

HIGHLIGHTS OF PRESCRIBING INFORMATION

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

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

RECENT MAJOR CHANGES

Indications and Usage (1.1) 08/2019
Dosage and Administration (2.1, 2.2) 08/2019

INDICATIONS AND USAGE

DULERA is a combination product containing a corticosteroid and a long-acting beta₂-adrenergic agonist (LABA) indicated for:

- Treatment of asthma in patients 5 years of age and older. (1.1)
- Important Limitation of Use:
- Not indicated for the relief of acute bronchospasm. (1.1)

DOSAGE AND ADMINISTRATION

For oral inhalation only. (2.1)
Treatment of asthma in patients ≥12 years: 2 inhalations twice daily of DULERA 100 mcg/5 mcg or 200 mcg/5 mcg. Starting dosage is based on disease severity. (2.2)
Treatment of asthma in patients aged 5 to less than 12 years: 2 inhalations twice daily of DULERA 50 mcg/5 mcg. (2.2)

DOSAGE FORMS AND STRENGTHS

Inhalation aerosol containing a combination of mometasone furoate (50, 100, or 200 mcg) and formoterol fumarate dihydrate (5 mcg) per actuation. (3)

CONTRAINDICATIONS

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

WARNINGS AND PRECAUTIONS

- LABA monotherapy increases the risk of serious asthma-related events. (5.1)
- Deterioration of disease and acute episodes: Do not initiate in acutely deteriorating asthma or to treat acute symptoms. (5.2)
- Use with additional long-acting beta₂-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. After dosing, advise patients to rinse their mouth with water and spit out contents without swallowing. (5.4)
- Immunosuppression: Potential worsening of existing tuberculosis, fungal, bacterial, viral, or parasitic infection; or ocular herpes simplex infections. More serious or even fatal course of chickenpox or measles can occur in susceptible patients. Use with caution in patients with these infections because of the potential for worsening of these infections. (5.5)
- Transferring patients from systemic corticosteroids: Risk of impaired adrenal function when transferring from oral steroids. Taper patients slowly from systemic corticosteroids if transferring to DULERA. (5.6)

- Hypercorticism and adrenal suppression: May occur with very high dosages or at the regular dosage in susceptible individuals. If such changes occur, discontinue DULERA slowly. (5.7)
- Strong cytochrome P450 3A4 inhibitors (e.g., ritonavir): Risk of increased systemic corticosteroid effects. Exercise caution when used with DULERA. (5.8)
- Paradoxical bronchospasm: Discontinue DULERA and institute alternative therapy if paradoxical bronchospasm occurs. (5.9)
- Patients with cardiovascular disorders: Use with caution because of beta-adrenergic stimulation. (5.11)
- Decreases in bone mineral density: Monitor patients with major risk factors for decreased bone mineral content. (5.12)
- Effects on growth: Monitor growth of pediatric patients. (5.13)
- Glaucoma and cataracts: Consider referral to an ophthalmologist in patients who develop ocular symptoms or use DULERA long term. (5.14)
- Coexisting conditions: Use with caution in patients with aneurysm, pheochromocytoma, convulsive disorders, thyrotoxicosis, diabetes mellitus, and ketoacidosis. (5.15)
- Hypokalemia and hyperglycemia: Be alert to hypokalemia and hyperglycemia. (5.16)

ADVERSE REACTIONS

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

- Nasopharyngitis, sinusitis and headache. (6.1)

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

DRUG INTERACTIONS

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

USE IN SPECIFIC POPULATIONS

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

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

Revised: 08/2019

FULL PRESCRIBING INFORMATION: CONTENTS*

1 INDICATIONS AND USAGE

1.1 Treatment of Asthma

2 DOSAGE AND ADMINISTRATION

2.1 Administration Information

2.2 Recommended Dosage

3 DOSAGE FORMS AND STRENGTHS

4 CONTRAINDICATIONS

4.1 Status Asthmaticus

4.2 Hypersensitivity

5 WARNINGS AND PRECAUTIONS

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

5.2 Deterioration of Disease and Acute Episodes

5.3 Excessive Use of DULERA and Use with Other Long-Acting Beta₂-Agonists

5.4 Local Effects

5.5 Immunosuppression

5.6 Transferring Patients from Systemic Corticosteroid Therapy

5.7 Hypercorticism and Adrenal Suppression

5.8 Drug Interactions with Strong Cytochrome P450 3A4 Inhibitors

5.9 Paradoxical Bronchospasm and Upper Airway Symptoms

5.10 Immediate Hypersensitivity Reactions

5.11 Cardiovascular and Central Nervous System Effects

5.12 Reduction in Bone Mineral Density

5.13 Effect on Growth

5.14 Glaucoma and Cataracts

5.15 Coexisting Conditions

5.16 Hypokalemia and Hyperglycemia

6 ADVERSE REACTIONS

6.1 Clinical Trials Experience

6.2 Postmarketing Experience

7 DRUG INTERACTIONS

7.1 Inhibitors of Cytochrome P450 3A4

7.2 Adrenergic Agents

7.3 Xanthine Derivatives

7.4 Diuretics

7.5	Monoamine Oxidase Inhibitors, Tricyclic Antidepressants, and Drugs Known to Prolong the QTc Interval
7.6	Beta-Adrenergic Receptor Antagonists
7.7	Halogenated Hydrocarbons
8	USE IN SPECIFIC POPULATIONS
8.1	Pregnancy
8.2	Lactation
8.4	Pediatric Use
8.5	Geriatric Use
8.6	Hepatic Impairment
10	OVERDOSAGE
10.1	Signs and Symptoms
10.2	Treatment
11	DESCRIPTION
12	CLINICAL PHARMACOLOGY

