

FORADIL[®] CERTIHALER[®]

(formoterol fumarate inhalation powder)

For Oral Inhalation Only

Rx only

Prescribing Information

WARNING: ASTHMA RELATED DEATH

Long-acting beta₂-adrenergic agonists (LABA), such as formoterol the active ingredient in FORADIL CERTIHALER, increase the risk of asthma-related death. Data from a large placebo-controlled US study that compared the safety of another LABA (salmeterol) or placebo added to usual asthma therapy showed an increase in asthma-related deaths in patients receiving salmeterol. This finding with salmeterol is considered a class effect of LABA, including formoterol (see WARNINGS). Currently available data are inadequate to determine whether concurrent use of inhaled corticosteroids or other long-term asthma control drugs mitigates the increased risk of asthma-related death from LABA.

Because of this risk, use of FORADIL CERTIHALER for the treatment of asthma without concomitant use of a long-term asthma control medication, such as an inhaled corticosteroid, is contraindicated. Use FORADIL CERTIHALER only as additional therapy for patients with asthma who are currently taking but are inadequately controlled on a long-term asthma control medication, such as an inhaled corticosteroid. Once asthma control is achieved and maintained, assess the patient at regular intervals and step down therapy (e.g. discontinue FORADIL CERTIHALER) if possible without loss of asthma control, and maintain the patient on a long-term asthma control medication, such as an inhaled corticosteroid. Do not use FORADIL CERTIHALER for patients whose asthma is adequately controlled on low or medium dose inhaled corticosteroids.

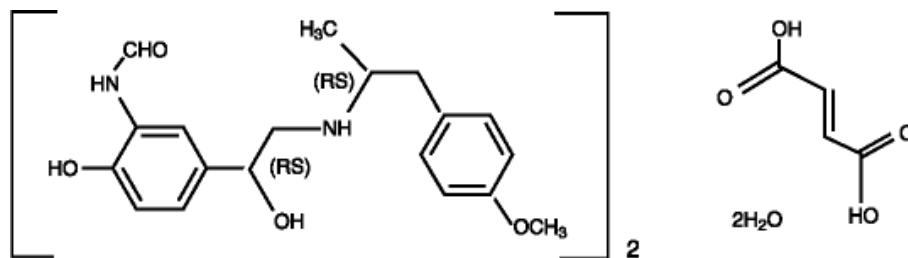
Pediatric and Adolescent Patients

Available data from controlled clinical trials suggest that LABA increase the risk of asthma-related hospitalization in pediatric and adolescent patients. For pediatric and adolescent patients with asthma who require addition of a LABA to an inhaled corticosteroid, a fixed-dose combination product containing both an inhaled corticosteroid and LABA should ordinarily be considered to ensure adherence with both drugs. In cases where use of a separate long-term asthma control medication (e.g. inhaled corticosteroid) and LABA is clinically indicated, appropriate steps must be taken to ensure adherence with both treatment components. If adherence cannot be assured, a fixed-dose combination product containing both an inhaled corticosteroid and LABA is recommended.

DESCRIPTION

FORADIL[®] CERTIHALER[®] is a breath-actuated multi-dose dry powder inhaler, which contains a powder formulation of formoterol fumarate intended for oral inhalation only. Each actuation of FORADIL CERTIHALER delivers approximately 8.5 mcg of formoterol fumarate from the mouthpiece (based on *in vitro* testing at 60 L/min for 2 sec), corresponding to a metered dose of 10 mcg of formoterol fumarate. The weight of the formulation metered is approximately 5.6 mg. Ten mcg of formoterol fumarate metered is equivalent to 8.2 mcg of formoterol base. The delivered inhalation powder also contains lactose monohydrate (which contains trace levels of milk proteins) and magnesium stearate.

The active component of FORADIL is formoterol fumarate, a racemate. Formoterol fumarate is a selective beta₂-adrenergic bronchodilator. Its chemical name is (±)-2-hydroxy-5-[(1RS)-1-hydroxy-2-[[[(1RS)-2-(4-methoxyphenyl)-1-methylethyl]-amino]ethyl]formanilide fumarate dihydrate; its structural formula is



Formoterol fumarate has a molecular weight of 840.9, and its empirical formula is (C₁₉H₂₄N₂O₄)₂•C₄H₄O₄•2H₂O. Formoterol fumarate is a white to yellowish crystalline 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.

The CERTIHALER Inhaler is a plastic device used for inhaling FORADIL and contains 60 doses. The amount of drug delivered to the lung will depend on patient factors, such as inspiratory flow rate and inspiratory time, which may vary for different patient populations. Under standardized *in vitro* testing at a fixed flow

rate of 60 L/min for 2 seconds, the FORADIL CERTIHALER delivered 8.5 mcg of formoterol fumarate from the mouthpiece. In 38 adult and 17 adolescent patients with asthma, mean peak inspiratory flow rates (PIF) through the CERTIHALER Inhaler were 63 (45-80) L/min and 70 (56-95) L/min, respectively. Similar results [mean PIF 63 (44-79) L/min] were obtained in 27 asthmatic children (aged 5 to 12 years).

Patients should be carefully instructed on the correct use of this drug product to assure optimal dose delivery (please refer to the accompanying Medication Guide).

CLINICAL PHARMACOLOGY

Mechanism of Action

Formoterol fumarate is a long-acting selective beta₂-adrenergic receptor agonist (beta₂-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 beta₂-receptors than at beta₁-receptors. Although beta₂-receptors are the predominant adrenergic receptors in bronchial smooth muscle and beta₁-receptors are the predominant receptors in the heart, there are also beta₂-receptors in the human heart comprising 10%-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 beta₂-agonists may have cardiac effects.

The pharmacologic effects of beta₂-adrenoceptor agonist drugs, including formoterol, are at least in part attributable to stimulation of intracellular adenyl cyclase, the enzyme that catalyzes the conversion of adenosine triphosphate (ATP) to cyclic-3',5'-adenosine monophosphate (cyclic AMP). Increased cyclic AMP levels cause relaxation of bronchial smooth muscle and inhibition of release of mediators of immediate hypersensitivity from cells, especially from mast cells.

In vitro tests show that formoterol is an inhibitor of the release of mast cell mediators, such as histamine and leukotrienes, from the human lung. Formoterol also inhibits histamine-induced plasma albumin extravasation in anesthetized

guinea pigs and inhibits allergen-induced eosinophil influx in dogs with airway hyper-responsiveness. The relevance of these in vitro and animal findings to humans is unknown.

Animal Pharmacology

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.

Pharmacokinetics

Information on the pharmacokinetics of formoterol in plasma has been obtained in asthma patients following inhalation of formoterol fumarate via FORADIL CERTIHALER at the therapeutic dose. In addition, information on the pharmacokinetics of formoterol in plasma has been obtained in healthy subjects by oral inhalation of formoterol fumarate doses via FORADIL[®] AEROLIZER[®] higher than the recommended dose. FORADIL AEROLIZER consists of a single-dose dry powder inhaler and capsules containing formoterol fumarate and lactose. Urinary excretion of unchanged formoterol was used as an indirect measure of systemic exposure. Plasma drug disposition data parallel urinary excretion, and the elimination half-lives calculated for urine and plasma are similar.

Absorption

Formoterol was rapidly absorbed in patients with asthma treated with formoterol fumarate 10 mcg twice daily via FORADIL CERTIHALER for 12 weeks; the maximum mean drug concentration of 18 pg/mL (n=12) in plasma was reached by 10 minutes post-dosing, and the systemic exposure (AUC_{0-12h}) at steady state was 67 pg.hr/mL (n=9). In this study of adult and adolescent patients, the mean accumulation index based on the urinary excretion of unchanged formoterol was 1.59 in comparison with the first dose. This suggests some limited accumulation of formoterol in plasma with multiple dosing. The excreted amounts of formoterol at steady-state were close to those predicted based on single-dose kinetics.

Following inhalation of a single 120 mcg dose of formoterol fumarate via FORADIL AEROLIZER by 12 healthy subjects, formoterol reached a maximum plasma drug concentration of 92 pg/mL within 5 minutes of dosing.

Following inhalation of 12 to 96 mcg of formoterol fumarate by 10 healthy males, urinary excretion of both (R,R)- and (S,S)-enantiomers of formoterol increased proportionally to the dose. Thus, absorption of formoterol following inhalation appeared linear over the dose range studied.

As with many drug products for oral inhalation, it is likely that the majority of the inhaled formoterol fumarate delivered is swallowed and then absorbed from the gastrointestinal tract.

Distribution

The binding of formoterol to human plasma proteins *in vitro* was 61%-64% at concentrations from 0.1 to 100 ng/mL. Binding to human serum albumin *in vitro* was 31%-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 via FORADIL AEROLIZER.

Metabolism

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. *In vitro* studies showed that multiple isozymes catalyze the glucuronidation (UGT1A1, 1A8, 1A9, 2B7 and 2B15 were the most predominant isozymes) and O-demethylation (CYP2D6, 2C19, 2C9, and 2A6) 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

Following oral administration of 80 mcg of radiolabeled formoterol fumarate to 2 healthy subjects, 59%-62% of the radioactivity was eliminated in the urine and 32%-34% in the feces over a period of 104 hours. Renal clearance of formoterol from blood in these subjects was about 150 mL/min.

When adults and adolescents with asthma were treated with 10 mcg formoterol fumarate twice daily via FORADIL CERTIHALER for 12 weeks, 11.5% of the dose was excreted in the urine as unchanged formoterol. Renal clearance of formoterol from plasma was 330 mL/min, which is similar to that seen previously following treatment of healthy volunteers with FORADIL AEROLIZER (300 mL/min).

