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® 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
FOR ORAL INHALATION
Initial U.S. Approval: 2010

WARNING: ASTHMA-RELATED DEATH
See full prescribing information for complete boxed warning.

- **Long-acting beta$_2$-adrenergic agonists (LABA), such as formoterol, one of the active ingredients in DULERA, increase the risk of asthma-related death. Data from a large placebo-controlled U.S. study that compared the safety of another LABA (salmeterol) or placebo added to usual asthma therapy showed an increase in asthma-related deaths in patients receiving salmeterol. This finding with salmeterol is considered a class effect of the LABA, including formoterol. Currently available data are inadequate to determine whether concurrent use of inhaled corticosteroids or other long-term asthma control drugs mitigates the increased risk of asthma-related death from LABA. Available data from controlled clinical trials suggest that LABA increase the risk of asthma-related hospitalization in pediatric and adolescent patients.**
- **When treating patients with asthma, prescribe DULERA only for patients with asthma not adequately controlled on a long-term asthma control medication, such as an inhaled corticosteroid or whose disease severity clearly warrants initiation of treatment with both an inhaled corticosteroid and LABA. Once asthma control is achieved and maintained, assess the patient at regular intervals and step down therapy (e.g., discontinue DULERA) if possible without loss of asthma control, and maintain the patient on a long-term asthma control medication, such as an inhaled corticosteroid. Do not use DULERA for patients whose asthma is adequately controlled on low or medium dose inhaled corticosteroids. (1.1, 5.1)**

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

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

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

Important limitations:

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

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

For oral inhalation only.
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 prior asthma therapy. (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 ----------

- Asthma-related death: Long-acting beta$_2$-adrenergic agonists increase the risk. Prescribe only for recommended patient populations. (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: Monitor patients with change in vision or with a history of increased intraocular pressure, glaucoma, and/or cataracts closely. (5.14)
- Coexisting conditions: Use with caution in patients with 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% of patients) included:

- Nasopharyngitis, sinusitis and headache. (6.1)

To report SUSPECTED ADVERSE REACTIONS, contact Schering Corporation, a subsidiary of Merck & Co., Inc., at 1-800-526-4099 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, 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)

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

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

See 17 for PATIENT COUNSELING INFORMATION and Medication Guide.

Revised: 07/2011

FULL PRESCRIBING INFORMATION: CONTENTS*

*****Sections or subsections omitted from the full prescribing information are not listed.

FULL PRESCRIBING INFORMATION

WARNING: ASTHMA-RELATED DEATH

Long-acting beta$_2$-adrenergic agonists (LABA), such as formoterol, one of the active ingredients in DULERA, increase the risk of asthma-related death. Data from a large placebo-controlled U.S. study that compared the safety of another long-acting beta$_2$-adrenergic agonist (salmeterol) or placebo added to usual asthma therapy showed an increase in asthma-related deaths in patients receiving salmeterol. This finding with salmeterol is considered a class effect of the LABA, including formoterol. Currently available data are inadequate to determine whether concurrent use of inhaled corticosteroids or other long-term asthma control drugs mitigates the increased risk of asthma-related death from LABA. Available data from controlled clinical trials suggest that LABA increase the risk of asthma-related hospitalization in pediatric and adolescent patients. Therefore, when treating patients with asthma, DULERA should only be used for patients not adequately controlled on a long-term asthma control medication, such as an inhaled corticosteroid or whose disease severity clearly warrants initiation of treatment with both an inhaled corticosteroid and LABA. Once asthma control is achieved and maintained, assess the patient at regular intervals and step down therapy (e.g., discontinue DULERA) if possible without loss of asthma control, and maintain the patient on a long-term asthma control medication, such as an inhaled corticosteroid. Do not use DULERA for patients whose asthma is adequately controlled on low or medium dose inhaled corticosteroids. *[See Warnings and Precautions (5.1).]*

1 INDICATIONS AND USAGE

1.1 Treatment of Asthma

DULERA is indicated for the treatment of asthma in patients 12 years of age and older.

Long-acting beta$_2$-adrenergic agonists, such as formoterol, one of the active ingredients in DULERA, increase the risk of asthma-related death. Available data from controlled clinical trials suggest that LABA increase the risk of asthma-related hospitalization in pediatric and adolescent patients *[see Warnings and Precautions (5.1)]*. Therefore, when treating patients with asthma, DULERA should only be used for patients not adequately controlled on a long-term asthma control medication, such as an inhaled corticosteroid or whose disease severity clearly warrants initiation of treatment with both an inhaled corticosteroid and LABA. Once asthma control is achieved and maintained, assess the patient at regular intervals and step down therapy (e.g., discontinue DULERA) if possible without loss of asthma control, and maintain the patient on a long-term asthma control medication, such as an inhaled corticosteroid. Do not use DULERA for patients whose asthma is adequately controlled on low or medium dose inhaled corticosteroids.

Important Limitation of Use

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

2 DOSAGE AND ADMINISTRATION

2.1 General

DULERA should be administered only by the orally inhaled route (see Instructions for Using DULERA in the Medication Guide). After each dose, the patient should be advised to rinse his/her mouth with water without swallowing.

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 Dosing

DULERA should be administered as two inhalations twice daily every day (morning and evening) by the orally inhaled route.
Shake well prior to each inhalation.

The recommended starting dosages for DULERA treatment are based on prior asthma therapy.

Table 1: Recommended Dosages for DULERA

Previous Therapy	Recommended Dose	Maximum Recommended Daily Dose
Inhaled medium dose corticosteroids	DULERA 100 mcg/5 mcg, 2 inhalations twice daily	400 mcg/20 mcg
Inhaled high dose corticosteroids	DULERA 200 mcg/5 mcg, 2 inhalations twice daily	800 mcg/20 mcg

The maximum daily recommended dose is two inhalations of DULERA 200 mcg/5 mcg twice daily. 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 reevaluated 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.

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 ≥12 years of age who do not respond adequately after 2 weeks of therapy, higher strength may provide additional asthma control.

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 Asthma-Related Death

Long-acting beta$_2$-adrenergic agonists, such as formoterol, one of the active ingredients in DULERA, increase the risk of asthma-related death. Currently available data are inadequate to determine whether concurrent use of inhaled corticosteroids

or other long-term asthma control drugs mitigates the increased risk of asthma-related death from LABA. Available data from controlled clinical trials suggest that LABA increase the risk of asthma-related hospitalization in pediatric and adolescent patients. Therefore, when treating patients with asthma, physicians should only prescribe DULERA for patients with asthma not adequately controlled on a long-term asthma control medication, such as an inhaled corticosteroid or whose disease severity clearly warrants initiation of treatment with both an inhaled corticosteroid and LABA. Once asthma control is achieved and maintained, assess the patient at regular intervals and step down therapy (e.g., discontinue DULERA) if possible without loss of asthma control, and maintain the patient on a long-term asthma control medication, such as an inhaled corticosteroid. Do not use DULERA for patients whose asthma is adequately controlled on low or medium dose inhaled corticosteroids.

A 28-week, placebo-controlled US study comparing 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; RR 4.37, 95% CI 1.25, 15.34). This finding with salmeterol is considered a class effect of the LABAs, including formoterol, one of the active ingredients in DULERA. No study adequate to determine whether the rate of asthma-related death is increased with DULERA has been conducted.

Clinical studies with formoterol suggested a higher incidence of serious asthma exacerbations in patients who received formoterol fumarate than in those who received placebo. The sizes of these studies were not adequate to precisely quantify the differences in serious asthma exacerbation rates 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 prescribing DULERA, the physician must also provide the patient with an inhaled, short-acting beta$_2$-agonist (e.g., albuterol) for treatment of acute symptoms, despite regular twice-daily (morning and evening) use of DULERA.

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 (FEV1 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, 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 inhaled 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. Therefore, close monitoring is warranted in patients with a change in vision or with a history of increased intraocular pressure, glaucoma, and/or cataracts *[see Adverse Reactions (6)]*.

5.15 Coexisting Conditions

DULERA, like other medications containing sympathomimetic amines, should be used with caution in patients with 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

Long-acting beta$_2$-adrenergic agonists, such as formoterol, one of the active ingredients in DULERA, increase the risk of asthma-related death. Currently available data are inadequate to determine whether concurrent use of inhaled corticosteroids or other long-term asthma control drugs mitigates the increased risk of asthma-related death from LABA. Available data from controlled clinical trials suggest that LABA increase the risk of asthma-related hospitalization in pediatric and adolescent patients. Data from a large placebo-controlled US trial that compared the safety of another long-acting beta$_2$-adrenergic agonist (salmeterol) or placebo added to usual asthma therapy showed an increase in asthma-related deaths in patients receiving salmeterol *[see Warnings and Precautions (5.1)]*.

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-week 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. 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.

Immune system disorders: anaphylactic reaction

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. Caution should be exercised when considering the coadministration of DULERA with long-term ketoconazole and other known strong CYP3A4 inhibitors (e.g., ritonavir, atazanavir, clarithromycin, indinavir, itraconazole, nefazodone, nelfinavir, saquinavir, telithromycin) *[see Warnings and Precautions (5.8) and Clinical Pharmacology (12.3)]*.

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, 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.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

DULERA: Teratogenic Effects: Pregnancy Category C

There are no adequate and well-controlled studies of DULERA, mometasone furoate only or formoterol fumarate only in pregnant women. Animal reproduction studies of mometasone furoate and formoterol in mice, rats, and/or rabbits revealed evidence of teratogenicity as well as other developmental toxic effects. Because animal reproduction studies are not always predictive of human response, DULERA should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Mometasone Furoate: Teratogenic Effects

When administered to pregnant mice, rats, and rabbits, mometasone furoate increased fetal malformations and decreased fetal growth (measured by lower fetal weights and/or delayed ossification). Dystocia and related complications were also observed when

mometasone furoate was administered to rats late in gestation. However, experience with oral corticosteroids suggests that rodents are more prone to teratogenic effects from corticosteroid exposure than humans.

