HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use DULERA safely and effectively. See full prescribing information for DULERA.

DULERA® (mometasone furoate and formoterol fumarate dihydrate) inhalation aerosol, for oral inhalation use
Initial U.S. Approval: 2010

----------RECENT MAJOR CHANGES----------

Boxed Warning (removed)	12/2017
Indications and Usage (1.1)	12/2017
Dosage and Administration (2.1, 2.2)	06/2017
Warnings and Precautions (5.1, 5.2, 5.8, 5.14)	03/2018

---------- INDICATIONS AND USAGE----------

DULERA is a combination product containing a corticosteroid and a long-acting beta$_2$-adrenergic agonist (LABA) indicated for:

- Treatment of asthma in patients 12 years of age and older. (1.1)

Important Limitation of Use:

- Not indicated for the relief of acute bronchospasm. (1.1)

----------DOSAGE AND ADMINISTRATION----------

For oral inhalation only. (2.1)

Treatment of asthma in patients ≥12 years: 2 inhalations twice daily of DULERA 100 mcg/5 mcg or 200 mcg/5 mcg. Starting dosage is based on disease severity. (2.2)

---------- DOSAGE FORMS AND STRENGTHS----------

Inhalation aerosol containing a combination of mometasone furoate (100 or 200 mcg) and formoterol fumarate dihydrate (5 mcg) per actuation. (3)

---------- CONTRAINDICATIONS ----------

- Primary treatment of status asthmaticus or acute episodes of asthma requiring intensive measures. (4.1)
- Hypersensitivity to any of the ingredients of DULERA. (4.2)

---------- WARNINGS AND PRECAUTIONS----------

- LABA monotherapy increases the risk of serious asthma-related events. (5.1)
- Deterioration of disease and acute episodes: Do not initiate in acutely deteriorating asthma or to treat acute symptoms. (5.2)
- Use with additional long-acting beta$_2$-agonist: Do not use in combination because of risk of overdose. (5.3)
- Localized infections: *Candida albicans* infection of the mouth and throat may occur. Monitor patients periodically for signs of adverse effects on the oral cavity. Advise patients to rinse the mouth following inhalation. (5.4)
- Immunosuppression: Potential worsening of existing tuberculosis, fungal, bacterial, viral, or parasitic infection; or ocular herpes simplex infections. More serious or even fatal course of chickenpox or measles can occur in susceptible patients. Use with caution in patients with these infections because of the potential for worsening of these infections. (5.5)
- Transferring patients from systemic corticosteroids: Risk of impaired adrenal function when transferring from oral steroids. Taper patients slowly from systemic corticosteroids if transferring to DULERA. (5.6)
- Hypercorticism and adrenal suppression: May occur with very high dosages or at the regular dosage in susceptible individuals. If such changes occur, discontinue DULERA slowly. (5.7)
- Strong cytochrome P450 3A4 inhibitors (e.g., ritonavir): Risk of increased systemic corticosteroid effects. Exercise caution when used with DULERA. (5.8)
- Paradoxical bronchospasm: Discontinue DULERA and institute alternative therapy if paradoxical bronchospasm occurs. (5.9)
- Patients with cardiovascular disorders: Use with caution because of beta-adrenergic stimulation. (5.11)
- Decreases in bone mineral density: Monitor patients with major risk factors for decreased bone mineral content. (5.12)
- Effects on growth: Monitor growth of pediatric patients. (5.13)
- Glaucoma and cataracts: Consider referral to an ophthalmologist in patients who develop ocular symptoms or use DULERA long term. (5.14)
- Coexisting conditions: Use with caution in patients with aneurysm, pheochromocytoma, convulsive disorders, thyrotoxicosis, diabetes mellitus, and ketoacidosis. (5.15)
- Hypokalemia and hyperglycemia: Be alert to hypokalemia and hyperglycemia. (5.16)

---------- ADVERSE REACTIONS ----------

Most common adverse reactions (reported in ≥3% in any treatment arm and greater than placebo) included:

- Nasopharyngitis, sinusitis and headache. (6.1)

To report SUSPECTED ADVERSE REACTIONS, contact Merck Sharp & Dohme Corp., a subsidiary of Merck & Co., Inc., at 1-877-888-4231 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

---------- DRUG INTERACTIONS----------

- Strong cytochrome P450 3A4 inhibitors (e.g., ritonavir): Use with caution. May cause increased systemic corticosteroid effects. (7.1)
- Adrenergic agents: Use with caution. Additional adrenergic drugs may potentiate sympathetic effects. (7.2)
- Xanthine derivatives and diuretics: Use with caution. May potentiate ECG changes and/or hypokalemia. (7.3, 7.4)
- MAO inhibitors, tricyclic antidepressants, macrolides, and drugs that prolong QTc interval: Use with extreme caution. May potentiate effect on the cardiovascular system. (7.5)
- Beta-blockers: Use with caution and only when medically necessary. May decrease effectiveness and produce severe bronchospasm. (7.6)
- Halogenated hydrocarbons: There is an elevated risk of arrhythmias in patients receiving concomitant anesthesia with halogenated hydrocarbons. (7.7)

---------- USE IN SPECIFIC POPULATIONS ----------

- Hepatic impairment: Monitor patients for signs of increased drug exposure. (8.6)

See 17 for PATIENT COUNSELING INFORMATION and FDA-approved patient labeling.

Revised: 03/2018

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FULL PRESCRIBING INFORMATION

1 INDICATIONS AND USAGE

1.1 Treatment of Asthma

DULERA is indicated for the twice-daily treatment of asthma in patients 12 years of age and older. DULERA should be used for patients not adequately controlled on a long-term asthma-control medication such as an inhaled corticosteroid (ICS) or whose disease warrants initiation of treatment with both an ICS and long-acting beta$_2$-adrenergic agonist (LABA).

Important Limitation of Use:

- DULERA is NOT indicated for the relief of acute bronchospasm.

2 DOSAGE AND ADMINISTRATION

2.1 Administration Information

DULERA should be administered as two inhalations twice daily every day (morning and evening) by the orally inhaled route (see Patient Instructions for Use in the Patient Information leaflet). Shake well prior to each inhalation. After each dose, the patient should be advised to rinse his/her mouth with water without swallowing.

The cap from the mouthpiece of the actuator should be removed before using DULERA.

DULERA should be primed before using for the first time by releasing 4 test sprays into the air, away from the face, shaking well before each spray. In cases where the inhaler has not been used for more than 5 days, prime the inhaler again by releasing 4 test sprays into the air, away from the face, shaking well before each spray.

The DULERA canister should only be used with the DULERA actuator. The DULERA actuator should not be used with any other inhalation drug product. Actuators from other products should not be used with the DULERA canister.

2.2 Recommended Dosage

Adults and Adolescents 12 Years of Age and Older

The dosage is either 2 inhalations twice daily of DULERA 100 mcg/5 mcg or DULERA 200 mcg/5 mcg. The maximum recommended dosage is two inhalations of DULERA 200 mcg/5 mcg twice daily (maximum daily dosage 800 mcg/20 mcg).

When choosing the starting dosage strength of DULERA, consider the patients' disease severity, based on their previous asthma therapy, including the inhaled corticosteroid dosage, as well as the patients' current control of asthma symptoms and risk of future exacerbation.

The maximum benefit may not be achieved for 1 week or longer after beginning treatment. Individual patients may experience a variable time to onset and degree of symptom relief. For patients who do not respond adequately after 2 weeks of therapy with two inhalations of DULERA 100 mcg/5 mcg twice daily (morning and evening), increasing the dosage to two inhalations of DULERA 200 mcg/5 mcg twice daily (morning and evening) may provide additional asthma control.

Do not use more than two inhalations twice daily of the prescribed strength of DULERA 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.

If a previously effective dosage regimen of DULERA fails to provide adequate control of asthma, the therapeutic regimen should be re-evaluated and additional therapeutic options, e.g., replacing the current strength of DULERA with a higher strength, adding additional inhaled corticosteroid, or initiating oral corticosteroids, should be considered.

3 DOSAGE FORMS AND STRENGTHS

DULERA is a pressurized metered dose inhaler that is available in 2 strengths.