12.1	Mechanism of Action
12.2	Pharmacodynamics
12.3	Pharmacokinetics
13	NONCLINICAL TOXICOLOGY
13.1	Carcinogenesis, Mutagenesis, Impairment of Fertility
13.2	Animal Toxicology and/or Pharmacology
14	CLINICAL STUDIES
14.1	Asthma
16	HOW SUPPLIED/STORAGE AND HANDLING
16.1	How Supplied
16.2	Storage and Handling
17	PATIENT COUNSELING INFORMATION

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

FULL PRESCRIBING INFORMATION

1 INDICATIONS AND USAGE

1.1 Treatment of Asthma

DULERA is indicated for the twice-daily treatment of asthma in patients 5 years of age and older. DULERA should be used for patients not adequately controlled on a long-term asthma-control medication such as an inhaled corticosteroid (ICS) or whose disease warrants initiation of treatment with both an ICS and long-acting beta₂-adrenergic agonist (LABA).

Important Limitation of Use:

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

2 DOSAGE AND ADMINISTRATION

2.1 Administration Information

Administer DULERA as two inhalations twice daily every day (morning and evening) by the orally inhaled route (see Patient Instructions for Use in the Patient Information leaflet). 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 beta₂-agonist should be taken for immediate relief. Shake well prior to each inhalation. After each dose, advise patients to rinse their mouth with water and, without swallowing, spit out the contents to help reduce the risk of oropharyngeal candidiasis.

Remove the cap from the mouthpiece of the actuator before using DULERA.

Prime DULERA 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.

Only use the DULERA canister with the DULERA actuator. Do not use the DULERA actuator with any other inhalation drug product. Do not use actuators from other products with the DULERA canister.

2.2 Recommended Dosage

Administer DULERA as two inhalations twice daily every day (morning and evening) by the orally inhaled route. Shake well prior to each inhalation. Individual patients may experience a variable time to onset and degree of symptom relief. If symptoms arise between doses, use an inhaled short-acting beta₂-agonist for immediate relief. Improvement in lung function following administration of DULERA can occur within 5 minutes of treatment, although the maximum benefit may not be achieved for 1 week or longer after beginning treatment.

Adult and Adolescent Patients Aged 12 Years and Older

For patients 12 years and older, the dosage is either 2 inhalations twice daily of DULERA 100 mcg/5 mcg or DULERA 200 mcg/5 mcg. When choosing the starting dosage strength of DULERA, consider the patients' disease severity, based on their previous asthma therapy, including the inhaled corticosteroid dosage, as well as the patients' current control of asthma symptoms and risk of future exacerbation. For patients who do not respond adequately after 2 weeks of therapy with two inhalations of DULERA 100 mcg/5 mcg twice daily (morning and evening), increasing the dosage to two inhalations of DULERA 200 mcg/5 mcg twice daily (morning and evening) may provide additional asthma control. The maximum recommended dosage is two inhalations of DULERA 200 mcg/5 mcg twice daily (maximum daily dosage 800 mcg/20 mcg).

After asthma stability has been achieved, it may be desirable to titrate to the lowest effective dosage to reduce the possibility of side effects.

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

Pediatric Patients Aged 5 to Less Than 12 Years

For patients aged 5 to less than 12 years, the dosage is 2 inhalations of DULERA 50 mcg/5 mcg twice daily. The maximum daily dosage is 200 mcg/20 mcg.

3 DOSAGE FORMS AND STRENGTHS

DULERA is a pressurized metered dose inhaler (MDI) that is available in 2 strengths (100 mcg/5 mcg or 200 mcg/5 mcg) for adult and adolescent patients aged 12 and older and 1 strength (50 mcg/5 mcg) for pediatric patients aged 5 to less than 12 years.

DULERA 50 mcg/5 mcg delivers 50 mcg of mometasone furoate and 5 mcg of formoterol fumarate dihydrate per actuation.

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.

Each strength of DULERA is supplied with a blue colored actuator and green dust cap [see *How Supplied/Storage and Handling (16.1)*].

4 CONTRAINDICATIONS

4.1 Status Asthmaticus

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

4.2 Hypersensitivity

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

5 WARNINGS AND PRECAUTIONS

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

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

Serious Asthma-Related Events with ICS/LABA

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

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

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

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

ICS = Inhaled Corticosteroid, LABA = Long-acting Beta₂-adrenergic Agonist.

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

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

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

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

Salmeterol Multicenter Asthma Research Trial (SMART)

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

Formoterol Monotherapy Studies

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

5.2 Deterioration of Disease and Acute Episodes

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

Increasing use of inhaled, short-acting beta₂-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 beta₂-agonist, not DULERA, should be used to relieve acute symptoms such as shortness of breath.

When beginning treatment with DULERA, patients who have been taking oral or inhaled, short-acting beta₂-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 Beta₂-Agonists

As with other inhaled drugs containing beta₂-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 beta₂-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 beta₂-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, treat 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. To reduce the risk of oropharyngeal candidiasis, after dosing with DULERA, advise patients to rinse their mouth with water and spit out the contents without swallowing.