Based on plasma concentrations measured following inhalation of a single 120 mcg dose of formoterol fumarate via FORADIL AEROLIZER by 12 healthy subjects, the mean terminal elimination half-life was determined to be 10 hours. From urinary excretion rates measured in these subjects, the mean terminal elimination half-lives for the (R,R)- and (S,S)-enantiomers were determined to be 13.9 and 12.3 hours, respectively. The (R,R)- and (S,S)-enantiomers represented about 40% and 60% of unchanged drug excreted in the urine, respectively, following single inhaled doses between 12 and 120 mcg in healthy volunteers and single and repeated doses of 12 and 24 mcg in patients with asthma. Thus, the relative proportion of the two enantiomers remained constant over the dose range studied and there was no evidence of relative accumulation of one enantiomer over the other after repeated dosing.

Special Populations

Gender: After correction for body weight, formoterol pharmacokinetics did not differ significantly between males and females.

Geriatric and Pediatric: The pharmacokinetics of formoterol have not been studied in the elderly population, and limited data are available in pediatric patients.

In a study of children with asthma who were 5 to 12 years of age, when formoterol fumarate 10 mcg was given twice daily by oral inhalation via FORADIL CERTIHALER for 8 weeks, the maximum mean drug concentration of 17 pg/mL (n=13) in plasma was seen at 10 minutes post-dosing and the systemic exposure (AUC_{0-12h}) at steady state was 82 pg.hr/mL (n=8), while the mean accumulation index was 1.58 based on urinary excretion of unchanged formoterol. Hence, rate of absorption and accumulation in children were similar to those in adults. About 12% of the dose was recovered in the urine of the children as unchanged formoterol.

Hepatic/Renal Impairment: The pharmacokinetics of formoterol have not been studied in subjects with hepatic or renal impairment.

Pharmacodynamics

Systemic Safety and Pharmacokinetic/Pharmacodynamic Relationships

The major adverse effects of inhaled beta₂-agonists occur as a result of excessive activation of the systemic beta-adrenergic receptors. The most common adverse effects in adults and adolescents include skeletal muscle tremor and cramps, insomnia, tachycardia, decreases in plasma potassium, and increases in plasma glucose.

Pharmacokinetic/pharmacodynamic (PK/PD) relationships between heart rate, ECG parameters, and serum potassium levels and the urinary excretion of formoterol were evaluated in 10 healthy male volunteers (25 to 45 years of age) following inhalation of single doses containing 12, 24, 48, or 96 mcg of formoterol fumarate. There was a linear relationship between urinary formoterol excretion and decreases in serum potassium, increases in plasma glucose, and increases in heart rate.

In a second study, PK/PD relationships between plasma formoterol levels and pulse rate, ECG parameters, and plasma potassium levels were evaluated in

12 healthy volunteers following inhalation of a single 120 mcg dose of formoterol fumarate via FORADIL AEROLIZER (10 times the recommended clinical dose). Reductions of plasma potassium concentration were observed in all subjects. Maximum reductions from baseline ranged from 0.55 to 1.52 mmol/L with a median maximum reduction of 1.01 mmol/L. The formoterol plasma concentration was highly correlated with the reduction in plasma potassium concentration. Generally, the maximum effect on plasma potassium was noted 1 to 3 hours after peak formoterol plasma concentrations were achieved. A mean maximum increase of pulse rate of 26 bpm was observed 6 hours post dose. The maximum increase of mean corrected QT interval (QTc) was 25 msec when calculated using Bazett's correction and was 8 msec when calculated using Fridericia's correction. The QTc returned to baseline within 12-24 hours post-dose. Formoterol plasma concentrations were weakly correlated with pulse rate and increase of QTc duration. The effects on plasma potassium, pulse rate, and QTc interval are known pharmacological effects of this class of study drug and were not unexpected at the very high formoterol dose (120 mcg single dose, 10 times the recommended single dose) tested in this study. These effects were well tolerated by the healthy volunteers.

The electrocardiographic effects of FORADIL CERTIHALER were compared with those of albuterol and placebo in two 12-week double-blind studies of adult and adolescent patients with asthma. ECGs were performed pre-dose and 90 minutes post-dose on the first day of treatment and after 12 weeks of treatment. A total of 166 patients were treated with FORADIL CERTIHALER 10 mcg twice daily in these two studies. There were no statistically significant differences between FORADIL CERTIHALER and placebo treatment groups for QTc at any timepoint assessed (for both Bazett's and Fridericia's formulae).

Additionally, the electrocardiographic effects of FORADIL CERTIHALER were compared with those of placebo in a 12-week double-blind study of pediatric patients with asthma. ECGs were performed pre-dose and 90 minutes post-dose on the first day of treatment and after 12 weeks of treatment. In this study, 127 patients were treated with FORADIL CERTIHALER 10 mcg twice

daily. There were no significant differences between treatments in mean QTc interval at any timepoint assessed using Bazett's formula. Similar results were found using Fridericia's formula, with the exception of the post-dose week 12 value where a significant decrease in QTc interval was observed with FORADIL CERTIHALER compared to placebo.

Continuous electrocardiographic monitoring was not included in the clinical studies of FORADIL CERTIHALER. However, in two 12-week double-blind studies that studied FORADIL AEROLIZER (FORADIL AEROLIZER consists of a single-dose dry powder inhaler and capsules containing formoterol fumarate and lactose) in patients with asthma a subset of patients underwent continuous electrocardiographic monitoring during three 24-hour periods. No important differences in ventricular or supraventricular ectopy between treatment groups were observed. In these two studies, the total number of patients with asthma exposed to any dose of FORADIL AEROLIZER who had continuous electrocardiographic monitoring was about 200.

Tachyphaxis/Tolerance

In a clinical study in 19 adult patients with mild asthma, the bronchoprotective effect of formoterol via FORADIL AEROLIZER, as assessed by methacholine challenge, was studied following an initial dose of 24 mcg (twice the recommended dose) and after 2 weeks of 24 mcg twice daily. Tolerance to the bronchoprotective effects of formoterol was observed as evidenced by a diminished bronchoprotective effect on FEV₁ after 2 weeks of dosing, with loss of protection at the end of the 12 hour dosing period.

Rebound bronchial hyper-responsiveness after cessation of chronic formoterol therapy has not been observed.

In three large clinical trials in patients with asthma, while efficacy of formoterol versus placebo was maintained, a slightly reduced bronchodilatory response (as measured by 12-hour FEV₁ AUC) was observed within the formoterol arms over time.

CLINICAL TRIALS

Adolescent and Adult Asthma Trials

In two 12-week, multi-center, randomized, double-blind, parallel group studies, FORADIL CERTIHALER 10 mcg twice daily was compared to albuterol 180 mcg four times daily by pressurized metered-dose inhaler, and placebo in a total of 504 adult and adolescent patients 13 years of age and above with persistent asthma (defined as FEV₁ greater than, or equal to 40% of the patient's predicted normal value).

The results of both studies showed that FORADIL CERTIHALER 10 mcg twice daily resulted in significantly greater post-dose bronchodilation (as measured by 12 hour AUC of FEV₁ post-dose) than placebo throughout the 12-week treatment period. Mean FEV₁ in liters from both studies are shown below for the first and last treatment days (see Figures 1 and 2).

