionate 400 micrograms, formoterol 24 micrograms given as a single dose) have been studied in asthmatic patients. The cumulative treatments did not cause abnormal clinical effect on vital signs and neither serious nor severe adverse events were observed (see section 4.8).

For the pressurized inhalation formulation, inhaled doses of up to 12 cumulative actuations of the beclometasone dipropionate/formoterol combination (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, hypokalemia, hyperglycemia.

In case of overdose of formoterol, supportive and symptomatic treatment is indicated. Serious cases should be hospitalized. Use of cardioselective 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.

In the event of chronic inhalation of higher than recommended doses of beclometasone dipropionate (see section 4.4), monitoring of adrenal reserve may be required. In this group of patients, the treatment should be continued at the most appropriate dose to control asthma.

Single supra-therapeutic doses up to 800 micrograms of beclometasone dipropionate, 48 micrograms of formoterol, administered via FOREBEC are generally safe and well tolerated.

5. PHARMACOLOGICAL PROPERTIES

5.1. Pharmacodynamic properties

Pharmacotherapeutic group: Drugs for obstructive airway diseases; Adrenergics in combination with corticosteroids or other drugs, excl. anticholinergics.
ATC code: R03AK08

Mechanism of action

FOREBEC contains beclometasone dipropionate and formoterol in a multi-dose dry powder formulation resulting in an extrafine aerosol with an average mass median aerodynamic diameter (MMAD) of 1.4-1.7 micrometers and co-deposition of the two components. The aerosol particles of FOREBEC are on average much smaller than the particles delivered in non-extrafine formulations.

A radio-labelled drug deposition study in asthmatic adults has demonstrated that a high proportion of beclometasone dipropionate/formoterol fumarate dihydrate (estimated 42% of the nominal dose) is deposited in the lung, with a homogenous deposition through the airways. These delivery characteristics support the use of a low corticosteroid dose with enhanced local pharmacodynamic effects, which were shown to be equivalent to the extrafine formulation of beclometasone dipropionate/formoterol fumarate dihydrate (BDP/FF) corresponding beclometasone dipropionate/formoterol fumarate dihydrate dry powder inhaler as a pressurized-metered-dose inhaler (PMDI) (see ‘Clinical experience’).

The two actives of FOREBEC 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 with the respective components. These two components are as follows:

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

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

Clinical experience
The efficacy of the two components of beclometasone dipropionate/formoterol fumarate dihydrate dry powder inhaler and 100 mcg/6 mcg beclometasone dipropionate/formoterol fumarate dihydrate pressurized metered dose inhaler solution has been compared and assessed in three separate studies in moderate to severe patients with persistent asthma. Overall, the efficacy of the two inhalers is expected to be equivalent in clinical practice at both 1 and 2 inhalations bid.

In one study, the primary objective was the efficacy evaluation of the inhaled corticosteroid component measured on bronchodilation (pre-dose FEV_1). A clinically significant improvement in FEV_1 was seen in 696 patients with moderate to severe symptomatic asthma at the end of a 3 months treatment period in comparison with baseline values, with 1 inhalation bid and 2 inhalations bid of both formulations. A mean increase in FEV_1 from baseline of at least 250 mL was observed. There was no clinically relevant difference in pre-dose FEV_1 between the dry powder inhaler and pressurized inhalation solution formulations of beclometasone dipropionate/formoterol at either dosage. A significant dose-response was observed for morning peak expiratory flow (PEF). Statistical significance for the dose-response in pre-dose FEV_1 was not reached. Measurements of control of asthma such as morning and evening asthma symptoms scores and percentage of days without symptoms improved significantly from baseline through to the end of the treatment period, particularly for the two high doses of both formulations.

In the second study, the primary aim was the efficacy evaluation on the long-acting beta$_2$-agonist component of the dry powder inhaler and pressurized metered dose inhaler (PMDI) formulations of beclometasone dipropionate/formoterol. In this study, bronchodilation at the onset and up to 12 hours after single doses administration was measured by serial spirometric evaluations of FEV_1 (FEV_1 AUC over at least 80% of formoterol duration of action). Compared with placebo, one inhalation and four inhalations of both beclometasone dipropionate/formoterol formulations significantly improved the FEV_1 $AUC_{0\text{-}12}$. The bronchodilation in 1 and 4 doses administration of beclometasone dipropionate/formoterol fumarate dihydrate dry powder inhaler is equivalent to the bronchodilator efficacy of the pressurized metered dose inhaler formulation. A statistically significant dose-response was found with both formulations between the low and high dose.