In a mouse reproduction study, subcutaneous mometasone furoate produced cleft palate at approximately one-third of the maximum recommended daily human dose (MRHD) on a mcg/m^2 basis and decreased fetal survival at approximately 1 time the MRHD. No toxicity was observed at approximately one-tenth of the MRHD on a mcg/m^2 basis.

In a rat reproduction study, mometasone furoate produced umbilical hernia at topical dermal doses approximately 6 times the MRHD on a mcg/m^2 basis and delays in ossification at approximately 3 times the MRHD on a mcg/m^2 basis.

In another study, rats received subcutaneous doses of 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 a dose that was approximately 8 times the MRHD on an area under the curve (AUC) basis. Similar effects were not observed at approximately 4 times MRHD on an AUC basis.

In rabbits, mometasone furoate caused multiple malformations (e.g., flexed front paws, gallbladder agenesis, umbilical hernia, hydrocephaly) at topical dermal doses approximately 3 times the MRHD on a mcg/m^2 basis. In an oral study, mometasone furoate increased resorptions and caused cleft palate and/or head malformations (hydrocephaly and domed head) at a dose less than the MRHD based on AUC. At a dose approximately 2 times the MRHD based on AUC, most litters were aborted or resorbed *[see Nonclinical Toxicology (13.2)]*.

Nonteratogenic Effects:
Hypoadrenalism may occur in infants born to women receiving corticosteroids during pregnancy. Infants born to mothers taking substantial corticosteroid doses during pregnancy should be monitored for signs of hypoadrenalism.

Formoterol Fumarate: Teratogenic Effects
Formoterol fumarate administered throughout organogenesis did not cause malformations in rats or rabbits following oral administration. When given to rats throughout organogenesis, oral doses of approximately 80 times the MRHD on a mcg/m^2 basis and above delayed ossification of the fetus, and doses of approximately 2,400 times the MRHD on a mcg/m^2 basis and above decreased fetal weight. Formoterol fumarate has been shown to cause stillbirth and neonatal mortality at oral doses of approximately 2,400 times the MRHD on a mcg/m^2 basis and above in rats receiving the drug during the late stage of pregnancy. These effects, however, were not produced at a dose of approximately 80 times the MRHD on a mcg/m^2 basis.

In another testing laboratory, formoterol was shown to be teratogenic in rats and rabbits. Umbilical hernia, a malformation, was observed in rat fetuses at oral doses approximately 1,200 times and greater than the MRHD on a mcg/m^2 basis. Brachygnathia, a skeletal malformation, was observed in rat fetuses at an oral dose approximately 6,100 times the MRHD on a mcg/m^2 basis. In another study in rats, no teratogenic effects were seen at inhalation doses up to approximately 500 times the MRHD on a mcg/m^2 basis. Subcapsular cysts on the liver were observed in rabbit fetuses at an oral dose approximately 49,000 times the MRHD on a mcg/m^2 basis. No teratogenic effects were observed at oral doses up to approximately 3,000 times the MRHD on a mcg/m^2 basis *[see Nonclinical Toxicology (13.2)]*.

8.2 Labor and Delivery
There are no adequate and well-controlled human studies that have studied the effects of DULERA during labor and delivery.

Because beta-agonists may potentially interfere with uterine contractility, DULERA should be used during labor only if the potential benefit justifies the potential risk *[see Nonclinical Toxicology (13.2)]*.

8.3 Nursing Mothers
DULERA: It is not known whether DULERA is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when DULERA is administered to a nursing woman.

Since there are no data from well-controlled human studies on the use of DULERA on nursing mothers, based on data for the individual components, a decision should be made whether to discontinue nursing or to discontinue DULERA, taking into account the importance of DULERA to the mother.

Mometasone Furoate: It is not known if mometasone furoate is excreted in human milk. However, other corticosteroids are excreted in human milk.

Formoterol Fumarate: In reproductive studies in rats, formoterol was excreted in the milk. It is not known whether formoterol is excreted in human milk.

8.4 Pediatric Use

The safety and effectiveness of DULERA have been established in patients 12 years of age and older in 3 clinical trials up to 52 weeks in duration. In the 3 clinical trials, 101 patients 12 to 17 years of age were treated with DULERA. Patients in this age-group demonstrated efficacy results similar to those observed in patients 18 years of age and older. There were no obvious differences in the type or frequency of adverse drug reactions reported in this age group compared to patients 18 years of age and older. Similar efficacy and safety results were observed in an additional 22 patients 12 to 17 years of age who were treated with DULERA in another clinical trial. The safety and efficacy of DULERA have not been established in children less than 12 years of age.

Controlled clinical studies have shown that inhaled corticosteroids may cause a reduction in growth velocity in pediatric patients. In these studies, the mean reduction in growth velocity was approximately 1 cm per year (range 0.3 to 1.8 per year) and appears to depend upon dose and duration of exposure. This effect was observed in the absence of laboratory evidence of hypothalamic-pituitary-adrenal (HPA) axis suppression, suggesting that growth velocity is a more sensitive indicator of systemic corticosteroid exposure in pediatric patients than some commonly used tests of HPA axis function. The long-term effects of this reduction in growth velocity associated with orally inhaled corticosteroids, including the impact on final adult height, are unknown. The potential for "catch up" growth following discontinuation of treatment with orally inhaled corticosteroids has not been adequately studied.

The growth of children and adolescents receiving orally inhaled corticosteroids, including DULERA, should be monitored routinely (e.g., via stadiometry). If a child or adolescent on any corticosteroid appears to have growth suppression, the possibility that he/she is particularly sensitive to this effect should be considered. The potential growth effects of prolonged treatment should be weighed against clinical benefits obtained and the risks associated with alternative therapies. To minimize the systemic effects of orally inhaled corticosteroids, including DULERA, each patient should be titrated to his/her lowest effective dose *[see Dosage and Administration (2.2)]*.

8.5 Geriatric Use

A total of 77 patients 65 years of age and older (of which 11 were 75 years and older) have been treated with DULERA in 3 clinical trials up to 52 weeks in duration. Similar efficacy and safety results were observed in an additional 28 patients 65 years of age and older who were treated with DULERA in another clinical trial. No overall differences in safety or effectiveness were observed between these patients and younger patients, but greater sensitivity of some older individuals cannot be ruled out. As with other products containing $beta_2$-agonists, special caution should be observed when using DULERA in geriatric patients who have concomitant cardiovascular disease that could be adversely affected by $beta_2$-agonists. Based on available data for DULERA or its active components, no adjustment of dosage of DULERA in geriatric patients is warranted.

8.6 Hepatic Impairment

Concentrations of mometasone furoate appear to increase with severity of hepatic impairment *[see Clinical Pharmacology (12.3)]*.

10 OVERDOSAGE

10.1 Signs and Symptoms

DULERA: DULERA contains both mometasone furoate and formoterol fumarate; therefore, the risks associated with overdosage for the individual components described below apply to DULERA.

Mometasone Furoate: Chronic overdosage may result in signs/symptoms of hypercorticism *[see Warnings and Precautions (5.7)]*. Single oral doses up to 8000 mcg of mometasone furoate have been studied on human volunteers with no adverse reactions reported.

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, 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 MRHD on a mcg/m^2 basis). The median lethal oral doses in Chinese hamsters, rats, and mice provide even higher multiples of the MRHD.

10.2 Treatment

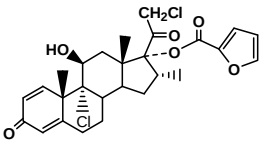
DULERA: Treatment of overdosage consists of discontinuation of DULERA together with institution of appropriate symptomatic and/or supportive therapy. The judicious use of a cardioselective beta-receptor blocker may be considered, bearing in mind that such

medication can produce bronchospasm. There is insufficient evidence to determine if dialysis is beneficial for overdosage of DULERA. Cardiac monitoring is recommended in cases of overdosage.

11 DESCRIPTION

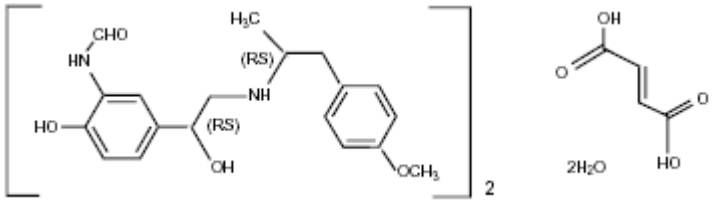
DULERA 100 mcg/5 mcg and DULERA 200 mcg/5 mcg, are combinations of mometasone furoate and formoterol fumarate dihydrate for oral inhalation only.

One active component of DULERA is mometasone furoate, a corticosteroid having the chemical name 9,21-dichloro-11(Beta),17-dihydroxy-16 (alpha)-methylpregna-1,4-diene-3,20-dione 17-(2-furoate) with the following chemical structure:



Mometasone furoate is a white powder with an empirical formula of $C_{27}H_{30}Cl_2O_6$, and molecular weight 521.44. It is practically insoluble in water; slightly soluble in methanol, ethanol, and isopropanol; soluble in acetone.

