HIGHLIGHTS OF PRESCRIBING INFORMATION

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

STRIVERDI® RESPIMAT® (olodaterol) Inhalation Spray
FOR ORAL INHALATION
Initial U.S. Approval: 2014~~xx~~

WARNING: ASTHMA-RELATED DEATH

See full prescribing information for complete boxed warning

- **Long-acting beta$_2$-adrenergic agonists (LABA) increase the risk of asthma-related death (5.1)**
- **A placebo-controlled study with another long-acting beta$_2$-adrenergic agonist (salmeterol) showed an increase in asthma-related deaths in patients receiving salmeterol (5.1)**
- **This finding of an increased risk of asthma-related death with salmeterol is considered a class effect of LABA, including olodaterol, the active ingredient in STRIVERDI RESPIMAT. The safety and efficacy of STRIVERDI RESPIMAT in patients with asthma have not been established. STRIVERDI RESPIMAT is not indicated for the treatment of asthma. (4, 5.1)**

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

STRIVERDI RESPIMAT Inhalation Spray is a long-acting beta$_2$-adrenergic agonist indicated for:

The long-term, once-daily maintenance bronchodilator treatment of airflow obstruction in patients with chronic obstructive pulmonary disease (COPD), including chronic bronchitis and/or emphysema (1.1)

Important limitations:

- STRIVERDI RESPIMAT is NOT indicated to treat acute deterioration of COPD (1.2)
- STRIVERDI RESPIMAT is NOT indicated to treat asthma (1.2)

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

- For oral inhalation only
- Two inhalations of STRIVERDI RESPIMAT once-daily at the same time of day (2)

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

Inhalation spray: Each actuation from the mouthpiece contains 2.7 mcg olodaterol hydrochloride, equivalent to 2.5 mcg olodaterol. Two actuations equal one dose (3)

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

All LABA are contraindicated in patients with asthma without use of a long-term asthma control medication. (4) STRIVERDI RESPIMAT is not indicated for the treatment of asthma. (1.2)

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

- Do not initiate STRIVERDI RESPIMAT in acutely deteriorating COPD patients (5.2)
- Do not use for relief of acute symptoms. Concomitant short-acting beta$_2$-agonists can be used as needed for acute relief. (5.2)
- Do not exceed the recommended dose. Excessive use of STRIVERDI RESPIMAT, or use in conjunction with other medications containing LABA can result in clinically significant cardiovascular effects and may be fatal. (5.3)
- Life-threatening paradoxical bronchospasm can occur. Discontinue STRIVERDI RESPIMAT immediately. (5.4)
- Use with caution in patients with cardiovascular or convulsive disorders, thyrotoxicosis or sensitivity to sympathomimetic drugs (5.5, 5.6)

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

Most common adverse reactions (incidence ≥2% and more than placebo) are nasopharyngitis, upper respiratory tract infection, bronchitis, urinary tract infection, cough, dizziness, rash, diarrhea, back pain and arthralgia (6.1)

To report SUSPECTED ADVERSE REACTIONS, contact Boehringer Ingelheim Pharmaceuticals, Inc. at (800) 542-6257 or (800) 459-9906 TTY, or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

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

- Other adrenergic drugs may potentiate effect. Use with caution. (5.3, 7.1)
- Xanthine derivatives, steroids, diuretics or non-potassium sparing diuretics may potentiate hypokalemia or ECG changes. Use with caution. (7.2, 7.3)
- MAO inhibitors, tricyclic antidepressants, and drugs that prolong QTc interval may potentiate effect on cardiovascular system. Use with extreme caution. (7.4)
- Beta-blockers may decrease effectiveness. Use with caution and only when medically necessary. (7.5)

See 17 for PATIENT COUNSELING INFORMATION, Medication Guide, and Instructions for Use.

Revised: 7/2014

FULL PRESCRIBING INFORMATION: CONTENTS*

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

FULL PRESCRIBING INFORMATION

WARNING: ASTHMA-RELATED DEATH

Long-acting beta$_2$-adrenergic agonists (LABA) increase the risk of asthma-related death. Data from a large, placebo-controlled US study that compared the safety of another long-acting beta$_2$-adrenergic agonist (salmeterol) or placebo added to usual asthma therapy showed an increase in asthma-related deaths in patients receiving salmeterol. This finding with salmeterol is considered a class effect of LABA, including olodaterol, the active ingredient in STRIVERDI RESPIMAT. The safety and efficacy of STRIVERDI RESPIMAT in patients with asthma have not been established. STRIVERDI RESPIMAT is not indicated for the treatment of asthma [*see Contraindications (4), Warnings and Precautions (5.1)*].