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, cobicistat-containing products, atazanavir, clarithromycin, indinavir, itraconazole, nefazodone, nelfinavir, saquinavir, telithromycin) because adverse effects related to increased systemic exposure to mometasone furoate may occur [*see Drug Interactions (7.1) and Clinical Pharmacology (12.3)*].

5.9 Paradoxical Bronchospasm and Upper Airway Symptoms

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

5.10 Immediate Hypersensitivity Reactions

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

5.11 Cardiovascular and Central Nervous System Effects

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

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

5.12 Reduction in Bone Mineral Density

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

In a 2-year double-blind study in 103 male and female asthma patients 18 to 50 years of age previously maintained on bronchodilator therapy (Baseline FEV₁ 85%-88% predicted), treatment with mometasone furoate dry powder inhaler (DPI) 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 FEV₁ 82%-83% predicted), treatment with mometasone furoate 400 mcg twice daily demonstrated no statistically significant changes in lumbar spine BMD at the end of the treatment period compared to placebo. The mean change from Baseline to Endpoint in the lumbar spine BMD was -0.018 (-1.57%) for the mometasone furoate group compared to -0.006 (-0.43%) for the placebo group.

5.13 Effect on Growth

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

5.14 Glaucoma and Cataracts

Glaucoma, increased intraocular pressure, and cataracts have been reported following the use of long-term administration of inhaled corticosteroids, including mometasone furoate, a component of DULERA. Consider referral to an ophthalmologist in patients who develop ocular symptoms or use DULERA long term [*see Adverse Reactions (6)*].

5.15 Coexisting Conditions

DULERA, like other medications containing sympathomimetic amines, should be used with caution in patients with aneurysm, pheochromocytoma, convulsive disorders, or thyrotoxicosis; and in patients who are unusually responsive to sympathomimetic amines. Doses of the related beta₂-agonist albuterol, when administered intravenously, have been reported to aggravate preexisting diabetes mellitus and ketoacidosis.

5.16 Hypokalemia and Hyperglycemia

Beta₂-agonist medications may produce significant hypokalemia in some patients, possibly through intracellular shunting, which has the potential to produce adverse cardiovascular effects. The decrease in serum potassium is usually transient, not requiring supplementation. Clinically significant changes in blood glucose and/or serum potassium were seen infrequently during clinical studies with DULERA at recommended doses.

6 ADVERSE REACTIONS

LABA use may result in the following:

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

Systemic and local corticosteroid use may result in the following:

- *Candida albicans* infection [see Warnings and Precautions (5.4)]
- Immunosuppression [see Warnings and Precautions (5.5)]
- Hypercorticism and adrenal suppression [see Warnings and Precautions (5.7)]
- Growth effects in pediatrics [see Warnings and Precautions (5.13)]
- Glaucoma and cataracts [see Warnings and Precautions (5.14)]

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

6.1 Clinical Trials Experience

Adult and Adolescent Patients Aged 12 Years and Older

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% Caucasian, 27% non-Caucasian. 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% Caucasian, 53% non-Caucasian 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 events associated with DULERA in Table 2 below is based upon pooled data from 2 clinical trials 12 to 26 weeks in duration in patients 12 years and older treated with two inhalations twice daily of DULERA (100 mcg/5 mcg or 200 mcg/5 mcg), mometasone furoate MDI (100 mcg or 200 mcg), formoterol MDI (5mcg) or placebo.

Table 2: Treatment-Emergent Adverse Events in DULERA Groups Occurring at an Incidence of $\geq 3\%$ 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.

Pediatric Patients Aged 5 to Less Than 12 Years

The safety data for pediatric patients aged 5 to less than 12 years are primarily based on a clinical trial of 24 weeks treatment duration with a 2-week safety follow-up. A total of 181 patients with asthma (92 male and 89 female) who were receiving any ICS/LABA therapy at trial entry were randomized to either DULERA 50 mcg/5 mcg (n=91) or mometasone furoate MDI 50 mcg (n=90), administered as 2 inhalations twice daily. The mean age was 9.1 years, 22.1% were between the ages of 5 to 7, and more than half (53.6%) of the population was non-Caucasian, with 38.7% of the total population reporting at least two races (i.e., multiracial). Common treatment-emergent adverse events that occurred in patients treated with DULERA with an incidence of $\geq 3\%$ and more frequently than patients treated with mometasone furoate alone included influenza, upper respiratory tract infection, and headache.

Overall, the safety profile for pediatric patients is similar to that observed in patients aged 12 years and older.

6.2 Postmarketing Experience

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

Cardiac disorders: angina pectoris, cardiac arrhythmias, e.g., atrial fibrillation, ventricular extrasystoles, tachyarrhythmia

Eye disorders: vision blurred [*see Warnings and Precautions (5.14)*]

Immune system disorders: immediate and delayed hypersensitivity reactions including anaphylactic reaction, angioedema, severe hypotension, rash, pruritus

Investigations: electrocardiogram QT prolonged, blood pressure increased (including hypertension)

Metabolism and nutrition disorders: hypokalemia, hyperglycemia

Respiratory, thoracic and mediastinal disorders: asthma aggravation, which may include cough, dyspnea, wheezing and bronchospasm

7 DRUG INTERACTIONS

In clinical trials, concurrent administration of DULERA and other drugs, such as short-acting beta₂-agonist and intranasal corticosteroids have not resulted in an increased frequency of adverse drug reactions. No formal drug interaction studies have been performed with DULERA. The drug interactions of the combination are expected to reflect those of the individual components.