One active component of DULERA is formoterol fumarate dihydrate, a racemate. Formoterol fumarate dihydrate is a selective $beta_2$-adrenergic bronchodilator having the chemical name of (±)-2-hydroxy-5-[(1RS)-1-hydroxy-2-[[(1RS)-2-(4-methoxyphenyl)-1-methylethyl]-amino]ethyl]formanilide fumarate dihydrate with the following chemical structure:



Formoterol fumarate dihydrate has a molecular weight of 840.9, and its empirical formula is $(C_{19}H_{24}N_2O_4)_2 \cdot C_4H_4O_4 \cdot 2H_2O$. Formoterol fumarate dihydrate is a white to yellowish powder, which is freely soluble in glacial acetic acid, soluble in methanol, sparingly soluble in ethanol and isopropanol, slightly soluble in water, and practically insoluble in acetone, ethyl acetate, and diethyl ether.

Each DULERA 100 mcg/5 mcg and 200 mcg/5 mcg is a hydrofluoroalkane (HFA-227) propelled pressurized metered dose inhaler containing sufficient amount of drug for 120 inhalations *[see How Supplied/Storage and Handling (16)]*. After priming, each actuation of the inhaler delivers 115 or 225 mcg of mometasone furoate and 5.5 mcg of formoterol fumarate dihydrate in 69.6 mg of suspension from the valve and delivers 100 or 200 mcg of mometasone furoate and 5 mcg of formoterol fumarate dihydrate from the actuator. The actual amount of drug delivered to the lung may depend on patient factors, such as the coordination between actuation of the device and inspiration through the delivery system. DULERA also contains anhydrous alcohol as a cosolvent and oleic acid as a surfactant.

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.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

DULERA: DULERA contains both mometasone furoate and formoterol fumarate; therefore, the mechanisms of actions described below for the individual components apply to DULERA. 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.

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. The clinical significance of these findings is unknown.

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.

12.2 Pharmacodynamics

Cardiovascular Effects:

DULERA:

In a single dose, double blind placebo controlled crossover trial in 25 patients with asthma, single dose treatment of 10 mcg formoterol fumarate in combination with 400 mcg of mometasone furoate delivered via DULERA 200 mcg/5 mcg were compared to formoterol fumarate 10 mcg MDI, formoterol fumarate 12 mcg dry powder inhaler (DPI; nominal dose of formoterol fumarate delivered 10 mcg), or placebo. The degree of bronchodilation at 12 hours after dosing with DULERA was similar to formoterol fumarate delivered alone via MDI or DPI.

ECGs and blood samples for glucose and potassium were obtained prior to dosing and post dose. No downward trend in serum potassium was observed and values were within the normal range and appeared to be similar across all treatments over the 12 hour period. Mean blood glucose appeared similar across all groups for each time point. There was no evidence of significant hypokalemia or hyperglycemia in response to formoterol treatment.

No relevant changes in heart rate or changes in ECG data were observed with DULERA in the trial. No patients had a QTcB (QTc corrected by Bazett's formula) ≥500 msec during treatment.

In a single dose crossover trial involving 24 healthy subjects, single dose of formoterol fumarate 10, 20, or 40 mcg in combination with 400 mcg of mometasone furoate delivered via DULERA were evaluated for safety (ECG, blood potassium and glucose changes). ECGs and blood samples for glucose and potassium were obtained at baseline and post dose. Decrease in mean serum potassium was similar across all three treatment groups (approximately 0.3 mmol/L) and values were within the normal range. No clinically significant increases in mean blood glucose values or heart rate were observed. No subjects had a QTcB >500 msec during treatment.

Three active- and placebo-controlled trials (study duration ranging from 12, 26, and 52 weeks) evaluated 1913 patients 12 years of age and older with asthma. No clinically meaningful changes were observed in potassium and glucose values, vital signs, or ECG parameters in patients receiving DULERA.

HPA Axis Effects:

The effects of inhaled mometasone furoate administered via DULERA on adrenal function were evaluated in two clinical trials in patients with asthma. HPA-axis function was assessed by 24-hour plasma cortisol AUC. Although both these trials have open-label design and contain small number of subjects per treatment arm, results from these trials taken together demonstrated suppression of 24-hour plasma cortisol AUC for DULERA 200 mcg/5 mcg compared to placebo consistent with the known systemic effects of inhaled corticosteroid.

In a 42-day, open-label, placebo and active-controlled study 60 patients with asthma 18 years of age and older were randomized to receive two inhalations twice daily of 1 of the following treatments: DULERA 100 mcg/5 mcg, DULERA 200 mcg/5 mcg, fluticasone

propionate/salmeterol xinafoate 230 mcg/21 mcg, or placebo. At Day 42, the mean change from baseline plasma cortisol AUC (0-24 hr) was 8%, 22% and 34% lower compared to placebo for the DULERA 100 mcg/5 mcg (n=13), DULERA 200 mcg/5 mcg (n=15) and fluticasone propionate/salmeterol xinafoate 230 mcg/21 mcg (n=16) treatment groups, respectively.

In a 52-week, open-label safety study, primary analysis of the plasma cortisol 24-hour AUC was performed on 57 patients with asthma who received 2 inhalations twice daily of DULERA 100 mcg/5 mcg, DULERA 200 mcg/5 mcg, fluticasone propionate/salmeterol xinafoate 250/50, or fluticasone propionate/salmeterol xinafoate 500/50. At Week 52, the mean plasma cortisol AUC (0-24 hr) was 2.2%, 29.6%, 16.7%, and 32.2% lower from baseline for the DULERA 100 mcg/5 mcg (n=18), DULERA 200 mcg/5 mcg (n=20), fluticasone propionate/salmeterol xinafoate 250/50 mcg (n=8), and fluticasone propionate/salmeterol xinafoate 500/50 mcg (n=11) treatment groups, respectively.

Other Mometasone Products

HPA Axis Effects:

The potential effect of mometasone furoate via a dry powder inhaler (DPI) on the HPA axis was assessed in a 29-day study. A total of 64 adult patients with mild to moderate asthma were randomized to one of 4 treatment groups: mometasone furoate DPI 440 mcg twice daily, mometasone furoate DPI 880 mcg twice daily, oral prednisone 10 mg once daily, or placebo. The 30-minute post-Cosyntropin stimulation serum cortisol concentration on Day 29 was 23.2 mcg/dl for the mometasone furoate DPI 440 mcg twice daily group and 20.8 mcg/dl for the mometasone furoate DPI 880 mcg twice daily group, compared to 14.5 mcg/dl for the oral prednisone 10 mg group and 25 mcg/dl for the placebo group. The difference between mometasone furoate DPI 880 mcg twice daily (twice the maximum recommended dose) and placebo was statistically significant.

12.3 Pharmacokinetics

Absorption

Mometasone furoate:

Healthy Subjects: The systemic exposures to mometasone furoate from DULERA versus mometasone furoate delivered via DPI were compared. Following oral inhalation of single and multiple doses of the DULERA, mometasone furoate was absorbed in healthy subjects with median Tmax values ranging from 0.50 to 4 hours. Following single-dose administration of higher than recommended dose of DULERA (4 inhalations of DULERA 200 mcg/5 mcg) in healthy subjects, the arithmetic mean (CV%) Cmax and AUC (0-12h) values for MF were 67.8 (49) pg/mL and 650 (51) pg.hr/mL, respectively while the corresponding estimates following 5 days of BID dosing of DULERA 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 DULERA 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 DULERA administration compared to mometasone furoate via a DPI.

Asthma Patients: Following oral inhalation of single and multiple doses of the DULERA, mometasone furoate was absorbed in asthma patients with median Tmax values ranging from 1 to 2 hours. Following single-dose administration of DULERA 400 mcg/10 mcg, the arithmetic mean (CV%) Cmax and AUC (0-12h) values for MF were 20 (88) pg/mL and 170 (94) pg.hr/mL, respectively while the corresponding estimates following BID dosing of DULERA 400 mcg/10 mcg at steady-state were 60 (36) pg/mL and 577 (40) pg.hr/mL.

Formoterol fumarate:

Healthy Subjects: When DULERA was administered to healthy subjects, formoterol was absorbed with median Tmax values ranging from 0.167 to 0.5 hour. In a single-dose study with DULERA 400 mcg/10 mcg in healthy subjects, arithmetic mean (CV%) Cmax 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 DULERA, the exposure to formoterol was dose proportional.

Asthma Patients: When DULERA was administered to patients with asthma, formoterol was absorbed with median Tmax values ranging from 0.58 to 1.97 hours. In a single-dose study with DULERA 400 mcg/10 mcg in patients with asthma, arithmetic mean (CV%) Cmax and AUC (0-12h) for formoterol were 22 (29) pmol/L and 125 (42) pmol*h/L, respectively. Following multiple-dose administration of DULERA 400 mcg/10 mcg, the steady-state arithmetic mean (CV%) Cmax and AUC (0-12h) for formoterol were 41 (59) pmol/L and 226 (54) pmol*hr/L.

Distribution

Mometasone furoate: Based on the study employing a 1000 mcg inhaled dose of tritiated mometasone furoate inhalation powder in humans, 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).

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.

Metabolism
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 P-450 3A4 (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.

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.

Excretion
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 DULERA was 25 hours in healthy subjects and in patients with asthma.

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 DULERA, 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 healthy subjects from the MFF 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.

Special Populations
Hepatic/Renal Impairment: There are no data regarding the specific use of DULERA in patients with hepatic or renal impairment.

A study evaluating the administration of a single inhaled dose of 400 mcg mometasone furoate by a dry powder inhaler to subjects with mild (n=4), moderate (n=4), and severe (n=4) hepatic impairment resulted in only 1 or 2 subjects 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.

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/m2 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.