DULERA 100 mcg/5 mcg delivers 100 mcg of mometasone furoate and 5 mcg of formoterol fumarate dihydrate per actuation.

DULERA 200 mcg/5 mcg delivers 200 mcg of mometasone furoate and 5 mcg of formoterol fumarate dihydrate per actuation.

4 CONTRAINDICATIONS

4.1 Status Asthmaticus

DULERA is contraindicated in the primary treatment of status asthmaticus or other acute episodes of asthma where intensive measures are required.

4.2 Hypersensitivity

DULERA is contraindicated in patients with known hypersensitivity to mometasone furoate, formoterol fumarate, or any of the ingredients in DULERA *[see Warnings and Precautions (5.10)]*.

5 WARNINGS AND PRECAUTIONS

5.1 Serious Asthma-Related Events – Hospitalizations, Intubations, and Death

Use of LABA as monotherapy (without ICS) for asthma is associated with an increased risk of asthma-related death *[see Salmeterol Multicenter Asthma Research Trial (SMART)]*. Available data from controlled clinical trials also suggest that use of LABA as monotherapy increases the risk of asthma-related hospitalization in pediatric and adolescent patients. These findings are considered a class effect of LABA monotherapy. When LABA are used in fixed-dose combination with ICS, data from large clinical trials do not show a significant increase in the risk of serious asthma-related events (hospitalizations, intubations, death) compared to ICS alone *[see Serious Asthma-Related Events with ICS/LABA]*.

Serious Asthma-Related Events with ICS/LABA

Four large, 26-week, randomized, blinded, active-controlled clinical safety trials were conducted to evaluate the risk of serious asthma-related events when LABA were used in fixed-dose combination with ICS compared to ICS alone in patients with asthma. Three trials included adult and adolescent patients aged ≥12 years: one trial compared mometasone furoate/formoterol (DULERA) to mometasone furoate *[see Clinical Studies (14.1)]*; one trial compared fluticasone propionate/salmeterol inhalation powder to fluticasone propionate inhalation powder; and one trial compared budesonide/formoterol to budesonide. The fourth trial included pediatric patients 4 to 11 years of age and compared fluticasone propionate/salmeterol inhalation powder to fluticasone propionate inhalation powder. The primary safety endpoint for all four trials was serious asthma-related events (hospitalizations, intubations and death). A blinded adjudication committee determined whether events were asthma-related.

The three adult and adolescent trials were designed to rule out a risk margin of 2.0, and the pediatric trial was designed to rule out a risk of 2.7. Each individual trial met its pre-specified objective and demonstrated non-inferiority of ICS/LABA to ICS alone. A meta-analysis of the three adult and adolescent trials did not show a significant increase in risk of a serious asthma-related event with ICS/LABA fixed-dose combination compared with ICS alone (Table 1). These trials were not designed to rule out all risk for serious asthma-related events with ICS/LABA compared with ICS.

Table 1: Meta-Analysis of Serious Asthma-Related Events in Patients with Asthma Aged 12 Years and Older

	ICS/LABA (N=17,537)*	ICS (N=17,552)*	ICS/LABA vs. ICS Hazard ratio (95% CI)†
Serious asthma-related event‡	116	105	1.10 (0.85, 1.44)
Asthma-related death	2	0	
Asthma-related intubation (endotracheal)	1	2	
Asthma-related hospitalization (≥24 hour stay)	115	105	

ICS = Inhaled Corticosteroid, LABA = Long-acting $Beta_2$-adrenergic Agonist.

* Randomized patients who had taken at least 1 dose of study drug. Planned treatment used for analysis.

† Estimated using a Cox proportional hazards model for time to first event with baseline hazards stratified by each of the 3 trials.

‡ Number of patients with events that occurred within 6 months after the first use of study drug or 7 days after the last date of study drug, whichever date was later. Patients can have one or more events, but only the first event was counted for analysis. A single, blinded, independent adjudication committee determined whether events were asthma-related.

The pediatric safety trial included 6208 pediatric patients 4 to 11 years of age who received ICS/LABA (fluticasone propionate/salmeterol inhalation powder) or ICS (fluticasone propionate inhalation powder). In this trial, 27/3107 (0.9%) patients randomized to ICS/LABA and 21/3101 (0.7%) patients randomized to ICS experienced a serious asthma-related event. There were no asthma-related deaths or intubations. ICS/LABA did not show a significantly increased risk of a serious asthma-related event compared to ICS based on the pre-specified risk margin (2.7), with an estimated hazard ratio of time to first event of 1.29 (95% CI: 0.73, 2.27).

Salmeterol Multicenter Asthma Research Trial (SMART)
A 28-week, placebo-controlled U.S. trial that compared the safety of salmeterol with placebo, each added to usual asthma therapy, showed an increase in asthma-related deaths in patients receiving salmeterol (13/13,176 in patients treated with salmeterol vs. 3/13,179 in patients treated with placebo; relative risk: 4.37 [95% CI: 1.25, 15.34]). Use of background ICS was not required in SMART. The increased risk of asthma-related death is considered a class effect of LABA monotherapy.

Formoterol Monotherapy Studies
Clinical studies with formoterol used as monotherapy suggested a higher incidence of serious asthma exacerbation in patients who received formoterol than in those who received placebo. The sizes of these studies were not adequate to precisely quantify the difference in serious asthma exacerbations between treatment groups.

5.2 Deterioration of Disease and Acute Episodes

DULERA should not be initiated in patients during rapidly deteriorating or potentially life-threatening episodes of asthma. DULERA has not been studied in patients with acutely deteriorating asthma. The initiation of DULERA in this setting is not appropriate.

Increasing use of inhaled, short-acting beta$_2$-agonists is a marker of deteriorating asthma. In this situation, the patient requires immediate re-evaluation with reassessment of the treatment regimen, giving special consideration to the possible need for replacing the current strength of DULERA with a higher strength, adding additional inhaled corticosteroid, or initiating systemic corticosteroids. Patients should not use more than 2 inhalations twice daily (morning and evening) of DULERA.

DULERA is not indicated for the relief of acute symptoms, i.e., as rescue therapy for the treatment of acute episodes of bronchospasm. An inhaled, short-acting beta$_2$-agonist, not DULERA, should be used to relieve acute symptoms such as shortness of breath.

When beginning treatment with DULERA, 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.

5.3 Excessive Use of DULERA and Use with Other Long-Acting Beta$_2$-Agonists

As with other inhaled drugs containing beta$_2$-adrenergic agents, DULERA 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 DULERA should not use an additional long-acting beta$_2$-agonist (e.g., salmeterol, formoterol fumarate, arformoterol tartrate) for any reason, including prevention of exercise-induced bronchospasm (EIB) or the treatment of asthma.

5.4 Local Effects

In clinical trials, the development of localized infections of the mouth and pharynx with *Candida albicans* have occurred in patients treated with DULERA. If oropharyngeal candidiasis develops, it should be treated with appropriate local or systemic (i.e., oral) antifungal therapy while remaining on treatment with DULERA therapy, but at times therapy with DULERA may need to be interrupted. Advise patients to rinse the mouth after inhalation of DULERA.

5.5 Immunosuppression

Persons 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. (See the respective package inserts for complete VZIG and IG prescribing information.) If chickenpox develops, treatment with antiviral agents may be considered.

DULERA 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.

5.6 Transferring Patients from Systemic Corticosteroid Therapy

Particular care is needed for patients who are transferred from systemically active corticosteroids to DULERA 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 DULERA 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 identification card indicating that they may need supplementary systemic corticosteroids during periods of stress or severe asthma attack.

Patients requiring systemic corticosteroids should be weaned slowly from systemic corticosteroid use after transferring to DULERA. 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 DULERA 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, lassitude, and depression, despite maintenance or even improvement of respiratory function.

5.7 Hypercorticism and Adrenal Suppression

Mometasone furoate, a component of DULERA, will often help control asthma symptoms with less suppression of HPA function than therapeutically equivalent oral doses of prednisone. Since mometasone furoate is absorbed into the circulation and can be systemically active at higher doses, the beneficial effects of DULERA in minimizing HPA dysfunction may be expected only when recommended dosages are not exceeded and individual patients are titrated to the lowest effective dose.