Figures 1a and 1b: Mean (adjusted) FEV₁ from Clinical Trial A

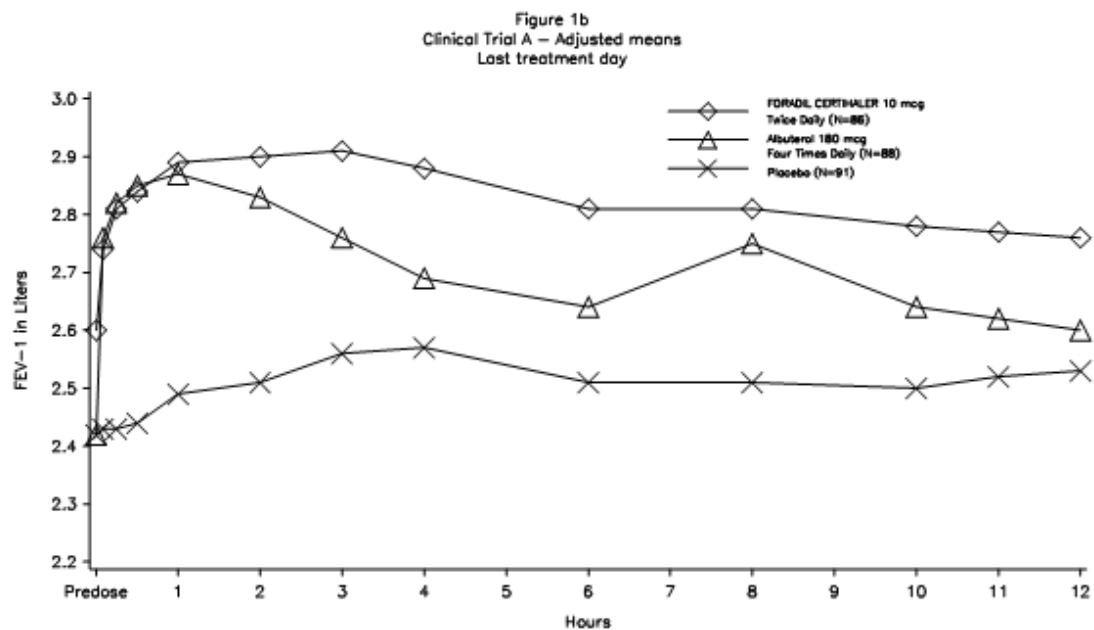
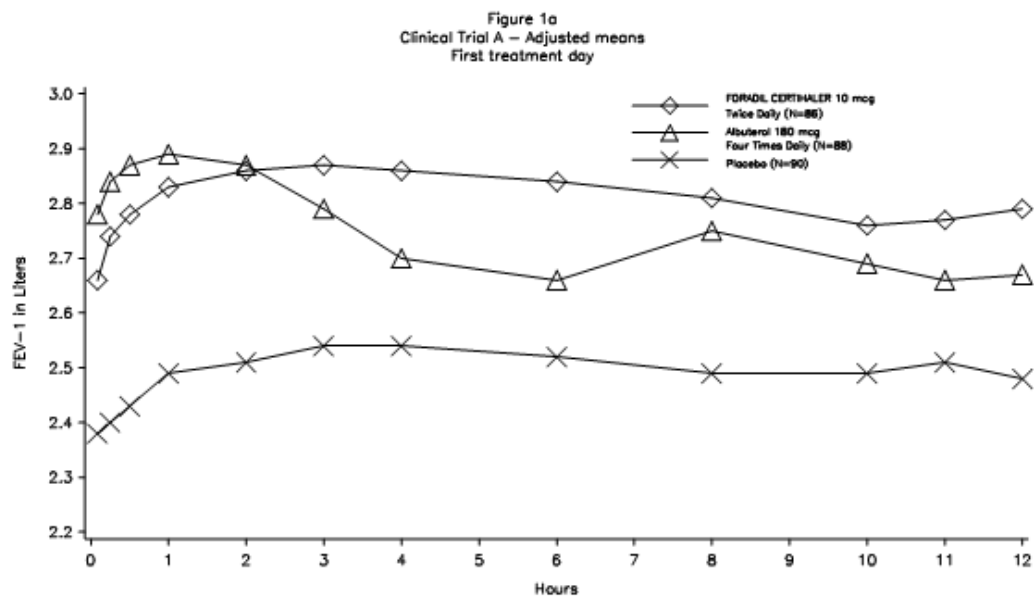
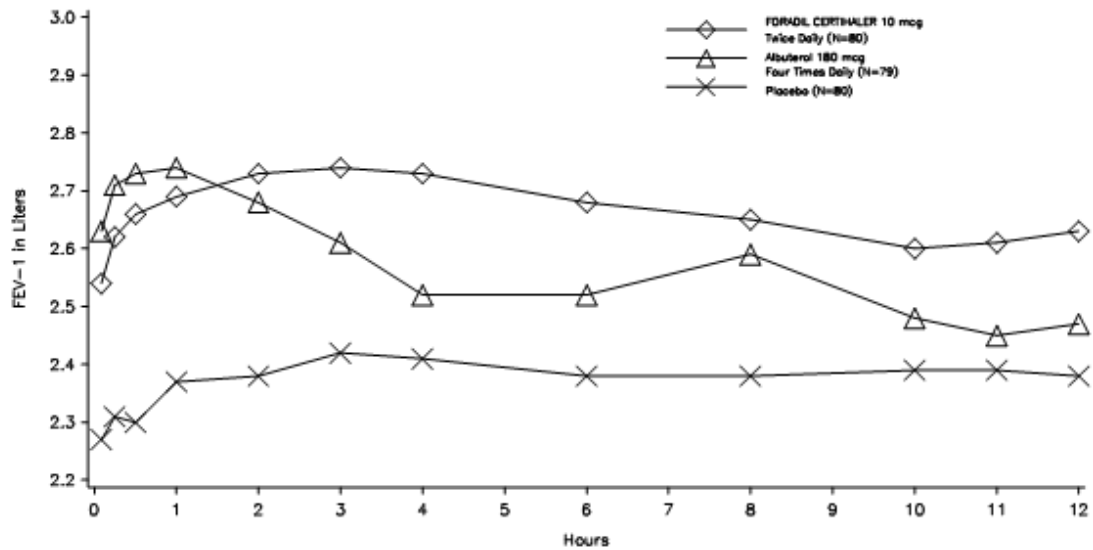
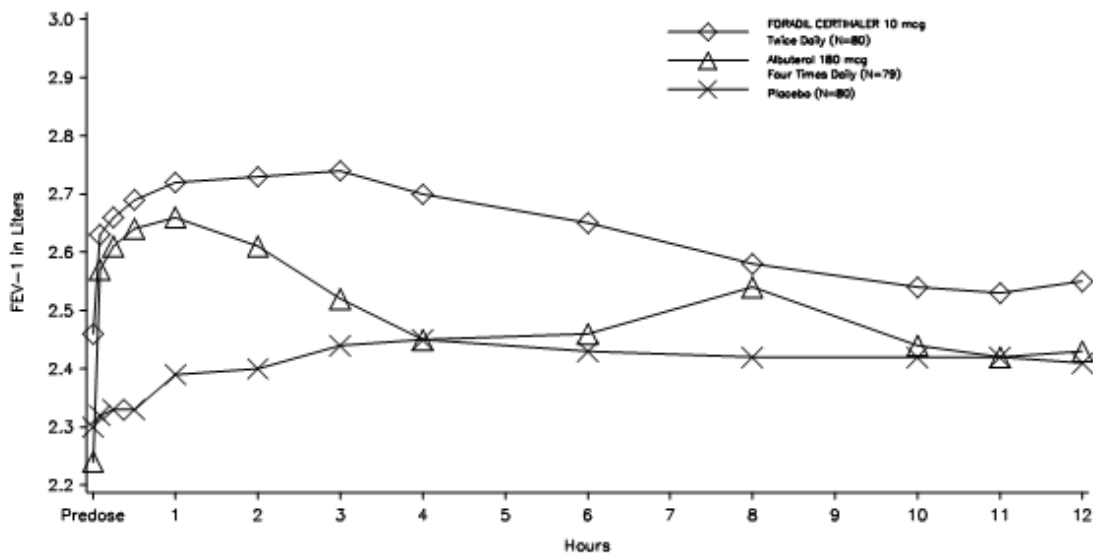


Figure 2a
Clinical Trial B – Adjusted means
First treatment day



Plotted means are least squares means adjusted for baseline

Figure 2b
Clinical Trial B – Adjusted means
Last treatment day



Plotted means are least squares means adjusted for baseline

FORADIL CERTIHALER 10 mcg demonstrated an onset of bronchodilation (defined as a 15% or greater increase from baseline in FEV₁)

comparable to albuterol, as demonstrated by FEV₁ measurements at the early post-dose time points.

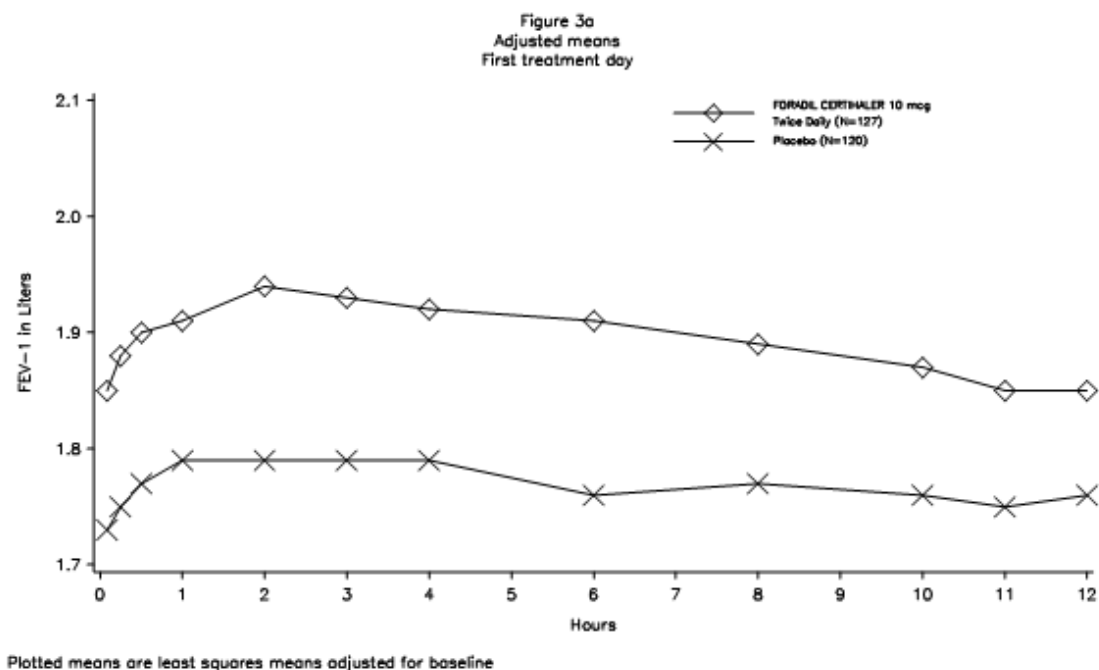
Compared with placebo, patients treated with FORADIL CERTIHALER 10 mcg also demonstrated improvement in the following secondary efficacy endpoints: increased morning and evening peak flow and reduction in rescue medication usage over a 24 hour period.

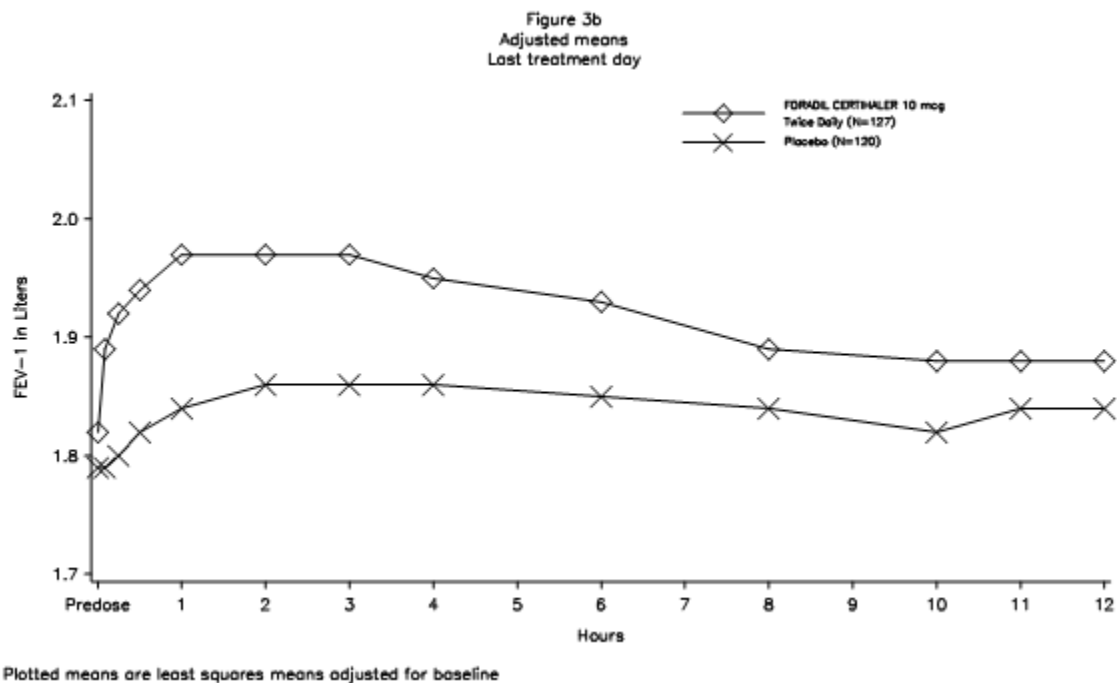
Pediatric Asthma Trial

A 12-week, multi-center, randomized, double-blind, parallel-group, study compared FORADIL CERTIHALER 10 mcg and placebo in a total of 249 children with persistent asthma (ages 5-12 years) who required daily bronchodilators. Efficacy was evaluated on the first day of treatment, after one month, and at the end of treatment.

