SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

FOSTHMA 20 mcg/2 ml Single-Dose Inhalation Solution for Nebulization

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Active substance:
Each vial contains 21 mcg formoterol fumarate dihydrate equivalent to 20 mcg formoterol fumarate.
Excipient(s):
For a full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Solution for inhalation.
Clear solution, free from visible particles.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

FOSTHMA is indicated as long-term maintenance treatment of bronchospasm, including chronic bronchitis and emphysema, in patients with chronic obstructive pulmonary disease (COPD).

It should not be used in patients with acutely worsening COPD. Do not use for asthma patients.

4.2 Posology and method of administration

Posology/frequency and duration of administration:
The recommended dose of FOSTHMA is a single-dose vial of 20 mcg administered by nebulization twice daily (morning and evening). The highest recommended dose is 40 mcg per day.

Medical advice should be sought if there is no response to maintenance therapy at the recommended dose, which may be a sign of destabilization of COPD and may require re-evaluation of treatment and new treatment options.

The incompatibility, efficacy and safety of the mixture of FOSTHMA with other drugs in the same nebulization device have not been determined.

Method of administration:
FOSTHMA is only administered by inhalation.

FOSTHMA should always be kept in aluminum foil packaging and should only be removed from the packaging when it is to be used. Residues from the used vial should be disposed of.

Additional information on special populations:
Renal / Hepatic impairment:
There have been no clinical studies on the use of formoterol in patients with hepatic or renal impairment. However, there is no theoretical reason for the need for dose adjustment in the use of FOSTHMA in patients with renal and hepatic impairment.

Paediatric population:
FOSTHMA is not indicated for use in children under 18 years of age. Safety and efficacy studies have not been conducted in pediatric patients.

Geriatric population:
In a study of 586 subjects taking formoterol, 284 were aged 65 years or older, while 89 were aged 75 years or older. Of the 123 subjects who received formoterol in the 12-week safety and efficacy study, 48 (39%) were aged 65 years or older. There were no differences in safety and efficacy between younger and older subjects. In other reported clinical trials, there was no difference in response to the drug between younger and older patients. However, it should be taken into account that older people may be more sensitive to the drug.

4.3 Contraindications
Contraindicated in case of hypersensitivity to the active substance formoterol or any of its excipients.

The use of all long-acting beta$_2$-agonists, including FOSTHMA, is contraindicated in asthma patients not taking long-term asthma control medication;

- In patients who are well controlled with another asthma control medicine such as an inhaled corticosteroid given in a low to moderate dose,
- In patients who (rarely) require only short-acting beta$_2$-agonist drugs.

4.4 Special warnings and precautions for use
Formoterol should not be used as monotherapy alone in patients with asthma.

Asthma-related breathing problems associated with long-acting beta-agonist preparations can rarely occur, which can be serious and sometimes fatal.

FOSTHMA is not recommended for the initial treatment of asthma.

Long-acting beta agonists should be used for the shortest period of time that allows controlling asthma symptoms and your doctor will discontinue it, if possible, once asthma control is achieved. Patients should then be maintained with a control treatment.

In pediatric and adolescent patients receiving long-acting beta-agonists in addition to inhaled corticosteroids, it is recommended to use a combination preparation containing both inhaled corticosteroids and long-acting beta-agonists to ensure compliance with both medicines.

Treatment with long-acting beta-agonists should not be initiated if patients are in exacerbation periods or have asthma symptoms that are significantly or acutely worsening.

Asthma-related deaths
Data from a large placebo-controlled study in asthma patients showed that long-acting beta$_2$-adrenergic agonists may increase the risk of asthma-related death. There are no data to determine whether mortality in COPD patients is increased by long-acting beta$_2$-adrenergic agonists.

A 28-day, placebo-controlled study comparing the safety of salmeterol versus placebo, each added to usual asthma treatment, showed an increase in asthma-related deaths in patients receiving salmeterol (13/13,176 in those treated with salmeterol and 3/13,179 in those treated

with placebo; RR 4.37, 95% CI 1.25-15.34). The increased risk of asthma-related death is considered a class effect of long-acting beta$_2$-adrenergic agonists such as formoterol fumarate. No appropriate studies have been conducted to determine whether asthma-related mortality is increased in patients treated with formoterol fumarate. The safety and efficacy of formoterol fumarate in patients with asthma have not been established. All long-acting beta agonists (LABAs), including formoterol fumarate, are contraindicated in patients with asthma without long-term use of an asthma control medication (see Section 4.3.).

Clinical studies with formoterol fumarate administered as a dry powder inhaler have shown a higher incidence of severe asthma exacerbations in patients receiving formoterol compared with those receiving placebo. The volume of these studies is not sufficient to fully characterize differences in rates of severe asthma exacerbations between treatment groups.

Worsening of the disease and acute attacks
Formoterol fumarate treatment should not be initiated in patients with acutely worsening COPD. Otherwise, a life-threatening situation may arise. Formoterol fumarate has not been studied in patients with acutely worsening COPD. The use of formoterol fumarate is not appropriate in this situation.

