SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

DULAMON 200 mcg/5 mcg Pressurized Inhalation, Suspension

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Per actuation delivered to the patient:
Active substance:
Mometasone furoate 200 mcg
Formoterol fumarate dihydrate 5 mcg
Excipients:
For the full list of excipients, see 6.1.

3. PHARMACEUTICAL FORM

Pressurized inhalation, suspension
Aerosol inhaler form in aluminum tubes with metering valve

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

DULAMON is used to relieve and control asthma symptoms. It is given as of the third step in the stepwise treatment of asthma.

4.2 Posology and method of administration

Posology/frequency and duration of administration:
Two inhalations of DULAMON should be administered twice daily (morning and evening).
The recommended initial dose for DULAMON depends on previous asthma therapy.

Recommended initial dose for DULAMON		
Previous Therapy	**Recommended dose**	**Maximum daily dose**
Medium-dose inhaled corticosteroid	Two inhalations of mometasone furoate/formoterol fumarate 200 mcg/5 mcg twice daily	400/20 mcg
High-dose inhaled corticosteroid	Two inhalations DULAMON 200 mcg/5 mcg twice daily	800/20 mcg

The maximum recommended daily dose is two inhalations DULAMON 200 mcg/5 mcg twice a day (morning and evening).

DULAMON should not be used for more than two inhalations twice daily, as some patients are more likely to experience adverse effects with higher doses of formoterol. If symptoms arise between doses, an inhaled short-acting beta$_2$-agonist should be taken for immediate relief.

DULAMON is not indicated for the relief of acute bronchospasm. DULAMON is not indicated for use in patients in whom full asthma control is achieved with low or medium dose inhaled corticosteroids.

If a previously effective dosage regimen of DULAMON fails to provide adequate control of asthma, re-evaluate the therapeutic regimen and consider additional therapeutic options, e.g., replacing the current strength of mometasone furoate/formoterol fumarate combination 100 mcg/5 mcg with a higher strength DULAMON 200 mcg/5 mcg, or adding additional inhaled corticosteroid, or initiating oral corticosteroids.

Maximum benefit may not be achieved for 1 week or longer after initiation of treatment. Individual patients may experience a variable time to onset and degree of symptom relief. Additional asthma control can be achieved with higher doses in patients 12 years of age and above who do not respond adequately to 2 weeks of therapy.

Method of administration
For inhalation use only.

The proper use of the inhalation spray should be demonstrated to the patient by the doctor or pharmacist. Patients should preferably be sitting or standing during inhalation. The inhalation spray is intended for use in an upright position.

For the proper use of the inhalation spray, the instructions given below should be carefully followed.

Instructions for use of the inhalation spray
Testing the inhalation spray:

(Figure 1)

Before using the inhaler for the first time, patients should remove the mouthpiece cap by gently squeezing its sides; shake the inhaler well; hold it with the thumb at the base of the inhaler under the mouthpiece, that is, between the fingers and the thumb; squeeze the inhalation spray into the air. The inhaler should be shaken before each use.

In cases where the inhaler has not been used for a week or longer period of time, mouthpiece cap should be removed and the inhalation spray should be squeezed into the air twice.
Patients should sit or stand upright when using the inhalation spray.

1. The mouthpiece cap should be removed as shown in Figure 1. The mouthpiece should be checked inside and out to make sure it is clean.
2. The inhalation spray should be well shaken before each use.

3. The inhaler should be held upright with the thumb at the base of it, under the mouthpiece.

4. The mouthpiece should be put between the teeth and the lips should be closed tightly.

5. While breathing slowly and deeply through the mouth, the top of the inhaler should be pressed simultaneously to release a puff of medicine.

6. While holding the breath for about 10 seconds or as long as it is comfortable to hold, the inhaler should be pulled from the mouth and the thumb from the top of the inhaler. Then breathe out slowly through the mouth. Exhaling into the inhaler should be avoided.

7. Wait for about half a minute between each puff intake and then repeat steps 2 to 6.

8. Afterwards, the mouth should be rinsed with water, then spit out. Doing so is important for the prevention of oral thrush and hoarseness.
9. The mouthpiece cap should be closed immediately after use to protect the mouthpiece from dust. When the cap is placed correctly it will click into position. If it does not fit, turn the cap the other way round and try again. Do not use too much force.

The steps 4, 5 and 6 should not be rushed. It is important to breathe as slowly as possible just before actuating the inhaler. Patients should use their inhaler whilst standing in front of a mirror for the first few times. If mist seen coming from the top of the inhaler or the sides of the mouth, the procedure should be restarted from step 2.

Cleaning the inhaler
The inhaler should be cleaned at least once a week.
1. The mouthpiece cap should be removed.
2. Tube must not be removed from plastic body.
3. With a dry cloth or tissue, wipe the plastic body and the inside and outside of the mouthpiece.
4. The mouthpiece cap should be inserted correctly. Do not apply too much force to insert the cover.

Warning!
Inhalation spray must not be sprayed into the eyes. In case of accidental spraying, the eyes should be rinsed with water. If redness or irritation occurs, consult a doctor.

Additional information on special populations

Renal insufficiency
No data are available on the specific use of the mometasone furoate/formoterol fumarate combination in patients with renal impairment.

Hepatic insufficiency
No data are available on the specific use of mometasone furoate/formoterol fumarate combination in patients with hepatic impairment. However, the concentrations of mometasone furoate in the content of DULAMON may increase in relation to the severity of hepatic failure.

Pediatric population
Since the efficacy and safety of mometasone furoate/formoterol fumarate combination has not been proven in children younger than 12 years of age, DULAMON should not be used in this age group.

Geriatric population
No dose adjustment is required for DULAMON in the geriatric population.

4.3 Contraindications
DULAMON is contraindicated in the following cases:
- In patients with hypersensitivity to formoterol fumarate, mometasone furoate or any of the excipients in this product.
- In the treatment of status asthmaticus, or other acute episodes of asthma requiring intensive measures.

4.4 Special warnings and precautions for use

Long-acting beta$_2$-adrenergic agonists (LABA) such as formoterol, one of the active ingredients of DULAMON, increase the risk of asthma-related deaths. The available data are insufficient to determine whether concomitant use of inhaled corticosteroids or other long-term asthma-controlling drugs would reduce the increased risk of LABA-induced asthma-related deaths. Data obtained from controlled clinical trials indicate that LABAs increase asthma-related hospitalizations in pediatric and adolescent patients. Therefore, when treating asthma patients, DULAMON should only be prescribed for patients whose asthma cannot be adequately controlled with medications that provide long-term asthma control, such as inhaled corticosteroids, or when treatment must be initiated with both inhaled corticosteroids and LABA due to the severity of the disease. Once asthma control is achieved, the patient should be evaluated at regular intervals and the treatment should be reviewed by taking care not to lose asthma control (e.g., DULAMON should be terminated), and the patients should be maintained with drugs that provide long-term asthma control such as inhaled corticosteroids. DULAMON should not be used in patients whose asthma is adequately controlled with low or medium dose inhaled corticosteroids.

A 28-week study conducted in the United States showed an increase in asthma-related deaths in patients who added salmeterol to their usual asthma treatment (13 of 13,176 patients treated with salmeterol compared with 3 of 13,179 patients who received placebo). This finding is thought to be a class effect of LABAs, including formoterol, one of the active excipients of DULAMON. No studies have been conducted to determine whether the use of mometasone furoate/formoterol fumarate combination increases the rate of asthma-related mortality.

Clinical studies with formoterol have shown a higher incidence of severe asthma exacerbations in patients receiving formoterol compared with patients receiving placebo.

Rare, serious and sometimes fatal asthma-related respiratory problems may occur with long-acting beta-agonist preparations.

DULAMON is not recommended for the initial treatment of asthma.

Long-acting beta-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. Subsequently, the patients should be maintained with a control treatment.

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

Treatment with long-acting beta-agonists should not be initiated if patients are in exacerbations or have severe or acutely worsening asthma.

<u>Deterioration of disease and acute episodes</u>

Treatment with DULAMON should not be initiated in patients during rapidly deteriorating or potentially life-threatening episodes of asthma. No studies have been conducted on the use of mometasone furoate/formoterol fumarate combination in patients with acutely deteriorating asthma. Therefore, it is not appropriate to initiate DULAMON treatment in such a setting.

Increasing use of inhaled, short-acting beta$_2$-agonists is a marker of deteriorating of asthma. In such

a situation, it is necessary to re-evaluate the therapeutic regimen and consider additional therapeutic options, e.g., replacing the current strength of mometasone furoate/formoterol fumarate combination 100 mcg/5 mcg with a higher strength of DULAMON 200 mcg/5 mcg or adding additional inhaled corticosteroid, or initiating oral corticosteroids. Patients should not use DULAMON for more than two inhalations twice daily (morning and evening).