FORADIL CERTIHALER 10 mcg twice daily demonstrated a greater 12-hour FEV₁ AUC compared to placebo on the first day of treatment, after one month of treatment, and after three months of treatment. Mean FEV₁ in liters is shown below for the first and last treatment days.

Figures 3a and 3b: Mean (adjusted) FEV₁ from Pediatric Clinical Trial





INDICATIONS AND USAGE

FORADIL CERTIHALER is indicated for the treatment of asthma and in the prevention of bronchospasm only as concomitant therapy with a long-term asthma control medication, such as an inhaled corticosteroid, in adults and children 5 years of age and older with reversible obstructive airway disease. Long-acting beta₂-adrenergic agonists (LABA), such as formoterol, the active ingredient in FORADIL CERTIHALER, increase the risk of asthma-related death (see WARNINGS). Use of FORADIL CERTIHALER for the treatment of asthma without concomitant use of a long-term asthma control medication, such as an inhaled corticosteroid, is contraindicated (see CONTRAINDICATIONS). Use FORADIL CERTIHALER only as additional therapy for patients with asthma who are currently taking but are inadequately controlled on a long-term asthma control medication, such as an inhaled corticosteroid. Once asthma control is achieved and maintained, assess the patient at regular intervals and step down therapy (e.g. discontinue FORADIL CERTIHALER) if possible without loss of

asthma control, and maintain the patient on a long-term asthma control medication, such as an inhaled corticosteroid. Do not use FORADIL CERTIHALER for patients whose asthma is adequately controlled on low or medium dose inhaled corticosteroids.

Pediatric and Adolescent Patients

Available data from controlled clinical trials suggest that LABA increase the risk of asthma-related hospitalization in pediatric and adolescent patients (see WARNINGS). For pediatric and adolescent patients with asthma who require addition of a LABA to an inhaled corticosteroid, a fixed-dose combination product containing both an inhaled corticosteroid and LABA should ordinarily be used to ensure adherence with both drugs. In cases where use of a separate long-term asthma control medication (e.g. inhaled corticosteroid) and LABA is clinically indicated, appropriate steps must be taken to ensure adherence with both treatment components. If adherence cannot be assured, a fixed-dose combination product containing both an inhaled corticosteroid and LABA is recommended.

CONTRAINDICATIONS

Because of the risk of asthma-related death and hospitalization, use of FORADIL CERTIHALER for the treatment of asthma without concomitant use of a long-term asthma control medication, such as an inhaled corticosteroid, is contraindicated (see Warnings – Asthma Related Death). FORADIL (formoterol fumarate) is contraindicated in patients with a history of hypersensitivity to formoterol fumarate or to any components of this product.

WARNINGS

ASTHMA RELATED DEATH

Long-acting beta₂-adrenergic agonists, such as formoterol, the active ingredient in FORADIL CERTIHALER, increase the risk of asthma-related

death. Currently available data are inadequate to determine whether concurrent use of inhaled corticosteroids or other long-term asthma control drugs mitigates the increased risk of asthma-related death from LABA.

Because of this risk, use of FORADIL CERTIHALER for the treatment of asthma without concomitant use of a long-term asthma control medication, such as an inhaled corticosteroid, is contraindicated. Use FORADIL CERTIHALER only as additional therapy for patients with asthma who are currently taking but are inadequately controlled on a long-term asthma control medication, such as an inhaled corticosteroid. Once asthma control is achieved and maintained, assess the patient at regular intervals and step down therapy (e.g. discontinue FORADIL CERTIHALER) if possible without loss of asthma control, and maintain the patient on a long-term asthma control medication, such as an inhaled corticosteroid. Do not use FORADIL CERTIHALER for patients whose asthma is adequately controlled on low or medium dose inhaled corticosteroids.

Pediatric and Adolescent Patients

Available data from controlled clinical trials suggest that LABA increase the risk of asthma-related hospitalization in pediatric and adolescent patients. For pediatric and adolescent patients with asthma who require addition of a LABA to an inhaled corticosteroid, a fixed-dose combination product containing both an inhaled corticosteroid and LABA should ordinarily be considered to ensure adherence with both drugs. In cases where use of a separate long-term asthma control medication (e.g. inhaled corticosteroid) and LABA is clinically indicated, appropriate steps must be taken to ensure adherence with both treatment components. If adherence cannot be assured, a fixed-dose combination product containing both an inhaled corticosteroid and LABA is recommended.

A 28-week, placebo-controlled US study comparing the safety of salmeterol with placebo, each added to usual asthma therapy, showed an increase in asthma-

related deaths in patients receiving salmeterol (13/13,176 in patients treated with salmeterol vs. 3/13,179 in patients treated with placebo; RR 4.37, 95% CI 1.25, 15.34). The increased risk of asthma-related death is considered a class effect of the long-acting beta₂-adrenergic agonists, including formoterol. No study adequate to determine whether the rate of asthma-related death is increased with FORADIL CERTIHALER has been conducted.

Clinical studies with FORADIL AEROLIZER suggested a higher incidence of serious asthma exacerbations in patients who received FORADIL AEROLIZER than in those who received placebo (See ADVERSE REACTIONS). The sizes of these studies were not adequate to precisely quantify the differences in serious asthma exacerbation rates between treatment groups.

The studies described above enrolled patients with asthma. No studies have been conducted that were adequate to determine whether the rate of death in patients with COPD is increased by long-acting beta₂-adrenergic agonists.

- **FORADIL CERTIHALER should not be initiated in patients with significantly worsening or acutely deteriorating asthma, which may be a life-threatening condition. The use of FORADIL CERTIHALER in this setting is inappropriate.**
- **FORADIL CERTIHALER should not be used in conjunction with an inhaled, long-acting beta₂-agonist. FORADIL CERTIHALER should not be used with other medications containing long-acting beta₂-agonists.**
- **FORADIL CERTIHALER is not a substitute for inhaled or oral corticosteroids. Corticosteroids should not be stopped or reduced at the time FORADIL CERTIHALER is initiated.**
- **When beginning treatment with FORADIL CERTIHALER, patients who have been taking inhaled, short-acting beta₂-agonists on a regular basis (e.g., four times a day) should be instructed to discontinue the regular**

use of these drugs and use them only for symptomatic relief of acute asthma symptoms.

- **See PRECAUTIONS, Information for Patients and the accompanying Medication Guide.**

Paradoxical Bronchospasm

As with other inhaled beta₂-agonists, formoterol can produce paradoxical bronchospasm, that may be life-threatening. If paradoxical bronchospasm occurs, FORADIL CERTIHALER should be discontinued immediately and alternative therapy instituted.

Deterioration of Asthma

Asthma may deteriorate acutely over a period of hours or chronically over several days or longer. It is important to watch for signs of worsening asthma, such as increasing use of inhaled, short-acting beta₂-adrenergic agonists or a significant decrease in peak expiratory flow (PEF) or lung function. Such findings require immediate evaluation. Patients should be advised to seek immediate attention should their condition deteriorate. Increasing the daily dosage of FORADIL CERTIHALER beyond the recommended dose in this situation is not appropriate. FORADIL CERTIHALER should not be used more frequently than twice daily (morning and evening) at the recommended dose.

Use of Anti-inflammatory Agents

There are no data demonstrating that FORADIL has any clinical anti-inflammatory effect and therefore it cannot be expected to take the place of corticosteroids. Patients who require oral or inhaled corticosteroids for treatment of asthma should be continued on this type of treatment even if they feel better as a result of initiating FORADIL CERTIHALER. Any change in corticosteroid dosage, in particular a reduction, should be made ONLY after clinical evaluation (see PRECAUTIONS, Information for Patients).

Cardiovascular Effects

Formoterol fumarate, like other beta₂-agonists, can produce a clinically significant cardiovascular effect in some patients as measured by increases in pulse rate,

blood pressure, and/or symptoms. Although such effects are uncommon after administration of FORADIL CERTIHALER 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. Therefore, formoterol fumarate, like other sympathomimetic amines, should be used with caution in patients with cardiovascular disorders, especially coronary insufficiency, cardiac arrhythmias, and hypertension (see PRECAUTIONS, General).

Immediate Hypersensitivity Reactions

Immediate hypersensitivity reactions may occur after administration of FORADIL CERTIHALER, as demonstrated by cases of anaphylactic reactions, urticaria, angioedema, rash, and bronchospasm.

Do Not Exceed Recommended Dose

Fatalities have been reported in association with excessive use of inhaled sympathomimetic drugs in patients with asthma. The exact cause of death is unknown, but cardiac arrest following an unexpected development of a severe acute asthmatic crisis and subsequent hypoxia is suspected. In addition, data from clinical trials with FORADIL AEROLIZER suggest that the use of doses higher than recommended is associated with an increased risk of serious asthma exacerbations (see ADVERSE REACTIONS).

