SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

FOTEROL-B 6 mcg/100 mcg aerosol inhalation solution

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each metered dose contains:

Active substance:

Beclometasone dipropionate: 100 mcg (84.6 mcg each dose delivered to patient)
Formoterol fumarate dihydrate: 6 mcg (5 mcg each dose delivered to patient)

Excipient(s):

Anhydrous ethanol..... 6.96 mg
For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Aerosol containing inhalation solution

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

As with treatments involving long-acting beta-$_2$-agonist+ inhaled corticosteroid combinations, FOTEROL-B is indicated for the improvement and control of asthma symptoms starting from Step 3 of the stepped-care therapy for asthma, and for the reduction of symptoms and frequency of exacerbations in moderate to severe COPD

4.2 Posology and method of administration

Posology:

FOTEROL-B is for inhalation use.

ASTHMA

FOTEROL-B is not intended for the initial treatment of asthma. Since the doses of the components in FOTEROL-B are different, the medication must be adjusted according to the severity of the disease. This should be considered not only when treatment is initiated with a fixed-dose combination product but also when dose adjustments are being made. If a patient requires a dose combination different from the combinations available in the inhaler, appropriate doses of the beta$_2$-agonist and/or corticosteroid from different inhalers should be prescribed.

When changing the treatment that patients are already receiving, care should be taken to ensure that the total daily dose of beclomethasone dipropionate recommended for

FOTEROL-B is below the dose given for the current product containing beclomethasone dipropionate and not extra thin, and that the dose is adjusted according to the needs of each patient.

Two treatment approaches are applicable for FOTEROL-B.

For adults aged 18 years and over:
A. Maintenance therapy with FOTEROL-B: A rescue fast-acting bronchodilator is used together with FOTEROL-B as regular maintenance therapy.

The necessity of using a separate fast-acting bronchodilator should always be considered, and patients should be informed about this.

The medication is administered in one or two inhalations daily.

The maximum daily dose is 4 inhalations.

B. Maintenance and reliever therapy with FOTEROL-B: FOTEROL-B is used for daily maintenance therapy and also, as needed, to relieve asthma symptoms.
Patients should always be advised to keep FOTEROL-B with them for relief use.

The use of FOTEROL-B as maintenance and reliever therapy should be especially considered for the following patients:

- Patients whose asthma is not fully controlled and who require a reliever medication.
- Patients with a history of asthma exacerbations requiring medical intervention.

Patients taking FOTEROL-B frequently and in large numbers require close monitoring for dose-related adverse effects.

The recommended maintenance dose of FOTEROL-B is 1 inhalation twice daily (1 inhalation in the morning and 1 in the evening).

Patients should take an additional inhalation if needed to relieve symptoms. If symptoms persist after a few minutes, an additional inhalation should be administered.

The maximum daily dose is 8 inhalations.

Patients who frequently use their relief inhalations daily must be advised to seek medical attention.

These patients should be re-evaluated, and their maintenance therapy should be reviewed.

COPD
For adults aged 18 years and over, the recommended dose of FOTEROL-B is 2 inhalations twice daily

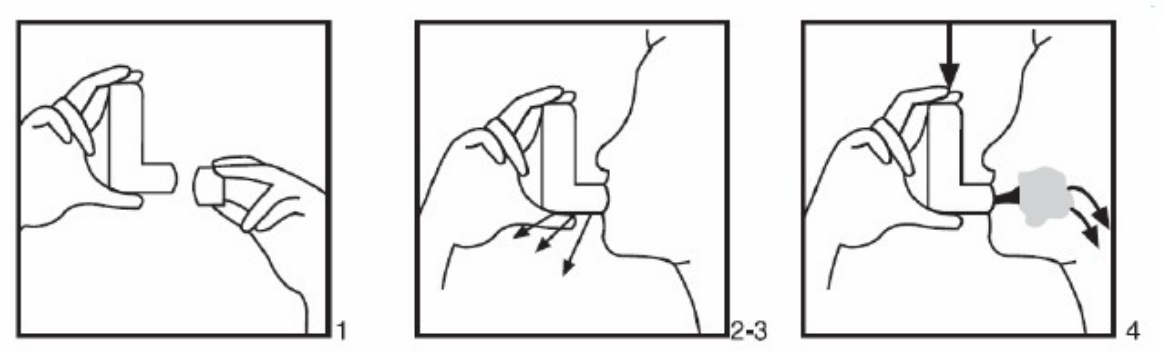
Method of administration:
For the appropriate use of the medicine, the patient should occasionally be shown how to use the inhaler by a doctor or other healthcare professional.

When the inhaler is used for the first time, and when it has not been used for more than 14 days, one puff must be released into the air to ensure faultless function. The patient should sit or stand upright, if possible, during the inhalation.
To ensure appropriate continuation of the dosage, patients should be regularly evaluated by a doctor and should only be changed based on medical advice. The treatment dose should be reduced to the lowest dose at which symptoms are effectively controlled. When symptoms are controlled at the lowest dose, the next step should involve testing the use of an inhaled corticosteroid alone. Patients should be informed to take FOTEROL-B every day, even when they are asymptomatic.