7.1 Inhibitors of Cytochrome P450 3A4

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

7.2 Adrenergic Agents

If additional adrenergic drugs are to be administered by any route, they should be used with caution because the pharmacologically predictable sympathetic effects of formoterol, a component of DULERA, may be potentiated.

7.3 Xanthine Derivatives

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

7.4 Diuretics

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

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

DULERA should be administered with caution to patients being treated with monoamine oxidase inhibitors, tricyclic antidepressants, macrolides, or drugs known to prolong the QTc interval or within 2 weeks of discontinuation of such agents, because the action of

formoterol, a component of DULERA, on the cardiovascular system may be potentiated by these agents. Drugs that are known to prolong the QTc interval have an increased risk of ventricular arrhythmias.

7.6 Beta-Adrenergic Receptor Antagonists

Beta-adrenergic receptor antagonists (beta-blockers) and formoterol may inhibit the effect of each other when administered concurrently. Beta-blockers not only block the therapeutic effects of beta₂-agonists, such as formoterol, a component of DULERA, but may produce severe bronchospasm in patients with asthma. Therefore, patients with asthma should not normally be treated with beta-blockers. However, under certain circumstances, e.g., as prophylaxis after myocardial infarction, there may be no acceptable alternatives to the use of beta-blockers in patients with asthma. In this setting, cardioselective beta-blockers could be considered, although they should be administered with caution.

7.7 Halogenated Hydrocarbons

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

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Risk Summary

There are no randomized clinical studies of DULERA, mometasone furoate, or formoterol fumarate in pregnant women. There are clinical considerations with the use of DULERA in pregnant women [see *Clinical Considerations*]. Animal reproduction studies with DULERA are not available; however, studies are available with its individual components, mometasone furoate and formoterol fumarate. In animal reproduction studies, subcutaneous administration of mometasone furoate to pregnant mice, rats, or rabbits caused increased fetal malformations and decreased fetal survival and growth following administration of doses that produced exposures approximately 1/3 to 8 times the maximum recommended human dose (MRHD) on a mcg/m² or AUC basis [see *Data*]. However, experience with oral corticosteroids suggests that rodents are more prone to teratogenic effects from corticosteroid exposure than humans. In animal reproduction studies, oral administration of formoterol fumarate to pregnant rats and rabbits caused increased fetal malformations (rats and rabbits), decreased fetal weight (rats), and increased neonatal mortality (rats) following administration of doses that produced exposures approximately 1200 to 49,000 times the MRHD on a mg/m² or AUC basis [see *Data*]. These adverse effects generally occurred at large multiples of the MRHD when formoterol fumarate was administered by the oral route to achieve high systemic exposures. No effects were observed in a study with rats that received formoterol fumarate by the inhalation route at an exposure approximately 500 times the MRHD.

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

Clinical Considerations

Disease-associated maternal and/or embryo/fetal risk

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

Labor or delivery

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

Data

Animal Data

Mometasone Furoate

In an embryofetal development study with pregnant mice dosed throughout the period of organogenesis, mometasone furoate produced cleft palate at an exposure approximately one-third of the MRHD (on a mcg/m² basis with maternal subcutaneous doses of 60 mcg/kg and above) and decreased fetal survival at an exposure approximately equivalent to the MRHD (on a mcg/m² basis with a maternal subcutaneous dose of 180 mcg/kg). No toxicity was observed with a dose that produced an exposure approximately one-tenth of the MRHD (on a mcg/m² basis with maternal topical dermal doses of 20 mcg/kg and above).

In an embryofetal development study with pregnant rats dosed throughout the period of organogenesis, mometasone furoate produced fetal umbilical hernia at exposures approximately 6 times the MRHD (on a mcg/m² basis with maternal topical dermal doses of 600 mcg/kg and above) and delays in fetal ossification at exposures approximately 3 times the MRHD (on a mcg/m² basis with maternal topical dermal doses of 300 mcg/kg and above).

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

Embryofetal development studies were conducted with pregnant rabbits dosed with mometasone furoate by either the topical dermal route or oral route throughout the period of organogenesis. In the study using the topical dermal route, mometasone furoate caused multiple malformations in fetuses (e.g., flexed front paws, gallbladder agenesis, umbilical hernia, hydrocephaly) at an exposure approximately 3 times the MRHD (on a mcg/m² basis with maternal topical dermal doses of 150 mcg/kg and above). In the study using the oral route, mometasone furoate caused increased fetal resorptions and cleft palate and/or head malformations (hydrocephaly and domed head) at an exposure approximately 1/2 of the MRHD (on AUC basis with a maternal oral dose of 700 mcg/kg). At an exposure approximately 2 times the MRHD (on an AUC basis with a maternal oral dose of 2800 mcg/kg), most litters were aborted or resorbed. No effects were observed at an exposure approximately 1/10 of the MRHD (on an AUC basis with a maternal oral dose of 140 mcg/kg).