PRECAUTIONS

General

FORADIL CERTIHALER should not be used to treat acute symptoms of asthma. FORADIL CERTIHALER has not been studied in the relief of acute asthma symptoms and extra doses should not be used for that purpose. When prescribing FORADIL CERTIHALER, the physician should also provide the patient with an inhaled, short-acting beta₂-agonist for treatment of symptoms that occur acutely, despite regular twice-daily (morning and evening) use of FORADIL CERTIHALER. Patients should also be cautioned that increasing inhaled beta₂-

agonist use is a signal of deteriorating asthma. (See Information for Patients and the accompanying Medication Guide.)

Formoterol fumarate, like other sympathomimetic amines, should be used with caution in patients with cardiovascular disorders, especially coronary insufficiency, cardiac arrhythmias, and hypertension; in patients with convulsive disorders or thyrotoxicosis; and in patients who are unusually responsive to sympathomimetic amines. Clinically significant changes in systolic and/or diastolic blood pressure, pulse rate and electrocardiograms have been seen infrequently in individual patients in controlled clinical studies with formoterol. Doses of the related beta₂-agonist albuterol, when administered intravenously, have been reported to aggravate preexisting diabetes mellitus and ketoacidosis.

Beta-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 infrequent during clinical studies with administration of FORADIL CERTIHALER at the recommended dose.

FORADIL CERTIHALER contains lactose, which contains trace levels of milk protein. Allergic reactions to products containing milk proteins may occur in patients with severe milk protein allergy.

Information for Patients

Patients should be instructed to read the accompanying Medication Guide with each new prescription and refill. The complete text of the Medication Guide is reprinted at the end of this document. Patients should be given the following information:

- 1. Patients should be informed that long-acting beta₂-adrenergic agonists (LABA), including formoterol, the active ingredient in FORADIL CERTIHALER, increase the risk of asthma-related death and may**

increase the risk of asthma-related hospitalizations in pediatric and adolescent patients. Currently available data are inadequate to determine whether concurrent use of inhaled corticosteroids or other long-term asthma control drugs mitigates the increased risk of asthma-related death from LABA. Patients should be informed that FORADIL CERTIHALER should not be the only therapy for the treatment of asthma and must only be used as additional therapy when other long-term asthma control medications (e.g., inhaled corticosteroids) do not adequately control asthma symptoms. Patients should be informed that when FORADIL CERTIHALER is added to their treatment regimen they must continue to use their long-term asthma control medication.

2. FORADIL CERTIHALER is not indicated to relieve acute asthma symptoms and extra doses should not be used for that purpose. Acute symptoms should be treated with an inhaled, short-acting, beta₂-agonist (the health-care provider should prescribe the patient with such medication and instruct the patient in how it should be used). Patients should be instructed to seek medical attention if their symptoms worsen, if FORADIL CERTIHALER treatment becomes less effective, or if they need more inhalations of a short-acting beta₂-agonist than usual. Patients should not inhale more than one dose at any one time. The daily dosage of FORADIL CERTIHALER should not exceed one inhalation twice daily (20 mcg total daily dose).
3. FORADIL CERTIHALER should not be used as a substitute for oral or inhaled corticosteroids. The dosage of these medications should not be changed and they should not be stopped without consulting the physician, even if the patient feels better after initiating treatment with FORADIL CERTIHALER.
4. The active ingredient of FORADIL (formoterol fumarate) is a long-acting, bronchodilator used for the treatment of asthma. FORADIL CERTIHALER provides bronchodilation for up to 12 hours. Patients should be advised not to increase the dose or frequency of FORADIL CERTIHALER without consulting

the prescribing physician. Patients should be warned not to stop or reduce concomitant asthma therapy without medical advice.

5. Patients should be informed that treatment with beta₂-agonists may lead to adverse events which include palpitations, chest pain, rapid heart rate, tremor or nervousness.
6. Patients should be informed never to use FORADIL CERTIHALER with a spacer and never to exhale into the device.
7. The CERTIHALER Inhaler should never be washed and should be kept dry.
8. Women should be advised to contact their physician if they become pregnant or if they are nursing.
9. It is important that patients understand how to use the CERTIHALER Inhaler appropriately and how it should be used in relation to other asthma medications they are taking (see the accompanying Medication Guide).

Drug Interactions

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 may be potentiated.

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

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

Formoterol, as with other beta₂-agonists, should be administered with extreme caution to patients being treated with monamine oxidase inhibitors, tricyclic antidepressants, or drugs known to prolong the QTc interval because the

action of adrenergic agonists 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.

Beta-adrenergic receptor antagonists (beta-blockers) and formoterol may inhibit the effect of each other when administered concurrently. Beta-blockers not only block the therapeutic effects of beta-agonists, such as formoterol, but may produce severe bronchospasm in asthmatic patients. 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.

Carcinogenesis, Mutagenesis, Impairment of Fertility

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 (AUC exposure approximately 1000 times human exposure at the maximum recommended daily inhalation dose), but not at dietary doses up to 5 mg/kg (AUC exposure approximately 250 times human exposure at the maximum recommended daily inhalation dose). 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 was approximately 25 times human exposure at the maximum recommended daily inhalation dose). This finding was not observed in the drinking water study.

In mice, the incidence of adrenal subcapsular adenomas and carcinomas was increased in males at doses of 69 mg/kg (AUC exposure approximately 460 times human exposure at the maximum recommended daily inhalation dose) and above in the drinking water study, but not at doses up to 50 mg/kg (AUC exposure approximately 330 times human exposure at the maximum recommended daily inhalation dose) in the dietary study. The incidence of

hepatocarcinomas was increased in the dietary study at doses of 20 and 50 mg/kg in females (AUC exposure approximately 130 and 330 times human exposure at the maximum recommended daily inhalation dose, respectively) and 50 mg/kg in males, but not at doses up to 5 mg/kg (AUC exposure approximately 33 times human exposure at the maximum recommended daily inhalation dose). Also in the dietary study, the incidence of uterine leiomyomas and leiomyosarcomas was increased at doses of 2 mg/kg and above (AUC exposure was approximately 15 times human exposure at the maximum recommended daily inhalation dose). 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 maximum recommended daily inhalation dose in adults on a mg/m^2 basis).

Pregnancy, Teratogenic Effects, Pregnancy Category C

Formoterol fumarate administered throughout organogenesis did not cause malformations in rats or rabbits following oral administration. When given to rats throughout organogenesis, oral doses of 0.2 mg/kg (approximately 80 times the maximum recommended daily inhalation dose in humans on a mg/m^2 basis) and above delayed ossification of the fetus, and doses of 6 mg/kg (approximately 2400 times the maximum recommended daily inhalation dose in adults on a mg/m^2 basis) and above decreased fetal weight. Formoterol fumarate has been shown to cause stillbirth and neonatal mortality at oral doses of 6 mg/kg and above in rats receiving the drug during the late stage of pregnancy. These effects, however, were not produced at a dose of 0.2 mg/kg. Because there are no adequate and well-controlled studies in pregnant women, FORADIL

CERTIHALER should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Use in Labor and Delivery

Because beta-agonists may potentially interfere with uterine contractility, FORADIL CERTIHALER should be used during labor only if the potential benefit justifies the potential risk.

Nursing Mothers

In reproductive studies in rats, formoterol was excreted in the milk. It is not known whether formoterol is excreted in human milk, but because many drugs are excreted in human milk, caution should be exercised if FORADIL CERTIHALER is administered to nursing women.

Pediatric Use

Asthma

Available data from controlled clinical trials suggest that LABA increase the risk of asthma-related hospitalization in pediatric and adolescent patients. For pediatric and adolescent patients with asthma who require addition of a LABA to an inhaled corticosteroid, a fixed-dose combination product containing both an inhaled corticosteroid and LABA should ordinarily be used to ensure adherence with both drugs (see INDICATIONS AND USAGE and WARNINGS).

A total of 326 children 5 years of age and older with asthma were studied in two multiple-dose controlled clinical trials. Of the 204 children who received FORADIL CERTIHALER, all were 5-12 years of age, and 69, approximately one third, were 5-8 years of age.

The safety and effectiveness of FORADIL CERTIHALER in pediatric patients below 5 years of age has not been established. (See CLINICAL TRIALS, Pediatric Asthma Trial, and ADVERSE REACTIONS, Experience in Pediatric, Adolescent and Adult Patients.)

Geriatric Use

Of the total number of patients who received FORADIL CERTIHALER in adolescent and adult chronic dosing asthma clinical trials, 30 (5.4%) were 65 years of age or older and 2 (0.4%) were 75 years of age and older. No overall differences in safety or effectiveness were observed between these subjects and younger subjects. However, the number of elderly patients studied with FORADIL CERTIHALER is low. Additionally, there is experience with FORADIL AEROLIZER (FORADIL AEROLIZER consists of a single-dose dry powder inhaler and capsules containing formoterol fumarate and lactose) and of the total number of patients who received FORADIL AEROLIZER in adolescent and adult chronic dosing asthma clinical trials, 318 were 65 years of age or older and 39 were 75 years of age and older. Of the 811 patients who received FORADIL AEROLIZER in two pivotal multiple-dose controlled clinical studies in patients with COPD, 395 (48.7%) were 65 years of age or older while 62 (7.6%) were 75 years of age or older. No overall differences in safety or effectiveness were observed between these subjects and younger subjects. A slightly higher frequency of chest infection was reported in the 39 asthma patients 75 years of age and older, although a causal relationship with FORADIL has not been established. Other reported clinical experience has not identified differences in responses between the elderly and younger adult patients, but greater sensitivity of some older individuals cannot be ruled out. (See PRECAUTIONS, Drug Interactions.)