Formoterol fumarate should not be used for the relief of acute symptoms (e.g. as rescue therapy in the treatment of acute attacks of bronchospasm). Formoterol fumarate has not been studied for the relief of acute symptoms and extra doses should not be administered for this purpose. Acute symptoms should be treated with a short-acting inhaled beta$_2$-agonist.

When starting formoterol fumarate treatment, patients who are regularly taking short-acting inhaled beta$_2$-agonists (four times daily) should be instructed to discontinue their regular use and use them only for the relief of acute respiratory symptoms. When prescribing formoterol fumarate, the healthcare professional should also prescribe a short-acting inhaled beta$_2$-agonist and describe how it should be used. Increased use of inhaled beta$_2$-agonists is a sign of worsening disease and requires immediate medical attention. COPD can worsen acutely within hours or chronically over several days or longer. If formoterol fumarate no longer controls the symptoms of bronchoconstriction, or if the patient's short-acting inhaled beta$_2$-agonist has become less effective, or if the patient requires more short-acting beta$_2$-agonist inhalations than usual, these may be signs of worsening disease. In this context, the patient and COPD treatment should be rapidly reassessed. In this case, it is not appropriate to increase formoterol fumarate above the recommended daily dose (20 mcg twice daily).

Overuse and concomitant use with other long-acting beta$_2$-agonists
As with other inhaled beta$_2$-adrenergic drugs, formoterol fumarate should not be used more frequently and in higher doses than recommended and should not be used concomitantly with other drugs containing long-acting beta$_2$-agonists, as this may result in overdose. Clinically significant cardiovascular effects and fatalities have been reported in association with overuse of inhaled sympathomimetic drugs.

Paradoxical bronchospasm
As with other inhaled beta$_2$-adrenergic drugs, formoterol fumarate may produce paradoxical bronchospasm that may be life-threatening. If paradoxical bronchospasm occurs, formoterol fumarate should be discontinued immediately and alternative treatment initiated.

Cardiovascular effects

As with other inhaled beta$_2$-adrenergic agonists, formoterol fumarate may produce clinically significant cardiovascular effects in some patients, as measured by increases in pulse rate, systolic and/or diastolic blood pressure and/or symptoms. If such effects occur, formoterol fumarate may need to be stopped. Furthermore, beta-agonists have been reported to cause ECG changes such as flattening of the T wave, prolongation of the QTc interval and ST segment depression. The clinical relevance of these findings is unknown. Therefore, as with other sympathomimetic amines, formoterol fumarate should be used with caution in patients with cardiovascular disorders (especially coronary insufficiency, cardiac arrhythmias and hypertension).

Coexisting diseases
As with other sympathomimetic amines, formoterol fumarate should be used with caution in patients with convulsive disorders or thyrotoxicosis and in patients with an unusual response to sympathomimetric amines. When administered intravenously, doses of the beta$_2$-agonist albuterol have been reported to exacerbate pre-existing diabetes and ketoacidosis.

Caution should be exercised in the presence of the following conditions in patients treated with FOSTHMA: third-degree atrioventricular block, persistent diabetes mellitus, thyrotoxicosis, pheochromocytoma, hypertrophic obstructive cardiomyopathy, idiopathic subvalvular aortic stenosis, severe hypertension, aneurysm or other serious cardiovascular diseases such as ischemic heart disease, tachyarrhythmia or occlusive vascular diseases including severe heart failure and especially atherosclerosis.

Formoterol can induce progression of the QTc interval. Care should be taken when treating patients with prolongation of the QTc interval, e.g. congenital or drug-induced (QTc > 0.44 seconds) and in patients treated with drugs that affect the QTc interval (see section 4.5).

Because of the hyperglycemic effects of β_2-agonists, additional initial blood glucose monitoring is recommended in patients with diabetes.

Hypokalemia and hyperglycemia
Beta-agonist drugs may cause significant hypokalemia (with the potential for adverse cardiovascular effects) in some patients, possibly via intracellular shunting. Decreased serum potassium levels are usually transient and do not require supplementation. Beta-agonist drugs may cause transient hyperglycemia in some patients.

Potentially severe hypokalemia can result from β_2 agonist therapy. Particular caution is recommended in acute severe asthma as the risk of hypoxia may be increased. The hypokalemic effect may be increased by the concomitant use of xanthine derivatives, steroids and diuretics with beta-agonists. Therefore, serum potassium levels should be monitored.

For this reason, potassium levels should be monitored regularly, especially in patients with low potassium levels. Serum levels should be monitored even if potassium levels have not decreased during previous short-acting β_2-sympathomimetic therapy. Potassium supplements should be given when necessary.

The occurrence of low serum potassium levels enhances the effect of medicinal products containing digitalis.

In clinical studies with long-term administration of formoterol fumarate at recommended

doses, clinically significant changes in serum potassium and blood glucose levels were rarely observed.

Early hypersensitivity reactions
Early hypersensitivity reactions may occur after administration of formoterol fumarate (demonstrated by cases of anaphylactic reactions, urticaria, angioedema, rash and bronchospasm).

4.5 Interaction with other medicinal products and other forms of interaction
Adrenergic drugs
If additional adrenergic drugs are to be administered by any route, they should be used with caution because the sympathetic effects of formoterol may be potentiated.