In the third study, after a 4-week run-in period with beclometasone dipropionate/formoterol pressurized metered-dose inhalation solution (1 inhalation bid), 755 controlled asthmatic patients

were randomized to 8 weeks of treatment with the same inhaler (PMDI), with beclometasone dipropionate/formoterol fumarate dihydrate dry powder inhaler or with beclometasone dipropionate 100 micrograms per dose inhalation powder, all given at 1 inhalation bid. The primary objective was the change from baseline over the entire treatment period in mean morning expiratory flow (PEF). After 8 weeks of treatment, there was no difference in the primary endpoint between the two combination inhalers, both formulations of beclometasone dipropionate/formoterol fumarate dihydrate (PMDI and dry powder inhaler) being significantly better in morning peak expiratory flow (PEF) than beclometasone dipropionate dry powder monotherapy. No differences were found between the two combination inhalers in measures of symptoms such as the asthma control questionnaire score and the number of rescue-free days.

Pediatric population
There is no clinical experience regarding the safety of beclometasone dipropionate/formoterol fumarate dihydrate in children 5-11 years of age, only limited information is available for adolescents 12-17 years of age.

In a 3-month randomized clinical trial, 162 adolescents aged 12-17 years with a diagnosis of moderate-to-severe asthma were randomized to either a beclometasone dipropionate/formoterol fumarate dihydrate dry powder inhaler or the corresponding pressurized inhalation solution formulation (PMDI), 1 or 2 inhalations bid. The change in pre-dose FEV_1 at the end of treatment was greater in the adolescents than in adults.

See also sections 4.2 and 4.8 for information on pediatric use.

5.2 Pharmacokinetic properties
General properties
Beclometasone dipropionate:
Absorption:
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, and binds strongly to the glucocorticoid receptor. The systemic availability of the active metabolite, beclometasone-17-monopropionate, arises from lung 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 being absorbed as the active metabolite. The absolute bioavailability following inhalation from a pressurized metered dose inhaler is approximately 2% and 62% of the nominal dose for unchanged beclometasone dipropionate and beclometasone-17-monopropionate respectively.

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

Metabolic disposition of beclometasone dipropionate mainly (82%) results in its active metabolite beclometasone-17-monopropionate. Plasma protein binding is moderately high (87%).

Biotransformation:

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

Elimination:
Fecal 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.

Linearity / Non-linearity:
A clinical pharmacology study was conducted to evaluate the lung bioavailability and total systemic exposure of the two components across two different dose strengths of the inhalation powder (beclometasone dipropionate/formoterol fumarate dihydrate 100 mcg/6 mcg and 200 mcg/6 mcg). These parameters were assessed after a single dose (4 inhalations) of each formulation, both with and without activated charcoal block. The study had an open-label, 6-way crossover, single-dose design. A total of 30 adult asthmatic patients with an FEV1 $\geq$ 70% of the predicted values were enrolled and treated with low daily doses of inhaled corticosteroids (e.g., budesonide or equivalent $\leq$ 400 mcg/day) or low dose of inhaled corticosteroids/long-acting β_2-agonists fixed combinations. The lung bioavailability and the total systemic exposure of B17MP (active metabolite of beclometasone dipropionate) were dose-proportional between the 200/6 mcg and 100/6 mcg strength in both study conditions (with and without activated charcoal). Formoterol bioequivalence in terms of lung bioavailability and total systemic exposure was not fully demonstrated in this study as the lower 90% confidence interval of C_{max} and AUC_t were below the 80% lower bioequivalence limit when the two dose strengths were compared. Since no differences in systemic effects (including glucose, potassium and cardiovascular parameters) have been observed, this reduced systemic exposure (which amounts to 20-14% in C_{max} and AUC_t) indicated that beclometasone dipropionate/formoterol fumarate dihydrate 200/6 micrograms was at least as safe as beclometasone dipropionate/formoterol fumarate dihydrate 100/6 micrograms. In terms of lung deposition, the difference was 20% and 22% for C_{max} and AUC_t respectively. The equivalent efficacy in terms of bronchodilation of the two dose strengths (100/6 micrograms and 200/6 micrograms) has been demonstrated in a specific pharmacodynamics study (see section 5.1).

Characteristics in patients
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:
Following inhalation, formoterol is absorbed from both the lung and 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.
Distribution:
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.

Biotransformation:
Formoterol is widely metabolized 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 to 96 micrograms 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 micrograms 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 active substance 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 micrograms), 6% to 10% of the dose was recovered in urine as unchanged active substance 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 its metabolites) and the remainder in the feces. The renal clearance of formoterol is 150 ml/min.