Reproductive Toxicology Studies

Mometasone furoate: In mice, mometasone furoate caused cleft palate at subcutaneous doses of 60 mcg/kg and above (approximately 1/3 of the maximum recommended human dose MRHD on a mcg/m^2 basis). Fetal survival was reduced at 180 mcg/kg (approximately equal to the MRHD on a mcg/m^2 basis). No toxicity was observed at 20 mcg/kg (approximately one-tenth of the MRHD on a mcg/m^2 basis).

In rats, mometasone furoate produced umbilical hernia at topical dermal doses of 600 mcg/kg and above (approximately 6 times the MRHD on a mcg/m^2 basis). A dose of 300 mcg/kg (approximately 3 times the MRHD on a mcg/m^2 basis) produced delays in ossification, but no malformations.

When rats received subcutaneous doses of mometasone furoate throughout pregnancy or during the later stages of pregnancy, 15 mcg/kg (approximately 8 times the MRHD on an AUC basis) caused prolonged and difficult labor and reduced the number of live births, birth weight, and early pup survival. Similar effects were not observed at 7.5 mcg/kg (approximately 4 times the MRHD on an AUC basis).

In rabbits, mometasone furoate caused multiple malformations (e.g., flexed front paws, gallbladder agenesis, umbilical hernia, hydrocephaly) at topical dermal doses of 150 mcg/kg and above (approximately 3 times the MRHD on a mcg/m^2 basis). In an oral study, mometasone furoate increased resorptions and caused cleft palate and/or head malformations (hydrocephaly and domed head) at 700 mcg/kg (less than the MRHD on an area under the curve [AUC] basis). At 2800 mcg/kg (approximately 2 times the MRHD on an AUC basis) most litters were aborted or resorbed. No toxicity was observed at 140 mcg/kg (less than the MRHD on an AUC basis).

Formoterol fumarate: Formoterol fumarate administered throughout organogenesis did not cause malformations in rats or rabbits following oral administration. When given to rats throughout organogenesis, oral doses of 0.2 mg/kg (approximately 80 times the MRHD on a mcg/m^2 basis) and above delayed ossification of the fetus, and doses of 6 mg/kg (approximately 2400 times the MRHD on a mcg/m^2 basis) and above decreased fetal weight. Formoterol fumarate has been shown to cause stillbirth and neonatal mortality at oral doses of 6 mg/kg (approximately 2400 times the MRHD on a mcg/m^2 basis) and above in rats receiving the drug during the late stage of pregnancy. These effects, however, were not produced at a dose of 0.2 mg/kg (approximately 80 times the MRHD on a mcg/m^2 basis).

In another testing laboratory, formoterol fumarate was shown to be teratogenic in rats and rabbits. Umbilical hernia, a malformation, was observed in rat fetuses at oral doses of 3 mg/kg/day and above (approximately 1,200 times greater than the MRHD on a mcg/m^2 basis). Brachygnathia, a skeletal malformation, was observed for rat fetuses at an oral dose of 15 mg/kg/day (approximately 6,100 times the MRHD on a mcg/m^2 basis). In another study in rats, no teratogenic effects were seen at inhalation doses up to 1.2 mg/kg/day (approximately 500 times the MRHD on a mcg/m^2 basis). Subcapsular cysts on the liver were observed for rabbit fetuses at an oral dose of 60 mg/kg (approximately 49,000 times the MRHD on a mcg/m^2 basis). No teratogenic effects were observed at oral doses up to 3.5 mg/kg (approximately 3,000 times the MRHD on a mcg/m^2 basis).

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 FEV1 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).

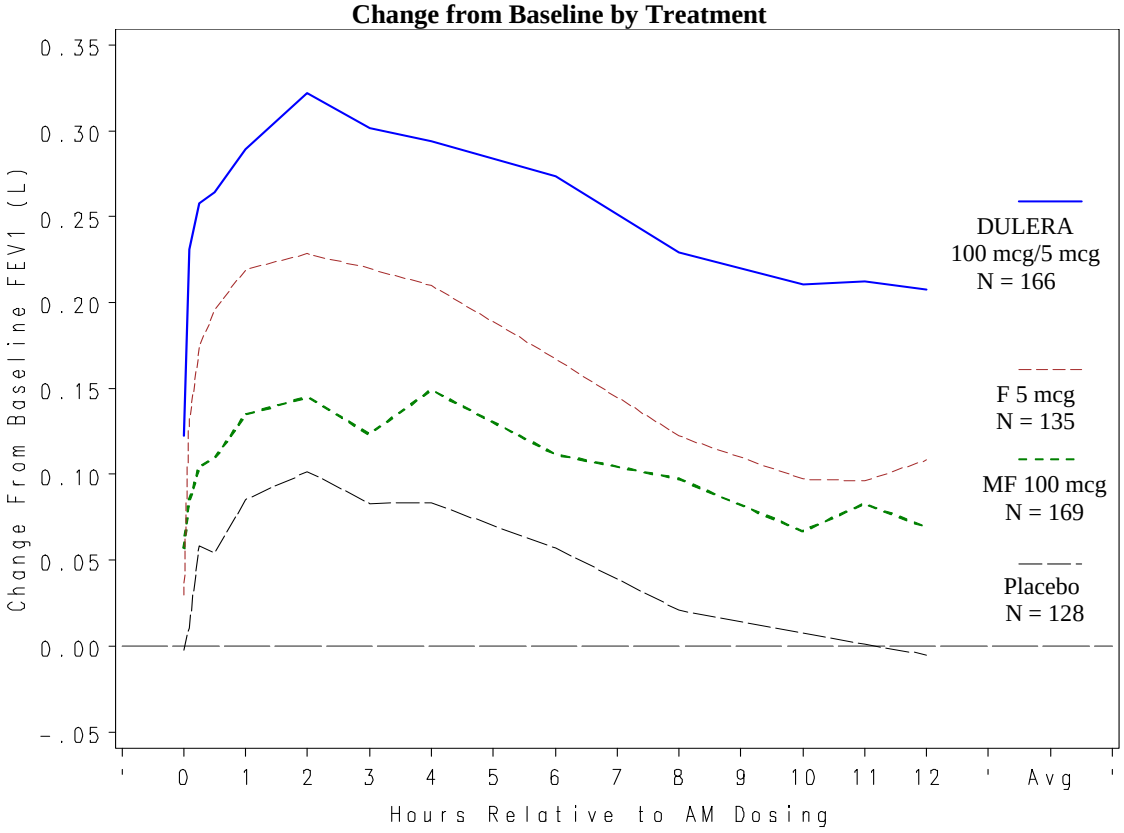
Trial 1: Clinical Trial with DULERA 100 mcg/5 mcg

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 FEV1 and mean percent predicted FEV1 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.

FEV1 AUC (0-12hr) 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 FEV1 AUC (0-12 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 FEV1 evaluations in Trial 1.

Figure 1

TRIAL 1 - DULERA 100 mcg/5 mcg - FEV1 Serial Evaluations for Observed Cases at Week 12
Change from Baseline by Treatment



MF = Mometasone furoate
F = Formoterol fumarate
Mean FEV1 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 FEV1; 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 FEV1**	18 (9%)	19 (10%)	31 (15%)	41 (21%)
Decrease in PEF†	37	41	62	61

	(19%)	(21%)	(31%)	(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.

** Decrease in absolute FEV1 below the treatment period stability limit (defined as 80% of the average of the two predose FEV1 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.

§ Two inhalations, twice daily.

The change in mean trough FEV1 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 FEV1 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 FEV1 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 FEV1 and mean percent predicted FEV1 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 FEV1 AUC (0-12 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 FEV1 AUC (0-12 hr) compared to mometasone furoate 200 mcg. The difference was maintained over 12 weeks of therapy.

Mean change in trough FEV1 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 FEV1 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 FEV1 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 FEV1; 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 FEV1**	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.

** Decrease in absolute FEV1 below the treatment period stability limit (defined as 80% of the average of the two predose FEV1 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.

§ Two inhalations, twice daily.

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 FEV1 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.

16 HOW SUPPLIED/STORAGE AND HANDLING

16.1 How Supplied

DULERA is available in two strengths (Table 7):

Table 7

Package	NDC
DULERA 100 mcg/5 mcg	0085-7206-01

DULERA 200 mcg/5 mcg	0085-4610-01

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

Initially the dose counter will display “124” actuations. After the initial priming with 4 actuations, the dose counter will read “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 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].

For best results, the canister should be at room temperature before use. Shake well 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

[See Medication Guide.]

17.1 Asthma-Related Death

[See Medication Guide.]

Patients should be informed that formoterol, one of the active ingredients in DULERA, increases the risk of asthma-related death. In pediatric and adolescent patients, formoterol may increase the risk of asthma-related hospitalization. They should also be informed that data are not adequate to determine whether the concurrent use of inhaled corticosteroids, the other component of DULERA, or other long-term asthma-control therapy mitigates or eliminates this risk *[see Warnings and Precautions (5.1)]*.

17.2 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)]*.

17.3 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)]*.

17.4 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)]*.

17.5 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)]*.

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

Distributed by: Schering Corporation, a subsidiary of
MERCK & CO., INC., Whitehouse Station, NJ 08889, USA

U.S. Patent Nos. 6,068,832; 7,067,502; and 7,566,705.

Issued Month Year

XXXXXXX

Medication Guide

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

What is the most important information I should know about DULERA?