Anesthesia drugs
If the patient is to receive halogenated anesthesia, FOSTHMA should be taken at least 12 hours before anesthesia is given.

Xanthine derivatives, steroids or diuretics
Concomitant treatment with xanthine derivatives, steroids or diuretics may potentiate the hypokalemic effect of adrenergic agonists.

Non-potassium-sparing diuretics
ECG changes and/or hypokalemia, which may result from the administration of non-potassium-sparing diuretics (loop or thiazide diuretics), may be acutely worsened by beta agonists (especially when the recommended dose of beta agonist is exceeded). Although the clinical significance of these effects is unknown, caution is advised when beta-agonists are administered with non-potassium-sparing diuretics.

MAO inhibitors, tricyclic antidepressants, drugs that prolong the QTc interval
Like other beta$_2$-agonists, formoterol should be administered with extreme caution in patients treated with monoamine oxidase inhibitors, tricyclic antidepressants, phenothiazine derivatives or drugs known to prolong the QTc interval (antihistamines such as terfenadine, astemizole and mizolastine; antiarrhythmics such as quinidine, disopyramide and procainamide; erythromycin and tricyclic antidepressants), because the effect of adrenergic agonists on the cardiovascular system may be potentiated by these agents. Drugs known to prolong the QTc interval have a high risk of ventricular arrhythmias.

Beta-blockers
Beta-adrenergic receptor antagonists (beta-blockers) and formoterol may inhibit each other's action when administered concomitantly. Beta-blockers not only block the therapeutic effects of beta-agonists, but also induce severe bronchospasm in COPD patients. Therefore, COPD patients should not normally be treated with beta-blockers. However, in certain circumstances (e.g. as prophylaxis after myocardial infarction), there may be no other acceptable alternative to the use of beta-blockers in COPD patients. In this situation, cardioselective beta-blockers should be considered, but these should also be administered with caution.

The concomitant use of formoterol and theophylline may lead to potentiation of their mutual effects and may also cause undesirable effects such as increased heart rate. Substances such as L-dopa, L-thyroxine, oxytocin or alcohol, which themselves potentiate sympathomimetic effects, may affect the cardiovascular system when used with formoterol.

Caution should be exercised before prescribing formoterol fumarate to patients treated with monoamine oxidase inhibitors or tricyclic antidepressants, because formoterol fumarate may potentiate the effects of β_2-adrenergic stimulants on the cardiovascular system.

Concomitant treatment with xanthine derivatives, steroids or diuretics such as thiazide and loop diuretics may increase hypokalemia, a rare adverse effect of β_2-agonists. Hypokalemia may increase susceptibility to arrhythmias in patients treated with digital glycosides.

The risk of arrhythmia is increased in patients receiving halogenated hydrocarbon anesthesia with formoterol.

The bronchodilating effects of formoterol may be enhanced by anticholinergic drugs.

β-adrenergic blockers may weaken or inhibit the effect of formoterol. Therefore, formoterol fumarate should not be given with β-adrenergic blockers (including eye drops) unless there are compelling reasons for their use.

Additional information on special populations
No clinical interaction studies have been conducted on special populations.

Paediatric population:
No interaction studies have been conducted for paediatric population.

4.6 Pregnancy and lactation
General advice
Pregnancy category: C

Women of childbearing potential / Birth Control (Contraception)
If pregnancy is detected during the use of FOSTHMA, the patient is advised to consult a doctor.

Pregnancy
There are limited amount of data from the use of FOSTHMA in pregnant women.

Animal studies have shown reproductive toxicity (See section 5.3). The potential risk for humans is unknown.

In the absence of adequate and well-controlled clinical trials during pregnancy, it should only be used during pregnancy if the benefit to the mother outweighs the risk to the fetus.

There are no adequate and well-controlled clinical studies on the use of formoterol fumarate inhalation during labor and delivery. Since beta agonists have the potential to inhibit uterine contractions, FOSTHMA should not be used during pregnancy unless necessary.

Lactation
After oral administration, formoterol was detected in the milk of lactating rats. It is not known whether formoterol passes into human milk, but breastfeeding mothers should be careful when using FOSTHMA as many medicines pass into breast milk. There have been no clinical studies on the use of formoterol in breastfeeding mothers. Formoterol should be given to

breastfeeding women only if the benefit outweighs the risk to the patient and the baby.

If the mother will use FOSTHMA during breastfeeding, it is recommended to consult her doctor.

Reproductive ability/Fertility
See Section 5.3.

4.7 Effects on ability to drive and use machines
FOSTHMA has no effect on driving and using machines.

4.8 Undesirable effects
The most commonly reported adverse effects of β_2-agonist treatment (such as tremor and palpitations) have been mild and resolved after the first few days of treatment. Adverse reactions associated with formoterol are listed below by system organ class and frequency. Frequencies are defined as follows:
Very common (≥ 1/10); common (≥ 1/100 to < 1/10); uncommon (≥ 1/1000 to < 1/100); rare (≥ 1/10000 to < 1/1000); very rare (< 1/10000); unknown (cannot be estimated from the available data).