1 INDICATIONS AND USAGE

1.1 Maintenance Treatment of COPD

STRIVERDI RESPIMAT is a long-acting beta$_2$-agonist indicated for long-term, once-daily maintenance bronchodilator treatment of airflow obstruction in patients with chronic obstructive pulmonary disease (COPD), including chronic bronchitis and/or emphysema.

1.2 Important Limitations of Use

STRIVERDI RESPIMAT is not indicated to treat acute deteriorations of COPD [*see Warnings and Precautions (5.2)*].

STRIVERDI RESPIMAT is not indicated to treat asthma. The safety and effectiveness of STRIVERDI RESPIMAT in asthma have not been established.

2 DOSAGE AND ADMINISTRATION

The recommended dose of STRIVERDI RESPIMAT is two inhalations once-daily at the same time of the day. Do not use STRIVERDI RESPIMAT more than two inhalations every 24 hours.

Prior to first use, the STRIVERDI RESPIMAT cartridge is inserted into the STRIVERDI RESPIMAT inhaler and the unit is primed. When using the unit for the first time, patients are to actuate the inhaler toward the ground until an aerosol cloud is visible and then repeat the process three more times. The unit is then considered primed and ready for use. If not used for more than 3 days, patients are to actuate the inhaler once to prepare the inhaler for use. If not used for more than 21 days, patients are to actuate the inhaler until an aerosol cloud is visible and then repeat the process three more times to prepare the inhaler for use [*see Patient Counseling Information (17.2)*].

No dosage adjustment is required for geriatric patients, patients with mild and moderate hepatic impairment, or renally-impaired patients. There are no data available for use of STRIVERDI RESPIMAT in severe hepatically impaired patients [*see Clinical Pharmacology (12.3)*].

3 DOSAGE FORMS AND STRENGTHS

STRIVERDI RESPIMAT consists of a STRIVERDI RESPIMAT inhaler and an aluminum cylinder (STRIVERDI RESPIMAT cartridge) containing olodaterol (as the hydrochloride). The STRIVERDI RESPIMAT cartridge is intended for use with the STRIVERDI RESPIMAT inhaler only.

Each actuation from the STRIVERDI RESPIMAT inhaler delivers 2.7 mcg olodaterol hydrochloride, equivalent to 2.5 mcg olodaterol. Two actuations equal one dose.

4 CONTRAINDICATIONS

All LABA are contraindicated in patients with asthma without use of a long-term asthma control medication [*see Warnings and Precautions (5.1)*]. STRIVERDI RESPIMAT is not indicated for the treatment of asthma.

5 WARNINGS AND PRECAUTIONS

5.1 Asthma-Related Death [*see Boxed Warning*]

- **Data from a large placebo-controlled study in asthma patients showed that long-acting beta$_2$-adrenergic agonists may increase the risk of asthma-related death. Data are not available to determine whether the rate of death in patients with COPD is increased by long-acting beta$_2$-adrenergic agonists.**
- **A 28-week, placebo-controlled US study comparing the safety of another long-acting beta$_2$-adrenergic agonist (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 long-acting beta$_2$-adrenergic agonists, including STRIVERDI RESPIMAT. No study adequate to determine whether the rate of asthma-related death is increased in patients treated with STRIVERDI RESPIMAT has been conducted. The safety and efficacy of STRIVERDI RESPIMAT in patients with asthma have not been established. STRIVERDI RESPIMAT is not indicated for the treatment of asthma [*see Contraindications (4)*].**

5.2 Deterioration of Disease and Acute Episodes

STRIVERDI RESPIMAT should not be initiated in patients with acutely deteriorating COPD, which may be a life-threatening condition. STRIVERDI RESPIMAT has not been studied in patients with acutely deteriorating COPD. The use of STRIVERDI RESPIMAT in this setting is inappropriate.

STRIVERDI RESPIMAT should not be used for the relief of acute symptoms, i.e., as rescue therapy for the treatment of acute episodes of bronchospasm. STRIVERDI RESPIMAT has not been studied in the relief of acute symptoms and extra doses should not be used for that purpose. Acute symptoms should be treated with an inhaled short-acting beta$_2$-agonist.

When beginning STRIVERDI RESPIMAT, patients who have been taking inhaled, short-acting beta$_2$-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 respiratory symptoms. When prescribing STRIVERDI RESPIMAT, the healthcare provider should also prescribe an inhaled, short-acting beta$_2$-agonist and instruct the patient on how it should be used. Increasing inhaled beta$_2$-agonist use is a signal of deteriorating disease for which prompt medical attention is indicated.