ADVERSE REACTIONS

Long-acting beta₂-adrenergic agonists (LABA), including formoterol, the active ingredient in FORADIL CERTIHALER, increase the risk of asthma-related death and may increase the risk of asthma-related hospitalizations in pediatric and adolescent patients. Clinical trials with FORADIL AEROLIZER (consists of a single-dose dry powder inhaler and capsules containing formoterol fumarate and lactose) suggested a higher incidence

of serious asthma exacerbations in patients who received FORADIL AEROLIZER than in those who received placebo. (See WARNINGS)

Experience in Pediatric, Adolescent and Adult Patients with Asthma

Of the 1,118 patients in multiple-dose controlled clinical trials of more than one month exposure, 414 were treated with FORADIL CERTIHALER at the recommended dose of 10 mcg twice daily. The following table shows adverse events where the frequency was greater than or equal to 1% in the FORADIL 10 mcg twice daily group and where the rates in the FORADIL group exceeded placebo.

**NUMBER AND FREQUENCY OF ADVERSE EXPERIENCES IN
PATIENTS 5 YEARS OF AGE AND OLDER FROM MULTIPLE-DOSE
CONTROLLED CLINICAL TRIALS OF MORE THAN ONE MONTH EXPOSURE**

Adverse Event	FORADIL CERTIHALER 10 mcg twice daily		Placebo	
	n	(%)	n	(%)
Total Patients	414	(100)	416	(100)
Nasopharyngitis	34	(8.2)	24	(5.8)
Headache NOS	34	(8.2)	33	(7.9)
Upper respiratory tract infection NOS	33	(8.0)	31	(7.5)
Cough	21	(5.1)	17	(4.1)
Pyrexia	19	(4.6)	11	(2.6)
Vomiting NOS	15	(3.6)	7	(1.7)
Tremor	11	(2.7)	2	(0.5)
Nasal congestion	10	(2.4)	8	(1.9)
Rhinitis allergic NOS	10	(2.4)	1	(0.2)
Viral infection NOS	10	(2.4)	5	(1.2)
Influenza	9	(2.2)	4	(1.0)
Bronchitis NOS	9	(2.2)	2	(0.5)
Upper respiratory tract infection viral NOS	7	(1.7)	4	(1.0)
Back pain	7	(1.7)	4	(1.0)
Conjunctivitis	6	(1.4)	2	(0.5)
Rash NOS	6	(1.4)	0	0
Dyspepsia	6	(1.4)	2	(0.5)
Pharyngitis streptococcal	5	(1.2)	3	(0.7)
Urinary tract infection NOS	4	(1.0)	3	(0.7)
Diarrhea NOS	4	(1.0)	3	(0.7)
Bronchitis acute NOS	4	(1.0)	1	(0.2)
Respiratory tract infection	4	(1.0)	1	(0.2)
Muscle cramps	4	(1.0)	1	(0.2)
Insomnia	4	(1.0)	2	(0.5)
Asthma NOS	4	(1.0)	3	(0.7)

NOS = not otherwise specified

In two 12-week controlled trials for FORADIL AEROLIZER with combined enrollment of 1095 patients 12 years of age and older, FORADIL AEROLIZER 12 mcg twice daily was compared to FORADIL AEROLIZER 24 mcg twice daily, albuterol 180 mcg four times daily, and placebo. Serious asthma exacerbations (acute worsening of asthma resulting in hospitalization) occurred more commonly with FORADIL AEROLIZER 24 mcg twice daily than with the recommended dose

of FORADIL AEROLIZER 12 mcg twice daily, albuterol, or placebo. The results are shown in the following table.

NUMBER AND FREQUENCY OF SERIOUS ASTHMA EXACERBATIONS IN PATIENTS 12 YEARS OF AGE AND OLDER FROM TWO 12-WEEK CONTROLLED CLINICAL TRIALS

	Foradil Aerolizer 12 mcg twice daily	Foradil Aerolizer 24 mcg twice daily	Albuterol 180 mcg four times daily	Placebo
Trial #1				
Serious asthma exacerbations	0/136	4/135 (3.0%) ¹	2/134 (1.5%)	0/136 (0)
Trial #2				
Serious asthma exacerbations	1/139 (0.7%)	5/136 (3.7%) ²	0/138 (0)	2/141 (1.4%)

¹ 1 patient required intubation

² 2 patients had respiratory arrest; 1 of the patients died

A 16-week, randomized, multi-center, double-blind, parallel-group study of FORADIL AEROLIZER enrolled 1568 patients 12 years of age and older with mild-to-moderate asthma (defined as FEV1 $\geq$ 40% of the patient's predicted normal value) in three treatment groups. The study's primary endpoint was the incidence of serious asthma-related adverse events. Patients who received either 24 mcg or 12 mcg twice daily doses of FORADIL AEROLIZER experienced more serious asthma exacerbations than patients who received placebo. The results are shown in the following table.

NUMBER AND FREQUENCY OF SERIOUS ASTHMA EXACERBATIONS IN PATIENTS 12 YEARS OF AGE AND OLDER FROM A 16-WEEK TRIAL

	Foradil Aerolizer 12 mcg twice daily	Foradil Aerolizer 24 mcg twice daily	Placebo
Serious asthma exacerbations	3/527 (0.6%)	2/527 (0.4%)	1/514 (0.2%)

The size of this study was not adequate to precisely quantify the differences in serious asthma exacerbation rates between treatment groups. All serious asthma exacerbations resulted in hospitalizations. While there were no deaths in

the study, the duration and size of this study were not adequate to quantify the rate of asthma-related death. See WARNINGS for information about a study which compared another long-acting beta₂-adrenergic agonist to placebo.

Experience in Children with Asthma

The safety of FORADIL CERTIHALER compared to placebo was investigated in a large, 12-week, multicenter, randomized, double-blind clinical trial in 249 children with asthma (ages 5-12 years) in need of daily bronchodilators. The numbers and percent of patients who reported adverse events were comparable in the 10 mcg twice daily and placebo groups. In general, the adverse events observed in children were similar to those described above for the overall asthma population in multiple-dose controlled trials of at least one month exposure. Adverse events that were frequently occurring (incidence of at least 1% and greater than placebo) only for children included viral gastroenteritis, acute sinusitis, pharyngitis, abrasion, rash and contact dermatitis.

The safety of FORADIL AEROLIZER 12 mcg twice daily compared to FORADIL AEROLIZER 24 mcg twice daily and placebo was investigated in one large, multicenter, randomized, double-blind, 52-week clinical trial in 518 children with asthma (ages 5-12 years) in need of daily bronchodilators and anti-inflammatory treatment. More children who received FORADIL AEROLIZER 24 mcg twice daily than children who received FORADIL AEROLIZER 12 mcg twice daily or placebo experienced serious asthma exacerbations, as shown in the next table.

NUMBER AND FREQUENCY OF SERIOUS ASTHMA EXACERBATIONS IN PATIENTS 5-12 YEARS OF AGE FROM A 52-WEEK TRIAL

	Foradil Aerolizer 12 mcg twice daily	Foradil Aerolizer 24 mcg twice daily	Placebo
Serious asthma exacerbations	8/171 (4.7%)	11/171 (6.4%)	0/176 (0)

Other adverse reactions to FORADIL are similar in nature to other selective beta₂-adrenoceptor agonists; e.g., angina, hypertension or hypotension, tachycardia, arrhythmias, nervousness, headache, tremor, dry mouth, palpitation,

muscle cramps, nausea, dizziness, fatigue, malaise, hypokalemia, hyperglycemia, metabolic acidosis and insomnia.

Post Marketing Experience

In extensive worldwide marketing experience with FORADIL, serious exacerbations of asthma, including some that have been fatal, have been reported. While most of these cases have been in patients with severe or acutely deteriorating asthma (see WARNINGS), a few have occurred in patients with less severe asthma. It is not possible to determine from these individual case reports whether FORADIL contributed to the events.

Rare reports of anaphylactic reactions, including severe hypotension and angioedema, have also been received in association with the use of formoterol fumarate inhalation powder.

DRUG ABUSE AND DEPENDENCE

There was no evidence in clinical trials of drug dependence with the use of FORADIL.

OVERDOSAGE

The expected signs and symptoms with overdosage of FORADIL CERTIHALER are those of excessive beta-adrenergic stimulation and/or occurrence or exaggeration of any of the signs and symptoms listed under ADVERSE REACTIONS, e.g., 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. As with all inhaled sympathomimetic medications, cardiac arrest and even death may be associated with an overdose of FORADIL CERTIHALER.

Treatment of overdosage consists of discontinuation of FORADIL CERTIHALER 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 FORADIL CERTIHALER. Cardiac monitoring is recommended in cases of overdosage.

The minimum lethal inhalation dose of formoterol fumarate in rats is 156 mg/kg (approximately 63,000 and 30,000 times the maximum recommended daily inhalation dose in adults and children, respectively, on a mg/m² basis). The median lethal oral doses in Chinese hamsters, rats, and mice provide even higher multiples of the maximum recommended daily inhalation dose in humans.

DOSAGE AND ADMINISTRATION

FORADIL CERTIHALER should be administered only by the oral inhalation route (see the accompanying Medication Guide).

Treatment of Asthma

Long-acting beta₂-adrenergic agonists, such as formoterol, the active ingredient in FORADIL CERTIHALER, increase the risk of asthma-related death. **Because of this risk, use of FORADIL CERTIHALER for the treatment of asthma without concomitant use of a long-term asthma control medication, such as an inhaled corticosteroid, is contraindicated.** Use FORADIL CERTIHALER only as additional therapy for patients with asthma who are currently taking but are inadequately controlled on a long-term asthma control medication, such as an inhaled corticosteroid. Once asthma control is achieved and maintained, assess the patient at regular intervals and step down therapy (e.g. discontinue FORADIL CERTIHALER) if possible without loss of asthma control, and maintain the patient on a long-term asthma control medication, such as an inhaled corticosteroid. Do not use FORADIL CERTIHALER for patients whose asthma is adequately controlled on low or medium dose inhaled corticosteroids.