DULAMON is not indicated for the relief of acute symptoms, i.e., as rescue therapy for the relief of acute episodes of bronchospasm. An inhaled short-acting beta$_2$-agonist should be used to relieve of acute symptoms such as shortness of breath. When physicians prescribe DULAMON, they should also prescribe an inhaled short-acting beta$_2$-agonist (e.g. albuterol) for the treatment of acute symptoms, along with the regular use of DULAMON twice daily (morning and evening).

When beginning treatment with DULAMON, patients who have been taking oral or inhaled, short-acting beta$_2$-agonists on a regular basis (e.g., 4 times a day) should be instructed to discontinue the regular use of these drugs.

Excessive use of DULAMON and use with other long-acting beta$_2$-agonists
As with other inhaled drugs containing beta$_2$-adrenergic agents, DULAMON should not be used more often than recommended, at higher doses than recommended, or in conjunction with other medications containing long-acting beta$_2$-agonists, as an overdose may result. Clinically significant cardiovascular effects and fatalities have been reported in association with excessive use of inhaled sympathomimetic drugs. Patients using DULAMON should not use an additional long-acting beta$_2$-agonist (e.g., salmeterol, formoterol fumarate, and arformoterol tartrate) for any reason, including prevention of exercise-induced bronchospasm (EIB) or the treatment of asthma.

Oral candidiasis
In clinical trials, the development of localized infections of the mouth and pharynx with *Candida albicans* have occurred in patients treated with formoterol fumarate and mometasone furoate combination. If oropharyngeal candidiasis (*Candida albicans* infection) develops, patients should be treated with an appropriate local or systemic (i.e., oral) antifungal medication while remaining on DULAMON therapy, but at times therapy with DULAMON may need to be interrupted. To reduce the risk of oropharyngeal candidiasis, after dosing with DULAMON, advise patients to rinse their mouth with water and spit out the contents without swallowing.

Immunosuppression
Patients who are using drugs that suppress the immune system are more susceptible to infections than healthy individuals.

Chickenpox and measles, for example, can have a more serious or even fatal course in susceptible children or adults using corticosteroids. In such children or adults who have not had these diseases or who are not properly immunized, particular care should be taken to avoid exposure. How the dose, route, and duration of corticosteroid administration affect the risk of developing a disseminated infection is not known. The contribution of the underlying disease and/or prior corticosteroid treatment to the risk is also not known. If exposed to chickenpox, prophylaxis with varicella zoster immune globulin (VZIG) or pooled intravenous immunoglobulin (IVIG) may be indicated. If exposed to measles, prophylaxis with pooled intramuscular immunoglobulin (IG) may be indicated. If chickenpox develops, treatment with antiviral agents may be considered.

DULAMON should be used with caution, if at all, in patients with active or quiescent tuberculosis infection of the respiratory tract, untreated systemic fungal, bacterial, viral, or parasitic infections; or

ocular herpes simplex.

Transferring patients on systemic corticosteroid therapy to DULAMON
Particular care is needed for patients who are transferred from systemically active corticosteroids to DULAMON because deaths due to adrenal insufficiency have occurred in asthmatic patients during and after transfer from systemic corticosteroids to less systemically available inhaled corticosteroids. After withdrawal from systemic corticosteroids, a number of months are required for recovery of hypothalamic-pituitary-adrenal (HPA) function.

Patients who have been previously maintained on 20 mg or more per day of prednisone (or its equivalent) may be most susceptible, particularly when their systemic corticosteroids have been almost completely withdrawn. During this period of HPA suppression, patients may exhibit signs and symptoms of adrenal insufficiency when exposed to trauma, surgery, or infection (particularly gastroenteritis) or other conditions associated with severe electrolyte loss. Although DULAMON may improve control of asthma symptoms during these episodes, in recommended doses it supplies less than normal physiological amounts of corticosteroid systemically and does not provide the mineralocorticoid activity necessary for coping with these emergencies.

During periods of stress or severe asthma attack, patients who have been withdrawn from systemic corticosteroids should be instructed to resume oral corticosteroids (in large doses) immediately and to contact their physicians for further instruction. These patients should also be instructed to carry a medical warning/identification card indicating that they may need supplementary systemic corticosteroids during periods of stress or severe asthma attack.

Patients requiring systemic corticosteroids should be discontinued slowly from systemic corticosteroid use after transferring to DULAMON. Lung function (FEV_1 or PEF), beta-agonist use, and asthma symptoms should be carefully monitored during withdrawal of systemic corticosteroids.

In addition to monitoring asthma signs and symptoms, patients should be observed for signs and symptoms of adrenal insufficiency such as fatigue, lassitude, weakness, nausea and vomiting, and hypotension.

Transfer of patients from systemic corticosteroid therapy to DULAMON may unmask allergic conditions previously suppressed by the systemic corticosteroid therapy, e.g., rhinitis, conjunctivitis, eczema, arthritis, and eosinophilic conditions.

During withdrawal from oral corticosteroids, some patients may experience symptoms of systemically active corticosteroid withdrawal, e.g., joint and/or muscular pain, fatigue/lassitude, and depression, despite maintenance or even improvement of respiratory function.

Hypercorticism and adrenal suppression
Because of the possibility of systemic absorption of inhaled corticosteroids, patients treated with DULAMON should be observed carefully for any evidence of systemic corticosteroid effects.

It is possible that systemic corticosteroid effects such as hypercorticism and adrenal suppression (including adrenal crisis) during periods of stress or elective surgery where additional systemic corticosteroids are needed may appear in a small number of patients, particularly when mometasone furoate is administered at higher than recommended doses over prolonged periods of time. If such effects occur, the dosage of DULAMON should be reduced slowly.

Drug interactions with potent cytochrome P450 3A4 inhibitors
Caution should be exercised when considering the co-administration of DULAMON with ketoconazole, and other known strong P450 3A4 inhibitors (e.g., ritonavir, atazanavir, clarithromycin, indinavir, itraconazole, nefazodone, nelfinavir, saquinavir, telithromycin) because adverse effects related to increased systemic exposure to mometasone furoate may occur (see section 4.5).

Paradoxical bronchospasm and upper respiratory tract symptoms
DULAMON may produce inhalation-induced bronchospasm with a sudden increase in wheezing after dosing that may be life-threatening. If inhalation-induced bronchospasm occurs, patients should be treated immediately with an inhaled, short-acting bronchodilator. In this case, DULAMON should be discontinued immediately and alternative therapy initiated.

Immediate hypersensitivity reactions
Immediate hypersensitivity reactions may occur after administration of DULAMON, as demonstrated by cases of urticaria, flushing, allergic dermatitis, and bronchospasm.

Cardiovascular and central nervous system effects
Caution should be exercised when treating patients with thyrotoxicosis, pheochromocytoma, hypertrophic obstructive cardiomyopathy, idiopathic subvalvular aortic stenosis, severe hypertension, aneurysm or other serious cardiovascular conditions such as ischemic heart disease, tachyarrhythmias, or severe heart failure.

Excessive beta-adrenergic stimulation has been associated with seizures, angina, hypertension or hypotension, tachycardia with rates up to 200 beats/min, arrhythmias, nervousness, headache, tremor, palpitation, nausea, dizziness, fatigue, malaise, and insomnia. Therefore, DULAMON should be used with caution in patients with cardiovascular disorders, especially coronary insufficiency, cardiac arrhythmias, and hypertension.

Formoterol fumarate, a component of DULAMON, can produce a clinically significant cardiovascular effect in some patients as measured by pulse rate, blood pressure, and/or symptoms. Although such effects are uncommon after administration of mometasone furoate/formoterol fumarate combination at recommended doses, if they occur, the drug may need to be discontinued. In addition, beta-agonists have been reported to produce electrocardiogram (ECG) changes, such as flattening of the T wave, prolongation of the QTc interval, and ST segment depression. The clinical significance of these findings is unknown. Fatalities have been reported in association with excessive use of inhaled sympathomimetic drugs.

Formoterol can cause prolongation of the QTc interval. Caution should be exercised during treatment in patients with QTc prolongation who are being treated with drugs that affect the QTc interval (see section 4.5).

Reduction in bone mineral density
Decreases in bone mineral density (BMD) have been observed with long-term administration of products containing inhaled corticosteroids, including mometasone furoate, one of the components of DULAMON. The clinical significance of small changes in BMD with regard to long-term outcomes, such as fracture, is unknown. Patients with major risk factors for decreased bone mineral content, such as prolonged immobilization, family history of osteoporosis, or chronic use of drugs that can reduce bone mass (e.g., anticonvulsants and corticosteroids) should be monitored and treated with established standards of care.