The following instructions should be followed during the application of FOTEROL-B:
1. Remove the protective cap from the mouthpiece.
2. Exhale as slowly and deeply as possible through your mouth.
3. Regardless of your body position, hold the canister vertically with the bottom facing up, place the mouthpiece between your teeth, and close your lips tightly.
4. Inhale slowly and deeply through your mouth and, at the same time, press the top of the inhaler to release one puff of aerosol.
5. Hold your breath for as long as possible without straining, and finally, remove the inhaler from your mouth and exhale through your nose.
6. After use, close the protective cap.

If another puff of aerosol is required, hold the inhaler upright for about half a minute and then repeat steps 2 to 5.

Important: Do not perform steps 2 through 4 too quickly.



If you see a 'mist' coming from the top of the inhaler or the sides of the mouthpiece, you must start the procedure again from step 2.

If your hands are weak, it may be easier to hold the inhaler with both hands; in this case, hold the top of the inhaler with both index fingers and the bottom with both thumbs.

To reduce the risk of a fungal infection in the mouth and throat, rinse your mouth with water or brush your teeth after every puff.

The dose specified in these instructions relates to the inhalation of FOTEROL-B using a standard inhaler. There is insufficient data on the use of FOTEROL-B with a different spacer device. If it is to be used with a different spacer, the dose may need to be adjusted.

Cleaning
Clean the outside of the mouthpiece regularly (once a week) with a dry cloth. Do not use water or any other liquid to clean the mouthpiece.

Additional information for special populations:
Kidney/ Liver failure:
Data on the use of FOTEROL-B are unavailable (see section 5.2).

Paediatric population:
The safety and efficacy of FOTEROL-B have not yet been established for children and adolescents under 18 years of age. Limited data are available for adolescents between 12 and 17 years. Therefore, its use is not recommended for children under 12 years and adolescents between 12 and 17 years until more data are available.

Geriatric population:
No dose adjustment is necessary for the elderly.

4.3 Contraindications

FOTEROL-B is contraindicated in patients with known hypersensitivity to beclometasone dipropionate, formoterol fumarate dihydrate, and/or any of the excipients contained in the product.

4.4.Special warnings and precautions for use

FOTEROL-B should be used with caution and the patient monitored in cases of cardiac arrhythmias, especially third-degree atrioventricular block and tachyarrhythmias (accelerated and/or irregular heartbeat), idiopathic subvalvular aortic stenosis, hypertrophic obstructive cardiomyopathy, severe heart disease, particularly acute myocardial infarction, ischemic heart disease, congestive heart failure, occlusive vascular diseases, especially arteriosclerosis, arterial hypertension, and aneurysm. Caution should be exercised during the treatment of patients with known or suspected congenital or drug-induced QTc interval prolongation (QTc > 0.44 seconds). Also formoterol itself may prolong the QTc interval.

FOTEROL-B should be used with caution in patients with thyrotoxicosis, pheochromocytoma, diabetes mellitus, and untreated hypokalemia.

Beta$_2$-agonist therapy can potentially cause serious hypokalemia. Since this effect can be potentiated by hypoxia, special attention should be paid during the treatment of severe asthma, and concomitant therapy is recommended. Hypokalemia may also be potentiated by concomitant treatment with hypokalemia-inducing drugs such as xanthine derivatives, steroids, and diuretics (see section 4.5). Special caution is also required in unstable asthma where rapid-acting bronchodilators are used. In such situations, monitoring of serum potassium levels is recommended.

Formoterol inhalation may cause an increase in blood glucose levels. Therefore, this parameter must be closely monitored in diabetic patients.

When anesthesia with halogenated anesthetics is planned, it is necessary to ensure that FOTEROL-B has not been used for at least 12 hours prior to the start of anesthesia due to the risk of cardiac arrhythmias.

As with all inhaled medications containing corticosteroids, FOTEROL-B should be administered with caution in patients with active or latent pulmonary tuberculosis and in patients with fungal and viral infections of the respiratory tract.

It is recommended that FOTEROL-B not be discontinued suddenly.

If a patient finds the treatment ineffective, medical attention should be sought. An increase in the use of short-acting reliever bronchodilators indicates the deterioration of the disease and necessitates a re-evaluation of the asthma treatment. Sudden and progressively worsening

control of asthma or COPD is potentially life-threatening, and the patient must undergo an urgent medical evaluation for treatment modification. Caution should be exercised if there is an increased need for oral or inhaled corticosteroid therapy, or if an antibiotic treatment should be started if an infection is suspected.

Treatment with long-acting beta-agonists should not be initiated if patients are in a period of exacerbation or have significantly or acutely deteriorating asthma complaints. Serious asthma-related adverse events and exacerbations may occur during treatment with FOTEROL-B. If asthma symptoms do not improve or worsen after starting treatment with FOTEROL-B, patients should continue their treatment but be advised to seek medical help.

As with other inhalation therapies, paradoxical bronchospasm, which is a sudden increase in wheezing, cough, and shortness of breath following dosing, may occur. This condition must be treated immediately with a fast-acting inhaled bronchodilator. Furthermore, FOTEROL-B use must be discontinued immediately, the patient re-evaluated, and alternative treatment implemented if necessary.