DULERA can cause serious side effects, including:

1. **People with asthma who take long-acting beta$_2$-adrenergic agonist (LABA) medicines such as formoterol (one of the medicines in DULERA), have an increased risk of death from asthma problems**. It is not known whether mometasone furoate, the other medicine in DULERA, reduces the risk of death from asthma problems seen with formoterol.
    - **Call your healthcare provider if breathing problems worsen over time while using DULERA. You may need different treatment.**
    - **Get emergency medical care if:**
        - breathing problems worsen quickly, and
        - you use your rescue inhaler medicine, but it does not relieve your breathing problems**.**
2. **DULERA should be used only if your healthcare provider decides that your asthma is not well controlled with a long-term asthma control medicine, such as an inhaled corticosteroid.**
3. When your asthma is well controlled, your healthcare provider may tell you to stop taking DULERA. Your healthcare provider will decide if you can stop DULERA without loss of asthma control. Your healthcare provider may prescribe a different long-term asthma-control medicine for you, such as an inhaled corticosteroid.
4. Children and adolescents who take LABA medicines may have an increased risk of being hospitalized for asthma problems.

What is DULERA?

DULERA combines an inhaled corticosteroid medicine, mometasone furoate (the same medicine found in ASMANEX TWISTHALER), and a long-acting beta$_2$-agonist medicine (LABA), formoterol (the same medicine found in FORADIL® AEROLIZER®).

- Inhaled corticosteroids help to decrease inflammation in the lungs. Inflammation in the lungs can lead to asthma symptoms.
- LABA medicines are used in people with asthma. LABA medicines help the muscles around the airways in your lungs stay relaxed to prevent asthma symptoms, such as wheezing and shortness of breath. These symptoms can happen when the muscles around the airways tighten. This makes it hard to breathe. In severe cases, wheezing can stop your breathing and may lead to death if not treated right away.

DULERA is used to control symptoms of asthma and prevent symptoms such as wheezing in people 12 years of age and older.

DULERA should not be used as a rescue inhaler.

DULERA contains formoterol (the same medicine found in FORADIL AEROLIZER). LABA medicines such as formoterol increase the risk of death from asthma problems.

DULERA is not for children and adults with asthma who:

- are well controlled with an asthma-control medicine, such as a low to medium dose of an inhaled corticosteroid medicine

- only need a rescue inhaler once in awhile

It is not known if DULERA is safe and effective in children less than 12 years of age.

Who should not use DULERA?

Do not use DULERA:

- to treat sudden severe symptoms of asthma
- if you are allergic to any of the ingredients in DULERA. See the end of the Medication Guide for a list of ingredients in DULERA.

What should I tell my healthcare provider before using DULERA?

Tell your healthcare provider about all of your health 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 any other medical problems**
- **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 non-prescription 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 Medication Guide. Do not use DULERA unless your healthcare provider has taught you and you understand everything. 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 medications, 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.
- Rinse your mouth with water after each dose (2 puffs) of DULERA. This will help to lessen the chance of getting a yeast infection (thrush) in the mouth and throat.
- 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 8 weeks' time
    - your peak flow meter results decrease. Your healthcare provider will tell you the numbers that are right for you.
    - you have asthma and your symptoms do not improve after using DULERA regularly for 1 to 2 weeks

What are the possible side effects of DULERA?

DULERA can cause serious side effects, including:

- **See "What is the most important information I should know about DULERA?"**
- **Thrush in the mouth and throat.** You may develop a yeast infection (Candida albicans) in your mouth or throat. Rinse your mouth with water after using DULERA to help prevent an infection in your mouth or throat.
- **Immune system effects and a higher chance for infections.**
- Tell your healthcare provider about any signs of infection such as:
    - 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 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**
- **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 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 with 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 Schering Corporation, a subsidiary of Merck & Co., Inc., at 1-800-526-4099.

How do I store DULERA?

- Store DULERA at room temperature between 59°F to 86°F (15°C to 30°C).
- 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 DULERA

Medicines are sometimes prescribed for purposes other than those listed in a Medication Guide. 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.

This Medication Guide summarizes the most important information about DULERA. If you would like more information, talk with your healthcare provider. You can ask your healthcare provider or pharmacist for information about DULERA that was written for healthcare professionals. For more information about DULERA, go to www.DULERA.com or call 1-800-526-4099.

What are the ingredients in DULERA?

Active ingredients: mometasone furoate and formoterol fumarate dihydrate

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

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 cap that covers the mouthpiece of the actuator (see **Figure 1**). The inhaler contains 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 “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 reinsertion may cause the counter to count down by 1 and 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.

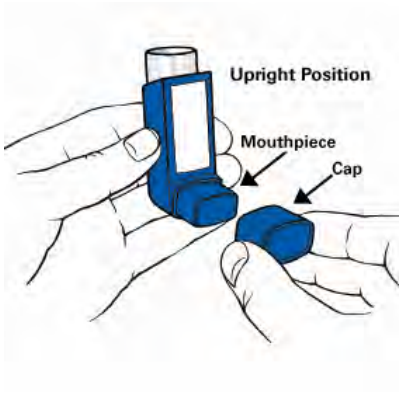


Figure 2

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 "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 2**). 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 3**). Close your lips around the mouthpiece.

Figure 3

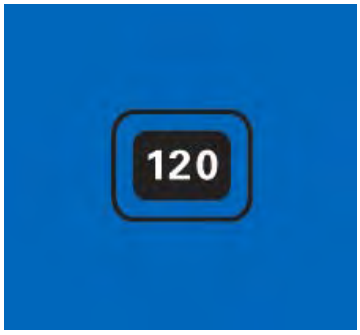
7. Take a deep breath (inhale) in slowly through your mouth. While doing this, press down firmly and fully on the top of the canister until it stops moving in the actuator. Take your finger off the canister.
8. When you have finished breathing in, hold your breath as long as you comfortably can, up to 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 before you take your second puff of DULERA.

After using your DULERA inhaler:

11. Replace the cap over the mouthpiece right away after use.
12. After you finish taking DULERA (2 puffs), rinse your mouth with water.

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 do I store DULERA?

- Store DULERA at room temperature between 59°F to 86°F (15°C to 30°C).
- 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. Put the cap back on the mouthpiece after cleaning.
- Do not attempt to unblock the actuator with a sharp object, such as a pin.
- Do not wash or put any parts of your inhaler in water.

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

Issued Month Year

This Medication Guide has been approved by the U.S. Food and Drug Administration.

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Initial REMA Approval : 06/2010
Most Recent Modificaion: 08/2011

NDA 022518 DULERA™ INHALATION AEROSOL
(mometasone furoate/formoterol fumarate)

Corticosteroid and Long-acting Beta$_2$-adrenergic Agonist

Schering Corporation a subsidiary of Merck & Co., Inc
2000 Galloping Hill Rd. Kenilworth, NJ 07033

Marty Huber, MD, Vice-President of Global Safety

RISK EVALUATION AND MITIGATION STRATEGY (REMS)

I. GOALS:

1. To inform healthcare providers and prescribers of the increased risk of asthma-related death and serious outcomes with the long-acting beta$_2$-adrenergic agonists (LABA) including DULERA.
2. To inform healthcare providers and prescribers of the appropriate use of long-acting beta$_2$-adrenergic agonists (LABA) including DULERA.

II. REMS ELEMENTS:

A. Communication Plan

Schering Corporation will implement a communication plan to healthcare providers to support implementation of this REMS. The communication plan will include the following:

1. A Dear Healthcare Provider Letter (DHCPL) will be distributed to current and potential prescribers of LABAs, Pulmonologists, Allergists/Immunologists, and select primary care physicians.
   Distribution of the Dear Healthcare Professional Letter will be by direct mail or e-mail communication with the following timeline:

   a) Initial distribution via mail or e-mail within 60 days of REMS approval
   b) Second distribution via mail or e-mail at or about 6 months post-marketing approval.

   The DHCPL will include the following safety information:
   a) Increased risk of asthma-related death in patients taking LABAs
   b) New prescribing guidelines:
      i. DULERA should only be used for patients not adequately controlled on a long-term asthma control medication, such as an

inhaled corticosteroid or whose disease severity clearly warrants initiation of treatment with both an inhaled corticosteroid and LABA

ii. Once asthma control is achieved and maintained, assess the patient at regular intervals and step down therapy (e.g. discontinue DULERA) if possible without loss of asthma control, and maintain the patient on a long-term asthma control medication, such as an inhaled corticosteroid.

iii. DULERA should not be used in patients whose asthma is adequately controlled on low or medium dose inhaled corticosteroids.

2. Printed or web-based information for health care providers will be posted on a Merck website within 10 days of the REMS approval. This information will remain on the website for 3 years. The content of the print or web-based material will, at a minimum, include the following:
   i. Information about the risk
   ii. Key data regarding the risk (e.g. SMART, SNS)
   iii. New prescribing guidelines
   iv. Currently available LABAs and approved uses
   v. Prescribing information for DULERA
   vi. Patient Counseling Information
   vii. Medication Guide for DULERA
   viii. Questions and Answers
   ix. DHCP letter (for a period of 1 year)

3. Schering Corporation will communicate via a letter to the leadership of the following professional societies:
   American College of Allergy, Asthma & Immunology (ACAAI)
   American Academy of Asthma Allergy & Immunology (AAAAI)
   American Thoracic Society (ATS)
   American College of Chest Physicians (ACCP)
   American College of Physicians (ACP)
   National Medical Association (NMA)
   American Academy of Nurse Practioners (AANP)
   American Academy of Physician Assistants (AAPA)

   The communication to medical societies will also include the information that is also available on the under 2) above. Schering Corporation will request that these societies disseminate this information to their members. A total number of recipients will be communicated to the agency prior to product launch.