Effect on growth
Inhaled corticosteroids, including DULAMON, may cause a reduction in growth velocity when administered to pediatric patients. The growth of pediatric patients taking DULAMON should be routinely monitored. To minimize the systemic effects of inhaled corticosteroids, including DULAMON, each patient's dose should be titrated to the lowest dosage that effectively controls his/her symptoms.

Glaucoma and cataracts
Glaucoma (increased intraocular pressure) and cataracts have been reported following the use of long-term administration of inhaled corticosteroids, including mometasone furoate, a component of DULAMON. Therefore, patients with altered vision or a history of increased intraocular pressure, glaucoma and/or cataracts should be closely monitored.

Coexisting conditions
DULAMON, like other medications containing sympathomimetic amines, should be used with caution in patients with aneurysm, pheochromocytoma, convulsive disorders, or thyrotoxicosis; and in patients who are unusually responsive to sympathomimetic amines. Doses of the related beta$_2$-agonist albuterol, when administered intravenously, have been reported to aggravate preexisting diabetes mellitus and ketoacidosis. Patients to be anesthetized with halogenated compounds should discontinue the drug at least 12 hours before anesthesia.

Hypokalemia and Hyperglycemia
Beta$_2$-agonist medications may produce hypokalemia in some patients, possibly through intracellular displacement, which has the potential to produce adverse cardiovascular effects. The decrease in serum potassium is usually transient, not requiring supplementation. Clinically significant changes in blood glucose and/or serum potassium were seen infrequently during clinical studies with mometasone furoate/formoterol fumarate combination at recommended doses. For this reason, serum potassium levels should be monitored.

4.5 Interaction with other medicinal products and other forms of interaction
In clinical trials, concurrent administration of mometasone furoate/formoterol fumarate combination and other drugs, such as short-acting beta$_2$-agonist and intranasal corticosteroids have not resulted in an increased frequency of adverse drug reactions. No formal drug interaction studies have been performed with mometasone furoate/formoterol fumarate combination. Drug interactions observed in clinical trials with specific drugs obtained from each component of DULAMON (mometasone furoate and formoterol fumarate) are expected to reflect the interactions that can be observed with concomitant use of these drugs with DULAMON.

Inhibitors of cytochrome P450 3A4
The main route of metabolism of corticosteroids, including mometasone furoate, a component of DULAMON, is via cytochrome P450 (CYP) isoenzyme 3A4 (CYP3A4). After oral administration of ketoconazole, an inhibitor of CYP3A4, the mean plasma concentration of inhaled mometasone furoate increased. Concomitant administration of CYP3A4 inhibitors may inhibit the metabolism of, and increase the systemic exposure to, mometasone furoate. Caution should be exercised when considering the co-administration of DULAMON with long-term ketoconazole and other known strong CYP3A4 inhibitors (e.g., ritonavir, atazanavir, clarithromycin, indinavir, itraconazole, nefazodone, nelfinavir, saquinavir, telithromycin).

Adrenergic agents
If additional adrenergic drugs are to be administered by any route, they should be used with caution

because the pharmacologically predictable sympathetic effects of formoterol, a component of DULAMON, may be potentiated.

Xanthine derivatives
Concomitant treatment with xanthine derivatives (e.g. theophylline, aminophylline) may potentiate any hypokalemic effect of formoterol, a component of DULAMON.

Diuretics
Concomitant treatment with diuretics may potentiate the possible hypokalemic effect of adrenergic agonists. The ECG changes and/or hypokalemia that may result from the administration of non-potassium-sparing diuretics (such as loop or thiazide diuretics) can be acutely worsened by beta-agonists, especially when the recommended dose of the beta-agonist is exceeded. Although the clinical significance of these effects is not known, caution is advised in the co-administration of DULAMON with non-potassium-sparing diuretics.

Monoamine oxidase inhibitors, tricyclic antidepressants, and drugs known to prolong the QTc interval
DULAMON should be administered with caution to patients being treated with monoamine oxidase inhibitors, tricyclic antidepressants or drugs known to prolong the QTc interval, or within 2 weeks of discontinuation of such agents, because the action of formoterol, a component of DULAMON, on the cardiovascular system may be potentiated by these agents. Drugs that are known to prolong the QTc interval (class IA and class III antiarrhythmics, arsenic trioxide, halofantrine, levomethadyl acetate, mesoridazine, thioridazine, pimozide, sparfloxacin, gatifloxacin, moxifloxacin, dolasetron mesylate, mefloquine, sertindole, dofetilide, sotalol, quinidine, chlorpromazine, droperidol, pentamidine, probucol, tacrolimus or cisapride) have an increased risk of ventricular arrhythmias.

There is a theoretical risk that concomitant therapy with other drugs known to prolong the QTc interval may result in a pharmacodynamic interaction with formoterol and increase the possible risk of ventricular arrhythmias. Examples of such drugs are some antihistamines (e.g., terfenadine, astemizole, and mizolastine), some antiarrhythmics (e.g., quinidine, disopyramide, and procainamide), erythromycin, and tricyclic antidepressants.

Patients receiving concomitant anesthesia with halogenated hydrocarbons have an increased risk of arrhythmias.

Beta-adrenergic receptor antagonists
Beta-adrenergic receptor antagonists (beta-blockers) and formoterol may inhibit the effect of each other when administered concurrently. Beta-blockers not only block the therapeutic effects of $beta_2$-agonists, such as formoterol, a component of DULAMON, but may produce severe bronchospasm in patients with asthma. Therefore, patients with asthma should not normally be treated with beta-blockers. However, under certain circumstances, e.g., as prophylaxis after myocardial infarction, there may be no acceptable alternatives to the use of beta-blockers in patients with asthma. In this setting, cardioselective beta-blockers could be considered, although they should be administered with caution.

Cardiac glycosides
In patients treated with cardiac glycosides, hypokalemia may increase susceptibility to arrhythmias.

Anticholinergics
Anticholinergic drugs can enhance the bronchodilator effect of DULAMON.

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

Pediatric population
No interaction studies have been conducted in the pediatric population.

4.6 Fertility, pregnancy and lactation

General Recommendation
Pregnancy category is "C".

Women of child-bearing potential/Contraception
It is recommended that women of childbearing potential use effective contraception methods during the treatment.

Pregnancy
Adequate data are not available from the use of mometasone furoate/formoterol fumarate combination, mometasone furoate alone, or formoterol fumarate alone in pregnant women.

Experimental animal reproduction studies with mometasone furoate and formoterol in mice, rats and/or rabbits have revealed that mometasone furoate and formoterol are teratogenic and show other developmental toxic effects.

Like other beta$_2$-adrenergic stimulants, formoterol can suppress the labor process due to its relaxant effect on uterine smooth muscle. Therefore, the benefit and risk ratio at birth should be carefully evaluated.

Infants of mothers using corticosteroids during pregnancy should be carefully observed for hypoadrenalism.

DULAMON should not be used during pregnancy unless necessary (if the expected benefits to the mother outweigh the potential risk to the fetus).

Breast-feeding
It is not known whether mometasone furoate/formoterol fumarate combination is excreted in breast milk, as there are no studies in lactating women. Reproductive studies in rats show that formoterol fumarate is excreted in milk. It is not known whether formoterol fumarate or mometasone furoate are excreted in breast milk. However, corticosteroids are excreted in human milk.

It is not known whether formoterol is excreted in human breast milk. Small amounts of formoterol have been detected in breast milk of rats. Administration of DULAMON in lactating women should only be considered if the expected benefit to the mother outweighs any potential risk to the child.

Because many drugs are excreted in breast milk, caution should be exercised when administering DULAMON to a nursing mother.

Fertility
There are no studies showing the effect of mometasone furoate/formoterol fumarate combination on fertility.

Animal reproduction studies with formoterol have shown some reduction in fertility in male rats at systemic exposures significantly higher than the clinical use. Thus, the results of these experimental animal studies do not appear to be relevant to humans.

In reproduction studies in rats, no impairment on fertility was observed of formoterol fumarate at oral doses up to 3 mg/kg (approximately 1200 times the maximum recommended human dose on a mcg/m^2 basis).

In reproduction studies in rats, no impairment on fertility was observed at doses of mometasone furoate administered subcutaneously at doses up to 15 mcg/kg (approximately 8 times the maximum recommended human dose based on AUC).

4.7 Effects on ability to drive and use machines

There are no studies showing the effects of mometasone furoate/formoterol fumarate combination on the ability to drive and use machines. However, if dizziness, tremors or similar undesirable effects are observed, vehicles and machines should not be used.