FOTEROL-B is not recommended for the initial treatment of asthma.

It is recommended that patients always have their FOTEROL-B and/or their fast-acting bronchodilator readily available for the treatment of acute asthma attacks.

Patients should be reminded to use FOTEROL-B every day regularly as prescribed, even when they are asymptomatic. If asthma symptoms occur, FOTEROL-B should be inhaled for relief, but it is not intended for regular prophylactic use (e.g., before exercise). A separate fast-acting bronchodilator should be considered for such use.

Once asthma symptoms are controlled, a reduction in the FOTEROL-B dose should be considered over time. It is important for patients to be regularly monitored while the dose is being reduced. The minimum effective dose of FOTEROL-B should be used in controlled asthma (see section 4.2).

Inhaled corticosteroids may produce systemic effects, particularly when prescribed at high doses for long periods. The likelihood of these effects occurring is much lower with inhaled corticosteroids than with oral corticosteroids. Possible systemic effects include: Cushing's syndrome, Cushingoid face appearance, adrenal suppression, decrease in bone mineral density, growth retardation in children and adolescents, cataract and glaucoma, and, more rarely, various psychological and behavioral effects including psychomotor hyperactivity, sleep disorders, anxiety, depression, or aggression (particularly in children). Therefore, it is important to regularly monitor the treated patient and to reduce the inhaled corticosteroid dose to the lowest dose at which effective control of asthma is maintained.

Single-dose pharmacokinetic data (see section 5.2) suggest that the use of FOTEROL-B with the Aerochamber Plus® spacer device does not increase the total systemic exposure to formoterol, reduces the systemic exposure to beclometasone-17-monopropionate, and increases the unchanged beclometasone dipropionate that reaches the systemic circulation in the lung, compared to the standard actuator. However, as the systemic exposure of beclometasone dipropionate and its active metabolite is unchanged, using FOTEROL-B with this device does not increase the risk of systemic effects.

Long-term treatment with high doses of inhaled corticosteroids may cause adrenal suppression and acute adrenal crisis. Children under 16 years of age inhaling higher than recommended doses of beclometasone dipropionate may be at risk. Potential situations that may trigger an acute adrenal crisis include trauma, surgery, infection, and rapid dose reduction. The resulting symptoms may be very indistinct but can include loss of appetite, abdominal pain, weight loss, fatigue, headache, nausea, vomiting, hypotension, decreased level of consciousness, hypoglycemia, and/or convulsions. The provision of supplementary systemic corticosteroids should be considered during periods of stress and elective surgery.

Caution should be exercised when switching these patients to FOTEROL-B therapy, especially if impaired adrenal function is suspected due to previous systemic steroid treatment.

Patients transferring from oral corticosteroids to inhaled steroids remain at risk of adrenal reserve deficiency for a quite a long time. Patients who have required high-dose emergency corticosteroid therapy in the past or who have been treated with high doses of inhaled corticosteroids for a long period may also be at risk. The possibility of this impairment should always be kept in mind during emergency and elective situations that may cause stress, and appropriate corticosteroid treatment should be applied. The degree of adrenal impairment may require specialist advice before elective procedures.

Rarely, serious and sometimes fatal asthma-related respiratory problems may occur due to long-acting beta-agonist preparations.

In pediatric and adolescent patients using a long-acting beta-agonist in addition to an inhaled corticosteroid, it is recommended to use a combination preparation containing both the inhaled corticosteroid and the long-acting beta-agonist to ensure compliance with both medications.

Long-acting beta-agonists should be used for the shortest duration that maintains asthma symptom control and should be discontinued, if possible, once asthma control is achieved. Patients should then be maintained on a controller therapy.

Formoterol should not be used alone as monotherapy in asthmatic patients.

Pneumonia in COPD Patients
An increased incidence of pneumonia, including pneumonia requiring hospitalization, has been observed in COPD patients receiving inhale medicines containing corticosteroids. There is evidence of an increased risk of pneumonia with increasing steroid dose, but this has not been conclusively demonstrated in all studies.

There is no definitive clinical evidence for a class difference regarding the magnitude of pneumonia risk from inhaled corticosteroids.

Physicians should be vigilant for the possible development of pneumonia in COPD patients, as the clinical features of infections may be obscured by the exacerbation of COPD symptoms.
Risk factors for pneumonia in COPD patients include smoking, advanced age, low body mass index, and severe COPD.

Vision Disorder
Vision disorders may be reported due to systemic and topical corticosteroid use. If a patient experiences blurred vision or other vision disturbances, they should be referred to an ophthalmologist to evaluate possible causes, which may include rare diseases such as cataract, glaucoma, or central serous chorioretinopathy (CSCR) reported after systemic and topical corticosteroid use.

To minimize the risk of oropharyngeal Candida infection, patients should be advised to rinse their mouth with water or brush their teeth after using the prescribed dose.

FOTEROL-B contains a small amount of anhydrous ethanol (6.96 mg per dose); at the administered doses, this does not pose a risk to patients.