Because of the possibility of systemic absorption of inhaled corticosteroids, patients treated with DULERA should be observed carefully for any evidence of systemic corticosteroid effects. Particular care should be taken in observing patients postoperatively or during periods of stress for evidence of inadequate adrenal response.

It is possible that systemic corticosteroid effects such as hypercorticism and adrenal suppression (including adrenal crisis) 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 DULERA should be reduced slowly, consistent with accepted procedures for reducing systemic corticosteroids and for management of asthma symptoms.

5.8 Drug Interactions with Strong Cytochrome P450 3A4 Inhibitors

Caution should be exercised when considering the coadministration of DULERA with ketoconazole, and other known strong CYP3A4 inhibitors (e.g., ritonavir, cobicistat-containing products, atazanavir, clarithromycin, indinavir, itraconazole, nefazodone, nelfinavir, saquinavir, telithromycin) because adverse effects related to increased systemic exposure to mometasone furoate may occur *[see Drug Interactions (7.1) and Clinical Pharmacology (12.3)]*.

5.9 Paradoxical Bronchospasm and Upper Airway Symptoms

DULERA may produce inhalation induced bronchospasm with an immediate increase in wheezing after dosing that may be life-threatening. If inhalation induced bronchospasm occurs, it should be treated immediately with an inhaled, short-acting bronchodilator. DULERA should be discontinued immediately and alternative therapy instituted.

5.10 Immediate Hypersensitivity Reactions

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

5.11 Cardiovascular and Central Nervous System Effects

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, DULERA should be used with caution in patients with cardiovascular disorders, especially coronary insufficiency, cardiac arrhythmias, and hypertension.

Formoterol fumarate, a component of DULERA, 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 DULERA at recommended doses, if they occur, the drug may need to be discontinued. In addition, beta-agonists have been reported to produce 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.

5.12 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 DULERA. 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.

In a 2-year double-blind study in 103 male and female asthma patients 18 to 50 years of age previously maintained on bronchodilator therapy (Baseline FEV_1 85%-88% predicted), treatment with mometasone furoate dry powder inhaler 200 mcg twice daily resulted in significant reductions in lumbar spine (LS) BMD at the end of the treatment period compared to placebo. The mean change from Baseline to Endpoint in the lumbar spine BMD was -0.015 (-1.43%) for the mometasone furoate group compared to 0.002 (0.25%) for the placebo group. In another 2-year double-blind study in 87 male and female asthma patients 18 to 50 years of age previously maintained on bronchodilator therapy (Baseline FEV_1 82%-83% predicted), treatment with mometasone furoate 400 mcg twice daily demonstrated no statistically significant changes in lumbar spine BMD at the end of the treatment period compared to placebo. The mean change from Baseline to Endpoint in the lumbar spine BMD was -0.018 (-1.57%) for the mometasone furoate group compared to -0.006 (-0.43%) for the placebo group.

5.13 Effect on Growth

Orally inhaled corticosteroids, including DULERA, may cause a reduction in growth velocity when administered to pediatric patients. Monitor the growth of pediatric patients receiving DULERA routinely (e.g., via stadiometry). To minimize the systemic effects of orally inhaled corticosteroids, including DULERA, titrate each patient's dose to the lowest dosage that effectively controls his/her symptoms *[see Use in Specific Populations (8.4)]*.

5.14 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 DULERA. Consider referral to an ophthalmologist in patients who develop ocular symptoms or use DULERA long term *[see Adverse Reactions (6)]*.

5.15 Coexisting Conditions

DULERA, 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.

5.16 Hypokalemia and Hyperglycemia

$Beta_2$-agonist medications may produce significant hypokalemia in some patients, possibly through intracellular shunting, 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 DULERA at recommended doses.

6 ADVERSE REACTIONS

LABA use may result in the following:

- Serious asthma-related events – hospitalizations, intubations, and death *[see Warnings and Precautions (5.1)]*.
- Cardiovascular and central nervous system effects *[see Warnings and Precautions (5.11)]*.

Systemic and local corticosteroid use may result in the following:

• *Candida albicans* infection *[see Warnings and Precautions (5.4)]*
• Immunosuppression *[see Warnings and Precautions (5.5)]*

• Hypercorticism and adrenal suppression *[see Warnings and Precautions (5.7)]*
• Growth effects in pediatrics *[see Warnings and Precautions (5.13)]*
• Glaucoma and cataracts *[see Warnings and Precautions (5.14)]*

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice.

6.1 Clinical Trials Experience

The safety data described below is based on 3 clinical trials which randomized 1913 patients 12 years of age and older with asthma, including 679 patients exposed to DULERA for 12 to 26 weeks and 271 patients exposed for 1 year. DULERA 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 26-week clinical trials, the population was 12 to 84 years of age, 41% male and 59% female, 73% Caucasians, 27% non-Caucasians. Patients received two inhalations twice daily of DULERA (100 mcg/5 mcg or 200 mcg/5 mcg), mometasone furoate MDI (100 mcg or 200 mcg), formoterol 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% Caucasians, 53% non-Caucasians and received two inhalations twice daily of DULERA 100 mcg/5 mcg or 200 mcg/5 mcg, or an active comparator.

The incidence of treatment emergent adverse reactions associated with DULERA in Table 2 below is based upon pooled data from 2 clinical trials 12 to 26 weeks in duration in patients 12 years and older treated with two inhalations twice daily of DULERA (100 mcg/5 mcg or 200 mcg/5 mcg), mometasone furoate MDI (100 mcg or 200 mcg), formoterol MDI (5mcg) or placebo.

Table 2: Treatment-Emergent Adverse Reactions in DULERA Groups Occurring at an Incidence of ≥3% and More Commonly than Placebo

Adverse Reactions	DULERA*		Mometasone Furoate*		Formoterol*	Placebo*
	100 mcg/5 mcg n=424 n (%)	200 mcg/5 mcg n=255 n (%)	100 mcg n=192 n (%)	200 mcg n=240 n (%)	5 mcg n=202 n (%)	n=196 n (%)
Nasopharyngitis	20 (4.7)	12 (4.7)	15 (7.8)	13 (5.4)	13 (6.4)	7 (3.6)
Sinusitis	14 (3.3)	5 (2.0)	6 (3.1)	4 (1.7)	7 (3.5)	2 (1.0)
Headache	19 (4.5)	5 (2.0)	10 (5.2)	8 (3.3)	6 (3.0)	7 (3.6)
Average Duration of Exposure (days)	116	81	165	79	131	138

*All treatments were administered as two inhalations twice daily.

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

Long-Term Clinical Trial Experience

In a long-term safety trial in patients 12 years and older treated for 52 weeks with DULERA 100 mcg/5 mcg (n=141), DULERA 200 mcg/5 mcg (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 DULERA 100 mcg/5 mcg and 5/130 (3.8%) patients receiving DULERA 200 mcg/5 mcg. No clinically significant changes in blood chemistry, hematology, or ECG were observed.

6.2 Postmarketing Experience

The following adverse reactions have been reported during post-approval use of DULERA or post-approval use with inhaled mometasone furoate or inhaled formoterol fumarate. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

Cardiac disorders: angina pectoris, cardiac arrhythmias, e.g., atrial fibrillation, ventricular extrasystoles, tachyarrhythmia
Eye disorders: vision blurred *[see Warnings and Precautions (5.14)]*
Immune system disorders: immediate and delayed hypersensitivity reactions including anaphylactic reaction, angioedema, severe hypotension, rash, pruritus
Investigations: electrocardiogram QT prolonged, blood pressure increased (including hypertension)
Metabolism and nutrition disorders: hypokalemia, hyperglycemia
Respiratory, thoracic and mediastinal disorders: asthma aggravation, which may include cough, dyspnea, wheezing and bronchospasm

7 DRUG INTERACTIONS

In clinical trials, concurrent administration of DULERA 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 DULERA. The drug interactions of the combination are expected to reflect those of the individual components.