   The timeline for REMS communication materials to professional societies will parallel the direct mail or e-mail program:
   i. Initial distribution at product approval
   ii. Second distribution at or about 6 months post-marketing approval

   The following materials are part of the REMS and are attached:

i. DHCPL
ii. Dear (Medical Society) Letter
iii. Printed or web-based information

C. Timetable for Submission of Assessments

Schering Corporation will submit REMS Assessments to FDA annually from approval of the initial REMS (June 22, 2010). To facilitate inclusion of as much information as possible while allowing reasonable time to prepare the submission, the reporting interval covered by each assessment should conclude no earlier than 60 days before the submission date for that assessment. Schering Corporation will submit each assessment so that it will be received by the FDA on or before the due date.

Attachment 1:
(Schering Corporation a subsidiary of Merck & Co. letterhead)

Dear Healthcare Professional:

Schering Corporation a subsidiary of Merck & Co., would like to inform you of important safety information for DULERA™ (mometasone furoate/formoterol fumarate). DULERA is a combination product containing a corticosteroid and a long acting beta$_2$-adrenergic agonist (LABA) indicated for treatment of asthma, in adults and patients 12 years of age and older. DULERA is not indicated for the relief of acute bronchospasm.

Important safety information related to DULERA includes:

- Increased risk of asthma-related death in patients taking LABAs.
- New prescribing guidelines.
    - DULERA should only be used for patients not adequately controlled on a long-term asthma control medication, such as an inhaled corticosteroid or whose disease severity clearly warrants initiation of treatment with both an inhaled corticosteroid and LABA.
    - Once asthma control is achieved and maintained, assess the patient at regular intervals and step down therapy (e.g. discontinue DULERA) if possible without loss of asthma control, and maintain the patient on a long-term asthma control medication, such as an inhaled corticosteroid.
    - DULERA should not be used in patients whose asthma is adequately controlled on low or medium dose inhaled corticosteroids

DULERA has a risk evaluation and a mitigation strategy (REMS) that consists of a Medication Guide and a communication program.

The DULERA labeling includes a boxed warning to highlight the safety issue of asthma-related death.

WARNING: ASTHMA-RELATED DEATH
See full prescribing information for complete boxed warning
Long-acting beta$_2$-adrenergic agonists (LABA), such as formoterol, one of the active ingredients in DULERA, increase the risk of asthma-related death. Data from a large placebo-controlled U.S. study that compared the safety of another long-acting beta$_2$-adrenergic agonist (salmeterol) or placebo added to usual asthma therapy showed an increase in asthma-related deaths in patients receiving salmeterol. This finding with salmeterol is considered a class effect of the LABA, including formoterol. Currently available data are inadequate to determine whether concurrent use of inhaled corticosteroids or other long-term asthma control drugs mitigates the increased risk of asthma-related death from LABA. Available data from controlled clinical trials suggest that LABA increase the risk of asthma-related hospitalization in pediatric and adolescent patients. Therefore, when treating patients with asthma, DULERA should only be used for patients not adequately controlled on a long-term asthma control medication, such as an inhaled corticosteroid or whose disease severity clearly warrants initiation of treatment with both an inhaled corticosteroid and LABA. Once asthma control is achieved and maintained, assess the patient at regular intervals and step down therapy (e.g. discontinue DULERA) if possible without loss of asthma control, and maintain the patient on a long-term asthma control medication, such as an inhaled corticosteroid. Do not use DULERA for

patients whose asthma is adequately controlled on low or medium dose inhaled corticosteroids.

Please note that DULERA should not be initiated in patients during rapidly deteriorating or potentially life-threatening episodes of asthma.

When prescribing DULERA, please also provide the patient with an inhaled, short-acting $beta_2$-agonist (e.g., albuterol) to be used as a rescue inhaler for treatment of acute symptoms. Increasing use of inhaled, short-acting $beta_2$-agonists is a marker for deteriorating asthma. In this situation, the patient requires immediate re-evaluation with reassessment of the treatment regimen.

Please instruct the patients to contact you if breathing problems worsen over time while using DULERA and get emergency medical care if breathing problems worsen quickly and are not being relieved by the use of the rescue inhaler.

Please take time to read the enclosed DULERA Package Insert for full prescribing information for complete description of this important safety information and the new prescribing guidelines.

In addition, please review the attached Medication Guide with each patient who is prescribed DULERA.

The Medication Guide will be enclosed in each carton packaging and must be provided by the authorized dispensers to each patient to whom the drug is dispensed.

To report adverse events potentially associated with DULERA, please call Schering Corporation at 1-800-672-6372

Alternatively, adverse event information may be reported to FDA's MedWatch Reporting System by:

- Phone at 1-800-FDA-1088 (1-800-332-1088)
- Facsimile at 1-800-FDA-0178 (1-800-332-0178)
- Mail using FDA Form 3500 located at http://www.fda.gov/medwatch

Please contact Schering Plough at 1-800-672-6372 if you have any questions about DULERA or the information in this letter.

Sincerely,

Marty Huber, MD
Vice President, Global Safety
Schering Corporation a subsidiary of Merck & Co.

Attachment 2:
(Schering Corporation a subsidiary of Merck & Co. letterhead)

Dear (Medical Society):

Schering Corporation a subsidiary of Merck & Co., would like to inform you of the U.S. Food and Drug Administration approval of DULERA™ (mometasone furoate/formoterol fumarate) a combination product containing a corticosteroid and a long acting $beta_2$-adrenergic agonist (LABA) indicated for treatment of asthma, in adults and patients 12 years of age and older. DULERA is not indicated for the relief of acute bronchospasm.

Important safety information related to DULERA includes:

- Increased risk of asthma-related death in patients taking LABAs.
- New prescribing guidelines.
    - DULERA should only be used for patients not adequately controlled on a long-term asthma control medication, such as an inhaled corticosteroid or whose disease severity clearly warrants initiation of treatment with both an inhaled corticosteroid and LABA.
    - Once asthma control is achieved and maintained, assess the patient at regular intervals and step down therapy (e.g. discontinue DULERA) if possible without loss of asthma control, and maintain the patient on a long-term asthma control medication, such as an inhaled corticosteroid.
    - DULERA should not be used in patients whose asthma is adequately controlled on low or medium dose inhaled corticosteroids

DULERA has a risk evaluation and a mitigation strategy (REMS) that consists of a Medication Guide and a communication program.

The DULERA labeling includes a boxed warning to highlight the safety issue of asthma-related death.

WARNING: ASTHMA-RELATED DEATH
See full prescribing information for complete boxed warning
Long-acting $beta_2$-adrenergic agonists (LABA), such as formoterol, one of the active ingredients in DULERA, increase the risk of asthma-related death. Data from a large placebo-controlled U.S. study that compared the safety of another long-acting $beta_2$-adrenergic agonist (salmeterol) or placebo added to usual asthma therapy showed an increase in asthma-related deaths in patients receiving salmeterol. This finding with salmeterol is considered a class effect of the LABA, including formoterol. Currently available data are inadequate to determine whether concurrent use of inhaled corticosteroids or other long-term asthma control drugs mitigates the increased risk of asthma-related death from LABA. Available data from controlled clinical trials suggest that LABA increase the risk of asthma-related hospitalization in pediatric and adolescent patients. Therefore, when treating patients with asthma, DULERA should only be used for patients not adequately controlled on a long-term asthma control medication, such as an inhaled corticosteroid or whose disease severity clearly warrants initiation of treatment with both an inhaled corticosteroid and LABA. Once asthma control is achieved and maintained, assess the patient at regular intervals and step down therapy (e.g. discontinue DULERA) if possible without loss of asthma control, and maintain the patient on a long-term asthma control medication, such as an inhaled corticosteroid. Do not use DULERA for patients whose asthma is adequately controlled on low or medium dose inhaled

corticosteroids.

Please note that DULERA should not be initiated in patients during rapidly deteriorating or potentially life-threatening episodes of asthma.

When prescribing DULERA, the healthcare professional should be guided to also provide the patient with an inhaled, short-acting beta$_2$-agonist (e.g., albuterol) to be used as a rescue inhaler for treatment of acute symptoms. Increasing use of inhaled, short-acting beta$_2$-agonists is a marker for deteriorating asthma. In this situation, the patient requires immediate re-evaluation with reassessment of the treatment regimen

The healthcare professional should instruct the patients to contact them if breathing problems worsen over time while using DULERA and get emergency medical care if breathing problems worsen quickly and are not being relieved by the use of the rescue inhaler.

Please take time to read the enclosed DULERA Package Insert for full prescribing information for complete description of this important safety information and the new prescribing guidelines.

Please share this communication with the members of your society and assure that they review the attached Medication Guide with each patient who is prescribed DULERA.

The Medication Guide will be enclosed in each carton packaging and must be provided by the authorized dispensers to each patient to whom the drug is dispensed.

To report adverse events potentially associated with DULERA, please call Schering Corporation at 1-800-672-6372

Alternatively, adverse event information may be reported to FDA's MedWatch Reporting System by:

- Phone at 1-800-FDA-1088 (1-800-332-1088)
- Facsimile at 1-800-FDA-0178 (1-800-332-0178)
- Mail using FDA Form 3500 located at http://www.fda.gov/medwatch

Please contact Schering Corporation at 1-800-672-6372 if you have any questions about DULERA or the information in this letter.

Sincerely,

Marty Huber, MD
Vice President, Global Safety
Schering Corporation a subsidiary of Merck & Co.

Attachment 3:
Printed / Web-based information:

The following content will be housed in a health care provider section of the product website.