4.5 Interaction with other medicinal products and other forms of interaction
Pharmacokinetic Interactions
Beclometasone dipropionate (BDP) is rapidly metabolized via esterase enzymes without involvement of cytochrome P-450 enzymes.

Beclometasone is less dependent on CYP3A metabolism compared to some other corticosteroids, and interactions are generally unlikely; however, the possibility of systemic effects due to the concomitant use of potent CYP3A inhibitors (e.g., ritonavir, cobicistat) cannot be excluded and therefore, caution is advised, and appropriate patient monitoring is recommended when such agents are used.

Pharmacodynamic Interactions
Beta-blocker therapy (including eye drops) should be avoided in asthmatic patients. If beta-blockers must be administered for compelling reasons, the effect of formoterol will be reduced or eliminated. On the other hand, concomitant use of beta-adrenergic drugs may have potentially additive effects, so caution should be exercised when prescribing theophylline or other beta-adrenergic drugs concurrently with formoterol.

Quinidine, disopyramide, procainamide, phenothiazines, antihistamines, monoamine oxidase inhibitors, and tricyclic antidepressants can increase the risk of ventricular arrhythmias by prolonging the QTc-interval.

Furthermore, L-dopa, L-thyroxine, oxytocin, and alcohol can reduce cardiac tolerance to beta$_2$-sympathomimetics.

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

The risk of arrhythmia may be increased in patients undergoing concurrent anesthesia with halogenated hydrocarbons.

Concomitant treatment with xanthine derivatives, steroids, or diuretics may potentiate the possible hypokalemic effects of beta$_2$-agonists (see section 4.4). In patients treated with digitalis glycosides, hypokalemia may facilitate the development of arrhythmias.
The low level of alcohol content may cause an interaction in susceptible patients using disulfiram or metronidazole.

Additional information on special populations:
No interaction studies have been conducted in cases of kidney/liver failure.

Pediatric population:
No interaction studies have been conducted in asthma and COPD patients under the age of 18.

4.6 Pregnancy and lactation

General recommendations
Pregnancy category C

There are insufficient data regarding the use or safety of the propellant HFA-134a in pregnant or breastfeeding women. However, studies conducted in animals regarding the effect of HFA-134a on reproductive function and embryofetal development have shown no clinically adverse effects.

Women of childbearing potential/Birth control (Contraception)
There are insufficient data on the use of FOTEROL-B in women of childbearing potential and for contraception.

Pregnancy
It is known that high-dose administration of corticosteroids to pregnant animals causes fetal developmental abnormalities such as cleft palate and intrauterine growth retardation. The tocolytic effects of beta-$_2$-sympathomimetic agents may also affect delivery.

There are insufficient clinical data on the use of FOTEROL-B in pregnant women. Animal studies using the combination of beclometasone dipropionate and formoterol have shown evidence of reproductive toxicity after high systemic exposure (see section 5.3). Due to the tocolytic effect of beta$_2$-sympathomimetic agents, necessary precautions should be taken as labor approaches. Unless another well-established alternative (safer) treatment is available, formoterol should not be used during pregnancy, and particularly late in pregnancy or during delivery.

FOTEROL-B should be used during pregnancy only if the expected benefits outweigh the potential risks.

Lactation
There are insufficient clinical data regarding the use of FOTEROL-B during lactation in humans. Although no data have been obtained from animal experiments, it can be assumed that beclometasone dipropionate, like other corticosteroids, passes into breast milk. Although it is unknown whether formoterol passes into human breast milk, it has been detected in the milk of animals. Therefore, FOTEROL-B should only be administered to breastfeeding women if the expected benefit to the mother is greater than the possible risk to the child.

Reproductive Ability/Fertility
Dose-dependent effects were observed in reproductive studies in rats (0.2, 2.0, and 20 mg/kg/day). While no effects were seen on male fertility, the No Observed Adverse Effect Level (NOAEL) on fetal development in female animals was 2 mg/kg/day. At higher doses (20 mg/kg/day), FOTEROL-B caused difficulty in parturition and resulted in findings of maternal (reduced implantation rate, reduced placental weight) and fetal toxicity (ossification disorders, reduced weight).

4.7 Effects on ability to drive and use machines
FOTEROL-B has no effect on the ability to drive and use machines.

4.8 Undesirable effects

As FOTEROL-B contains beclometasone dipropionate and formoterol fumarate dihydrate, adverse reactions of the type and severity associated with each individual compound are expected. No increase in additional adverse effects has been observed following the co-administration of both compounds. Undesirable effects associated with beclometasone dipropionate and formoterol fumarate when administered as a fixed combination (FOTEROL-B) are listed below and systematically shown by system organ class and frequency.

The incidence rates of undesirable effects obtained from clinical studies are defined as follows: Very common (≥1/10); common (≥1/100 to <1/10); uncommon (≥1/1,000 to <1/100); rare (≥1/10,000 to <1/1,000); very rare (≤1/10,000); not known (cannot be estimated from the available data).

Placebo incidences have not been taken into account.