Linearity / Non-linearity:
Absorption of formoterol is linear following inhalation of 12 to 96 mcg of formoterol fumarate.

Characteristics in patients
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.

Clinical Experience
The systemic exposure to beclometasone dipropionate and formoterol in the combination has been compared to the single components. There was no evidence of pharmacokinetic or pharmacodynamic (systemic) interactions between beclometasone dipropionate and formoterol.

The pharmacokinetics of the beclometasone dipropionate/formoterol fumarate dihydrate inhalation powder has been compared with that of the corresponding pressurized inhalation solution formulation. The analysis of the steroid component focused on beclometasone-17-monopropionate, the main active metabolite of beclometasone dipropionate.

Systemic absorption and metabolism of beclometasone dipropionate was rapid and C_{max} was reached 5 minutes postdose for both treatments but was higher (+68%) with the beclometasone dipropionate/formoterol fumarate dihydrate inhalation powder. AUC_t was about 3 times higher after inhalation of beclometasone dipropionate/formoterol fumarate dihydrate compared with the pressurized inhalation solution. C_{max} for beclometasone-17-monopropionate, the main active metabolite, representing about 82% of the total blood level, was reached on average after 30 minutes and 15 minutes with the dry powder inhaler and with the pressurized inhalation solution, respectively. Plasma concentration of beclometasone-17-monopropionate was lower (C_{max} -49% and AUC_t -29%), after inhalation of the inhalation powder than via the pressurized inhalation solution. After inhalation of beclometasone dipropionate/formoterol fumarate dihydrate, the peak concentration (C_{max}) of formoterol was reached within 5 minutes and was higher (+47%) for the inhalation powder, whereas the overall exposure (AUC_t) was comparable in the two treatments.

In one study, the relative lung delivery was investigated by using a charcoal blockade to exclude drug absorption from the gastrointestinal tract, and adopting an approved spacer for the reference product (the pressurized inhalation solution). In this setting, the beclometasone dipropionate/formoterol dry powder inhaler and the pressurized inhalation solution were shown to be equivalent for the AUC_t of both beclometasone-17-monopropionate and formoterol (the ratio inhalation powder/pressurized inhalation solution and the 90% confidence intervals were within 80-125%). However, C_{max} of beclometasone-17-monopropionate was lower (-38%) following inhalation from beclometasone dipropionate/formoterol fumarate dihydrate dry powder inhaler.

5.3 Preclinical safety data
Non-clinical data of the individual components of FOREBEC reveal no special hazard for humans based on conventional studies of safety pharmacology and repeated dose toxicity. The toxicity profile of the combination reflected that of single components with no increase in toxicity or unexpected findings.

Carcinogenicity
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.

Mutagenicity
Genotoxicity studies performed with a beclometasone dipropionate/formoterol combination do not indicate a mutagenic potential.

Reproduction toxicity
Reproduction studies in rats showed dose-dependent effects. The presence of beclometasone dipropionate at high doses was associated with reduced female fertility, decrease in the number of implantations and embryofetal toxicity. High doses of corticosteroids given 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 (more than 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 fumarate

dihydrate.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Lactose monohydrate (Inhalac 250) (from bovine milk)
Lactose monohydrate (Inhalac 400) (from bovine milk)

HPMC Capsule (No: 3) Composition
Hypromellose
Azorubine

6.2 Incompatibilities

The drug has no known incompatibility.

6.3 Shelf life

24 months.

6.4 Special precautions for storage

Store at room temperature below 25°C.
Keep in its original packaging to protect from moisture.

6.5 Nature and contents of container

The product is packaged in blisters consisting of OPA-Alu-PVC foil and aluminum foil. Blisters are packed in cardboard boxes. Each cardboard box contains 120 capsules, 1 device (monodose dry powder inhaler) in a plastic separator, and a package leaflet.

6.6 Special precautions for disposal and other handling

Any unused product or waste material should be disposed of in accordance with local disposal regulations.

7. MARKETING AUTHORIZATION HOLDER

DEVA Holding A.Ş.
Halkalı Merkez Mah. Basın Ekspres Cad. No:1
34303 Küçükçekmece – İSTANBUL/TÜRKİYE

8. MARKETING AUTHORIZATION NUMBER

2022/14

9. DATE OF FIRST AUTHORIZATION/RENEWAL OF THE AUTHORIZATION

Date of first authorization : 01.02.2022
Date of last renewal :

10. DATE OF REVISION OF THE TEXT