4.8 Undesirable effects

Candida albicans infection, immunosuppression, hypercorticism, adrenal suppression, glaucoma, cataracts, decrease in bone mineral density, and effects on growth in pediatric patients may occur with the use of systemic and local corticosteroids.

The safety data described below is based on three clinical trials which randomized 1913 asthmatic patients 12 years of age and older, including 679 patients exposed to mometasone furoate/formoterol fumarate combination administered via metered-dose inhaler (MDI) for 12 to 26 weeks and 271 patients exposed for one year. Mometasone furoate/formoterol fumarate combination MDI was studied in two placebo- and active-controlled trials (n=781 and n=728, respectively) and in a long-term 52-week safety trial (n=404). In the 12 to 26week clinical trials, the population was 12 to 84 years of age, 41% male and 59% female, 73% Caucasian, 27% non-Caucasian. Patients received two inhalations twice daily of mometasone furoate/formoterol fumarate combination (100 mcg/5 mcg or 200 mcg/5 mcg), mometasone furoate MDI (100 mcg or 200 mcg), formoterol fumarate MDI (5 mcg) or placebo. In the long-term 52-week active-comparator safety trial, the population was 12 years to 75 years of age with asthma, 37% male and 63% female, 47% Caucasian, 53% non-Caucasian and received two inhalations twice daily of mometasone furoate/formoterol fumarate combination 100 mcg/5 mcg or 200 mcg/5 mcg, or an active comparator.

Treatment-related adverse events with an incidence ≥3% and observed more frequently than placebo are listed below based on the data from two trials of 12-26 weeks in patients 12 years of age and older treated with two inhalations twice daily of mometasone furoate/formoterol fumarate combination 100 mcg/5 mcg or 200 mcg/5 mcg (n=424, n=255, respectively), mometasone furoate 100 mcg or 200 mcg MDI (n=192, n=240, respectively) and formoterol fumarate 5 mcg MDI (n=202).

The frequency of side effects is listed as follows: very common (≥1/10), common (≥1/100 and <1/10), uncommon (≥1/1,000 and <1/100), rare (≥1/10,000 <1/1,000), very rare (<1/10,000) and not known (cannot be estimated from the available data).

MedDRA System Organ Class	Adverse Event	Frequency		
		Formoterol	Mometasone	Mometasone/Formoterol
Infections and Infestations	Candidiasis		Very common	

Immune System Disorders	Anaphylactic reaction		Not known	Not known
	Angioedema	Very rare	Not known	Not known
	Severe hypotension			Not known
	Immediate and delayed hypersensitivity reactions including rash and pruritus	Very rare	Not known	Not known
	Hypersensitivity reactions including hypotension and exanthema	Very rare		
Endocrine Disorders	Adrenal suppression		Not known	
	Growth retardation in adolescents		Not known	
	Decreased bone mineral density		Not known	
	Cataract		Not known	
	Glaucoma		Not known	
Metabolism and Nutrition Disorders	Hypokalemia	Uncommon		Not known
	Hyperglycemia	Uncommon		Not known
Psychiatric Disorders	Agitation	Uncommon		
	Anxiety	Uncommon		
	Irritability	Uncommon		
	Insomnia	Uncommon		
	Dizziness	Uncommon		
	Dysgeusia	Very rare		
Nervous System Disorders	Headache	Common	Common	Common
	Tremor	Common		Not known
Cardiac Disorders	Atrial fibrillation	Uncommon		Not known
	Angina pectoris	Uncommon		Not known
	Ventricular extrasystoles	Not known		Not known
	Tachyarrhythmia	Uncommon		
	Palpitation	Common	Not known	
	Tachycardia	Uncommon		
	Peripheral edema	Very rare		
	Cardiac arrhythmias (e.g. supraventricular tachycardia, extrasystoles)	Uncommon		
	Prolonged QTc interval	Very rare		
Vascular Disorders	Changes in blood pressure	Uncommon		
Respiratory, Thoracic and Mediastinal	Nasopharyngitis			Common
	Sinusitis			Common

Disorders	Asthma exacerbation (including cough, dyspnea, wheezing and bronchospasm)	Uncommon	Not known	Not known
	Asthmatic attacks	Not known		
	Bronchospasm, including paradoxical bronchospasm	Uncommon		
	Throat irritation	Uncommon		
	Cough	Not known		
	Pharyngitis		Common	
	Dysphonia		Common	
Gastrointestinal disorders	Vomiting			Not known
	Nausea	Common		
	Dyspepsia		Not known	
	Weight gain		Not known	
	Dry mouth and throat		Not known	
Skin and Subcutaneous Tissue Disorders	Skin rash	Not known		
Musculoskeletal and Connective Tissue Disorders	Muscular cramps	Common		
	Myalgia	Uncommon		
General Disorders and Administration Site Conditions	Fever			Not known
	Fatigue			Not known
	Pain			Not known
Researches	QT prolongation on electrocardiogram			Not known
	Increased blood pressure, including hypertension	Not known		Not known

Oral candidiasis has been reported in clinical trials at an incidence of 0.7% in patients using mometasone furoate/formoterol fumarate combination 100 mcg/5 mcg, 0.8% in patients using mometasone furoate/formoterol fumarate combination 200 mcg/5 mcg, and 0.5% in the placebo group.

In a long-term safety trial in patients 12 years and older treated for 52 weeks with mometasone furoate/formoterol fumarate combination 100 mcg/5 mcg (n=141), mcg mometasone furoate/formoterol fumarate combination 200 mcg/5 (n=130) or an active comparator (n=133), safety outcomes in general were similar to those observed in the shorter 12 to 26 week controlled trials. No asthma-related deaths were observed. Dysphonia was observed at a higher frequency in the longer term treatment trial at a reported incidence of 7/141 (5%) patients receiving mometasone furoate/formoterol fumarate combination 100 mcg/5 mcg and 5/130 (3.8%) patients receiving mometasone furoate/formoterol fumarate combination 200 mcg/5 mcg. No clinically significant changes in blood chemistry, hematology, or ECG were observed.

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 to Turkey Pharmacovigilance Center (TÜFAM). (www.titck.gov.tr; e-mail: tufam@titck.gov.tr; phone number: +90 800 314 00 08; fax: +90 312 218 35 99)

4.9 Overdose
Signs and symptoms
Formoterol fumarate
The expected signs and symptoms with overdosage of formoterol are those of excessive beta-adrenergic stimulation and/or occurrence or exaggeration of any of the following signs and symptoms: angina, hypertension or hypotension, tachycardia, with rates up to 200 beats/min., arrhythmias, prolonged QT interval, nervousness, headache, tremor, seizures, muscle cramps, dry mouth, palpitation, nausea, dizziness, fatigue, malaise, hypokalemia, hyperglycemia, and insomnia. Metabolic acidosis may also occur. Cardiac arrest and even death may be associated with an overdose of formoterol.

The minimum acute lethal inhalation dose of formoterol fumarate in rats is 156 mg/kg (approximately 63,000 times the maximum recommended human dose [MRHD] on a mcg/m^2 basis).

Mometasone furoate
Chronic overdosage may result in signs/symptoms of hypercorticism (see section 4.4). Single oral doses up to 8000 mcg of mometasone furoate have been studied on adult subjects with no adverse reactions reported.

Treatment
Treatment of overdosage consists of discontinuation of DULAMON together with initiation of appropriate symptomatic and/or supportive therapy. The judicious use of a cardioselective beta-receptor blocker may be considered, bearing in mind that such medication can produce bronchospasm. There is insufficient evidence to determine if dialysis is beneficial for overdosage of mometasone furoate/formoterol fumarate combination. Cardiac monitoring is recommended in cases of overdosage.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties
Pharmacotherapeutic group: Adrenergics in combination with corticosteroids or other drugs, excluding anticholinergics
R03AK09
ATC code: R03AK09

Mechanism of Action
DULAMON contains both mometasone furoate and formoterol fumarate. These drugs represent two different classes of medications (a synthetic corticosteroid and a selective long-acting beta$_2$-adrenergic receptor agonist) that have different effects on clinical, physiological, and inflammatory indices of asthma.

Formoterol Fumarate

Formoterol fumarate is a long-acting selective beta$_2$-adrenergic receptor agonist (beta$_2$-agonist). Inhaled formoterol fumarate acts locally in the lung as a bronchodilator. *In vitro* studies have shown that formoterol has more than 200-fold greater agonist activity at beta$_2$-receptors than at beta$_1$-receptors. Although beta$_2$-receptors are the predominant adrenergic receptors in bronchial smooth muscle and beta$_1$-receptors are the predominant receptors in the heart, there are also beta$_2$-receptors in the human heart comprising 10% to 50% of the total beta-adrenergic receptors. The precise function of these receptors has not been established, but they raise the possibility that even highly selective beta$_2$-agonists may have cardiac effects.