Common and uncommon adverse drug reactions were obtained from clinical studies conducted in asthma and COPD patients.

Infections and Infestations

Common: Pharyngitis, oral candidiasis, pneumonia (in COPD patients)*

Uncommon: Flu, oral fungal infection, oropharyngeal and esophageal candidiasis, vulvovaginal candidiasis, gastroenteritis, sinusitis, rhinitis

Blood and Lymphatic System Disorders

Uncommon: Granulocytopenia

Very Rare: Thrombocytopenia

Immune System Disorders

Uncommon: Allergic dermatitis

Very Rare: Hypersensitivity reactions including erythema, edema of the lips, face, eyes, and pharynx

Endocrine Disorders

Very Rare: Adrenal suppression

Metabolism and Nutrition Disorders

Uncommon: Hypokalemia, hyperglycemia

Psychiatric Disorders

Uncommon: Restlessness

Not Known: Psychomotor hyperactivity, sleep disorders, anxiety, depression, aggression, behavioral changes (mostly in children)

Nervous System Disorders
Common: Headache
Uncommon: Tremor, dizziness

Eye Disorders
Very Rare: Glaucoma, cataract
Not Known: Blurred vision (see Section 4.4)

Ear and Labyrinth Disorders
Uncommon: Otosalpingitis

Cardiac Disorders
Uncommon: Palpitations; QTc interval prolongation on ECG; ECG changes, tachycardia, tachyarrhythmia, atrial fibrillation*
Rare: Ventricular extrasystoles, angina pectoris

Vascular Disorders
Uncommon: Hyperaemia; hot flushes

Respiratory, Thoracic and Mediastinal Disorders
Common: Dysphonia
Uncommon: Cough, productive cough, throat irritation, asthma crisis
Rare: Paradoxical bronchospasm
Very Rare: Dyspnoea, exacerbation of asthma

Gastrointestinal Disorders
Uncommon: Diarrhea, dry mouth, dyspepsia, dysphagia, burning sensation on the lips, nausea, taste disturbance

Skin and Subcutaneous Tissue Disorders
Uncommon: Itching, rash, hyperhidrosis, urticaria
Rare: Angioedema

Musculoskeletal, connective Tissue and bone Disorders
Uncommon: Muscle cramps, myalgia
Very Rare: Growth retardation in children and adolescents
Renal and Urinary Disorders
Rare: Nephritis

General Disorders and Administration Site Conditions

Very Rare:	Peripheral edema

Investigations

Uncommon:	Increased C-reactive protein, increased platelet count, increased free fatty acid, increased blood insulin, increased blood ketone bodies, decreased blood cortisol*
Rare:	Increased blood pressure, decreased blood pressure
Very Rare:	Decreased bone density

* A case of non-serious pneumonia was reported in one patient in a pivotal study conducted in COPD patients treated with the beclometasone dipropionate and formoterol combination. Other adverse reactions observed for the beclometasone dipropionate and formoterol combination in COPD clinical studies include decreased blood cortisol and atrial fibrillation.

As is also seen with other inhalation therapies, paradoxical bronchospasm may occur.

Adverse events typically associated with formoterol include: hypokalemia, headache, tremor, palpitations, cough, muscle cramps, and QTc interval prolongation.

Adverse events typically associated with Beclometasone include: oral fungal infections, oral candidiasis, dysphonia, and throat irritation

To reduce dysphonia and candidiasis, patients may gargle or rinse their mouth with water or brush their teeth after using the product. Symptomatic candidiasis that occurs while FOTEROL-B treatment continues can be treated with topical anti-fungal therapy.

Systemic effects of inhaled corticosteroids (e.g., beclometasone dipropionate) may occur, especially when administered in high doses for prolonged periods. These effects include: adrenal suppression, decreased bone mineral density, growth retardation in children and adolescents, glaucoma, and cataracts (see section 4.4).

Hypersensitivity reactions include rash, urticaria-like itching, erythema, and edema of the eyes, face, lips, and throat.

Reporting of Suspected Adverse Reactions

Reporting suspected adverse reactions after authorization of the medicinal product is essential. It allows continued monitoring of the benefit/risk ratio of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via the national reporting system.

4.9 Overdose and Treatment

Inhaled beclometasone dipropionate and formoterol combination doses of up to 12 cumulative actuations (a total of 1200 micrograms BDP and 72 micrograms formoterol) were studied in asthmatic patients. The cumulative treatment showed no abnormal effect on vital signs, and no serious or severe adverse events were observed.

Excessive doses of formoterol may lead to effects typical of beta-$_2$-adrenergic agonists: nausea, vomiting, headache, tremor, somnolence, palpitations, tachycardia, ventricular arrhythmias, QTc interval prolongation, metabolic acidosis, hypokalemia, hyperglycemia.

In the event of formoterol overdose, supportive and symptomatic treatment is indicated. Severe cases should be hospitalized. The use of cardioselective beta-adrenergic blockers may be considered, but they should be administered with extreme caution, as beta-adrenergic blocker use may lead to bronchospasm. The patient's serum potassium must be monitored.