Blood and lymphatic system disorders	
Very rare:	Thrombopenia
Immune system disorders	
Rare:	Hypersensitivity reactions such as angioedema, bronchospasm, exanthema, urticaria, pruritus
Metabolism and nutrition disorders	
Uncommon:	Hypokalemia, hyperglycemia
Psychiatric disorders	
Uncommon:	Agitation, restlessness, sleep disturbances
Very rare:	Abnormal behavior, hallucinations
Nervous system disorders	
Common:	Tremor, headache
Uncommon:	Dizziness, taste disturbances
Very rare:	Central nervous system stimulation
Cardiac disorders	
Common:	Palpitation
Uncommon:	Tachycardia
Rare:	Cardiac arrhythmias such as atrial fibrillation, supraventricular tachycardia, extrasystole; angina pectoris
Very rare:	Prolongation of the QTc interval
Vascular disorders	
Rare:	Unstable blood pressure
Respiratory, thoracic and mediastinal disorders	
Common:	Cough
Uncommon:	Throat irritation
Rare:	Paradoxical bronchospasm (see. Section 4.4)
Very rare:	Dyspnea, asthma exacerbation

Gastrointestinal disorders	
Uncommon:	Nausea
Skin and subcutaneous tissue disorders	
Uncommon:	Hyperhidrosis
Musculoskeletal and connective tissue disorders	
Uncommon:	Muscle cramps, myalgia
Renal and urinary disorders	
Rare:	Nephritis
General disorders and administration site conditions	
Very rare:	Oedema peripheral

Side effects such as nausea, taste disturbance, throat irritation, hyperhidrosis, restlessness, headache, dizziness and muscle cramps may resolve spontaneously within one to two weeks of ongoing treatment.

Central nervous system stimulant effects have been sporadically reported following inhalation of ß$_2$-sympathomimetic, manifesting as hyperexcitability. These effects were mainly observed in children up to 12 years of age.

Treatment with ß$_2$-agonists can lead to increased blood levels of insulin, free fatty acids, glycerol and ketone bodies.

Adverse reactions to FOSTHMA are expected to be similar to adverse reactions to other beta$_2$-adrenergic receptor agonists (such as angina, hypertension or hypotension, tachycardia, arrhythmias, nervousness, headache, tremor, dry mouth, muscle cramps, palpitations, nausea, dizziness, fatigue, weakness, insomnia, hypokalemia, hyperglycemia and metabolic acidosis).

Clinical Study Experience
Because clinical trials are conducted under a wide variety of conditions, adverse reaction rates observed in clinical trials of one medicinal product are not directly comparable to rates observed in clinical trials of another medicinal product and may not reflect rates observed in practice.

Adults with COPD
The data described below reflect the use of 20 mcg formoterol twice daily by oral inhalation in 586 patients (the drug was used by 232 patients for 6 months and 155 patients for at least 1 year). Formoterol was studied in a 12-week placebo and active-controlled study (123 subjects treated with formoterol) and a 52-week active-controlled study (463 subjects treated with formoterol). The patients were mostly Caucasian (88%), aged between 40 and 90 years (mean 64 years), and had a mean FEV1 of 1.33 L. Patients with significant cardiac or other medical disease were not included in the studies.

Table 1 shows the adverse reactions observed in the 12-week, double-blind, placebo-controlled study. In this study, the frequency of adverse reactions was 2% or higher in the formoterol group and the rate in the formoterol group exceeded the rate in the placebo group. The frequency of patients experiencing cardiovascular adverse events was 4.1% for the formoterol group and 4.4% for the placebo group. No specific frequently occurring cardiovascular adverse events were identified for formoterol (frequency of 1% or higher and higher than in the placebo group). The rate of COPD exacerbations was 4.1% for the

formoterol group and 7.9% for the placebo group.

TABLE 1 - Number of patients with adverse reactions in a 12-week multi-dose controlled clinical trial

Adverse reaction	Formoterol 20 mcg n	(%)	Placebo n	(%)
Total patients	123	(100)	114	(100)
Diarrhoea	6	(4.9)	4	(3.5)
Nausea	6	(4.9)	3	(2.6)
Nasopharyngitis	4	(3.3)	2	(1.8)
Dry mouth	4	(3.3)	2	(1.8)
Vomiting	3	(2.4)	2	(1.8)
Dizziness	3	(2.4)	1	(0.9)
Insomnia	3	(2.4)	0	0

In the 52-week open-label study, in patients treated with 20 mcg Formoterol twice daily, no increase in clinically significant adverse events above the number expected based on patients' medical condition and age was observed.

Post marketing experience
The following adverse reactions have been reported during the use of formoterol after marketing approval. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably calculate their frequency or to establish a cause and effect relationship with drug exposure.

Anaphylactic reactions, urticaria, angioedema (manifested as edema of the face, lips, tongue, eyes, pharynx or mouth), rash and bronchospasm.