7.1 Inhibitors of Cytochrome P450 3A4

The main route of metabolism of corticosteroids, including mometasone furoate, a component of DULERA, is via cytochrome P450 (CYP) isoenzyme 3A4 (CYP3A4). After oral administration of ketoconazole, a strong inhibitor of CYP3A4, the mean plasma concentration of orally inhaled mometasone furoate increased. Concomitant administration of CYP3A4 inhibitors may inhibit the metabolism of, and increase the systemic exposure to, mometasone furoate and potentially increase the risk for systemic corticosteroid side effects. Caution should be exercised when considering the coadministration of DULERA with long-term ketoconazole and other known strong CYP3A4 inhibitors (e.g., ritonavir, cobicistat-containing products, atazanavir, clarithromycin, indinavir, itraconazole, nefazodone, nelfinavir, saquinavir, telithromycin) *[see Warnings and Precautions (5.8) and Clinical Pharmacology (12.3)]*. Consider the benefit of coadministration versus the potential risk of systemic corticosteroid effects, in which case patients should be monitored for systemic corticosteroid side effects.

7.2 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 DULERA, may be potentiated.

7.3 Xanthine Derivatives

Concomitant treatment with xanthine derivatives may potentiate any hypokalemic effect of formoterol, a component of DULERA.

7.4 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 coadministration of DULERA with non-potassium-sparing diuretics.

7.5 Monoamine Oxidase Inhibitors, Tricyclic Antidepressants, and Drugs Known to Prolong the QTc Interval

DULERA should be administered with caution to patients being treated with monoamine oxidase inhibitors, tricyclic antidepressants, macrolides, 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 DULERA, on the cardiovascular system may be potentiated by these agents. Drugs that are known to prolong the QTc interval have an increased risk of ventricular arrhythmias.

7.6 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 DULERA, 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.

7.7 Halogenated Hydrocarbons

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

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Risk Summary

There are no randomized clinical studies of DULERA, mometasone furoate, or formoterol fumarate in pregnant women. There are clinical considerations with the use of DULERA in pregnant women *[see Clinical Considerations]*. Animal reproduction studies with DULERA are not available; however, studies are available with its individual components, mometasone furoate and formoterol fumarate. In animal reproduction studies, subcutaneous administration of mometasone furoate to pregnant mice, rats, or rabbits caused increased fetal malformations and decreased fetal survival and growth following administration of doses that produced exposures approximately 1/3 to 8 times the maximum recommended human dose (MRHD) on a mcg/m^2 or AUC basis *[see Data]*. However, experience with oral corticosteroids suggests that rodents are more prone to teratogenic effects from corticosteroid exposure than humans. In animal reproduction studies, oral administration of formoterol fumarate to pregnant rats and rabbits caused increased fetal malformations (rats and rabbits), decreased fetal weight (rats), and increased neonatal mortality (rats) following administration of doses that produced exposures approximately 1200 to 49,000 times the MRHD on a mg/m^2 or AUC basis *[see Data]*. These adverse effects generally occurred at large multiples of the MRHD when formoterol fumarate was administered by the oral route to achieve

high systemic exposures. No effects were observed in a study with rats that received formoterol fumarate by the inhalation route at an exposure approximately 500 times the MRHD.

The estimated background risk of major birth defects and miscarriage for the indicated population is unknown. In the U.S. general population, the estimated risk of major birth defects and miscarriage in clinically recognized pregnancies is 2 to 4% and 15 to 20%, respectively.

Clinical Considerations

Disease-associated maternal and/or embryo/fetal risk

In women with poorly or moderately controlled asthma, there is an increased risk of several perinatal adverse outcomes such as preeclampsia in the mother and prematurity, low birth weight, and small for gestational age in the neonate. Pregnant women with asthma should be closely monitored and medication adjusted as necessary to maintain optimal asthma control.

Labor or delivery

There are no adequate and well-controlled human studies that have studied the effects of DULERA during labor and delivery. Because of the potential for beta-agonist interference with uterine contractility, use of DULERA during labor should be restricted to those patients in whom the benefits clearly outweigh the risk.

Data

Animal Data

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).

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 findings with an exposure approximately 4 times the MRHD (on an AUC basis with a maternal subcutaneous dose of 7.5 mcg/kg).

Embryofetal development studies were conducted with pregnant rabbits dosed with mometasone furoate by either the topical dermal route or oral route throughout the period of organogenesis. In the study using the topical dermal route, mometasone furoate caused multiple malformations in fetuses (e.g., flexed front paws, gallbladder agenesis, umbilical hernia, 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 effects were observed at an exposure approximately 1/10 of the MRHD (on an AUC basis with a maternal oral dose of 140 mcg/kg).

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

Gender and Race: Specific studies to examine the effects of gender and race on the pharmacokinetics of DULERA have not been specifically studied.

Geriatrics: The pharmacokinetics of DULERA have not been specifically studied in the elderly population.

Drug-Drug Interactions
A single-dose crossover study was conducted to compare the pharmacokinetics of 4 inhalations of the following: mometasone furoate MDI, formoterol MDI, DULERA (mometasone furoate/formoterol fumarate MDI), and mometasone furoate MDI plus formoterol fumarate MDI administered concurrently. The results of the study indicated that there was no evidence of a pharmacokinetic interaction between the two components of DULERA.

Inhibitors of Cytochrome P450 Enzymes: Ketoconazole*:* In a drug interaction study, an inhaled dose of mometasone furoate 400 mcg delivered by a dry powder inhaler was given to 24 healthy subjects twice daily for 9 days and ketoconazole 200 mg (as well as placebo) were given twice daily concomitantly on Days 4 to 9. Mometasone furoate plasma concentrations were <150 pcg/mL on Day 3 prior to coadministration of ketoconazole or placebo. Following concomitant administration of ketoconazole, 4 out of 12 subjects in the ketoconazole treatment group (n=12) had peak plasma concentrations of mometasone furoate >200 pcg/mL on Day 9 (211-324 pcg/mL). Mometasone furoate plasma levels appeared to increase and plasma cortisol levels appeared to decrease upon concomitant administration of ketoconazole.

Specific drug-drug interaction studies with formoterol have not been performed.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility
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.

In reproductive studies in rats, impairment of fertility was not produced by subcutaneous doses up to 15 mcg/kg (approximately 8 times the MRHD on an AUC basis).

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.

Reproduction studies in rats revealed no impairment of fertility at oral doses up to 3 mg/kg (approximately 1200 times the MRHD on a mcg/m^2 basis).

13.2 Animal Toxicology and/or Pharmacology
Animal Pharmacology

Formoterol fumarate: Studies in laboratory animals (minipigs, rodents, and dogs) have demonstrated the occurrence of cardiac arrhythmias and sudden death (with histologic evidence of myocardial necrosis) when beta-agonists and methylxanthines are administered concurrently. The clinical significance of these findings is unknown.

14 CLINICAL STUDIES

14.1 Asthma

The safety and efficacy of DULERA 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 DULERA to placebo and the individual components, mometasone furoate and formoterol **(Trial 1)** and one clinical trial compared two different strengths of DULERA to mometasone furoate alone **(Trial 2)**.

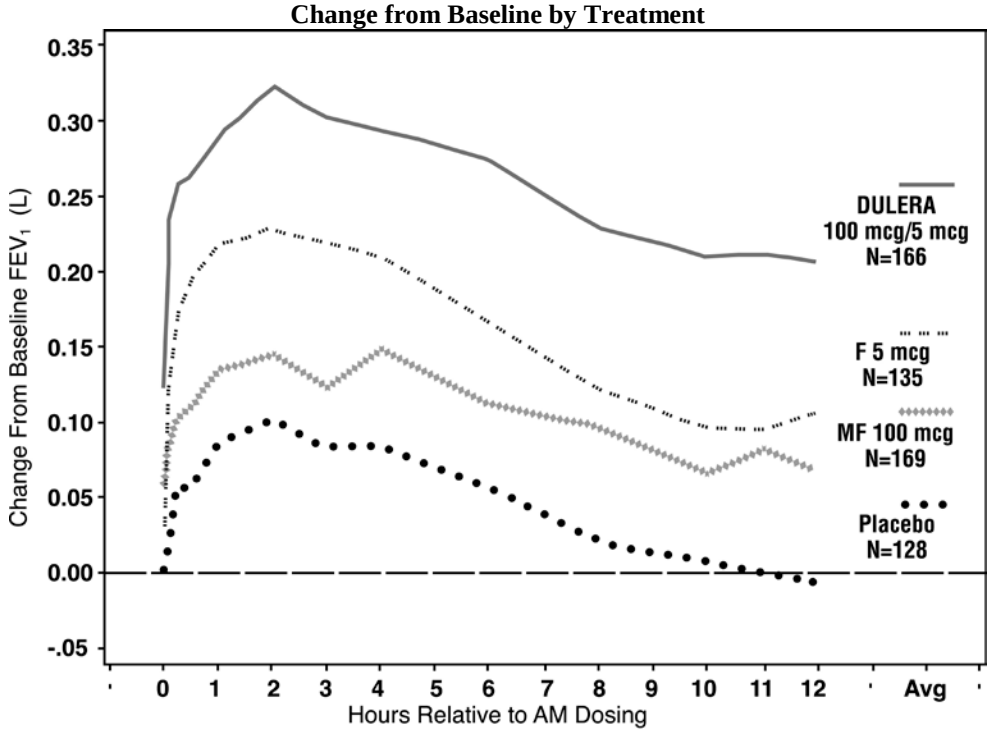
Trial 1: Clinical Trial with DULERA 100 mcg/5 mcg