Inhalation of acute doses of beclometasone dipropionate higher than recommended may cause transient suppression of adrenal function. This does not require emergency action, as the suppression disappears within a few days, as confirmed by plasma cortisol measurements. Treatment in these patients should be continued at doses sufficient to control their asthma.

Inhalation of chronic excessive doses of beclometasone dipropionate: Refer to Section 4.4 for the risk of adrenal suppression. Monitoring of the 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 used in obstructive airway diseases, Adrenergics in combination with corticosteroids or other drugs – excluding anticholinergics.
ATC Code: R03AK08

Mechanism of Action and Pharmacodynamic Effects:
FOTEROL-B contains beclometasone dipropionate and formoterol; these have different mechanisms of action and show an additive (synergistic) effect in reducing asthma exacerbations. The mechanism of action for these two substances is detailed below.

Beclometasone Dipropionate
When given by inhalation at recommended doses, beclometasone dipropionate has an anti-inflammatory effect in the lungs mediated by glucocorticoid and this effect provides a reduction in asthma symptoms and exacerbations while causing fewer adverse effects than systemically administered corticosteroids.

Formoterol

Formoterol is a selective beta$_2$-adrenergic agonist that causes the relaxation of the smooth muscles of the bronchi in patients with reversible airway obstruction. The bronchodilatory effects are rapid, starting 1-3 minutes after inhalation, and the duration of effect for a single dose is 12 hours.

ASTHMA

Clinical Efficacy of Beclometasone Dipropionate and Formoterol Combination in Maintenance Therapy

Clinical studies in adults have shown that the addition of formoterol to beclometasone dipropionate improves asthma symptoms and lung function and reduces exacerbations.

In a 24-week study examining the effects of the beclometasone dipropionate and formoterol combination on lung function, the combination was at least equivalent to beclometasone dipropionate and formoterol given separately, and the treatment efficacy was greater than beclometasone dipropionate alone.

Clinical Efficacy of Beclometasone Dipropionate and Formoterol Combination in Maintenance and Reliever Therapy

A 48-week parallel group study involving 1,701 asthma patients compared maintenance dosing (one inhalation twice daily) and reliever therapy (up to a total of 8 puffs per day) of the combination of beclometasone dipropionate and formoterol at a maintenance dose (one inhalation twice daily) plus salbutamol as needed in adult patients with uncontrolled moderate or severe asthma. The results show that the combination of beclomethasone dipropionate and formoterol, administered as maintenance and reliever therapy, significantly prolonged the time to first severe exacerbation compared to the maintenance plus as-needed salbutamol group ($p<0.001$ for both ITT and PP populations). The rate of serious asthma exacerbations was significantly reduced (per patient/year) in the maintenance and reliever therapy groups compared to the salbutamol group (0.1476 and 0.2239, respectively, statistically significant reduction: $p<0.001$). Patients in the beclomethasone dipropionate and formoterol combination maintenance and reliever therapy group achieved clinically significant asthma control. The mean number of reliever therapy inhalations and the number of patients receiving reliever therapy decreased similarly in both groups.

Note: Severe exacerbations were defined as a worsening of asthma resulting in hospitalization or emergency treatment, or an increase in the need for systemic steroids for more than 3 days.

In another clinical study, the bronchodilation achieved with a single dose (100/6 mcg) of the beclometasone dipropionate and formoterol combination was compared to salbutamol 200 mcg in asthmatic patients who developed bronchoconstriction with methacholine. The single dose of the beclometasone dipropionate and formoterol combination provided similarly rapid bronchodilation and a rapid improvement in dyspnea as salbutamol.

COPD
In two 48-week studies, the effects on lung function and the rate of exacerbations (defined as a course of oral steroids and/or antibiotics and/or hospitalization) were evaluated in patients with severe COPD (30%<FEV_1%<50%).

A pivotal trial showed that after 12 weeks of treatment, the combination of beclomethasone dipropionate and formoterol resulted in a significant improvement in lung function compared to formoterol (primary endpoint change in pre-dose FEV_1), with a mean difference (69 ml), and significant improvement was observed throughout the entire clinical study period (48 weeks). The study, involving a total of 1199 patients with severe COPD, demonstrated a statistically significant reduction in the mean number of exacerbations per patient/year (exacerbation rate, a co-primary endpoint) with the beclometasone dipropionate and formoterol combination compared to formoterol treatment over the 48-week treatment period (adjusted mean rate 0.80 versus 1.12 in the formoterol group, adjusted ratio 0.72, p<0.001). Additionally, the beclometasone dipropionate and formoterol combination statistically significantly prolonged the time to the first exacerbation when compared to formoterol. The superiority of the beclometasone dipropionate and formoterol combination over formoterol was also confirmed in terms of the exacerbation rate in subgroups of patients who did or did not receive tiotropium bromide as a concomitant medication (approximately 50% in each treatment arm).

Another important study, a three-arm, randomized, parallel-group study conducted on 718 patients, confirmed the superiority of the beclometasone dipropionate and formoterol combination treatment versus formoterol in terms of the change in pre-dose FEV_1 at the end of the treatment (48 weeks) and demonstrated the equivalent efficacy of the beclometasone dipropionate and formoterol combination compared to the fixed-dose combination of budesonide/formoterol for the same parameter.