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
Symptoms:
Due to overdose of FOSTHMA, typical signs and symptoms of excessive beta$_2$-adrenergic stimulation and/or the emergence or aggravation of the undesirable effects listed in section 4.8. Signs and symptoms include angina, hypertension or hypotension, tachycardia (up to 200 beats/min), arrhythmia, nervousness, headache, tremor, seizures, muscle cramps, dry mouth, palpitations, nausea, dizziness, fatigue, weakness, insomnia, hyperglycemia, hypokalemia and metabolic acidosis.

As with all inhaled sympathomimetic drugs, overdose of formoterol may be associated with cardiac arrest and death.

Treatment:
Upon discontinuation of FOSTHMA, an appropriate supportive and/or symptomatic treatment is applied. Appropriate use of cardioselective beta-blockers may be considered, but it should be kept in mind that these drugs may cause bronchospasm. There is insufficient evidence that

formoterol is removed by dialysis. Cardiac monitoring is recommended in case of overdose.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Drugs Used in Obstructive Respiratory Diseases, Selective $beta_2$-adrenoreceptor agonists

ATC code: R03AC13

Mechanism of action:
Formoterol fumarate is a long-acting, $beta_2$-adrenergic receptor agonist ($beta_2$-agonist). Inhaled formoterol fumarate exerts a bronchodilator effect locally in the lung. *In vitro* studies have shown that formoterol has 200 times more agonist activity at $beta_2$-receptors than at $beta_1$-receptors. Although $beta_2$-receptors predominate in bronchial smooth muscle cells and $beta_1$-receptors in the heart, $beta_2$-receptors account for 10-50% of total beta-adrenergic receptors in the heart. The function of these receptors has not been fully characterized but suggests that even highly selective $beta_2$-agonists may have cardiac effects.

The pharmacological effects of $beta_2$-adrenoreceptor agonist drugs such as formoterol are partly related to stimulation of intracellular adenylyl cyclase, the enzyme that catalyzes the conversion of adenosine triphosphate (ATP) to cyclic-3'-5'-adenosine monophosphate (cyclic AMP). The increase in cyclic AMP levels causes relaxation of bronchial smooth muscle cells and inhibits the release of mediators, especially those released from mast cells, which cause immediate hypersensitization of the cells.

According to *in vitro* tests, formoterol inhibits the release of mast cell mediators such as histamine and leukotrienes from human lung cells. Furthermore, formoterol inhibits histamine-induced plasma albumin extravasation in anesthetized guinea pigs and allergen-induced eosinophil entry in dogs with airway hypersensitivity. The relationship between *in vitro* tests and animal findings and COPD patients is unknown.

Systemic Safety and Pharmacokinetic/Pharmacodynamic Relationships
The major adverse effects of inhaled beta-agonists occur as a result of over-activation of systemic beta-adrenergic receptors. The most common side effects in adults include tremor and cramps involving skeletal muscle, insomnia, tachycardia, decreases in plasma potassium and increases in plasma glucose.

Changes in serum potassium and serum glucose in 12 COPD patients after single-dose inhalation of 10, 20, 244 mcg formoterol fumarate (calculated on anhydrous base) were examined in crossover studies. At 1 hour after treatment with formoterol fumarate inhalation solution, mean (± standard deviation) serum glucose was elevated to 26 ± 30, 29 ± 28 and 38 ± 44 mg/dL, respectively, and did not differ significantly from baseline or trough levels at 24 hours and within 24 hours. One hour after administration of formoterol fumarate inhalation solution at a dose of 244 mcg, the serum potassium level decreased by 0.68 ± 0.4 mEq/L and did not differ from baseline or trough levels 24 hours after dosing.

Electrophysiology
In line with the examination of the dose range of formoterol fumarate inhalation solution, 6 hours after a single-dose of 244 mcg, the heart rate determined by ECG increased by 6 ± 3 beats per minute. The heart rate returned to the pre-dose rate in 16-24 hours.

The effects of formoterol fumarate inhalation solution on heart rate and cardiac rhythm were studied in a 12-week clinical trial with placebo and active controlled treatment. 105 patients with COPD underwent continuous electrocardiography (Holter) monitoring for 24 hours after exposure to formoterol fumarate inhalation solution (baseline study started after 8-12 weeks of treatment of patients with formoterol fumarate inhalation solution). ECG was measured at baseline (before dosing) and 2 to 3 hours after dosing, and ECG was measured after 4, 8 and 12 weeks of treatment. Bazett and Fridericia methods were used to correct heart rate and QT interval (QTcB and QTcF, respectively). The mean increase from baseline in QTcB interval over the 12-week treatment period with formoterol inhalation solution was ≤ 4.8 msec and ≤ 4.6 msec for placebo. The percentage of patients who experienced a maximum change in QTc of more than 60 msec at any time during the 12-week treatment period was 0% and 1.8% and 1.6% and 0.9% for placebo, respectively, based on Bazett's adjustment and Fridericia's adjustment, respectively. Indefinite QT prolongation was reported as an adverse event in 1 patient (0.8%) after inhalation of formoterol fumarate inhalation solution and in 2 patients (1.8%) in the placebo group. During 24-hour Holter monitoring, atrial fibrillation or ventricular tachycardia were not observed or reported as adverse events in patients treated with formoterol fumarate inhalation solution after initiation of dose administration. No increase in supraventricular tachycardia was observed in placebo-treated patients. The mean increase in maximum heart rate from baseline was 0.6 beats per minute (bpm) 8-12 weeks after dose initiation and 1.2 bpm in placebo patients compared with patients treated twice daily with formoterol fumarate inhalation solution. There were no clinically significant differences in acute or chronic effects on heart rate, including QTcB and QTcF, in cardiac rhythm resulting from formoterol fumarate inhalation solution treatment in the active treatment and placebo treatment groups.