This 26-week, placebo-controlled trial evaluated 781 patients 12 years of age and older comparing DULERA 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 DULERA 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 DULERA. Patients receiving DULERA 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 shows the change from baseline post-dose serial FEV_1 evaluations in Trial 1.

Figure 1

Trial 1 - DULERA 100 mcg/5 mcg - FEV_1 Serial Evaluations for Observed Cases at Week 12
Change from Baseline by Treatment



MF = Mometasone furoate
F = Formoterol fumarate
Mean FEV_1 over 12 hours at Week 12 (shown as AVG)

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 DULERA 100 mcg/5 mcg (primary treatment comparison DULERA vs. formoterol). 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 DULERA 100 mcg/5 mcg reported an event compared to patients who received formoterol 5 mcg ($p<0.001$).

Table 3: Trial 1 - Clinically Judged Deterioration in Asthma or Reduction in Lung Function*

	DULERA 100 mcg/ 5 mcg† (n=191)	**Mometasone Furoate 100 mcg† (n=192)**	**Formoterol 5 mcg† (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 predose 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 DULERA 100 mcg/5 mcg. A significantly greater increase in mean trough FEV_1 was observed for DULERA 100 mcg/5 mcg compared to formoterol 5 mcg (the primary treatment comparison) as well as to placebo (Table 4).

Table 4: Trial 1 – 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**
DULERA 100 mcg/5 mcg	167	2.33	0.13	0.18	<0.001	<0.001
Mometasone furoate 100 mcg	175	2.36	0.07	0.12	<0.001	0.058
Formoterol fumarate 5 mcg	141	2.29	0.00	0.05	0.170	
Placebo	145	2.30	-0.05			

LS means and p-values are from Week 12 estimates of a longitudinal analysis model.

The effect of DULERA 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 DULERA 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 DULERA 100 mcg/5 mcg and placebo was 0.5 [95% CI 0.32, 0.68].

Trial 2: Clinical Trial With DULERA 200 mcg/5 mcg

This 12-week double-blind trial evaluated 728 patients 12 years of age and older comparing DULERA 200 mcg/5 mcg (n=255 patients) with DULERA 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 DULERA 100 mcg/5 mcg, 8 (3%) patients receiving DULERA 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 DULERA 100 mcg/5 mcg and DULERA 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 DULERA 100 mcg/5 mcg and DULERA 200 mcg/5 mcg (Table 5). A greater numerical increase in the mean trough FEV_1 was observed for DULERA 200 mcg/5 mcg compared to DULERA 100 mcg/5 mcg and mometasone furoate 200 mcg.

Table 5: Trial 2 – Change in Trough FEV_1 from Baseline to Week 12

Treatment Arm	N	Baseline (L)	Change from Baseline at Week 12 (L)
DULERA 100 mcg/5 mcg	232	2.10	0.14
DULERA 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 DULERA 200 mcg/5 mcg or DULERA 100/5 mcg compared to mometasone furoate 200 mcg alone reported an event, defined as in Trial 1 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 6: Trial 2 - Clinically Judged Deterioration in Asthma or Reduction in Lung Function*

	DULERA 100 mcg/ 5 mcg† (n=233)	DULERA 200 mcg/ 5 mcg† (n=255)	Mometasone Furoate 200 mcg† (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 (7%)	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 predose 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 DULERA 200 mcg / 5 mcg group.

Other Studies

In addition to Trial 1 and Trial 2, the safety and efficacy of the individual components, mometasone furoate MDI 100 mcg and 200 mcg, in comparison to placebo were demonstrated in three other, 12-week, placebo controlled trials which evaluated the mean change in FEV_1 from baseline as a primary endpoint. The safety and efficacy of formoterol MDI 5 mcg alone in comparison to placebo was replicated in another 26-week trial that evaluated a lower dose of mometasone furoate MDI in combination with formoterol.

Postmarketing Safety and Efficacy Trial with DULERA

This 26-week double-blind, randomized control trial evaluated 11,729 patients, 12 years of age and older, who received at least one dose of DULERA (100 mcg/5 mcg or 200 mcg/5 mcg, n=5868) or mometasone furoate monotherapy (100 mcg or 200 mcg, n=5861) each administered as 2 inhalations twice daily by metered dose inhalation aerosols (NCT01471340). The primary safety objective was to evaluate whether the addition of formoterol to mometasone furoate (DULERA) was non-inferior to mometasone furoate in risk of serious asthma-related events (adjudicated hospitalization, intubation, and death). A blinded adjudication committee determined whether events were asthma-related. The study was designed to rule out a pre-defined risk margin of 2.0. Enrolled patients had a diagnosis of persistent asthma, had been receiving a stable dose of asthma maintenance therapy for at least 4 weeks and had a history of one to four asthma exacerbations requiring hospitalization or systemic corticosteroid use in the previous year. The assigned dose level of inhaled corticosteroid was based on the patients' disease severity, considering their prior asthma medication and current level of asthma control. The study included patients ranging in age from 12 to 88 years (median age 47 years), and were 66% female and 77% Caucasian.

DULERA was non-inferior to mometasone furoate in terms of time to first serious asthma-related event based on the pre-specified risk margin with an estimated hazard ratio of 1.22 [95% CI: 0.76, 1.94].

Table 7: Serious Asthma-Related Event (Postmarketing Trial)

	DULERA* n (%)	**Mometasone Furoate* n (%)**	**Total n (%)**	**DULERA vs. Mometasone Furoate**
Patients in population	5868	5861	11,729	Hazard Ratio† (95% CI)
Serious Asthma-related Event‡,§	**39 (0.66)**	**32 (0.55)**	**71 (0.6)**	**1.22 (0.76, 1.94)**
Asthma-Related Hospitalization (≥24 hr stay)	39 (0.66)	32 (0.55)	71 (0.6)	
Asthma-Related Intubation (Endotracheal)	0	0	0	
Asthma-Related Death	0	0	0	

* Actual treatment used for analysis.

† The hazard ratio for time to first event was based on a Cox proportional hazard model with covariates of treatment (DULERA vs. mometasone furoate) and inhaled corticosteroid dose level (100 mcg vs. 200 mcg), as treated.

‡ Results provided for all randomized patients who received at least one dose of DULERA (100 mcg/5 mcg and 200 mcg/5 mcg, two inhalations, prescribed twice daily) or mometasone furoate (100 mcg and 200 mcg, two inhalations, prescribed twice daily).

§ Number of patients with an event that occurred within 6 months after the first use of study drug or 7 days after the last date of study drug, whichever date was later. Patients can have one or more events, but only the first event was counted for analysis. A blinded adjudication committee determined whether events were asthma related.

The key efficacy endpoint was time to first asthma exacerbation [defined as a clinical deterioration of asthma associated with systemic corticosteroid use for ≥3 consecutive days (or ≥1 depot injectable), emergency department visits <24 hours requiring systemic corticosteroid, or hospital stays of ≥24 hours]. The estimated hazard ratio for time to first exacerbation for DULERA relative to mometasone furoate was 0.89 [95% CI: 0.8, 0.98]. This outcome was primarily driven by a reduction in those events requiring systemic corticosteroid use, which accounted for 87% of the total number of first asthma exacerbations.