5.2 Pharmacokinetic properties

General properties
The systemic effects of the FOTEROL-B fixed combination were compared in a clinical study with the systemic effects of its active ingredients, beclometasone dipropionate (BDP) and formoterol.

For beclometasone dipropionate, AUC and maximum plasma concentration of the main active metabolite, beclometasone-17-monopropionate (B-17-MP), were lower after fixed-combination administration, but the rate of absorption was faster compared to beclometasone administered alone.

For formoterol, the maximum plasma concentration was similar after fixed or free combination administrations, and the systemic effect with the beclometasone dipropionate and formoterol combination was found to be slightly higher than with the free combination.

No pharmacokinetic or pharmacodynamic interaction was observed between beclometasone dipropionate and formoterol.

In a study conducted in healthy volunteers, the use of the Aerochamber Plus actuator increased the lung accessibility for beclometasone dipropionate's active metabolite, 17-monopropionate, and for formoterol fumarate by 41% and 45%, respectively, compared to the standard actuator.

The total systemic exposure for formoterol fumarate remained unchanged, showed a 10% decrease for beclometasone-17-monopropionate, and increased for unchanged beclometasone dipropionate.
In a study conducted in healthy volunteers, the use of the beclometasone dipropionate and formoterol combination with the Aerochamber Plus spacer increased the lung accessibility for beclometasone dipropionate's active metabolite, 17-monopropionate, and for formoterol fumarate by 41% and 45%, respectively. The total systemic exposure remained unchanged for formoterol, showed a 10% decrease for beclometasone-17-monopropionate, and increased for unchanged beclometasone dipropionate.

A lung deposition study conducted in stable COPD patients, healthy volunteers, and asthma patients showed that 33% of the nominal dose deposited in the lungs in COPD patients, compared to 34% in healthy subjects and 31% in asthmatic patients. The plasma exposure of beclometasone 17-monopropionate and formoterol was comparable across the three groups over the 24 hours following inhalation. The total exposure of beclometasone dipropionate was higher in COPD patients compared to asthma patients and healthy volunteers.

Beclometasone Dipropionate
Beclometasone dipropionate is a prodrug with a weak binding affinity to glucocorticoid receptors, which is hydrolyzed by esterase enzymes into the active metabolite, beclometasone-17-monopropionate. Beclometasone-17-monopropionate has a stronger topical anti-inflammatory activity than the prodrug, beclometasone dipropionate.

Absorption
Inhaled beclometasone dipropionate is rapidly absorbed from the lungs; prior to absorption, beclometasone dipropionate largely converts into its active metabolite, B-17-MP. The systemic bioavailability of B-17-MP is due to lung (36%) and gastrointestinal absorption of the swallowed dose. The bioavailability of swallowed beclometasone dipropionate is negligible, but its conversion to B-17-MP before systemic circulation ensures that 41% of the

absorbed amount is B-17-MP. There is an approximately linear increase in systemic effect with an increase in the swallowed dose. The absolute bioavailability after inhalation was 2% and 62% of the nominal dose for unchanged beclometasone dipropionate and B-17-MP, respectively.

Distribution
After an intravenous dose, the distribution of beclometasone dipropionate and B-17-MP is characterized by a high plasma clearance (150 and 120 l/hour, respectively), and the volume of distribution is small for beclometasone dipropionate (20 l) and greater for tissue distribution for B-17-MP (424 l) at steady state. Plasma protein binding is moderately high.

Biotransformation
Beclometasone dipropionate is metabolized in the systemic circulation via esterase enzymes found in most tissues and is cleared very rapidly from the systemic circulation. The main product of metabolism is the active metabolite (B-17-MP). Minor metabolites such as beclometasone-21-monopropionate (B-21-MP) and beclometasone (BOH) are also formed, but they contribute very little to systemic exposure.

Elimination
The main route of elimination for beclometasone dipropionate is through the feces as polar metabolites. Urinary excretion of beclometasone dipropionate and its metabolites is negligible. The terminal elimination half-life for beclometasone dipropionate and beclometasone-17-monopropionate is 0.5 and 2.7 hours, respectively.

Characteristics in Patients
The pharmacokinetics of beclometasone dipropionate have not been studied in patients with kidney or liver failure; however, since beclometasone dipropionate is metabolized very rapidly by esterase enzymes found in intestinal fluid, serum, lungs, and liver into more polar products B-21-MP, B-17-MP, and BOH, liver failure is not expected to alter the pharmacokinetics and safety profile of beclometasone dipropionate.

Since beclometasone dipropionate or its metabolites are not found in the urine, no increase in systemic exposure has been observed in patients with kidney failure.

Formoterol

Absorption
After inhalation, formoterol is absorbed from both the lungs and the gastrointestinal tract. The fraction of the inhaled dose that is swallowed after oral administration with a metered-dose inhaler (MDI) can be found between 60% and 90%. At least 65% of the swallowed dose is

absorbed in the gastrointestinal system. Peak plasma concentration of the unchanged drug is reached 0.5 to 1 hour after oral administration.