- Information about the risk

Due to an increased risk of asthma-related death, FDA has mandated that all Long-Acting Beta Agonists (LABAs) and LABA-containing products, like DULERA, carry a boxed warning. The boxed warning for DULERA reads as follows:

WARNING: ASTHMA RELATED DEATH
See full prescribing information for complete boxed warning
Long-acting beta$_2$-adrenergic agonists (LABA), such as formoterol, one of the active ingredients in DULERA, increase the risk of asthma-related death. Data from a large placebo-controlled U.S. study that compared the safety of another LABA (salmeterol) or placebo added to usual asthma therapy showed an increase in asthma-related deaths in patients receiving salmeterol. This finding with salmeterol is considered a class effect of the LABA, including formoterol. Currently available data are inadequate to determine whether concurrent use of inhaled corticosteroids or other long-term asthma control drugs mitigate the increased risk of asthma-related death from LABA. Available data from controlled clinical trials suggest that LABA increase the risk of asthma-related hospitalization in pediatric and adolescent patients.

When treating patients with asthma, prescribe DULERA only for patients with asthma not adequately controlled on a long-term asthma control medication, such as an inhaled corticosteroid or whose disease severity clearly warrants initiation of treatment with both an inhaled corticosteroid and LABA. Once asthma control is achieved and maintained, assess the patient at regular intervals and step down therapy (e.g., discontinue DULERA) if possible without loss of asthma control, and maintain the patient on a long-term asthma control medication, such as an inhaled corticosteroid. Do not use DULERA for patients whose asthma is adequately controlled on low or medium dose inhaled corticosteroids.

See the full Prescribing Information (Link) for a more complete description of the risks associated with the use of DULERA in the treatment of asthma.

- Key data regarding the risk (e.g. SMART, SNS)

FDA's decision to require a Risk Evaluation and Mitigation Strategy (REMS) and class-labeling changes to the drug labels for Long-Acting Beta Agonists (LABAs) is based on analyses from the Salmeterol Multi-center Asthma Research Trial (SMART), the Salmeterol Nationwide Surveillance study (SNS), and a meta-analysis conducted by FDA in 2008 and discussed at the joint Pulmonary Allergy Drugs, Drug Safety and Risk Management, and Pediatric Advisory Committees, held on December 10-11, 2008 (for complete safety reviews and background information discussed at this meeting see the following link: December 10-11 2008 AC meeting).

SMART was a large, randomized, 28-week, placebo-controlled trial that evaluated patients 12 years of age and older receiving standard asthma therapy and the addition of either salmeterol or placebo. A total of 26,355 patients were evaluated in this study. Results showed that patients receiving salmeterol were at an increased risk for asthma-related death compared to patients receiving placebo. Subgroup analyses were also performed and found that asthma-related death in Caucasians and African Americans occurred at a higher rate in patients using salmeterol compared to placebo. See Table 1 below for results from SMART.

Table 1. SMART Results

SMART Patients	Asthma-Related Deaths in Salmeterol Group n (%*)	Asthma-Related Deaths in Placebo Group n (%*)	Relative Risk of Asthma-Related Death (95% Confidence Interval)	Excess Deaths Expressed per 10,000 Patients+ (95% Confidence Interval)
All Patients§ salmeterol: n = 13,176 placebo: n = 13,179	13 (0.10%)	3 (0.02%)	4.37 (1.25, 15.34)	8 (3, 13)
Caucasian Patients Salmeterol: n = 9,281 Placebo: n = 9,361	6 (0.07%)	1 (0.01%)	5.82 (0.70, 48.37)	6 (1, 10)
African American Patients Salmeterol: n = 2,366 Placebo: n = 2,319	7 (0.31%)	1 (0.04%)	7.26 (0.89, 58.94)	27 (8, 46)

[*] *28-week estimate, adjusted according to actual lengths of exposure to study treatment to account for early withdrawal of patients from the study.*

[+] *Estimate of the number of additional asthma-related deaths in patients treated with salmeterol in SMART, assuming 10,000 patients received salmeterol for a 28-week treatment period. Estimate calculated as the difference between the salmeterol and placebo groups in the rates of asthma-related death multiplied by 10,000.*

[§] *The Total Population includes Caucasian, African American, Hispanic, Asian, and "Other" and "not reported". No asthma-related deaths occurred in the Hispanic*

(salmeterol n = 996, placebo n = 999), Asian (salmeterol n = 173, placebo n = 149), or "Other" (salmeterol n = 230, placebo n = 224) subpopulations. One asthma-related death occurred in the placebo group in the subpopulation whose ethnic origin was "not reported" (salmeterol n = 130, placebo n = 127).

The SNS was a 16-week, double-blind study that compared the addition of salmeterol or albuterol to standard asthma therapy in 25,180 asthma patients who were 12 years of age and older. In the study, there was an increase in the number of respiratory and asthma-related deaths in the salmeterol group (0.07% [12 out of 16,787 patients]) compared to the albuterol group (0.02% [2 out of 8,393 patients] relative risk of 3.0, p=0.105).

In preparation for the December 2008 Advisory Committee, FDA conducted a meta-analysis of 110 studies evaluating the use of LABAs in 60,954 patients with asthma. The meta-analysis used a composite endpoint to measure severe exacerbation of asthma symptoms (asthma-related death, intubation, and hospitalization). The results of the meta-analysis suggested an increased risk for severe exacerbation of asthma symptoms in patients using LABAs compared to those not using LABAs. The largest risk difference per 1000 treated patients was seen in children 4-11 years of age, see table 2 below. The results of the meta-analysis were primarily driven by asthma-related hospitalizations. Other meta-analyses evaluating the safety of LABAs in the treatment of asthma have not shown a significant increase in the risk for severe asthma exacerbations.

Table 2. Meta-Analysis Results: Number of Patients Experiencing an Event*

Patient Population	LABA Patients experiencing an event	Non-LABA Patients experiencing an event	Risk Difference Estimate per 1000 treated patients	95% Confidence Interval
All Patients n = 30,148 LABA patients n = 30,806 non-LABA patients	381	304	2.80	1.11 – 4.49
Patients ages 12 to 17 years n = 3,103 LABA patients n = 3,289 non-LABA patients	48	30	5.57	0.21 – 10.92

Patients ages 4 to 11 years n = 1,626 LABA patients n = 1,789 non-LABA patients	61	39	14.83	3.24 – 26.43

** Event defined as the composite endpoint (asthma-related death, intubation, and hospitalization)*

At this time, there are insufficient data to conclude whether using LABAs with an inhaled corticosteroid reduces or eliminates the risk of asthma-related death and hospitalizations. FDA is requiring the manufacturers of LABAs to conduct studies evaluating the safety of LABAs when used in conjunction with an inhaled corticosteroid.

Based on the available information, FDA concludes there is an increased risk for severe exacerbation of asthma symptoms, leading to hospitalizations in pediatric and adult patients as well as death in some patients using LABAs for the treatment of asthma. The agency is requiring the REMS and class-labeling changes to improve the safe use of these products.

See February 2010 LABA Drug Safety Communication for more information.

Link:
http://www.fda.gov/Drugs/DrugSafety/PostmarketDrugSafetyInformationforPatientsandProviders/ucm200776.htm

- New prescribing guidelines

Long-Acting Beta-Agonists (LABAs), a class of medications used for the treatment of asthma, now have new recommendations in their drug label intended to promote their safe use in the treatment of asthma.

In February 2010, the agency announced it was requiring manufacturers to revise their drug labels because of an increased risk of severe exacerbation of asthma symptoms, leading to hospitalizations, in pediatric and adult patients, as well as death in some patients using LABAs for the treatment of asthma (see February 2010 LABA Drug Safety Communication).

In June 2010, the agency issued updated recommendations on the appropriate use of LABAs. See June 2010 LABA Drug Safety Communication for more information.

Link:
http://www.fda.gov/Drugs/DrugSafety/PostmarketDrugSafetyInformationforPatientsandProviders/ucm213836.htm

The new recommendations in the updated labels state:

- Use of a LABA alone without use of a long-term asthma control medication, such as an inhaled corticosteroid, is contraindicated (absolutely advised against) in the treatment of asthma.
- LABAs should not be used in patients whose asthma is adequately controlled on low or medium dose inhaled corticosteroids.
- LABAs should only be used as additional therapy for patients with asthma who are currently taking but are not adequately controlled on a long-term asthma control medication, such as an inhaled corticosteroid.
- Once asthma control is achieved and maintained, patients should be assessed at regular intervals and step down therapy should begin (e.g., discontinue LABA), if possible without loss of asthma control, and the patient should continue to be treated with a long-term asthma control medication, such as an inhaled corticosteroid.

FDA has stated its belief that when LABAs are used according to the recommendations outlined above and in the approved drug labels, the benefits of LABAs in improving asthma symptoms outweigh their risks of increasing severe asthma exacerbations and deaths from asthma.

- Currently available LABAs and approved uses

FDA Approved Long-Acting Beta Agonists

Brand Name	LABA active ingredient	Corticosteroid active ingredient	FDA Approved Uses
DULERA Inhalation Aerosol	Formoterol	Mometasone	Asthma
Serevent Diskus	Salmeterol	None	Asthma, COPD, exercise-induced bronchospasm
Foradil Aerolizer	Formoterol	None	Asthma, COPD, exercise-induced bronchospasm
Foradil Certihaler*	Formoterol	None	Asthma
Advair Diskus	Salmeterol	Fluticasone	Asthma, COPD
Advair HFA	Salmeterol	Fluticasone	Asthma

Symbicort	Formoterol	Budesonide	Asthma, COPD
Brovana	Arformoterol	None	COPD
Perforomist	Formoterol	None	COPD

* not currently marketed in the U.S.

See June 2010 LABA Drug Safety Communication for more information.