Pediatric and Adolescent Patients

Available data from controlled clinical trials suggest that LABA increase the risk of asthma-related hospitalization in pediatric and adolescent patients. For patients with asthma less than 18 years of age who require addition of a LABA to an inhaled corticosteroid, a fixed-dose combination product containing both an inhaled corticosteroid and LABA should ordinarily be used to ensure adherence with both drugs. In cases where use of a separate long-term asthma control medication (e.g. inhaled corticosteroid) and LABA is clinically indicated, appropriate steps must be taken to ensure adherence with both treatment components. If adherence cannot be assured, a fixed-dose combination product containing both an inhaled corticosteroid and LABA is recommended.

For adults and children 5 years of age and older, the usual dosage is one 10 mcg inhalation from the FORADIL CERTIHALER every 12 hours. The patient must not exhale into the device. The total daily dose of FORADIL CERTIHALER should not exceed one inhalation twice daily (20 mcg total daily dose). More frequent administration or administration of a larger number of inhalations is not recommended. If symptoms arise between doses, an inhaled short-acting beta₂-agonist should be taken for immediate relief.

If a previously effective dosage regimen fails to provide the usual response, medical advice should be sought immediately as this is often a sign of destabilization of asthma. Under these circumstances, the therapeutic regimen should be re-evaluated.

HOW SUPPLIED

FORADIL CERTIHALER consists of a number of assembled plastic components, the main parts being the mouthpiece, dosing mechanism, reservoir, body, valve socket, and counter. The body of the inhaler is light blue; the mouthpiece is white, and the protective cap is dark blue. The target net content (fill weight) is approximately 560 mg of formoterol powder blend. FORADIL CERTIHALER delivers 8.5 mcg of formoterol fumarate per dose, with 60 doses contained within the inhaler. The inhaler device will lock closed after the final dose is administered.

FORADIL CERTIHALER contains: one CERTIHALER Inhaler and Instructions for Using FORADIL CERTIHALER (NDC XXXX_XXXX_XX).

Unit Dose

Box of 1 CERTIHALER Inhaler (60 doses) NDC xxxx-xxxx-xx

Store at 25°C (77°F). Excursions permitted to 15°C–30°C (59°F–86°F) [see USP Controlled Room Temperature]. Protect from heat and moisture.

Keep out of the reach of children.

XXXXXX 20XX

Printed in U.S.A.

T200X-XX
XXXXXXXXXX



Manufactured by*:

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* The agreement with SkyePharma has been terminated.

** Since approval, Foradil Certihaler has not been marketed in the United States.

Medication Guide

Foradil® [FOR-a-dil] Certihaler® (formoterol fumarate inhalation powder)

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

What is the most important information I should know about FORADIL CERTIHALER?

FORADIL CERTIHALER can cause serious side effects, including:

- 1. People with asthma who take long-acting beta₂-adrenergic agonist (LABA) medicines such as formoterol fumarate inhalation powder (FORADIL CERTIHALER), have an increased risk of death from asthma problems.**
 - Call your healthcare provider if breathing problems worsen over time while using FORADIL CERTIHALER. You may need a different treatment.
 - Get emergency medical care if:
 - breathing problems worsen quickly, and
 - you use your rescue inhaler medicine, but it does not relieve your breathing problems.
- 2. Do not use FORADIL CERTIHALER as your only asthma medicine. FORADIL CERTIHALER must only be used with a long-term asthma control medicine, such as an inhaled corticosteroid.**
3. When your asthma is well controlled, your healthcare provider may tell you to stop taking FORADIL CERTIHALER. Your healthcare provider will decide if you can stop FORADIL CERTIHALER without loss of asthma control. You will continue taking your long-term asthma control medicine, such as a long-term inhaled corticosteroid.
4. Children and adolescents who take LABA medicines may have an increased risk of being hospitalized for asthma problems.

What is FORADIL CERTIHALER?

FORADIL CERTIHALER is a long-acting beta₂-agonist (LABA). LABA medicines help the muscles around the airways in your lungs stay relaxed to prevent asthma symptoms, such as wheezing and shortness of breath. These symptoms can happen when the muscles around the airways tighten. This

makes it hard to breathe. In severe cases, wheezing can stop your breathing and cause death if not treated right away.

FORADIL CERTIHALER is used with other long-term asthma control medicines, such as an inhaled corticosteroid, in adults and children ages 5 and older:

- to control symptoms of asthma, and
- to prevent symptoms such as wheezing

LABA medicines, such as FORADIL CERTIHALER, increase the risk of death from asthma problems. FORADIL CERTIHALER is not for adults and children with asthma who:

- are well controlled with another long-term asthma control medicine, such as low to medium dose of an inhaled corticosteroid medicine.

Who should not use FORADIL CERTIHALER?

- Do not take FORADIL CERTIHALER to treat your asthma without an asthma control medicine, such as a long-term inhaled corticosteroid.
- If you are allergic to formoterol fumarate or any of the ingredients in FORADIL CERTIHALER. Ask your healthcare provider if you are not sure. See the end of the Medication Guide for a complete list of ingredients in FORADIL CERTIHALER.

What should I tell my healthcare provider before using FORADIL CERTIHALER?

Tell your healthcare provider about all of your health conditions, including if you:

- have heart problems
- have high blood pressure
- have seizures
- have thyroid problems
- have diabetes
- are pregnant or planning to become pregnant. It is not known if FORADIL CERTIHALER may harm your unborn baby.
- are breastfeeding. It is not known if FORADIL CERTIHALER passes into your milk and if it can harm your baby.
- are allergic to FORADIL CERTIHALER, any other medicines, or food products.

FORADIL CERTIHALER contains lactose (milk sugar) and a small amount of milk proteins. It is possible that allergic reactions may happen in patients who have a severe milk protein allergy.

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

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

How do I use the FORADIL CERTIHALER inhaler?

See the step-by-step instructions for using the FORADIL CERTIHALER inhaler at the end of this Medication Guide. Do not use FORADIL unless your healthcare provider has taught you and you understand everything. Ask your healthcare provider or pharmacist if you have any questions.

- Children should use FORADIL CERTIHALER with an adult's help, as instructed by the child's healthcare provider.
- Use FORADIL CERTIHALER exactly as prescribed. **Do not use FORADIL CERTIHALER more often than prescribed.**
- The usual dose is 1 inhalation through the CERTIHALER inhaler 2 times each day (morning and evening). The 2 doses should be about 12 hours apart.
- If you miss a dose of FORADIL CERTIHALER, just skip that dose. Take your next dose at your usual time. Never take 2 doses at one time.
- Do not use a spacer device with FORADIL CERTIHALER.
- Do not breathe into FORADIL CERTIHALER.
- While you are using FORADIL CERTIHALER 2 times each day, do not use other medicines that contain a long-acting beta2-agonist (LABA) for any reason. Ask your healthcare provider or pharmacist for a list of these medicines.
- Do not stop using FORADIL CERTIHALER or any of your asthma medicines unless told to do so by your healthcare provider because your symptoms might get worse. Your healthcare provider will change your medicines as needed.
- FORADIL CERTIHALER does not relieve sudden symptoms. Always have a rescue inhaler medicine with you to treat sudden symptoms. If you do not have an inhaled, short-acting bronchodilator, contact your healthcare provider to have one prescribed for you.

- **Call your healthcare provider or get medical care right away if:**
 - your breathing problems worsen with FORADIL CERTIHALER
 - you need to use your rescue inhaler medicine more often than usual
 - your rescue inhaler medicine does not work as well for you at relieving symptoms
 - you need to use 4 or more inhalations of your rescue inhaler medicine for 2 or more days in a row
 - you use 1 whole canister of your rescue inhaler medicine in 8 weeks time
 - your peak flow meter results decrease. Your healthcare provider will tell you the numbers that are right for you.
 - you have asthma and your symptoms do not improve after using FORADIL CERTIHALER regularly for 1 week.

What are the possible side effects with FORADIL CERTIHALER?

FORADIL CERTIHALER may cause serious side effects, including:

- **See “What is the most important information I should know about FORADIL CERTIHALER?”**
- **Bronchospasm with wheezing or coughing and difficulty breathing**
- **Low blood potassium (which may cause symptoms of muscle spasm, muscle weakness or abnormal heart rhythm)**
- **Fast or irregular heart beat (palpitations)**
- **Serious allergic reactions including rash, hives, swelling of the face, mouth, and tongue, and breathing problems.** Call your healthcare provider or get emergency medical care if you get any symptoms of a serious allergic reaction.

Other possible side effects with FORADIL CERTIHALER include:

- chest pain
- increased blood pressure
- nervousness
- dry mouth
- muscle cramps
- nausea
- dizziness
- tiredness
- high blood sugar
- high blood acid
- trouble sleeping

Common side effects with FORADIL CERTIHALER include:

- headache
- tremor
- cough
- rash

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

These are not all the side effects with FORADIL CERTIHALER. Ask your healthcare provider or pharmacist for more information. Call your doctor for medical advice about side effects. You may report side effects to FDA at 1-800-FDA-1088.

How do I store FORADIL CERTIHALER?

- Store FORADIL CERTIHALER at room temperature 59°F to 86°F (15°C to 30°C). Protect FORADIL CERTIHALER from heat and moisture.
- Use FORADIL CERTIHALER before the expiration date. The expiration date is marked on the label on the underside of the inhaler.
- **Keep FORADIL CERTIHALER and all medicines out of the reach of children.**

General Information about FORADIL CERTIHALER

Medicines are sometimes prescribed for purposes other than those listed in a Medication Guide. Do not use FORADIL CERTIHALER for a condition for which it was not prescribed. Do not give FORADIL CERTIHALER to other people, even if they have the same condition. It may harm them.

This Medication Guide summarizes the most important information about FORADIL CERTIHALER. If you would like more information or have any questions about the use of FORADIL CERTIHALER, talk with your healthcare provider. You can ask your healthcare provider or pharmacist for information about FORADIL CERTIHALER that was written for healthcare professionals.

What are the ingredients in FORADIL CERTIHALER?