COPD may deteriorate acutely over a period of hours or chronically over several days or longer. If STRIVERDI RESPIMAT no longer controls symptoms of bronchoconstriction, or the patient's inhaled, short-acting beta$_2$-agonist becomes less effective or the patient needs more inhalation of short-acting beta$_2$-agonist than usual, these may be markers of deterioration of disease. In this setting, a re-evaluation of the patient and the COPD treatment regimen should be undertaken at once. Increasing the daily dosage of STRIVERDI RESPIMAT beyond the recommended dose is not appropriate in this situation.

5.3 Excessive Use of STRIVERDI RESPIMAT and Use with Long-Acting Beta$_2$-Agonists
As with other inhaled drugs containing beta$_2$-adrenergic agents, STRIVERDI RESPIMAT should not be used more often than recommended, at higher doses than recommended, or in conjunction with other medications containing long-acting beta$_2$-agonists, as an overdose may result. Clinically significant cardiovascular effects and fatalities have been reported in association with excessive use of inhaled sympathomimetic drugs.

5.4 Paradoxical Bronchospasm
As with other inhaled beta$_2$-agonists, STRIVERDI RESPIMAT may produce paradoxical bronchospasm that may be life-threatening. If paradoxical bronchospasm occurs, STRIVERDI RESPIMAT should be discontinued immediately and alternative therapy instituted.

5.5 Cardiovascular Effects
STRIVERDI RESPIMAT, like other beta$_2$-agonists, can produce a clinically significant cardiovascular effect in some patients as measured by increases in pulse rate, systolic or diastolic blood pressure, and/or symptoms. If such effects occur, STRIVERDI RESPIMAT 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. Long acting beta$_2$-adrenergic agonists should be administered with caution in patients with cardiovascular disorders, especially coronary insufficiency, cardiac arrhythmias, hypertrophic obstructive cardiomyopathy, and hypertension.

5.6 Co-existing Conditions
STRIVERDI RESPIMAT, like other sympathomimetic amines, should be used with caution in patients with convulsive disorders or thyrotoxicosis, in patients with known or suspected prolongation of the QT interval, and in patients who are unusually responsive to sympathomimetic amines. Doses of the related beta$_2$-agonist albuterol, when administered intravenously, have been reported to aggravate pre-existing diabetes mellitus and ketoacidosis.

5.7 Hypokalemia and Hyperglycemia
Beta-adrenergic agonists may produce significant hypokalemia in some patients, which has the potential to produce adverse cardiovascular effects [*see Clinical Pharmacology (12.2)*]. The decrease in serum potassium is usually transient, not requiring supplementation. Inhalation of high doses of beta$_2$-adrenergic agonists may produce increases in plasma glucose.

In patients with severe COPD, hypokalemia may be potentiated by hypoxia and concomitant treatment [*see Drug Interactions (7.2)*], which may increase the susceptibility for cardiac arrhythmias.

Clinically notable decreases in serum potassium or changes in blood glucose were infrequent during clinical studies with long-term administration of STRIVERDI RESPIMAT with the rates similar to those for placebo controls. STRIVERDI RESPIMAT has not been investigated in patients whose diabetes mellitus is not well controlled.

5.8 Hypersensitivity Reactions
Immediate hypersensitivity reactions, including angioedema, may occur after administration of STRIVERDI RESPIMAT. If such a reaction occurs, therapy with STRIVERDI RESPIMAT should be stopped at once and alternative treatment should be considered.

6 ADVERSE REACTIONS

Long-acting beta$_2$-adrenergic agonists, such as STRIVERDI RESPIMAT, increase the risk of asthma-related death. STRIVERDI RESPIMAT is not indicated for the treatment of asthma [*see Boxed Warning and Warning and Precautions (5.1)*].

6.1 Clinical Trials Experience in Chronic Obstructive Pulmonary Disease
Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared with rates in the clinical trials of another drug and may not reflect the rates observed in practice.

The STRIVERDI RESPIMAT clinical development program included seven dose-ranging trials and eight confirmatory trials. Four of the confirmatory trials were 6-week cross-over trials and four were 48-week parallel group trials. Adverse reactions observed in the dose-ranging trials and four 6-week cross-over trials were consistent with those observed in the 48-week parallel group trials, which formed the primary safety database.