Formoterol Fumarate

In embryofetal development studies with pregnant rats and rabbits dosed throughout the period of organogenesis, formoterol fumarate did not cause malformations in either species. However, for pregnant rats dosed throughout organogenesis, formoterol fumarate caused delayed fetal ossification at an exposure approximately 80 times the MRHD (on a mcg/m² basis with maternal oral doses of 200 mcg/kg and higher) and decreased fetal weight at an exposure approximately 2400 times the MRHD (on a mcg/m² basis with maternal oral doses of 6000 mcg/kg and above). In a pre- and post-natal development study with rats dosed during the late stage of pregnancy, formoterol fumarate caused stillbirth and neonatal mortality at an exposure approximately 2400 times the MRHD (on a mcg/m² basis with maternal oral doses of 6000 mcg/kg and above). However, no effects were observed in this study at an exposure approximately 80 times the MRHD (on a mcg/m² basis with a maternal oral dose of 200 mcg/kg).

In embryofetal development studies, conducted by another testing laboratory, with pregnant rats and rabbits dosed throughout the period of organogenesis, formoterol fumarate was teratogenic in both species. Umbilical hernia, a malformation, was observed in rat fetuses at exposures approximately 1200 times the MRHD (on a mcg/m² basis with maternal oral doses of 3000 mcg/kg/day and above). Brachygnathia, a skeletal malformation, was observed in rat fetuses at an exposure approximately 6100 times the MRHD (on a mcg/m² basis with a maternal oral dose of 15,000 mcg/kg/day). In another study with rats, no teratogenic effects were observed with exposures up to approximately 500 times the MRHD (on a mcg/m² basis with a maternal inhalation dose of 1200 mcg/kg/day). Subcapsular cysts on the liver were observed in rabbit fetuses at an exposure approximately 49,000 times the MRHD (on a mcg/m² basis with a maternal oral dose of 60,000 mcg/kg/day). No teratogenic effects were observed with exposures up to approximately 3000 times the MRHD (on a mcg/m² basis with a maternal oral dose of 3500 mcg/kg).

8.2 Lactation

Risk Summary

There are no available data on the presence of DULERA, mometasone furoate, or formoterol fumarate in human milk, the effects on the breastfed child, or the effects on milk production. Other inhaled corticosteroids, similar to mometasone furoate, are present in human milk. Formoterol fumarate is present in rat milk; however, due to species specific differences in lactation physiology, animal lactation data may not reliably predict levels in human milk. The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for DULERA and any potential adverse effects on the breastfed infant from DULERA or from the underlying maternal condition.

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 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 effectiveness of DULERA 50 mcg/5 mcg, two inhalations twice daily, have been established in patients with asthma aged 5 to less than 12 years in clinical trials up to 24 weeks of treatment duration. Patients in this age group demonstrated efficacy and safety results similar to those observed in patients aged 12 years and older who were treated with DULERA [see *Adverse Reactions (6.1) and Clinical Studies (14.1)*].

The safety and effectiveness of DULERA have not been established in children younger than 5 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 (11 of whom 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 beta₂-agonists, special caution should be observed when using DULERA in geriatric patients who have concomitant cardiovascular disease that could be adversely affected by beta₂-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 adult subjects 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/m² basis). The median lethal oral doses in Chinese hamsters, rats, and mice provide even higher multiples of the MRHD.

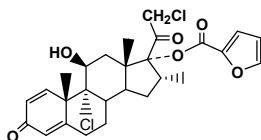
10.2 Treatment

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

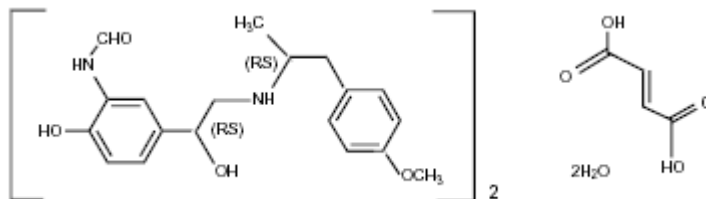
DULERA 50 mcg/5 mcg, DULERA 100 mcg/5 mcg, and DULERA 200 mcg/5 mcg are combinations of mometasone furoate and formoterol fumarate dihydrate for oral inhalation only.

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 β_2 -adrenergic bronchodilator having the chemical name of (\pm) -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.

DULERA 50 mcg/5 mcg, 100 mcg/5 mcg, and 200 mcg/5 mcg are each formulated as a hydrofluoroalkane (HFA-227; 1, 1, 1, 2, 3, 3, 3-heptafluoropropane) propelled pressurized metered dose inhaler containing sufficient amount of drug for 60 or 120 inhalations [see *How Supplied/Storage and Handling (16)*]. After priming, each actuation of the inhaler delivers 60, 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 50, 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 β_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 β_2 -adrenergic receptor agonist (β_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 β_2 -receptors than at β_1 -receptors. Although β_2 -receptors are the predominant adrenergic receptors in bronchial smooth muscle and β_1 -receptors are the predominant receptors in the heart, there are also β_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 β_2 -agonists may have cardiac effects.

The pharmacologic effects of β_2 -adrenoceptor agonist drugs, including formoterol, are at least in part attributable to stimulation of intracellular adenylyl 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

DULERA:

Adult and Adolescent Patients Aged 12 Years and Older

Cardiovascular Effects:

In a single-dose, double-blind placebo-controlled crossover trial in 25 adult 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 adult 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.