16 HOW SUPPLIED/STORAGE AND HANDLING

16.1 How Supplied

DULERA is available in two strengths and supplied in the following package sizes (Table 8):

Table 8

Package	NDC
DULERA 100 mcg/5 mcg 120 inhalations	0085-7206-01
DULERA 100 mcg/5 mcg 60 inhalations (institutional pack)	0085-7206-07
DULERA 200 mcg/5 mcg 120 inhalations	0085-4610-01
DULERA 200 mcg/5 mcg 60 inhalations (institutional pack)	0085-4610-05

Each strength is supplied as a pressurized aluminum canister that has a blue plastic actuator integrated with a dose counter and a green dust cap. Each 120-inhalation canister has a net fill weight of 13 grams and each 60-inhalation canister has a net fill weight of 8.8 grams. Each canister is placed into a carton. Each carton contains 1 canister and a Patient Information leaflet.

Initially the dose counter will display “64” or “124” actuations. After the initial priming with 4 actuations, the dose counter will read “60” or “120” and the inhaler is now ready for use.

16.2 Storage and Handling

The DULERA canister should only be used with the DULERA actuator. The DULERA actuator should not be used with any other inhalation drug product. Actuators from other products should not be used with the DULERA canister.

The canister should not be removed from the actuator because the correct amount of medication may not be discharged; the dose counter may not function properly; reinsertion may cause the dose counter to count down by 1 and discharge a puff.

The correct amount of medication in each inhalation cannot be ensured after the labeled number of actuations from the canister has been used, even though the inhaler may not feel completely empty and may continue to operate. The inhaler should be discarded when the labeled number of actuations has been used (the dose counter will read “0").

Store at controlled room temperature 20-25°C (68-77°F); excursions permitted to 15-30°C (59-86°F) [see USP Controlled Room Temperature].

The 120-inhalation inhaler does not require specific storage orientation. For the 60-inhalation inhaler, after priming, store the inhaler with the mouthpiece down or in a horizontal position.

For best results, the canister should be at room temperature before use. Shake well and remove the cap from the mouthpiece of the actuator before using. Keep out of reach of children. Avoid spraying in eyes.

Contents Under Pressure: Do not puncture. Do not use or store near heat or open flame. Exposure to temperatures above 120°F may cause bursting. Never throw container into fire or incinerator.

17 PATIENT COUNSELING INFORMATION

Advise the patient to read the FDA-approved patient labeling (Patient Information and Instructions for Use).

Serious Asthma-Related Events

Inform patients with asthma that LABA when used alone increases the risk of asthma-related hospitalization, or asthma-related death. Available data show that when ICS and LABA are used together, such as with DULERA, there is not a significant increase in risk of these events.

Not for Acute Symptoms

DULERA is not indicated to relieve acute asthma symptoms and extra doses should not be used for that purpose. Acute symptoms should be treated with an inhaled, short-acting, beta$_2$-agonist (the health care provider should prescribe the patient with such medication and instruct the patient in how it should be used).

Patients should be instructed to seek medical attention immediately if they experience any of the following:

- If their symptoms worsen
- Significant decrease in lung function as outlined by the physician
- If they need more inhalations of a short-acting beta$_2$-agonist than usual

Patients should be advised not to increase the dose or frequency of DULERA. The daily dosage of DULERA should not exceed two inhalations twice daily. If they miss a dose, they should be instructed to take their next dose at the same time they normally do. DULERA provides bronchodilation for up to 12 hours.

Patients should not stop or reduce DULERA therapy without physician/provider guidance since symptoms may recur after discontinuation *[see Warnings and Precautions (5.2)]*.

Do Not Use Additional Long-Acting Beta$_2$-Agonists
When patients are prescribed DULERA, other long-acting beta$_2$-agonists should not be used *[see Warnings and Precautions (5.3)]*.

Risks Associated With Corticosteroid Therapy
Local Effects: Patients should be advised that localized infections with *Candida albicans* occurred in the mouth and pharynx in some patients. If oropharyngeal candidiasis develops, it should be treated with appropriate local or systemic (i.e., oral) antifungal therapy while still continuing with DULERA therapy, but at times therapy with DULERA may need to be temporarily interrupted under close medical supervision. Rinsing the mouth after inhalation is advised *[see Warnings and Precautions (5.4)]*.

Immunosuppression: Patients who are on immunosuppressant doses of corticosteroids should be warned to avoid exposure to chickenpox or measles and, if exposed, to consult their physician without delay. Patients should be informed of potential worsening of existing tuberculosis, fungal, bacterial, viral, or parasitic infections, or ocular herpes simplex *[see Warnings and Precautions (5.5)]*.

Hypercorticism and Adrenal Suppression: Patients should be advised that DULERA may cause systemic corticosteroid effects of hypercorticism and adrenal suppression. Additionally, patients should be instructed that deaths due to adrenal insufficiency have occurred during and after transfer from systemic corticosteroids. Patients should taper slowly from systemic corticosteroids if transferring to DULERA *[see Warnings and Precautions (5.7)]*.

Reduction in Bone Mineral Density: Patients who are at an increased risk for decreased BMD should be advised that the use of corticosteroids may pose an additional risk and should be monitored and, where appropriate, be treated for this condition *[see Warnings and Precautions (5.12)]*.

Reduced Growth Velocity: Patients should be informed that orally inhaled corticosteroids, a component of DULERA, may cause a reduction in growth velocity when administered to pediatric patients. Physicians should closely follow the growth of pediatric patients taking corticosteroids by any route *[see Warnings and Precautions (5.13)]*.

Glaucoma and Cataracts: Long-term use of inhaled corticosteroids may increase the risk of some eye problems (glaucoma or cataracts); regular eye examinations should be considered *[see Warnings and Precautions (5.14)]*.

Risks Associated With Beta-Agonist Therapy
Patients should be informed that treatment with beta$_2$-agonists may lead to adverse events which include palpitations, chest pain, rapid heart rate, tremor or nervousness *[see Warnings and Precautions (5.11)]*.

Instructions for Use
Patients should be instructed regarding the following:

- Read the Patient Information before use and follow the Instructions for Use carefully.
- Patients should be reminded to:
    - Remove the cap from the mouthpiece of the actuator before use.
    - Rinse their mouth with water after breathing in the medicine. To spit out the water and not to swallow it.
    - Not remove the canister from the actuator.
    - Not wash inhaler in water. The mouthpiece should be cleaned using a dry wipe after every 7 days of use.

Manufactured by: 3M Health Care Ltd., Loughborough, United Kingdom.

For patent information: www.merck.com/product/patent/home.html

The trademarks depicted herein are owned by their respective companies.

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PATIENT INFORMATION

DULERA® [dew-LAIR-ah] 100 mcg/5 mcg

(mometasone furoate 100 mcg and formoterol fumarate dihydrate 5 mcg)

Inhalation Aerosol

DULERA® 200 mcg/5 mcg

(mometasone furoate 200 mcg and formoterol fumarate dihydrate 5 mcg)

Inhalation Aerosol

Read the Patient Information leaflet that comes with DULERA® before you start using it and each time you get a refill. There may be new information. The Patient Information leaflet does not take the place of talking to your healthcare provider about your medical condition or treatment.

What is DULERA?

- DULERA combines an inhaled corticosteroid medicine (ICS), mometasone furoate, and a long-acting $beta_2$-agonist medicine (LABA), formoterol.
- ICS medicines such as mometasone furoate help to decrease inflammation in the lungs. Inflammation in the lungs can lead to breathing problems.
- LABA medicines such as formoterol help the muscles around the airways in your lungs stay relaxed to prevent asthma symptoms, such as wheezing, cough, chest tightness, and shortness of breath. These symptoms can happen when the muscles around the airways tighten. This makes it hard to breathe.
- **DULERA is not used to relieve sudden breathing problems** and will not replace a rescue inhaler.
- It is not known if DULERA is safe and effective in children less than 12 years of age.
- DULERA is used for asthma as follows:
  - DULERA is a prescription medicine used to control symptoms of asthma and prevent symptoms such as wheezing in people 12 years of age and older.
  - DULERA contains formoterol. LABA medicines such as formoterol when used alone increase the risk of hospitalizations and death from asthma problems. DULERA contains an ICS and a LABA. When an ICS and LABA are used together, there is not a significant increased risk in hospitalizations and death from asthma problems.
  - DULERA is not for adults and adolescents with asthma who are well controlled with an asthma control medicine, such as a low to medium dose ICS medicine. DULERA is for adults and adolescents with asthma who need both an ICS and LABA medicine.