Distribution
The plasma protein binding rate of formoterol is 61-64%, with 34% binding to albumin. Binding saturation does not occur within the concentration range reached at therapeutic doses. The elimination half-life detected after oral administration is 2-3 hours. Formoterol absorption is linear over the range of 12-97 micrograms inhaled formoterol fumarate.

Biotransformation
Formoterol is extensively metabolized, and the prominent metabolic pathway is direct conjugation at the phenolic hydroxyl group. The glucuronide acid conjugate is inactive. The second major pathway is demethylation at the phenolic 2'-hydroxyl group, followed by conjugation. Cytochrome P-450 isoenzymes CYP2D6, CYP2C19, and CYP2C9 are involved in formoterol demethylation. The liver is considered to be the primary site of metabolism. Formoterol does not inhibit CYP-450 enzymes at therapeutically relevant concentrations.

Elimination
The cumulative urinary excretion of formoterol showed a linear increase over the 12-96 µg dose range after a single inhalation from a DPI (Dry Powder Inhaler). On average, 8% and 25% of the dose were excreted as unchanged drug and total formoterol, respectively.

Based on plasma concentrations measured following a single 120 µg dose inhalation in 12 healthy subjects, the mean terminal elimination half-life was determined to be 10 hours. The (R,R) and (S,S) enantiomers represent approximately 40% and 60%, respectively, of the unchanged drug excreted in the urine. The ratio of the two enantiomers remained constant over the dose range investigated, and there was no evidence of greater accumulation of one enantiomer relative to the other after repeated doses.

After oral administration (40-80 µg), up to 6%-10% of the dose was found as unchanged drug in the urine of healthy subjects, and up to 8% was found as the glucuronide. A total of 67% of the oral formoterol dose is excreted via the urine (mainly as metabolites), with the remainder excreted via the feces. The renal clearance of formoterol is 150 ml/min.

Characteristics in Patients
Liver /Kidney Failure: The pharmacokinetics of formoterol have not been studied in patients with liver and kidney failure. However, since formoterol is primarily eliminated via hepatic metabolism, increased exposure can be expected in patients with severe liver cirrhosis.

5.3 Preclinical Safety Data

The toxicity observed in animal studies with beclometasone dipropionate (BDP) and formoterol, given either in combination or alone, are effects related to an exaggerated pharmacological activity. These effects are primarily associated with the immunosuppressive effects of BDP and the known cardiovascular effects of formoterol, mainly in dogs. No increase in toxicity or unexpected findings were observed following the administration of the combination.

Carcinogenicity:
Carcinogenicity studies have not been performed with the suggested combination. However, data obtained from animals reported for the separate components do not suggest any potential carcinogenicity risk in humans.

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

Reproductive Toxicity:
Reproduction studies in rats showed dose-dependent effects. The combination was associated with reduced fertility in females and embryofetal toxicity. High corticosteroid doses in pregnant animals are known to cause fetal developmental anomalies, including cleft palate and intrauterine growth retardation, and the effects observed with the beclometasone dipropionate/formoterol combination are likely due to beclometasone dipropionate. These effects were only noticed with high systemic exposure to the active metabolite, beclometasone-17-monopropionate (more than 200 times the expected plasma levels in patients). Furthermore, studies in animals showed prolongation of the pregnancy and parturition period, an effect that can be attributed to the known tocolytic effects of beta$_2$-sympathomimetics. These effects were recorded when maternal plasma formoterol levels were below the levels expected in patients treated with the beclometasone dipropionate/formoterol combination.

No specific risks for humans have been revealed in preclinical conventional safety pharmacology, repeated dose toxicity, genotoxicity, carcinogenic potential, and reproductive toxicity studies related to the CFC-free propellant HFA-134a.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Anhydrous Ethanol
Hydrochloric Acid
HFA 134a

6.2 Incompatibilities

There is no known incompatibility.

6.3 Shelf life
20 months

6.4 Special precautions for storage
Instructions for Pharmacies and Wholesalers
Must be stored at 2°C–8°C in a refrigerator for a maximum of 15 months.

Instructions for Patients
Must be used within a maximum of 5 months provided that it is stored at room temperature, below 25°C.
Must be protected from freezing.

6.5 Nature and contents of the container
For our product named FOTEROL-B 6 mcg/100 mcg inhalation solution containing aerosol, aluminium vials (canisters) with a metering valve are used as the packaging material. Each canister (vial and valve) is placed inside a plastic actuator (activator) to ensure that the inhaler delivers the necessary spray for its intended use. Each container provides 120 doses.

6.6 Disposal of Unused Medicinal Product and Other Special Precautions
Any unused material should be disposed according to local disposal regulations.
Instructions for use are detailed in section '4.2 Posology and method of administration'.
Warning: The canister contains liquid under high pressure. Do not expose the canister to temperatures above 50°C, do not pierce it, and do not attempt to open it.

7 MARKETING AUTHORIZATION HOLDER
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Date of first authorisation: 29.03.2017
Date of latest renewal:

10 DATE OF REVISION OF THE SPC