Pediatric Patients: Among 91 children with asthma aged 5 to less than 12 years treated with DULERA for up to 24 weeks, there were no notable changes from baseline in heart rate or blood pressure. There were no reports of hypokalemia or hypoglycemia.

HPA Axis Effects: Adults

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 patients 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 125/25 mcg, or fluticasone propionate/salmeterol xinafoate 250/25 mcg. 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 125/25 mcg (n=8), and fluticasone propionate/salmeterol xinafoate 250/25 mcg (n=11) treatment groups, respectively.

Other Mometasone Products:

Systemic effects of inhaled corticosteroids are related to systemic exposure. Pharmacokinetic data have demonstrated that, in adults, systemic exposure to mometasone furoate administered as DULERA is the same or lower than that of equivalent doses of inhaled mometasone furoate administered via DPI [see *Clinical Pharmacology (12.3)*]. Based upon the pharmacokinetic data, the systemic effects (e.g., HPA-axis suppression and growth retardation) of mometasone furoate delivered from DULERA in adult and pediatric patients would be expected to be no greater than what is reported for inhaled mometasone furoate when administered at comparable doses via DPI [see *Use in Specific Populations (8.4)*].

HPA Axis Effects: Adults

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.

HPA Axis Effect: Pediatrics

The potential effect of mometasone furoate via a DPI on the HPA axis was assessed in 50 children aged 6 to 11 years in a 29-day, randomized, double-blind, placebo-controlled, parallel-group clinical trial. In this study, the mean difference from placebo in plasma cortisol $AUC_{(0-12hr)}$ for DPI 110 mcg twice daily was 3.4 mcg•hr/dL (95% CI: -14.0, 20.7) and for 220 mcg twice daily was -16.0 mcg•hr/dL (95% CI: -33.9, 1.9). The mean difference from placebo in plasma cortisol $AUC_{(0-12hr)}$ for the 440 mcg twice daily group (eight times the currently recommended mometasone furoate dose via a DPI in children ages 4-11) was -17.9 mcg•hr/dL (95% CI: -35.8, 0.0). The mean differences in urinary-free cortisol changes from baseline compared to placebo were 3.1 mcg/day (95% CI: -3.3, 9.6), 3.3 mcg/day (95% CI: -3.0, 9.7), and -2.0 mcg/day (95% CI: -8.6, 4.6) for the groups treated with 110 mcg twice daily, 220 mcg twice daily, and 440 mcg twice daily, respectively.

12.3 Pharmacokinetics

Absorption

Mometasone furoate:

Adult 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 T_{max} 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%) C_{max} and $AUC_{(0-12 hr)}$ values for MF were 67.8 (49) pg/mL and 650 (51) pg•hr/mL, respectively while the corresponding estimates following 5 days of 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.

Adult Asthma Patients: Following oral inhalation of single and multiple doses of the DULERA, mometasone furoate was absorbed in asthma patients with median T_{max} values ranging from 1 to 2 hours. Following single-dose administration of DULERA 400 mcg/10 mcg, the arithmetic mean (CV%) C_{max} and $AUC_{(0-12 hr)}$ 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:

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

Adult Asthma Patients: When DULERA was administered to patients with asthma, formoterol was absorbed with median T_{max} values ranging from 0.58 to 1.97 hours. In a single-dose study with DULERA 400 mcg/10 mcg in patients with asthma, arithmetic mean (CV%) C_{max} and $AUC_{(0-12 hr)}$ 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%) C_{max} and $AUC_{(0-12 hr)}$ 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 adult subjects, no appreciable accumulation of mometasone furoate in the red blood cells was found. Following an intravenous 400 mcg dose of mometasone furoate, the plasma concentrations showed a biphasic decline, with a mean steady-state volume of distribution of 152 liters. The *in vitro* protein binding for mometasone furoate was reported to be 98% to 99% (in a concentration range of 5 to 500 ng/mL).

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 $t_{1/2}$ for mometasone furoate following inhalation with DULERA was 25 hours in adult healthy subjects and in adult 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 $t_{1/2}$ 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 $t_{1/2}$ of 9 to 11 hour.

Following single inhaled doses ranging from 10 to 40 mcg to adult healthy subjects from the MF/F 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 adult patients with mild (n=4), moderate (n=4), and severe (n=4) hepatic impairment resulted in only 1 or 2 patients in each group having detectable peak plasma concentrations of mometasone furoate (ranging from 50-105 pg/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 adult 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.

14 CLINICAL STUDIES

14.1 Asthma

Adult and Adolescent Patients Aged 12 Years of Age and Older

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**).