At an exposure equal to approximately 12 times that of formoterol fumarate dry powder formulation and approximately 12 times that of formoterol fumarate inhalation solution, an average pulse rate increase of 26 bpm was observed in healthy subjects 6 hours after the dose. This study showed that the maximum increase of the mean corrected QT interval (QTc) was at 25 msec when calculated using Bazett's correction and 8 msec when calculated using Fridericia's correction. QTc returned to baseline within 12 to 24 hours post-dose. Formoterol plasma concentrations are weakly correlated with increased pulse rate and QTc duration. The effects on pulse rate and QTc interval are pharmacological effects of formoterol fumarate inhalation solution and this supratherapeutic formoterol fumarate inhalation dose is not unexpected.

Tachyphylaxis / Tolerance
Tolerance to the effects of inhaled beta-agonists may develop with regularly scheduled, chronic use.

In a placebo-controlled clinical trial in 351 adult patients with COPD, the bronchodilating effect of formoterol fumarate inhalation solution was determined by the FEV_1 area under the curve at day 1 dose and for 12 hours after 12 weeks of treatment. The effect of formoterol fumarate inhalation solution was not reduced for 12 weeks after twice-daily treatment (see Figures 1 and 2).

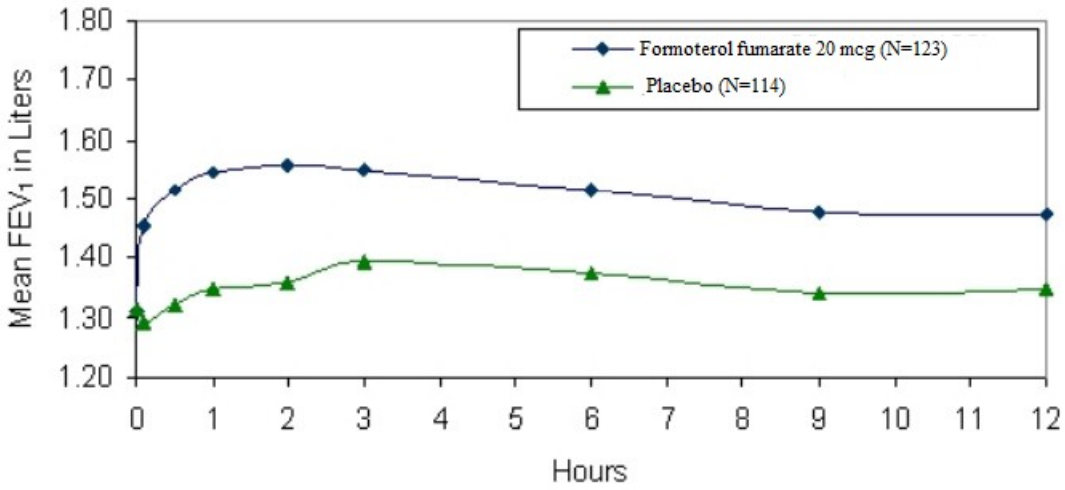

Figure 1: Mean FEV_1 in day 1

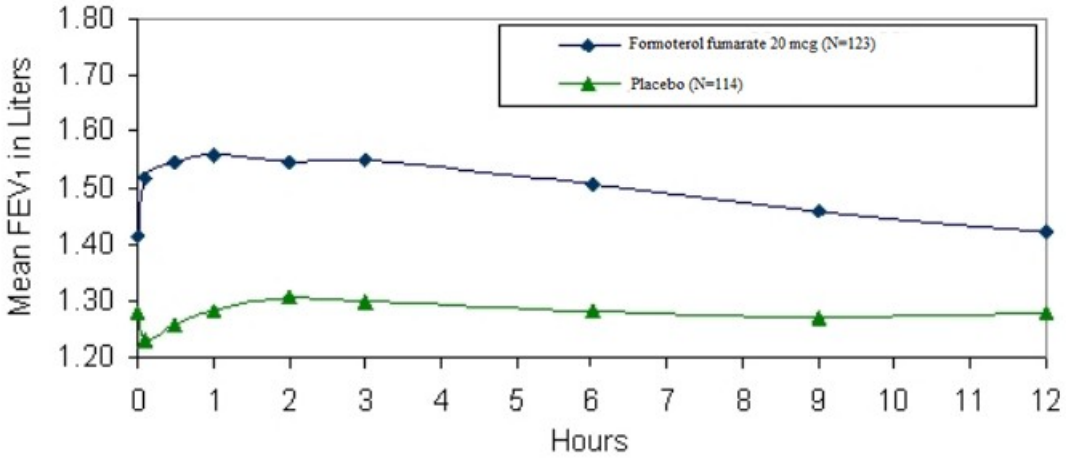

Figure 2: mean FEV_1 in day 1 (endpoint after 12 weeks of treatment)

5.2. Pharmacokinetic properties

General properties

Information on the pharmacokinetics of formoterol (dry powder and/or inhalation solution) in plasma and/or urine was obtained from oral inhalation of COPD patients and healthy volunteers at therapeutic and above therapeutic doses.