Do not use DULERA:

- to treat sudden severe symptoms of asthma.
- as a rescue inhaler.
- if you are allergic to any of the ingredients in DULERA. See the end of this Patient Information leaflet for a list of ingredients in DULERA.

Before you use DULERA, tell your healthcare provider about all of your medical conditions, including if you:

- have heart problems.
- have high blood pressure.
- have seizures.
- have thyroid problems.
- have diabetes.
- have liver problems.
- have osteoporosis.
- have an immune system problem.
- have eye problems such as increased pressure in the eye, glaucoma, or cataracts.
- are allergic to any medicines.
- are exposed to chickenpox or measles.
- have an aneurysm (swelling of an artery).
- have a pheochromocytoma (a tumor of the adrenal gland that can affect your blood pressure).
- are scheduled to have surgery.

- are pregnant or planning to become pregnant. It is not known if DULERA may harm your unborn baby.
- are breastfeeding. It is not known if DULERA passes into your milk and if it can harm your baby. You and your healthcare provider should decide if you will take DULERA while breastfeeding.

Tell your healthcare provider about all the medicines you take including prescription and over-the-counter medicines, vitamins, and herbal supplements. DULERA and certain other medicines may interact with each other. This may cause serious side effects.

Especially, tell your healthcare provider if you take antifungal medicines, such as ketoconazole, or anti-HIV medicines, such as ritonavir. The anti-HIV medicines NORVIR® (ritonavir capsules) Soft Gelatin, NORVIR® (ritonavir oral solution), and KALETRA® (lopinavir/ritonavir) Tablets contain ritonavir.

Know the medicines you take. Keep a list and show it to your healthcare provider and pharmacist each time you get a new medicine.

How should I use DULERA?

See the step-by-step instructions for using DULERA at the end of this Patient Information leaflet. Do not use DULERA unless your healthcare provider has taught you and you understand how to use it. Ask your healthcare provider or pharmacist if you have any questions.

- Use DULERA exactly as prescribed. **Do not use DULERA more often than prescribed.** DULERA comes in 2 strengths. Your healthcare provider has prescribed the strength that is best for you. Note the differences between DULERA and your other inhaled medicines, including the differences in prescribed use and physical appearance.
- DULERA should be taken every day as 2 puffs in the morning and 2 puffs in the evening.
- If you miss a dose of DULERA, skip your missed dose and take your next dose at your regular time. Do not take DULERA more often or use more puffs than you have been prescribed.
- **While you are using DULERA 2 times each day, do not use other medicines that contain a long-acting beta$_2$-agonist (LABA) for any reason.** Ask your healthcare provider or pharmacist if any of your other medicines are LABA medicines.
- If you take more DULERA than your healthcare provider has prescribed, get medical help right away if you have any unusual symptoms, such as problems breathing, palpitations, chest pain, increased heart rate, nervousness or shakiness.
- Do not change or stop using DULERA or other asthma medicines used to control or treat your breathing problems unless told to do so by your healthcare provider. Your healthcare provider will change your medicines as needed.
- DULERA does not relieve sudden asthma symptoms. Always have a rescue inhaler with you to treat sudden symptoms. Use your rescue inhaler if you have breathing problems between doses of DULERA. If you do not have a rescue inhaler, call your healthcare provider to have one prescribed for you.
- **Remove the cap from the mouthpiece of the actuator before using DULERA.**
- **Do not remove the canister from the actuator because:**
  - You may not receive the correct amount of medicine.
  - The dose counter may not function properly.
  - Reinsertion may cause the dose counter to count down by 1 and may discharge a puff.
- After each dose (2 puffs) of DULERA, rinse your mouth with water. Spit out the water. Do not swallow it. This will help to lessen the chance of getting a yeast infection (thrush) in the mouth and throat.
- Prime (sprays released into the air before use) your inhaler away from your face. Do not spray DULERA in your eyes. If you accidentally get DULERA in your eyes, rinse your eyes with water and if redness or irritation continues, call your healthcare provider.
- **Call your healthcare provider or get medical care right away if:**
  - your breathing problems worsen with DULERA
  - you need to use your rescue inhaler more often than usual
  - your rescue inhaler does not work as well for you at relieving symptoms
  - you need to use 4 or more inhalations of your rescue inhaler for 2 or more days in a row
  - you use 1 whole canister of your rescue inhaler in 4 weeks' time
  - your peak flow meter results decrease. Your healthcare provider will tell you the numbers that are right for you.
  - your asthma symptoms do not improve after using DULERA regularly for 2 weeks

What are the possible side effects of DULERA?

DULERA may cause serious side effects, including

- **Thrush in the mouth and throat.** You may develop thrush, a yeast infection (Candida albicans), in your mouth or throat. After each dose of DULERA (2 puffs), rinse your mouth with water. Spit out the water. Do not swallow it. This will

help to prevent thrush in your mouth or throat.

- **Immune system effects and a higher chance for infections.** Signs of infection may include:
  - fever
  - feeling tired
  - pain
  - nausea
  - body aches
  - vomiting
  - chills
- **Adrenal insufficiency**. Adrenal insufficiency is a condition in which the adrenal glands do not make enough steroid hormones. This can happen when you stop taking oral corticosteroid medicines and start inhaled corticosteroid medicines.
- **Increased wheezing right after taking DULERA.** Always have a rescue inhaler with you to treat sudden wheezing.
- **Serious allergic reactions.** Call your healthcare provider or get emergency medical care if you get any of the following symptoms of a serious allergic reaction:
  - rash
  - hives
  - swelling, including swelling of the face, mouth, and tongue
  - breathing problems
- **Using too much of a LABA medicine may cause:**
  - chest pain
  - increased or decreased blood pressure
  - a fast and irregular heartbeat
  - headache
  - tremor
  - nervousness
  - dizziness
  - weakness
  - seizures
  - electrocardiogram (ECG) changes
- **Lower bone mineral density.** This may be a problem for people who already have a higher chance for low bone density (osteoporosis).
- **Slowed growth in children.** A child's growth should be checked often.
- **Eye problems including glaucoma and cataracts.** You should have regular eye exams while using DULERA.
- **Decreases in blood potassium levels (hypokalemia).**
- **Increases in blood sugar levels (hyperglycemia).**

The most common reported side effects of DULERA include:

- inflammation of the nose and throat (nasopharyngitis)
- inflammation of the sinuses (sinusitis)
- headache

Tell your healthcare provider about any side effect that bothers you or that does not go away.

These are not all the side effects of DULERA. Ask your healthcare provider or pharmacist for more information.

Call your doctor for medical advice about side effects. You may report side effects to FDA at 1-800-FDA-1088.

You may also report side effects to Merck Sharp & Dohme Corp., a subsidiary of Merck & Co., Inc., at 1-877-888-4231.

How should I store DULERA?

- Store DULERA at room temperature between 68°F to 77°F (20°C to 25°C).
- The 120-actuation inhaler can be stored in any position. For the 60-actuation inhaler, after priming, store the inhaler with the mouthpiece down or sideways.
- The contents of your DULERA are under pressure. Do not puncture. Do not use or store near heat or open flame. Storage above 120°F may cause the canister to burst.
- Do not throw container into fire or incinerator.
- **Keep DULERA and all medicines out of the reach of children.**

General Information about the safe and effective use of DULERA.

Medicines are sometimes prescribed for purposes other than those listed in the Patient Information leaflet. Do not use DULERA for a condition for which it was not prescribed. Do not give your DULERA to other people, even if they have the same condition. It may harm them.

You can ask your healthcare provider or pharmacist for information about DULERA that was written for healthcare professionals.

What are the ingredients in DULERA?