The pharmacologic effects of beta$_2$-adrenoceptor agonist drugs, including formoterol, are at least in part attributable to stimulation of intracellular adenyl cyclase, the enzyme that catalyzes the conversion of adenosine triphosphate (ATP) to cyclic-3', 5'-adenosine monophosphate (cyclic AMP). Increased cyclic AMP levels cause relaxation of bronchial smooth muscle and inhibition of release of mediators of immediate hypersensitivity from cells, especially from mast cells.

In vitro tests show that formoterol is an inhibitor of the release of mast cell mediators, such as histamine and leukotrienes, from the human lung. Formoterol also inhibits histamine-induced plasma albumin extravasation in anesthetized guinea pigs and inhibits allergen-induced eosinophil influx in dogs with airway hyper-responsiveness. The relevance of these *in vitro* and animal findings to humans is unknown.

Mometasone Furoate

Mometasone furoate is a corticosteroid demonstrating potent anti-inflammatory activity. The precise mechanism of corticosteroid action on asthma is not known. Inflammation is an important component in the pathogenesis of asthma. Corticosteroids have been shown to have a wide range of inhibitory effects on multiple cell types (e.g., mast cells, eosinophils, neutrophils, macrophages, and lymphocytes) and mediators (e.g., histamine, eicosanoids, leukotrienes, and cytokines) involved in inflammation and in the asthmatic response. These anti-inflammatory actions of corticosteroids may contribute to their efficacy in asthma.

Mometasone furoate has been shown *in vitro* to exhibit a binding affinity for the human glucocorticoid receptor, which is approximately 12 times that of dexamethasone, 7 times that of triamcinolone acetonide, 5 times that of budesonide, and 1.5 times that of fluticasone.

Clinical Trials

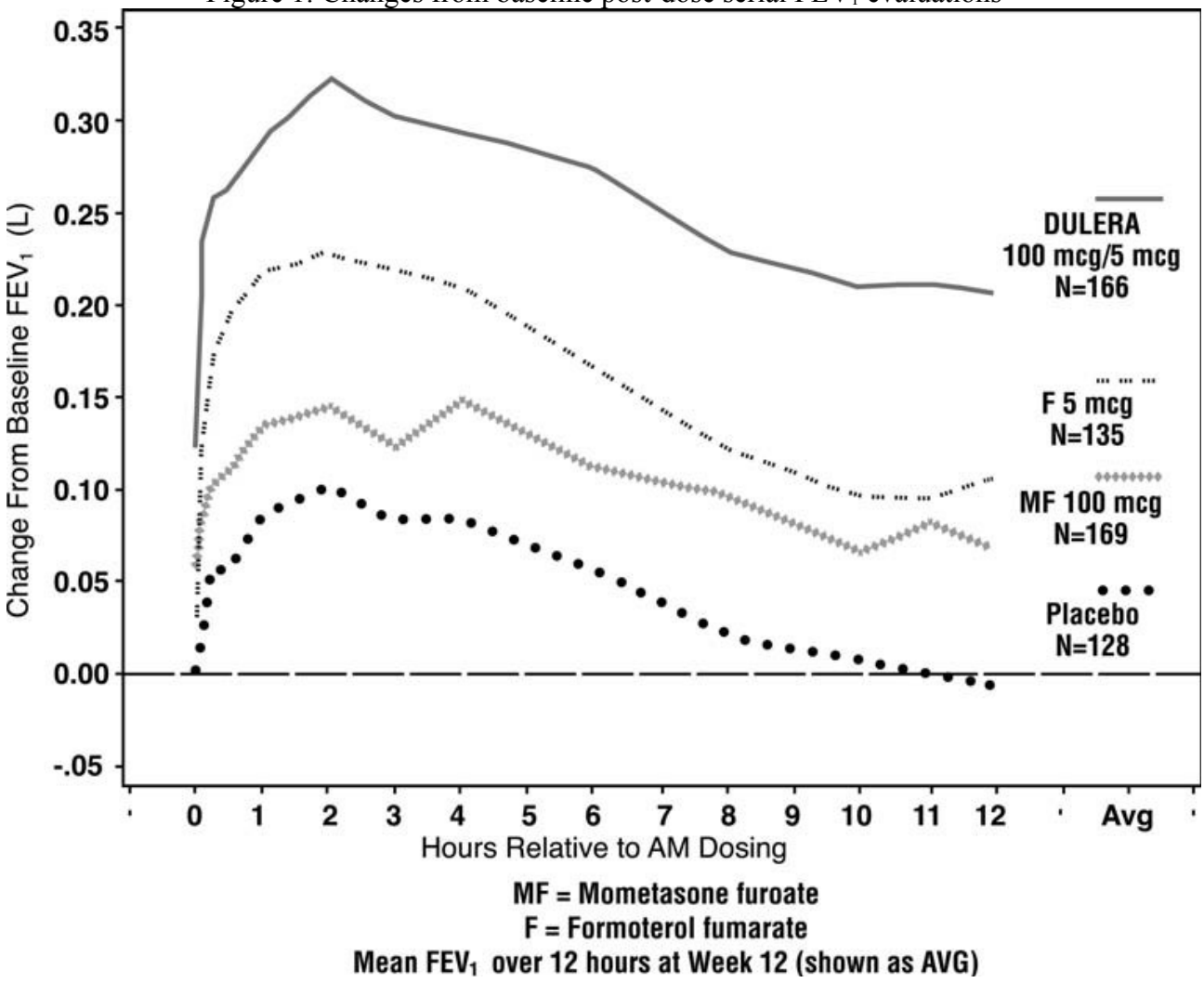
The safety and efficacy of mometasone furoate/formoterol fumarate combination were demonstrated in two randomized, double-blind, parallel group, multicenter clinical trials of 12 to 26 weeks in duration involving 1509 patients 12 years of age and older with persistent asthma uncontrolled on medium or high dose inhaled corticosteroids (baseline FEV_1 means of 66% to 73% of predicted normal). These studies included a 2 to 3-week run-in period with mometasone furoate to establish a certain level of asthma control. One clinical trial compared mometasone furoate/formoterol fumarate combination to placebo and the individual components, mometasone furoate and formoterol fumarate. Another clinical trial compared two different strengths (100 mcg/5 mcg and 200 mcg/5 mcg) of mometasone furoate/formoterol fumarate combination to mometasone furoate alone.

This 26-week, placebo-controlled trial evaluated 781 patients 12 years of age and older comparing mometasone furoate/formoterol fumarate combination 100 mcg/5 mcg (n=191 patients), mometasone furoate 100 mcg (n=192 patients), formoterol fumarate 5 mcg (n=202 patients) and placebo (n=196 patients); each administered as 2 inhalations twice daily by metered dose inhalation aerosols. All other maintenance therapies were discontinued. This study included a 2 to 3-week run-in period with

mometasone furoate 100 mcg, 2 inhalations twice daily. This trial included patients ranging from 12 to 76 years of age, 41% male and 59% female, and 72% Caucasian and 28% non-Caucasian. Patients had persistent asthma and were not well controlled on medium dose of inhaled corticosteroids prior to randomization. All treatment groups were balanced with regard to baseline characteristics. Mean FEV_1 and mean percent predicted FEV_1 were similar among all treatment groups (2.33 L, 73%). Eight (4%) patients receiving mometasone furoate/formoterol fumarate combination 100 mcg/5 mcg, 13 (7%) patients receiving mometasone furoate 100 mcg, 47 (23%) patients receiving formoterol fumarate 5 mcg and 46 (23%) patients receiving placebo discontinued the study early due to treatment failure.

FEV_1 $AUC_{(0\text{-}12\ hr)}$ was assessed as a co-primary efficacy endpoint to evaluate the contribution of the formoterol component to mometasone furoate/formoterol fumarate combination. Patients receiving mometasone furoate/formoterol fumarate combination 100 mcg/5 mcg had significantly higher increases from baseline at Week 12 in mean FEV_1 $AUC_{(0\text{-}12\ hr)}$ compared to mometasone furoate 100 mcg (the primary treatment comparison) and vs. placebo (both $p<0.001$) (Figure 1). These differences were maintained through Week 26.