Formoterol excreted unchanged in urine has been used as an indirect measure of systemic exposure. Drug plasma disposition data and urinary excretion are in parallel; they are also similar to the elimination half-lives calculated for urine and plasma.

Absorption:

The pharmacokinetic properties of formoterol fumarate were evaluated in 12 COPD patients following single-dose inhalation of 10, 20 and 244 mcg formoterol fumarate (calculated on anhydrous base) inhalation solution and 12 mcg dry powder formoterol fumarate followed by 36 hours post-inhalation. Following doses of 10 and 20 mcg of formoterol fumarate inhalation solution and 12 mcg of formoterol fumarate dry powder, plasma concentrations of formoterol fumarate were not measured or inconsistently measured at very low concentrations. After administration of a single-dose of 244 mcg (approximately 12 times the recommended clinical dose) of formoterol fumarate inhalation solution, formoterol fumarate concentrations were

rapidly absorbed into plasma and were measurable in plasma within a short time; a maximum drug concentration of 72 pg/mL was reached within approximately 12 minutes of dosing.

When COPD patients were given 12 mcg of dry powder formoterol fumarate twice daily by oral inhalation for 12 weeks, the accumulation index relative to the portion of formoterol excreted unchanged in urine was 1.19 to 1.38. This suggests that formoterol accumulates in plasma with multiple dose administration. Although there are no multiple-dose pharmacokinetic data from formoterol inhalation solution, its linear pharmacokinetics allows prediction of minimal accumulation based on single-dose pharmacokinetic data. Like many oral inhaled drugs, a significant proportion of inhaled formoterol reaches the target site and is absorbed from the gastrointestinal tract.

Distribution:
The binding of formoterol to human plasma proteins was found to be 61-64% in *in vitro* studies in the concentration range of 0.1 to 100 ng/mL. *In vitro* binding to human serum albumin in the range of 5 to 500 ng/mL is 31-38%. The concentration of formoterol used to determine its binding to plasma proteins is greater than that of 244 mcg formoterol inhalation solution inhaled as a single-dose.

Biotransformation:
Formoterol is mainly metabolized by direct glucronidation at phenolic or aliphatic hydroxyl groups and O-demethylation followed by glucronide conjugation at phenolic hydroxyl groups. Sulfate conjugation and deformylation followed by sulfate conjugation are the minor metabolic pathways of formoterol. The most prominent metabolic pathway involves direct conjugation at the phenolic hydroxyl group. The second major pathway is O-demethylation followed by conjugation at the phenolic 2'-hydroxyl group. *In vitro* studies have shown that the enzymes metabolizing many drugs catalyze the glucronidation (UGT1A1, 1A8, 1A9, 2B7 and 2B15 were the most dominant enzymes) and O-demethylation (CYP2D6, CYP2C19, CYP2C9 and CYP2A6) of formoterol. Formoterol did not inhibit CYP450 enzymes at therapeutically relevant concentrations. Some patients may have deficiency of CYP2D6, 2C19 or both. Whether deficiency of these isoenzymes, alone or in combination, results in increased systemic exposure or systemic adverse effects of formoterol has not been investigated.

Elimination:
Following single-dose administration of 10, 20 and 244 mcg (calculated on anhydrous base) of formoterol inhalation solution by nebulizer to 12 COPD patients, an average of approximately 1.1% to 1.7% of the dose was excreted as unchanged formoterol in the urine, compared to 3.4% unchanged following administration of 12 mcg of dry powder. In these patients, the renal clearance of formoterol in formoterol inhalation solution given by inhalation is 157 mL/min. Based on plasma concentrations measured after administration of a 244 mcg dose, the terminal half-life was 7 hours.

The mean amount of formoterol excreted unchanged in the urine 24 hours after a single oral inhalation dose of 10, 20 and 244 mcg formoterol inhalation solution was 109.7 ng, 349.6 ng and 3317.5 ng, respectively. These findings indicate a dose-proportional increase in systemic exposure over the dose range tested.

Linearity/Non-linearity
The linear pharmacokinetic/pharmacodynamic relationship between decreased urinary

formoterol excretion and serum potassium levels, increased plasma glucose levels and increased heart rate has been mostly observed in other inhaled formulations of formoterol. A similar relationship is expected to be seen in this dosage form of formoterol. Following a single-dose of 244 mcg (approximately 12 times the recommended dose) of formoterol inhalation solution in healthy subjects, formoterol plasma concentrations were highly correlated with a decrease in plasma potassium levels following a single-dose of 10 times the recommended dose of another formoterol inhalation formulation with comparable exposure. Based on the data in this study, the maximum decrease in plasma potassium levels from the cut-off line was 0.55-1.52 mmol/L and the median maximum decrease was 1.01 mmol/L. The effect on plasma potassium levels was generally seen 1-3 hours after the peak plasma concentration of formoterol was reached.