Active ingredients: mometasone furoate and formoterol fumarate dihydrate

Inactive ingredients: hydrofluoroalkane (HFA-227), anhydrous alcohol and oleic acid

For more information about DULERA:

Go to www.DULERA.com or call 1-800-622-4477.

This Patient Information has been approved by the U.S. Food and Drug Administration Revised: 12/2017

Patient Instructions for Use

DULERA®

DULERA® 100 mcg/5 mcg

(mometasone furoate 100 mcg and formoterol fumarate dihydrate 5 mcg) Inhalation Aerosol

DULERA® 200 mcg/5 mcg

(mometasone furoate 200 mcg and formoterol fumarate dihydrate 5 mcg) Inhalation Aerosol

How to use your DULERA

Before using your DULERA, read the complete instructions and use only as directed.

The parts of your DULERA:

There are 2 main parts to your DULERA inhaler – the metal canister that holds the medicine and the blue plastic actuator that sprays the medicine from the canister. The inhaler also has a green cap that covers the mouthpiece of the actuator (see **Figure 1**). The cap from the mouthpiece must be removed before use. The inhaler contains 60 or 120 actuations (puffs).

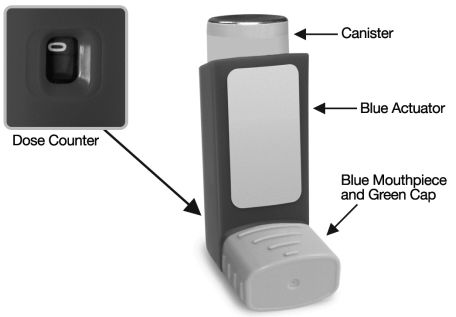


Figure 1

The inhaler comes with dose counter located on the plastic actuator. See **Figure 1.** The counter display will show the number of actuations (puffs) of medicine remaining. The dose counter will initially display “64” or “124” actuations remaining. Each time you press the canister, a puff of medicine is released and the counter will count down by 1. The counter will stop counting at 0.

- **YOU SHOULD NOT REMOVE THE CANISTER FROM THE ACTUATOR** because:
  - You may not receive the correct amount of medication.
  - The dose counter may not function properly.
  - Reinsertion may cause the counter to count down by 1 and may discharge a puff.
- Use the DULERA canister only with the actuator supplied with the product. Do not use parts of the DULERA inhaler with parts from any other inhalation medicine.

Before using your DULERA:

REMOVE THE CAP FROM THE MOUTHPIECE OF THE ACTUATOR (see **Figure 2**). Check the mouthpiece for objects before use. Make sure the canister is fully inserted into the actuator.

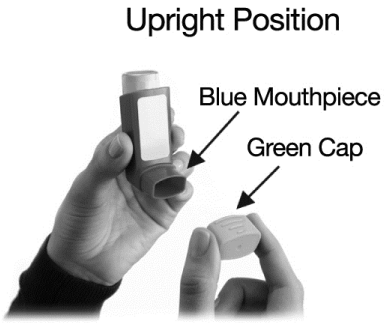


Figure 2

Priming your DULERA Inhaler:

Before you use DULERA for the first time, you must prime the inhaler.

1. To prime the inhaler, hold it in the upright position and release 4 actuations (puffs) into the air, away from your face.
2. Shake the inhaler well before each of the priming actuations. After priming 4 times, the dose counter should read either "60" or "120".
3. **If you do not use your DULERA for more than 5 days, you will need to prime it again before use.**

Using your DULERA

4. **REMOVE THE CAP FROM THE MOUTHPIECE OF THE ACTUATOR** (see **Figure 3**). Check the mouthpiece for objects before use. Make sure the canister is fully inserted into the actuator.
5. Shake the inhaler well before each use.
6. Breathe out as fully as you comfortably can through your mouth. Push out as much air from your lungs as possible. Hold the inhaler in the upright position and place the mouthpiece into your mouth (see **Figure 4**). Close your lips around the mouthpiece.

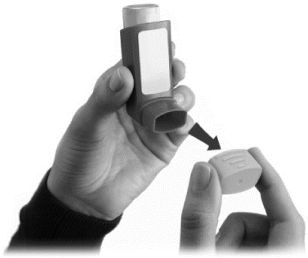


Figure 3

Figure 4

7. Take a deep breath (inhale) in slowly through your mouth. While doing this, press down firmly and fully on the top of the canister until it stops moving in the actuator. Take your finger off the canister.
8. When you have finished breathing in, hold your breath as long as you comfortably can, up to 10 seconds. Then remove the inhaler from your mouth and breathe out through your nose, while keeping your lips closed.

9. Wait at least **30 seconds** to take your second puff of DULERA.
10. Shake the inhaler well again and repeat steps 6 through 8 to take your second puff of DULERA.

After using your DULERA inhaler:

11. Replace the cap over the mouthpiece right away after use (see **Figure 5**).

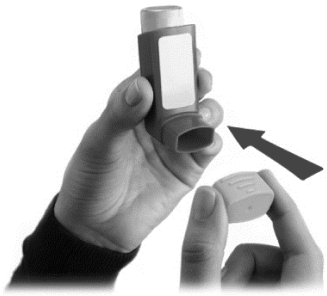
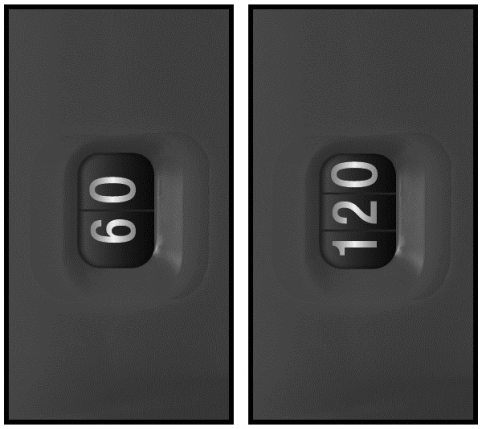


Figure 5

12. After you finish taking DULERA (2 puffs), rinse your mouth with water. Spit out the water. Do not swallow it.

Reading the counter

- The dose counter identifies the number of inhalations (puffs) left in your inhaler.
- The counter will count down each time you release a puff of medicine (either when preparing your DULERA inhaler for use or when taking the medicine).



When to replace your DULERA:

- It is important that you pay attention to the number of inhalations (puffs) left in your DULERA inhaler by reading the counter.
- When the counter reads 20, you should refill your prescription or ask your healthcare provider if you need a new prescription for DULERA.
- Throw away DULERA after the counter reaches 0, indicating that you have used the number of actuations on the product label and box. Your inhaler may not feel empty and it may continue to operate, but you will not get the right amount of medicine if you keep using it.
- Never try to change the numbers on the counter or remove the counter from the actuator.
- Do not use the inhaler after the expiration date.

How should I store DULERA?

- Store DULERA at room temperature between 68°F to 77°F (20°C to 25°C).
- The 120-actuation inhaler can be stored in any position. For the 60-actuation inhaler, after priming, store the inhaler with the mouthpiece down or sideways.
- The contents of your DULERA canister are under pressure. Do not puncture or throw the canister into a fire or incinerator. Do not use or store it near heat or open flame. Storage above 120ºF (50°C) may cause the canister to burst.
- **Keep DULERA and all medicines out of the reach of children.**

How to clean your DULERA:

The mouthpiece should be cleaned using a dry wipe after every 7 days of use.

Routine cleaning instructions:

- Remove the cap off the mouthpiece. Wipe the inside and outside surfaces of the actuator mouthpiece with a clean, dry, lint-free tissue or cloth. **Do not wash or put any parts of your inhaler in water.** Put the cap back on the mouthpiece after cleaning.
- Do not remove the canister from the actuator.
- Do not attempt to unblock the actuator with a sharp object, such as a pin.

Manufactured for: Merck Sharp & Dohme Corp., a subsidiary of
MERCK & CO., INC., Whitehouse Station, NJ 08889, USA

Manufactured by: 3M Health Care Ltd., Loughborough, United Kingdom.

This Instructions for Use has been approved by the U.S. Food and Drug Administration.

For patent information: www.merck.com/product/patent/home.html

Revised: 12/2017

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