Link:
http://www.fda.gov/Drugs/DrugSafety/PostmarketDrugSafetyInformationforPatientsandProviders/ucm213836.htm

- Prescribing information for DULERA

LINK - http://www.spfiles.com/pidulera.pdf (will be live once product is approved)

- Patient Counseling Information

Patient Counseling Information

See USPI and Medication Guide

Asthma-Related Death
See Medication Guide
Patients should be informed that formoterol, one of the active ingredients in DULERA, increases the risk of asthma-related death. In pediatric and adolescent patients, formoterol may increase the risk of asthma-related hospitalization. They should also be informed that data are not adequate to determine whether the concurrent use of inhaled corticosteroids, the other component of DULERA, or other long-term asthma-control therapy mitigates or eliminates this risk. See Warnings and Precautions Section 5.1 of the full Prescribing Information.

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 Section 5.2 of the full Prescribing Information.

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 Section 5.3 of the full Prescribing Information.

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 Section 5.4 of the full Prescribing Information.

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 Section 5.5 of the full Prescribing Information.

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 Section 5.7 of the full Prescribing Information.

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 Section 5.12 of the full Prescribing Information.

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 Section 5.13 of the full Prescribing Information.

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 Section 5.14 of the full Prescribing Information.

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 and death. See Warnings and Precautions Section 5.11 of the full Prescribing Information.

- Medication Guide for DULERA

LINK - http://www.spfiles.com/mgdulera.pdf (will be live at product approval)

- Questions and Answers

Questions about LABA Safety and Risk Evaluation and Mitigation Strategy (REMS) for LABAs

Q1. Why is FDA requiring LABA manufacturers to have a risk management program for these medicines?

Q2. What is the goal of the new risk management program for LABAs?

Q3. What are the key points people should know about the safe use of LABAs in patients with asthma?

Q4. What are the names of LABA-containing medicines used to treat asthma?

Q5. Why should LABAs only be used with a long-term asthma control medication, are they safer when used this way?

Q6. What information did FDA review to help the Agency decide to require a risk management program?

Questions about DULERA Inhalation Aerosol

Q1. Why does DULERA have a boxed warning?

Q2. What should I tell patients about the risk of asthma-related death?

Q3. Can DULERA be used for acute asthma symptoms?

Q4. Can additional LABAs be used with DULERA?

Q5. What are the risks of corticosteroid therapy?

Q6. What are the risks of Beta-Agonist Therapy

Questions about LABA safety

Q1. Why is FDA requiring LABA manufacturers to have a risk management program for these medicines?

A. Despite the benefits of long-acting beta$_2$-agonists (LABAs) in helping people with asthma, FDA's analyses indicate there is an increase in the risk of severe exacerbation of asthma symptoms leading to hospitalizations in pediatric and adult patients as well as death in some patients with asthma that use a LABA compared to patients with asthma that do not use a LABA. Because of this risk, FDA wants to make sure LABAs are used appropriately in patients with asthma. In order to ensure the safe use of these medicines, FDA is requiring the manufacturers of LABAs to develop this risk management program for healthcare professionals and patients.

Q2. What is the goal of the new risk management program for LABAs?

A. The risk management program for LABAs requires the manufacturers to better inform healthcare professionals about the risk of LABAs for patients with asthma and ways to decrease that risk while maintaining the benefits of the drug. In addition manufacturers of LABAs will update the prescribing information they provide to healthcare professionals to include the latest recommendations for safe use of these important medicines.

Q3. What are the key points people should know about the safe use of LABAs in patients with asthma?

A. The key points are:

- Use of a LABA alone without use of a long-term asthma control medication, such as an inhaled corticosteroid, is contraindicated (absolutely advised against) in the treatment of asthma.
- LABAs should not be used in patients whose asthma is adequately controlled on low or medium dose inhaled corticosteroids.
- LABAs should only be used as additional therapy for patients with asthma who are currently taking but are not adequately controlled on a long-term asthma control medication, such as an inhaled corticosteroid.
- Once asthma control is achieved and maintained, patients should be assessed at regular intervals and step down therapy should begin (e.g., discontinue LABA), if possible without loss of asthma control, and the patient should continue to be treated with a long-term asthma control medication, such as an inhaled corticosteroid.

Q4. What are the names of LABA-containing medicines used to treat asthma?

A. Below are the names of the LABA-containing medicines approved by FDA to treat asthma:

Brand Name(s)	Generic Name(s)	Description
DULERA Inhalation Aerosol	formoterol and mometasone	formoterol is a LABA and mometasone is a corticosteroid long-term asthma control medication
Advair Diskus, Advair HFA	salmeterol and fluticasone	salmeterol is a LABA and fluticasone is a corticosteroid long-term asthma control medication
Symbicort Inhalation Aerosol	formoterol and budesonide	formoterol is a LABA and budesonide is a corticosteroid long-term asthma control medication
Serevent Diskus	salmeterol	single ingredient LABA with no corticosteroid long-term asthma control medication
Foradil Aerolizer	formoterol	single ingredient LABA with no corticosteroid long-term asthma control medication

Q5. Why should LABAs only be used with a long-term asthma control medication, are they safer when used this way?

A. At this time, there is no conclusive evidence that the combination of a long-term asthma control medication with a LABA decreases or eliminates the risk of a LABA. More study and analysis is required in this area. FDA is requiring the manufacturers of LABAs to conduct studies evaluating the safety of LABAs when used with an inhaled corticosteroid to better understand this issue.

Because of the risks of LABAs, FDA recommends that a LABA should not be used for a patient whose asthma can be controlled with long-term asthma control medication, such as an inhaled corticosteroid. If a LABA needs to be added to that medicine, it should only be used until the patient's healthcare professional determines their asthma is under control, and then the LABA should be stopped if possible. This means it is always necessary for a patient to use a LABA in combination with a long-term asthma control medication.

Q6. What information did FDA review to help the Agency decide to require a risk management program?

A. FDA used a variety of studies and research in patients with asthma using a LABA. Two specific studies that provided valuable information were 1) the Salmeterol Multi-center Asthma Research Trial (SMART) and 2), the Serevent Nationwide Surveillance

study (SNS). Salmeterol is the LABA in Serevent. Each of these studies showed a higher risk of death for patients with asthma that used a LABA (salmeterol) compared to patients with asthma that did not use a LABA. In addition, FDA used a research method called a meta-analysis to further understand the risks associated with the use of LABAs in patients with asthma. A meta-analysis uses data from multiple studies on a particular topic to enable scientists to combine information from those studies to make scientific conclusions or recommendations in that area. For more information on these specific studies, please see February 2010 LABA Drug Safety Communication for more information.

Questions about DULERA

Q1. Why does DULERA have a boxed warning?

A. Due to an increased risk of asthma-related death, FDA has mandated that all Long-Acting Beta Agonists (LABAs) and LABA-containing products, like DULERA, carry a boxed warning. The boxed warning for DULERA reads as follows:

WARNING: ASTHMA RELATED DEATH
See full prescribing information for complete boxed warning
Long-acting beta$_2$-adrenergic agonists (LABA), such as formoterol, one of the active ingredients in DULERA, increase the risk of asthma-related death. Data from a large placebo-controlled U.S. study that compared the safety of another LABA (salmeterol) or placebo added to usual asthma therapy showed an increase in asthma-related deaths in patients receiving salmeterol. This finding with salmeterol is considered a class effect of the LABA, including formoterol. Currently available data are inadequate to determine whether concurrent use of inhaled corticosteroids or other long-term asthma control drugs mitigates the increased risk of asthma-related death from LABA. Available data from controlled clinical trials suggest that LABA increase the risk of asthma-related hospitalization in pediatric and adolescent patients.

When treating patients with asthma, prescribe DULERA only for patients with asthma not adequately controlled on a long-term asthma control medication, such as an inhaled corticosteroid or whose disease severity clearly warrants initiation of treatment with both an inhaled corticosteroid and LABA. Once asthma control is achieved and maintained, assess the patient at regular intervals and step down therapy (e.g., discontinue DULERA) if possible without loss of asthma control, and maintain the patient on a long-term asthma control medication, such as an inhaled corticosteroid. Do not use DULERA for patients whose asthma is adequately controlled on low or medium dose inhaled corticosteroids.

See the full Prescribing Information for a more complete description of the risks associated with the use of DULERA in the treatment of asthma.

Q2. What should I tell patients about the risk of asthma-related death?

A. Patients should be informed that formoterol, one of the active ingredients in DULERA, increases the risk of asthma-related death. In pediatric and adolescent patients, formoterol may increase the risk of asthma-related hospitalization. They should also be informed that data are not adequate to determine whether the concurrent use of inhaled

corticosteroids, the other component of DULERA, or other long-term asthma-control therapy mitigates this risk. See Warnings and Precautions Section 5.1 of the full Prescribing Information.

Q3. Can DULERA be used for acute asthma symptoms?
A. No. 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 Section 5.2 of the full Prescribing Information.

Q4. Can additional LABAs be used with DULERA?
A. No. When patients are prescribed DULERA, other long-acting beta$_2$-agonists should not be used. See Warnings and Precautions Section 5.3 of the full Prescribing Information.

Q5. What are the risks of Corticosteroid Therapy?

A. 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 Section 5.4 of the full Prescribing Information.

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 Section 5.5 of the full Prescribing Information.

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 Section 5.7 of the full Prescribing Information.

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 Section 5.12 of the full Prescribing Information.

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 Section 5.13 of the full Prescribing Information.

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 Section 5.14 of the full Prescribing Information.

Q6. What are the risks of Beta-Agonist Therapy?

A. 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 Section 5.11 of the full Prescribing Information.

For more information:
http://www.fda.gov/Drugs/DrugSafety/PostmarketDrugSafetyInformationforPatientsandProviders/ucm200776.htm

- DHCP letter (for a period of 1 year)

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

LADAN G JAFARI
08/18/2011

SALLY M SEYMOUR
08/18/2011