Active ingredient: formoterol fumarate

Inactive ingredients: lactose (contains milk proteins), magnesium stearate

Instructions for Using FORADIL CERTIHALER

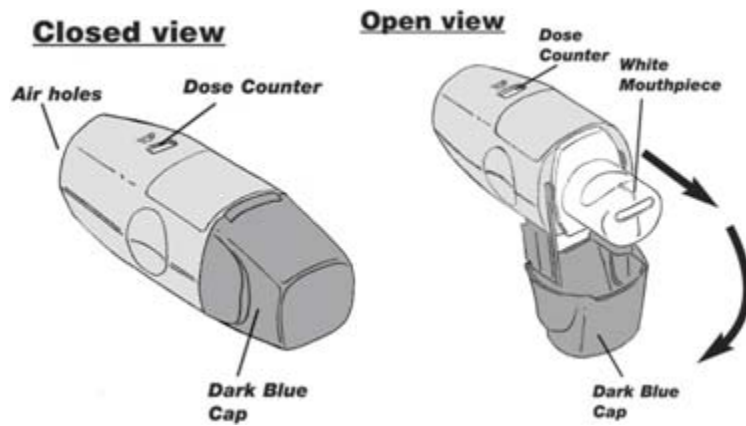
Follow the instructions below for using your FORADIL CERTIHALER. **You will breathe-in (inhale) the medicine from the FORADIL CERTIHALER.** If you have any questions, ask your healthcare provider or pharmacist.

FORADIL CERTIHALER

- Keep your FORADIL CERTIHALER Inhaler dry. Handle with DRY hands.

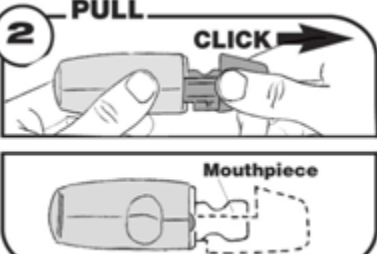
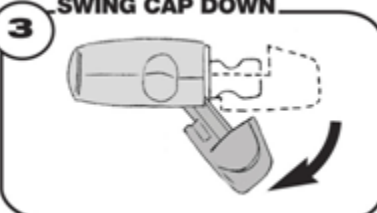
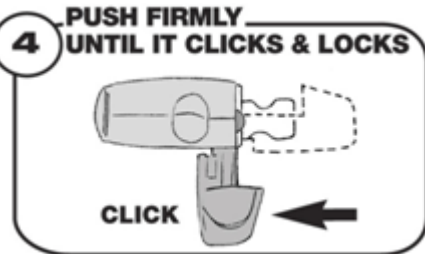
Note: The rattling sound heard when you move the device is normal.

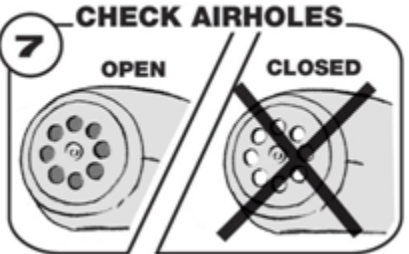
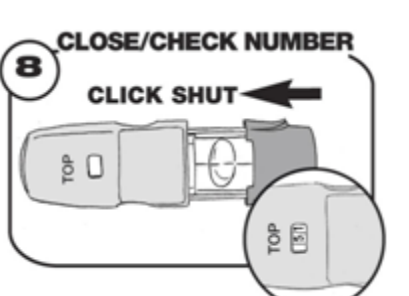
Picture 1



Taking a dose of FORADIL CERTIHALER requires the following steps:

Note the number on the dose counter before you start.

1 MUST HOLD LEVEL 	Hold the inhaler perfectly level with the dose counter facing the ceiling. IMPORTANT: The inhaler will not open unless it is level. TIP: Place the inhaler on a table or other flat surface while opening to keep level.
2 PULL 	Pull the dark blue cap completely away from the inhaler until you hear a click. (Fully open cap clears mouthpiece.) TIP: If the cap doesn't open fully, reclose it <u>all the way</u> before trying again.
3 SWING CAP DOWN 	Pull cap away from inhaler as you swing down.
4 PUSH FIRMLY UNTIL IT CLICKS & LOCKS 	Push cap firmly until it locks into place with a click. IMPORTANT: Cap must click to lock or the inhaler will not work. TIP: Pushing hard to lock won't damage the inhaler.

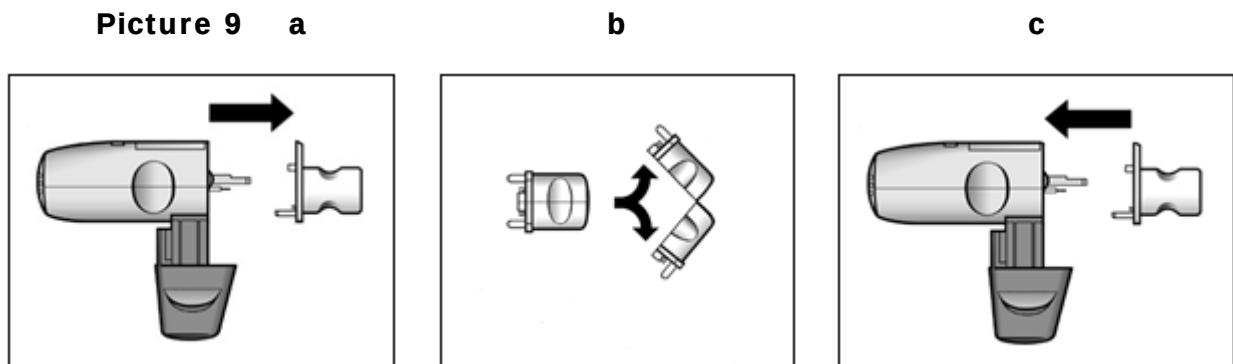
5 EXHALE 	While holding the inhaler level, breathe out (exhale) away from the inhaler, then close your lips firmly over mouthpiece. TIP: Keep fingers clear of air holes at back.
6 TAKE A FAST, DEEP BREATH 	Breathe in (inhale) quickly one fast, deep breath. Hold your breath at least 5 seconds. Exhale away from the inhaler. IMPORTANT: If you do not inhale fast enough the inhaler will not work. TIP: When you inhale fast and deep enough, you will hear a soft click as the air holes open.
7 CHECK AIRHOLES 	Double-check air holes to see if they opened completely. IMPORTANT: If air holes did not open, return to step 4. If the cap was locked down all the way, try inhaling faster and deeper.
8 CLOSE/CHECK NUMBER 	After you have received the dose, close the cap all the way until it clicks shut. The counter will now show you have one less dose left in the inhaler. TIP: Dose counter changes after you close the cap.

IMPORTANT: If the display number did not decrease by one after step 8 above, but you still received your dose of medicine, **stop using the inhaler and contact your pharmacist.** Remember, you will know that you received your dose of medicine, if the ring of air holes was open before you closed the Protective Cap (see step 7 above).

Taking care of your FORADIL CERTIHALER

Cleaning of the mouthpiece – The mouthpiece of your FORADIL CERTIHALER should be cleaned once weekly as follows:

- Open the Protective Cap
- Pull off the white mouthpiece as shown in Picture 9a.
- **IMPORTANT:** Once the mouthpiece is removed keep your open FORADIL CERTIHALER in a safe place where it cannot be damaged or get wet. It is important that you do not clean, blow on or touch any internal parts of your FORADIL CERTIHALER that are exposed when the mouthpiece is removed.
- After removal of the mouthpiece, unfold it as shown in Picture 9b and tap the mouthpiece gently onto a dry tissue to remove any powder residue.
- **IMPORTANT:** Never use water to clean the mouthpiece or any other parts of your FORADIL CERTIHALER, because moisture may damage the medicine.
- After cleaning the mouthpiece, fold it up and insert it gently into its original position (Picture 9c).
- Close the Protective Cap all the way once the mouthpiece has been replaced.

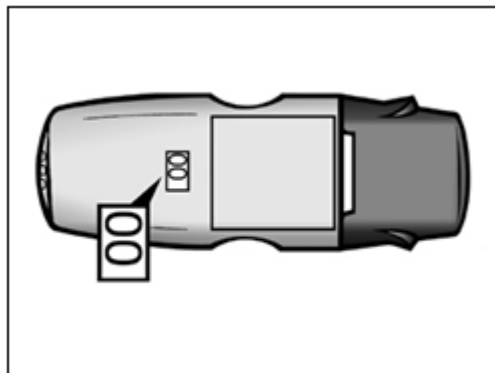


General recommendations

Stop using your FORADIL CERTIHALER when the Dose Counter window shows **00 (Picture 10)**. This indicates that you have used all 60 doses of medicine in the inhaler. You will need to start a new FORADIL CERTIHALER.

Note: If you try to use your FORADIL CERTIHALER after the Dose Counter window shows **00**, you will receive only one more dose. After this dose, the Dose Counter display will change to **999** and the Protective Cap will be permanently locked and the device cannot be opened any more.

Picture 10



Remember:

- Always keep the Protective Cap closed when you are not using your CERTIHALER unless you are cleaning the mouthpiece.
- Always clean the mouthpiece if the CERTIHALER Inhaler is dropped while the cap is open.
- Always open the CERTIHALER Inhaler in a level, horizontal position, with the counter in the upwards position.
- Make sure that the Protective Cap is clicked into place in its fully open position when inhaling.
- Never breathe into the CERTIHALER Inhaler.
- Never take the CERTIHALER Inhaler apart (aside from removing the mouthpiece for cleaning).
- Never wash the CERTIHALER Inhaler. **Keep it dry.**
- Always keep the CERTIHALER Inhaler in a dry place.

Rx only



Manufactured by*:

SkyePharma Production SAS, Saint Quentin-Fallavier, France

Distributed by:**

Novartis Pharmaceuticals Corp., East Hanover, NJ 07936

* The agreement with SkyePharma has been terminated.

** Since approval, Foradil Certihaler has not been marketed in the United States.

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