Figure 1: Changes from baseline post-dose serial FEV_1 evaluations



Clinically judged deteriorations in asthma or reductions in lung function were assessed as another primary endpoint to evaluate the contribution of mometasone furoate 100 mcg to mometasone

furoate/formoterol fumarate combination 100 mcg/5 mcg. Deteriorations in asthma were defined as any of the following: a 20% decrease in FEV_1; a 30% decrease in PEF on two or more consecutive days; emergency treatment, hospitalization, or treatment with systemic corticosteroids or other asthma medications not allowed per protocol. Fewer patients who received mometasone furoate/formoterol fumarate combination 100 mcg/5 mcg reported an event compared to patients who received formoterol 5 mcg ($p<0.001$).

Table 1: Clinically Judged Deterioration in Asthma or Reduction in Lung Function*

	100 mcg/5 mcg mometasone furoate/formoterol fumarate† (n=191)	**100 mcg mometasone furoate† (n=192)**	**5 mcg formoterol fumarate† (n=202)**	**Placebo† (n=196)**
Clinically judged deterioration in asthma or reduction in lung function*	58 (%30)	65 (%34)	109 (%54)	109 (%56)
Decrease in FEV_1‡	18 (%9)	19 (%10)	31 (%15)	41 (%21)
Decrease in PEF§	37 (%19)	41 (%21)	62 (%31)	61 (%31)
Emergency treatment	0	1 (<%1)	4 (%2)	1 (<%1)
Hospitalization	1 (<%1)	0	0	0
Treatment with excluded asthma medication¶	2 (%1)	4 (%2)	17 (%8)	8 (%4)

* Includes only the first event day for each patient. Patients could have experienced more than one event criterion.
† Two inhalations, twice daily.
‡ Decrease in absolute FEV_1 below the treatment period stability limit (defined as 80% of the average of the two pre-dose FEV_1 measurements taken 30 minutes and immediately prior to the first dose of randomized trial medication).
§ Decrease in AM or PM peak expiratory flow (PEF) on 2 or more consecutive days below the treatment period stability limit (defined as 70% of the AM or PM PEF obtained over the last 7 days of the run-in period).
¶ Thirty patients received glucocorticosteroids; 1 patient received formoterol via dry powder inhaler in the Formoterol 5 mcg Group.

The change in mean trough FEV_1 from baseline to Week 12 was assessed as another endpoint to evaluate the contribution of mometasone furoate 100 mcg to mometasone furoate/formoterol fumarate combination 100 mcg/5 mcg. A significantly greater increase in mean trough FEV_1 was observed for mometasone furoate/formoterol fumarate combination 100 mcg/5 mcg compared to formoterol 5 mcg (the primary treatment comparison) as well as to placebo (Table 2).

Table 2: Change in Trough FEV_1 from Baseline to Week 12

Treatment Arm	**N**	**Baseline (L)**	**Change From Baseline at Week 12 (L)**	**Treatment Difference from Placebo (L)**	**P-Value vs. Placebo**	**P-Value vs. Formoterol**
Mometasone furoate/formoterol fumarate 100 mcg/5 mcg	167	2,33	0,13	0,18	<0,001	<0,001
Mometasone furoate 100 mcg	175	2,36	0,07	0,012	<0,001	0,058
Formoterol furoate 5 mcg	141	2,29	0	0,05	0,17	
Placebo	145	2,3	0,05			

The effect of mometasone furoate/formoterol fumarate combination 100 mcg/5 mcg, two inhalations

twice daily on selected secondary efficacy endpoints, including proportion of nights with nocturnal awakenings (-60% vs. -15%), change in total rescue medication use (-0.6 vs. +1.1 puffs/day), change in morning peak flow (+18.1 vs. -28.4 L/min) and evening peak flow (+10.8 vs. -32.1 L/min) further supports the efficacy of mometasone furoate/formoterol fumarate combination 100 mcg/5 mcg compared to placebo.

The subjective impact of asthma on patients' health-related quality of life was evaluated by the Asthma Quality of Life Questionnaire (AQLQ(S)) (based on a 7-point scale where 1 = maximum impairment and 7 = no impairment). A change from baseline ≥0.5 points is considered a clinically meaningful improvement. The mean difference in AQLQ between patients receiving mometasone furoate/formoterol fumarate combination 100 mcg/5 mcg and placebo was 0.5 [95% CI 0.32, 0.68].

This 12-week double-blind trial evaluated 728 patients 12 years of age and older comparing mometasone furoate/formoterol fumarate combination 200 mcg/5 mcg (n=255 patients) with mometasone furoate/formoterol fumarate combination 100 mcg/5 mcg (n=233 patients) and mometasone furoate 200 mcg (n=240 patients), each administered as 2 inhalations twice daily by metered dose inhalation aerosols. All other maintenance therapies were discontinued. This trial included a 2 to 3-week run-in period with mometasone furoate 200 mcg, 2 inhalations twice daily. Patients had persistent asthma and were uncontrolled on high dose inhaled corticosteroids prior to study entry. All treatment groups were balanced with regard to baseline characteristics. This trial included patients ranging from 12 to 84 years of age, 44% male and 56% female, and 89% Caucasian and 11% non-Caucasian. Mean FEV_1 and mean percent predicted FEV_1 values were similar among all treatment groups (2.05 L, 66%). Eleven (5%) patients receiving mometasone furoate/formoterol fumarate combination 100 mcg/5 mcg, 8 (3%) patients receiving mometasone furoate/formoterol fumarate combination 200 mcg/5 mcg and 13 (5%) patients receiving mometasone furoate 200 mcg discontinued the trial early due to treatment failure.

The primary efficacy endpoint was the mean change in FEV_1 $AUC_{(0\text{-}12\ hr)}$ from baseline to Week 12. Patients receiving mometasone furoate/formoterol fumarate combination 100 mcg/5 mcg and mometasone furoate/formoterol fumarate combination 200 mcg/5 mcg had significantly greater increases from baseline at Day 1 in mean FEV_1 $AUC_{(0\text{-}12\ hr)}$ compared to mometasone furoate 200 mcg. The difference was maintained over 12 weeks of therapy.

Mean change in trough FEV_1 from baseline to Week 12 was also assessed to evaluate the relative contribution of mometasone furoate to mometasone furoate/formoterol fumarate combination 100 mcg/5 mcg and mometasone furoate/formoterol fumarate combination 200 mcg/5 mcg (Table 3). A greater numerical increase in the mean trough FEV_1 was observed for mometasone furoate/formoterol fumarate combination 200 mcg/5 mcg compared to mometasone furoate/formoterol fumarate combination 100 mcg/5 mcg and mometasone furoate 200 mcg.

Table 3: Change in Trough FEV_1 from Baseline to Week 12

Treatment Arm	N	Baseline (L)	Change from Baseline at Week 12 (L)
Mometasone furoate/formoterol fumarate 100 mcg/5 mcg	232	2.10	0.14
Mometasone furoate/formoterol fumarate 200 mcg/5 mcg	255	2.05	0.19
Mometasone furoate 200 mcg	239	2.07	0.10

Clinically judged deterioration in asthma or reduction in lung function was assessed as an additional endpoint. Fewer patients who received mometasone furoate/formoterol fumarate combination 200

mcg/5 mcg or mometasone furoate/formoterol fumarate combination 100 mcg/5 mcg compared to mometasone furoate 200 mcg alone reported an event by any of the following: a 20% decrease in FEV_1; a 30% decrease in PEF on two or more consecutive days; emergency treatment, hospitalization, or treatment with systemic corticosteroids or other asthma medications not allowed per protocol.

Table 4: Clinically Judged Deterioration in Asthma or Reduction in Lung Function*

	100 mcg/5 mcg mometasone furoate/formoterol fumarate† (n=233)	**200 mcg/5 mcg mometasone furoate/formoterol fumarate† (n=255)**	**200 mcg mometasone furoate† (n=240)**
Clinically judged deterioration in asthma or reduction in lung function*	29 (%12)	31 (%12)	44 (%18)
Decrease in FEV_1‡	23 (%10)	17 (%17)	33 (%14)
Decrease in PEF on two consecutive days§	2 (%1)	4 (%2)	3 (%1)
Emergency treatment	2 (%1)	1 (<%1)	1 (<%1)
Hospitalization	0	1 (<%1)	0
Treatment with excluded asthma medication¶	5 (%2)	8 (%3)	12 (%5)

* Includes only the first event day for each patient. Patients could have experienced more than one event criterion.
† Two inhalations, twice daily.
‡ Decrease in absolute FEV_1 below the treatment period stability limit (defined as 80% of the average of the two pre-dose FEV_1 measurements taken 30 minutes and immediately prior to the first dose of randomized trial medication).
§ Decrease in AM or PM peak expiratory flow (PEF) below the treatment period stability limit (defined as 70% of the AM or PM PEF obtained over the last 7 days of the run-in period).
¶ Twenty four patients received glucocorticosteroids; 1 patient received albuterol in the Mometasone furoate/formoterol fumarate combination 200 mcg/5 mcg Group.