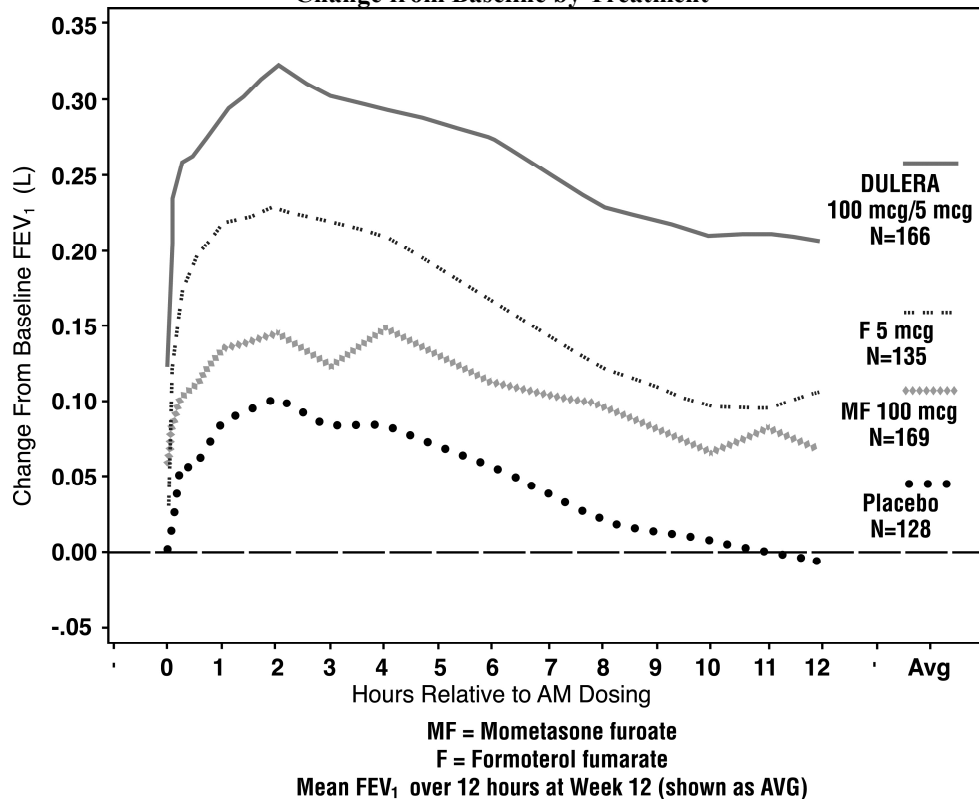
Trial 1: Clinical Trial with DULERA 100 mcg/5 mcg

This 26-week, placebo-controlled trial (NCT00383240) 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_(0-12 hr) was assessed as a co-primary efficacy endpoint to evaluate the contribution of the formoterol component to DULERA. Patients receiving DULERA 100 mcg/5 mcg had significantly higher increases from baseline at Week 12 in mean 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**



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 FEV ₁ [‡]	18 (9%)	19 (10%)	31 (15%)	41 (21%)
Decrease in PEF [§]	37 (19%)	41 (21%)	62 (31%)	61 (31%)
Emergency treatment	0	1 (<1%)	4 (2%)	1 (<1%)
Hospitalization	1 (<1%)	0	0	0
Treatment with excluded asthma medication [¶]	2 (1%)	4 (2%)	17 (8%)	8 (4%)

* Includes only the first event day for each patient. Patients could have experienced more than one event criterion.

[†] Two inhalations, twice daily.

[‡] Decrease in absolute 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.

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 (NCT00381485) 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 FEV ₁ [‡]	23 (10%)	17 (7%)	33 (14%)
Decrease in PEF on two consecutive days [§]	2 (1%)	4 (2%)	3 (1%)
Emergency treatment	2 (1%)	1 (<1%)	1 (<1%)
Hospitalization	0	1 (<1%)	0
Treatment with excluded asthma medication [¶]	5 (2%)	8 (3%)	12 (5%)

* Includes only the first event day for each patient. Patients could have experienced more than one event criterion.

[†] Two inhalations, twice daily.

[‡] Decrease in absolute 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.

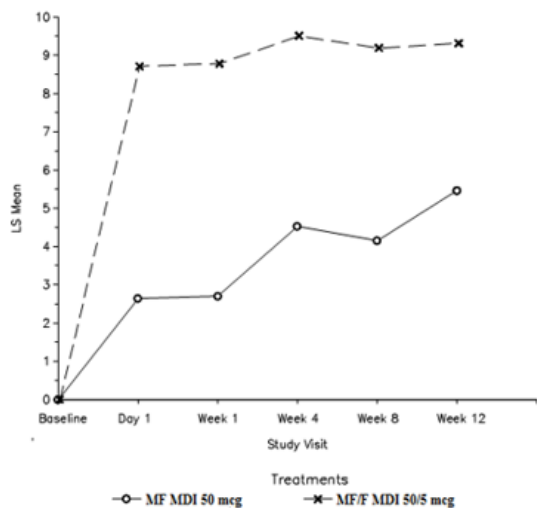
Other Studies in Adults

In addition to Trial 1 and Trial 2, the safety and efficacy of the individual components, mometasone furoate MDI 100 mcg and 200 mcg (each administered as 2 inhalations by MDI), in comparison to placebo were demonstrated in two other, 12-week, placebo-controlled trials that evaluated the mean change in FEV₁ from baseline as a primary endpoint. The safety and efficacy of formoterol MDI 5 mcg (administered as 2 inhalations twice daily) alone in comparison to placebo was replicated in another 26-week trial (NCT00383552) that also evaluated the same endpoint with a lower dose of mometasone furoate MDI in combination with formoterol.