Characteristics in patients
Liver / kidney failure:
The pharmacokinetics of formoterol in patients with hepatic or renal impairment have not been studied.

Paediatric population:
The pharmacokinetics of formoterol in pediatric patients have not been studied.

Geriatric population:
In clinical trials of formoterol inhalation solution, there were no differences in safety and efficacy between young and elderly subjects. In other clinical experiences, no difference in response to the drug was found between younger and older patients. However, it should be taken into account that some elderly people may be more sensitive to the drug.

The pharmacokinetics of formoterol in elderly patients has not been studied.

Gender
As reported for another formoterol fumarate inhalation formulation, there were no significant differences in the pharmacokinetics of formoterol fumarate between men and women when proportioned by weight.

5.3. Preclinical safety data

Mutagenicity:
Formoterol fumarate was not found to be mutagenic or clastogenic in the indicated tests: Mutagenicity test in bacterial and mammalian cells, chromosome analysis in mammalian cells, unprogrammed DNA synthesis repair test in rat hepatocytes and human fibroblast cells, transformation assay in mammalian fibroblasts and micronucleus test in mice and rats

Carcinogenicity
The carcinogenic potential of formoterol was evaluated in 2-year drinking water and dietary studies in both rats and mice. In rats, the incidence of ovarian leiomyomas was increased at doses of 15 mg/kg and above in the drinking water study and 20 mg/kg in the feeding study (AUC exposure approximately 2300 times the maximum recommended daily inhalation dose in humans). However, this was not seen at doses up to 5 mg/kg in the feeding study (AUC exposure 570 times the maximum recommended daily inhalation dose in humans). In the feeding study, doses of 0.5 mg/kg and above (approximately 57 times the maximum recommended daily inhalation dose in humans) increased the incidence of benign ovarian tabula cell tumors. These findings were not seen in drinking water studies or in mice.

In drinking water studies, doses of 69 mg/kg and above (AUC exposure 1000 times the maximum recommended daily inhalation dose in humans) given to male mice increased the incidence of adrenal subcapsular adenomas and carcinomas. However, this was not seen in feeding studies at doses up to 50 mg/kg (AUC exposure 750 times the maximum daily recommended inhalation dose in humans). In a feeding study, the incidence of hepatocarcinoma was increased in female mice at doses of 20 and 50 mg/kg (AUC exposure 300 and 750 times the human maximum daily recommended inhalation dose, respectively) and in male mice at 50 mg/kg, but not at doses up to 5 mg/kg (AUC exposure approximately 75 times the human maximum daily recommended inhalation dose). In addition, in nutritional studies, the incidence of uterine leiomyomas and leiomyosarcoma was increased at doses of 2 mg/kg and above (AUC exposure approximately 30 times the maximum daily recommended inhalation dose in humans). The increase of leiomyomas in the genital tract of female rodents was similar to that found with other beta-agonist drugs.

Fertility
In reproduction studies in rats, oral doses up to 3 mg/kg (approximately 600 times the maximum recommended daily inhalation dry dust dose in humans based on mg/m^2) had no adverse effect on fertility.

Teratogenicity
Orally administered formoterol fumarate did not cause malformations in rats or mice during organogenesis. However, formoterol fumarate was found to be teratogenic in rats and rabbits in another test laboratory. During organogenesis, oral doses of 0.2 mg/kg and above (approximately 40 times the maximum recommended human daily dose based on mg/m^2) administered to rats delayed fetal ossification. At doses of 6 mg/kg and above (approximately 1200 times the maximum recommended daily dose in humans based on mg/m^2) there was a decrease in fetal birth weight. Formoterol fumarate has been shown to cause stillbirth and neonatal death in rats given orally at doses of 6 mg/kg and above during late pregnancy. However, these effects did not occur at a dose of 0.2 mg/kg.

The minimum lethal inhalation dose of formoterol fumarate in rats is 156 mg/kg (approximately 32,000 times the maximum recommended daily inhalation dose in humans in mg/m^2). The average lethal oral doses administered to Chinese hamsters, rats and mice make the maximum recommended daily inhalation dose in humans much exponentially higher.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients
Citric acid monohydrate
Sodium citrate dihydrate
Sodium chloride
Water for injection

6.2 Incompatibilities
Not known.

6.3 Shelf life
24 months

6.4 Special precautions for storage

It should be stored between 2 - 8°C in the sachet in the refrigerator, protected from light.

6.5 Nature and contents of container
It is supplied in a box containing 6 or 12 sachets and 5 single-dose vials in each sachet, each vial containing 2 ml of finished product, together with package leaflet.

6.6 Special precautions for disposal and other handling
Any unused medicinal product or waste material should be disposed of in accordance with local requirement.

7. MARKETING AUTHORISATION HOLDER
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8. MARKETING AUTHORISATION NUMBER(S)
2018/586

9. DATE OF FIRST AUTHORIZATION / RENEWAL OF THE AUTHORIZATION
Date of first authorization: 18.10.2018
Renewal of the authorization:

10. DATE OF REVISION OF THE TEXT