5.2 Pharmacokinetic properties

General features

Absorption
Formoterol Fumarate
Healthy Volunteers:
When mometasone furoate/formoterol fumarate combination was administered to healthy subjects, formoterol was absorbed with median T_{max} values ranging from 0.167 to 0.5 hour. In a single-dose study with mometasone furoate/formoterol fumarate combination 400 mcg/10 mcg in healthy subjects, arithmetic mean (CV%) C_{max} and AUC for formoterol were 15 (50) pmol/L and 81 (51) pmol*h/L, respectively. Over the dose range of 10 to 40 mcg for formoterol from mometasone furoate/formoterol fumarate combination, the exposure to formoterol was dose proportional.

Asthma Patients:
When mometasone furoate/formoterol fumarate combination was administered to patients with asthma, formoterol was absorbed with median T_{max} values ranging from 0.58 to 1.97 hours. In a single-dose study with mometasone furoate/formoterol fumarate combination 400 mcg/10 mcg in patients with asthma, arithmetic mean (CV%) C_{max} and $AUC_{(0\text{-}12\,hr)}$ for formoterol were 22 (29) pmol/L and 125 (42) pmol*h/L, respectively. Following multiple-dose administration of mometasone furoate/formoterol fumarate combination 400 mcg/10 mcg, the steady-state arithmetic mean (CV%)

C_{max} and $AUC_{(0\text{-}12\ hr)}$ for formoterol were 41 (59) pmol/L and 226 (54) pmol*hr/L.

Mometasone Furoate
Healthy Volunteers:
The systemic exposures to mometasone furoate from mometasone furoate/formoterol fumarate combination versus mometasone furoate delivered via dry powder inhaler (DPI) were compared. Following oral inhalation of single and multiple doses of the mometasone furoate/formoterol fumarate combination, mometasone furoate was absorbed in healthy subjects with median T_{max} values ranging from 0.50 to 4 hours. Following single-dose administration of higher than recommended dose of mometasone furoate/formoterol fumarate combination (4 inhalations of mometasone furoate/formoterol fumarate combination 200 mcg/5 mcg) in healthy subjects, the arithmetic mean (CV%) C_{max} and $AUC_{(0\text{-}12\ hr)}$ values for MF were 67.8 (49) pg/mL and 650 (51) pg.hr/mL, respectively while the corresponding estimates following 5 days of twice daily dosing of mometasone furoate/formoterol fumarate combination 800 mcg/20 mcg were 241 (36) pg/mL and 2200 (35) pg.hr/mL. Exposure to mometasone furoate increased with increasing inhaled dose of mometasone furoate/formoterol fumarate combination 100 mcg/5 mcg to 200 mcg/5 mcg. Studies using oral dosing of labeled and unlabeled drug have demonstrated that the oral systemic bioavailability of mometasone furoate is negligible (<1%).

The above study demonstrated that the systemic exposure to mometasone furoate (based on AUC) was approximately 52% and 25% lower on Day 1 and Day 5, respectively, following mometasone furoate/formoterol fumarate combination administration compared to mometasone furoate via a DPI.

Asthma Patients:
Following oral inhalation of single and multiple doses of the mometasone furoate/formoterol fumarate combination, mometasone furoate was absorbed in asthma patients with median T_{max} values ranging from 1 to 2 hours. Following single-dose administration of mometasone furoate/formoterol fumarate combination 400 mcg/10 mcg, the arithmetic mean (CV%) C_{max} and $AUC_{(0\text{-}12\ hr)}$ values for mometasone furoate were 20 (88) pg/mL and 170 (94) pg.hr/mL, respectively while the corresponding estimates following BID dosing of mometasone furoate/formoterol fumarate combination 400 mcg/10 mcg at steady-state were 60 (36) pg/mL and 577 (40) pg.hr/mL.

Distribution
Formoterol Fumarate
The binding of formoterol to human plasma proteins *in vitro* was 61% to 64% at concentrations from 0.1 to 100 ng/mL. Binding to human serum albumin *in vitro* was 31% to 38% over a range of 5 to 500 ng/mL. The concentrations of formoterol used to assess the plasma protein binding were higher than those achieved in plasma following inhalation of a single 120 mcg dose.

Mometasone Furoate
Based on the study employing a 1000 mcg inhaled dose of tritiated (tritium-containing, labeled with tritium) mometasone furoate inhalation powder in adult subjects, no appreciable accumulation of mometasone furoate in the red blood cells was found. Following an intravenous 400 mcg dose of mometasone furoate, the plasma concentrations showed a biphasic decline, with a mean steady-state volume of distribution of 152 liters. The *in vitro* protein binding for mometasone furoate was reported to be 98% to 99% (in a concentration range of 5 to 500 ng/mL).

Biotransformation
Formoterol Fumarate

Formoterol is metabolized primarily by direct glucuronidation at either the phenolic or aliphatic hydroxyl group and O-demethylation followed by glucuronide conjugation at either phenolic hydroxyl groups. Minor pathways involve sulfate conjugation of formoterol and deformylation followed by sulfate conjugation. The most prominent pathway involves direct conjugation at the phenolic hydroxyl group. The second major pathway involves O-demethylation followed by conjugation at the phenolic 2'-hydroxyl group. Four cytochrome P450 isozymes (CYP2D6, CYP2C19, CYP2C9 and CYP2A6) are involved in the O-demethylation of formoterol. Formoterol did not inhibit CYP450 enzymes at therapeutically relevant concentrations. Some patients may be deficient in CYP2D6 or 2C19 or both. Whether a deficiency in one or both of these isozymes results in elevated systemic exposure to formoterol or systemic adverse effects has not been adequately explored.

Mometasone Furoate
Studies have shown that mometasone furoate is primarily and extensively metabolized in the liver of all species investigated and undergoes extensive metabolism to multiple metabolites. *In-vitro* studies have confirmed the primary role of human liver cytochrome CYP3A4 in the metabolism of this compound, however, no major metabolites were identified. Human liver CYP3A4 metabolizes mometasone furoate to 6-beta hydroxy mometasone furoate.

Elimination
Formoterol Fumarate
Following oral administration of 80 mcg of radiolabeled formoterol fumarate to 2 healthy subjects, 59% to 62% of the radioactivity was eliminated in the urine and 32% to 34% in the feces over a period of 104 hours. In an oral inhalation study with mometasone furoate/formoterol fumarate combination, renal clearance of formoterol from the blood was 217 mL/min. In single-dose studies, the mean t½ values for formoterol in plasma were 9.1 hours and 10.8 hours from the urinary excretion data. The accumulation of formoterol in plasma after multiple dose administration was consistent with the increase expected with a drug having a terminal t½ of 9 to 11 hour.

Following single inhaled doses ranging from 10 to 40 mcg to adult healthy subjects from the mometasone furoate/formoterol fumarate combination MDI, 6.2% to 6.8% of the formoterol dose was excreted in urine unchanged. The (R,R) and (S,S)-enantiomers accounted, respectively, for 37% and 63% of the formoterol recovered in urine. From urinary excretion rates measured in healthy subjects, the mean terminal elimination half-lives for the (R,R)- and (S,S)-enantiomers were determined to be 13 and 9.5 hours, respectively. The relative proportion of the two enantiomers remained constant over the dose range studied.

Mometasone Furoate
Following an intravenous dosing, the terminal half-life was reported to be about 5 hours. Following the inhaled dose of tritiated 1000 mcg mometasone furoate, the radioactivity is excreted mainly in the feces (a mean of 74%), and to a small extent in the urine (a mean of 8%) up to 7 days. No radioactivity was associated with unchanged mometasone furoate in the urine. Absorbed mometasone furoate is cleared from plasma at a rate of approximately 12.5 mL/min/kg, independent of dose. The effective t½ for mometasone furoate following inhalation with mometasone furoate/formoterol fumarate combination was 25 hours in adult healthy subjects and in adult patients with asthma.

Linearity/Non-linearity
The exposure to formoterol was linear from mometasone furoate/formoterol fumarate combination containing 10-40 mcg formoterol.

Characteristics in patients

Renal/Hepatic failure

No data are available on the specific use of mometasone furoate/formoterol fumarate combination in patients with renal or hepatic impairment.

A study evaluating the administration of a single inhaled dose of 400 mcg mometasone furoate by a dry powder inhaler to adult patients with mild (n=4), moderate (n=4), and severe (n=4) hepatic impairment resulted in only 1 or 2 patients in each group having detectable peak plasma concentrations of mometasone furoate (ranging from 50-105 pcg/mL). The observed peak plasma concentrations appear to increase with severity of hepatic impairment; however, the numbers of detectable levels were few.