Pediatric Patients Aged 5 to Less Than 12 Years

The efficacy of DULERA 50 mcg/5 mcg in children aged 5 to less than 12 years was demonstrated in a randomized, active-controlled, multicenter clinical trial (NCT02741271) in which DULERA 50 mcg/5 mcg (administered as two inhalations, twice daily; n=91) was compared with mometasone furoate MDI 50 mcg (administered as two inhalations, twice daily; n=90), in 181 asthma patients aged 5 to less than 12 years. These participants had been adequately controlled on an ICS/LABA for at least 4 weeks and had no symptoms of asthma worsening during a 2-week run-in on mometasone furoate MDI 50 mcg (administered as two inhalations twice daily). Primary endpoint results showed that patients receiving DULERA 50 mcg/5 mcg had a statistically significant change from baseline to Week 12 in 60-min AM post-dose % predicted FEV₁ compared to mometasone furoate MDI 50 mcg (5.21, 95% CI: 3.22, 7.20) [Figure 2]. Bronchodilatory improvement with DULERA 50 mcg/5 mcg relative to mometasone furoate MDI 50 mcg was significant from the first assessment at 5 minutes and was sustained through 4 hours post-dose. These improvements were evident as early as the first dose and were maintained through Week 12.

Figure 2: Change from Baseline AM Post-Dose in % Predicted FEV₁ Through Week 12



MF = mometasone furoate; MF/F = mometasone furoate/formoterol fumarate

Population consists of all subjects who received at least one dose of blinded treatment and completed at least one efficacy evaluation.

Treatment Effects were estimated using the Primary Analysis Method [i.e., a cLDA model with control-based multiple imputation, including terms for treatment, time, age strata (5-7 yrs., 8-11 yrs.), treatment by time interaction, and region (US, ex-US)].

Postmarketing Safety and Efficacy Trial with DULERA

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

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

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

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

* Actual treatment used for analysis.

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

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

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

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

16 HOW SUPPLIED/STORAGE AND HANDLING

16.1 How Supplied

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

Table 8

Package	NDC	Strength Identifier (Color Band)*
DULERA 50 mcg/5 mcg 120 inhalations	0085-2223-01	Blue
DULERA 100 mcg/5 mcg 120 inhalations	0085-7206-01	Yellow
DULERA 100 mcg/5 mcg 60 inhalations (institutional pack)	0085-7206-07	Yellow
DULERA 200 mcg/5 mcg 120 inhalations	0085-4610-01	Purple
DULERA 200 mcg/5 mcg 60 inhalations (institutional pack)	0085-4610-05	Purple

*Included on the outer carton, actuator, and canister labels

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

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

16.2 Storage and Handling

Only use the DULERA canister with the DULERA actuator. Do not use the DULERA actuator with any other inhalation drug product. Do not use actuators from other products with the DULERA canister.

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

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

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

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

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

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

17 PATIENT COUNSELING INFORMATION

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

Serious Asthma-Related Events

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

Not for Acute Symptoms

DULERA is not indicated to relieve acute asthma symptoms and extra doses should not be used for that purpose. Treat acute symptoms with an inhaled, short-acting, beta₂-agonist (the health care provider should prescribe the patient with such medication and instruct the patient in how it should be used).

Instruct patients 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 beta₂-agonist than usual

Advise patients not to increase the dose or frequency of DULERA. Do not exceed the daily dosage of DULERA of two inhalations twice daily. If they miss a dose, instruct patients to take their next dose at the same time they normally do. DULERA provides bronchodilation for up to 12 hours.

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

Do Not Use Additional Long-Acting Beta₂-Agonists

When patients are prescribed DULERA, other long-acting beta₂-agonists should not be used [see *Warnings and Precautions* (5.3)].

Risks Associated With Corticosteroid Therapy

Local Effects: Advise patients that localized infections with *Candida albicans* occurred in the mouth and pharynx in some patients. If oropharyngeal candidiasis develops, treat 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: Warn patients who are on immunosuppressant doses of corticosteroids to avoid exposure to chickenpox or measles and, if exposed, to consult their physician without delay. Inform patients 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: Advise patients that DULERA may cause systemic corticosteroid effects of hypercorticism and adrenal suppression. Additionally, instruct patients that deaths due to adrenal insufficiency have occurred during and after transfer

from systemic corticosteroids. Instruct patients to taper slowly from systemic corticosteroids if transferring to DULERA [see *Warnings and Precautions (5.7)*].

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

Reduced Growth Velocity: Inform patients 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); consider regular eye examinations [see *Warnings and Precautions (5.14)*].

Risks Associated With Beta-Agonist Therapy

Inform patients that treatment with beta₂-agonists may lead to adverse events which include palpitations, chest pain, rapid heart rate, tremor or nervousness [see *Warnings and Precautions (5.11)*].

Instructions for Use

Instruct patients regarding the following:

- Read the Patient Information before use and follow the Instructions for Use carefully.
- Remind patients to:
 - Remove the cap from the mouthpiece of the actuator before use.
 - After dosing, rinse their mouth with water without swallowing and spit out after breathing in the medicine. This will help reduce the risk of oropharyngeal candidiasis.
 - Not remove the canister from the actuator.
 - Not wash inhaler in water. The mouthpiece should be cleaned using a dry wipe after every 7 days of use.

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

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

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

The trademarks depicted herein are owned by their respective companies.

Copyright © 2010-2019 Merck Sharp & Dohme Corp., a subsidiary of **Merck & Co., Inc.**
All rights reserved.

uspi-mk0887a-ao-1908r031