Geriatric population

No studies have been conducted on the pharmacokinetics of mometasone furoate/formoterol fumarate combination in the geriatric population.

Gender and race

Specific studies evaluating the effects of gender and race on the pharmacokinetics of mometasone furoate/formoterol fumarate combination have not been performed.

5.3 Preclinical safety data

Carcinogenesis, mutagenesis, impairment of fertility

Formoterol fumarate

The carcinogenic potential of formoterol fumarate has been 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 at 20 mg/kg in the dietary study, but not at dietary doses up to 5 mg/kg (AUC exposure approximately 265 times human exposure at the MRHD). In the dietary study, the incidence of benign ovarian theca-cell tumors was increased at doses of 0.5 mg/kg and above (AUC exposure at the low dose of 0.5 mg/kg was approximately 27 times human exposure at the MRHD). This finding was not observed in the drinking water study, nor was it seen in mice (see below).

In mice, the incidence of adrenal subcapsular adenomas and carcinomas was increased in males at doses of 69 mg/kg and above in the drinking water study, but not at doses up to 50 mg/kg (AUC exposure approximately 350 times human exposure at the MRHD) in the dietary study. The incidence of hepatocarcinomas was increased in the dietary study at doses of 20 and 50 mg/kg in females and 50 mg/kg in males, but not at doses up to 5 mg/kg in either males or females (AUC exposure approximately 35 times human exposure at the MRHD). Also in the dietary study, the incidence of uterine leiomyomas and leiomyosarcomas was increased at doses of 2 mg/kg and above (AUC exposure at the low dose of 2 mg/kg was approximately 14 times human exposure at the MRHD). Increases in leiomyomas of the rodent female genital tract have been similarly demonstrated with other beta-agonist drugs.

Formoterol fumarate was not mutagenic or clastogenic in the following tests: mutagenicity tests in bacterial and mammalian cells, chromosomal analyses in mammalian cells, unscheduled DNA synthesis repair tests in rat hepatocytes and human fibroblasts, transformation assay in mammalian fibroblasts and micronucleus tests in mice and rats.

Mometasone furoate

In a 2-year carcinogenicity study in Sprague Dawley® rats, mometasone furoate demonstrated no

statistically significant increase in the incidence of tumors at inhalation doses up to 67 mcg/kg (approximately 14 times the MRHD on an AUC basis). In a 19-month carcinogenicity study in Swiss CD-1 mice, mometasone furoate demonstrated no statistically significant increase in the incidence of tumors at inhalation doses up to 160 mcg/kg (approximately 9 times the MRHD on an AUC basis).

Mometasone furoate increased chromosomal aberrations in an *in vitro* Chinese hamster ovary cell assay, but did not have this effect in an *in vitro* Chinese hamster lung cell assay. Mometasone furoate was not mutagenic in the Ames test or mouse lymphoma assay, and was not clastogenic in an *in vivo* mouse micronucleus assay, a rat bone marrow chromosomal aberration assay, or a mouse male germ-cell chromosomal aberration assay. Mometasone furoate also did not induce unscheduled DNA synthesis *in vivo* in rat hepatocytes.

Reproductive toxicology studies

Formoterol fumarate

In embryofetal development studies with pregnant rats and rabbits dosed throughout the period of organogenesis, formoterol fumarate did not cause malformations in either species. However, for pregnant rats dosed throughout organogenesis, formoterol fumarate caused delayed fetal ossification at an exposure approximately 80 times the MRHD (on a mcg/m^2 basis with maternal oral doses of 200 mcg/kg and higher) and decreased fetal weight at an exposure approximately 2400 times the MRHD (on a mcg/m^2 basis with maternal oral doses of 6000 mcg/kg and above). In a pre- and post-natal development study with rats dosed during the late stage of pregnancy, formoterol fumarate caused stillbirth and neonatal mortality at an exposure approximately 2400 times the MRHD (on a mcg/m^2 basis with maternal oral doses of 6000 mcg/kg and above). However, no effects were observed in this study at an exposure approximately 80 times the MRHD (on a mcg/m^2 basis with a maternal oral dose of 200 mcg/kg).

In embryofetal development studies, conducted by another testing laboratory, with pregnant rats and rabbits dosed throughout the period of organogenesis, formoterol fumarate was teratogenic in both species. Umbilical hernia, a malformation, was observed in rat fetuses at exposures approximately 1200 times the MRHD (on a mcg/m^2 basis with maternal oral doses of 3000 mcg/kg/day and above). Brachygnathia, a skeletal malformation, was observed in rat fetuses at an exposure approximately 6100 times the MRHD (on a mcg/m^2 basis with a maternal oral dose of 15,000 mcg/kg/day). In another study with rats, no teratogenic effects were observed with exposures up to approximately 500 times the MRHD (on a mcg/m^2 basis with a maternal inhalation dose of 1200 mcg/kg/day). Subcapsular cysts on the liver were observed in rabbit fetuses at an exposure approximately 49,000 times the MRHD (on a mcg/m^2 basis with a maternal oral dose of 60,000 mcg/kg/day). No teratogenic effects were observed with exposures up to approximately 3000 times the MRHD (on a mcg/m^2 basis with a maternal oral dose of 3500 mcg/kg).

Mometasone furoate

In an embryofetal development study with pregnant mice dosed throughout the period of organogenesis, mometasone furoate produced cleft palate at an exposure approximately one-third of the MRHD (on a mcg/m^2 basis with maternal subcutaneous doses of 60 mcg/kg and above) and decreased fetal survival at an exposure approximately equivalent to the MRHD (on a mcg/m^2 basis with a maternal subcutaneous dose of 180 mcg/kg). No toxicity was observed with a dose that produced an exposure approximately one-tenth of the MRHD (on a mcg/m^2 basis with maternal topical dermal doses of 20 mcg/kg and above).

In an embryofetal development study with pregnant rats dosed throughout the period of organogenesis, mometasone furoate produced fetal umbilical hernia at exposures approximately 6

times the MRHD (on a mcg/m^2 basis with maternal topical dermal doses of 600 mcg/kg and above) and delays in fetal ossification at exposures approximately 3 times the MRHD (on a mcg/m^2 basis with maternal topical dermal doses of 300 mcg/kg and above), but no malformations were observed.

In another reproductive toxicity study, pregnant rats were dosed with mometasone furoate throughout pregnancy or late in gestation. Treated animals had prolonged and difficult labor, fewer live births, lower birth weight, and reduced early pup survival at an exposure that was approximately 8 times the MRHD (on an area under the curve (AUC) basis with a maternal subcutaneous dose of 15 mcg/kg). There were no similar findings with an exposure approximately 4 times the MRHD (on an AUC basis with a maternal subcutaneous dose of 7.5 mcg/kg).

In the study using the topical dermal route, mometasone furoate caused multiple malformations in fetuses (e.g., flexed front paws, gallbladder agenesis, umbilical hernia, and hydrocephaly) at an exposure approximately 3 times the MRHD (on a mcg/m^2 basis with maternal topical dermal doses of 150 mcg/kg and above). In the study using the oral route, mometasone furoate caused increased fetal resorptions and cleft palate and/or head malformations (hydrocephaly and domed head) at an exposure approximately 1/2 of the MRHD (on AUC basis with a maternal oral dose of 700 mcg/kg). At an exposure approximately 2 times the MRHD (on an AUC basis with a maternal oral dose of 2800 mcg/kg), most litters were aborted or resorbed. No toxicity was observed at an exposure approximately 1/10 of the MRHD (on an AUC basis with a maternal oral dose of 140 mcg/kg).

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients
Ethyl alcohol (anhydrous)
Oleic acid
HFA-227 ea Pharma Grade

6.2 Incompatibilities
Not applicable.

6.3 Shelf life
24 months.

6.4 Special precautions for storage
Store at room temperature below 25°C. Protect from direct sunlight and freezing. Do not puncture, break or burn the aluminum vials, even when apparently empty.

6.5 Nature and contents of container
DULAMON 200 mcg/5 mcg is supplied in the form of pressurized inhalation, suspension, and in aluminum vials (tubes) with metering valve for 60 or 120 doses. Each canister (tube and valve) is placed in a metered plastic sprayer (activator) consisting of a blue body and a green cap. The device is presented with a package leaflet in a cardboard box.

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. 34303 No:1
Küçükçekmece / İSTANBUL / TURKEY

8. MARKETING AUTHORIZATION NUMBER

2019/286

9. DATE OF FIRST AUTHORIZATION/RENEWAL OF THE AUTHORIZATION

Date of first authorization : 12.06.2019
Date of last renewal :

10. DATE OF REVISION OF THE TEXT