The primary safety database consisted of pooled data from the four 48-week double-blind, active and placebo-controlled, parallel group confirmatory clinical trials. These trials included 3104 adult COPD patients (77% males and 23% females) 40 years of age and older. Of these patients, 876 and 883 patients were treated with STRIVERDI RESPIMAT 5 mcg and 10 mcg once-daily, respectively. The STRIVERDI RESPIMAT groups were composed of mostly Caucasians (66%) with a mean age of 64 years and a mean percent predicted FEV_1 at baseline of 44% for both the 5 mcg and 10 mcg treatment groups. Control arms for comparison included placebo in all four trials plus formoterol 12 mcg in two trials.

In these four clinical trials, seventy-two percent (72%) of patients exposed to any dose of STRIVERDI RESPIMAT reported an adverse reaction compared to 71% in the placebo group. The proportion of patients who discontinued due to an adverse reaction was 7.2% for STRIVERDI RESPIMAT treated patients compared to 8.8% for placebo treated patients. The adverse reaction most commonly leading to discontinuation was worsening COPD. The most common serious adverse reactions were COPD exacerbation, pneumonia, and atrial fibrillation.

Table 1 shows all adverse drug reactions reported by at least 2% of patients (and higher than placebo) who received STRIVERDI RESPIMAT 5 mcg during the 48-week trials.

Table 1: Number and frequency of adverse drug reactions greater than 2% (and higher than placebo) in COPD patients exposed to STRIVERDI RESPIMAT 5 mcg: Pooled data from the four 48-week, double-blind, active- and placebo-controlled clinical trials in COPD patients 40 years of age and older

Treatment	**STRIVERDI 5 mcg once-daily**	**Placebo**
Body system (adverse drug reaction)	**n=876 n (%)**	**n=885 n (%)**
Infections and infestations		
Nasopharyngitis	99 (11.3)	68 (7.7)
Upper Respiratory Tract Infection	72 (8.2)	66 (7.5)
Bronchitis	41 (4.7)	32 (3.6)
Urinary Tract Infection	22 (2.5)	9 (1.0)
Respiratory, thoracic, and mediastinal disorders		
Cough	37 (4.2)	35 (4.0)
Nervous system disorders		
Dizziness	20 (2.3)	19 (2.1)
Skin and subcutaneous tissue disorders		
Rash*	19 (2.2)	10 (1.1)
Gastrointestinal disorders		
Diarrhea	25 (2.9)	22 (2.5)
Musculoskeletal and connective tissue disorders		
Back Pain	31 (3.5)	24 (2.7)
Arthralgia	18 (2.1)	7 (0.8)

* Rash includes a grouping of similar terms.

Additional adverse reactions that occurred in greater than 2% (and higher than placebo) of patients exposed to STRIVERDI RESPIMAT 10 mcg were pneumonia, constipation, and pyrexia.

Lung cancers were reported in 6 (0.7%), 3 (0.3%), and 2 (0.2%) patients who received STRIVERDI RESPIMAT 10 mcg, 5 mcg, and placebo, respectively.

7 DRUG INTERACTIONS

7.1 Adrenergic Drugs

If additional adrenergic drugs are to be administered by any route, they should be used with caution because the sympathetic effects of STRIVERDI RESPIMAT may be potentiated [*see Warnings and Precautions (5.3, 5.5, 5.6, 5.7)*].

7.2 Xanthine Derivatives, Steroids, or Diuretics

Concomitant treatment with xanthine derivatives, steroids, or diuretics may potentiate any hypokalemic effect of STRIVERDI RESPIMAT [*see Warnings and Precautions (5.7)*].

7.3 Non-Potassium Sparing Diuretics

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-agonists with non-potassium-sparing diuretics.

7.4 Monoamine Oxidase Inhibitors, Tricyclic Antidepressants, QTc Prolonging Drugs

STRIVERDI RESPIMAT, as with other beta$_2$-agonists, should be administered with extreme caution to patients being treated with monoamine oxidase inhibitors or tricyclic antidepressants or other 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 may be associated with an increased risk of ventricular arrhythmias.

7.5 Beta-Blockers

Beta-adrenergic receptor antagonists (beta-blockers) and STRIVERDI RESPIMAT may interfere with the effect of each other when administered concurrently. Beta-blockers not only block the therapeutic effects of beta-agonists, but may produce severe bronchospasm in COPD patients. Therefore, patients with COPD 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 COPD. In this setting, cardioselective beta-blockers could be considered, although they should be administered with caution.

7.6 Inhibitors of Cytochrome P450 and P-gp Efflux Transporter

In a drug interaction study using the strong dual CYP and P-gp inhibitor ketoconazole, a 1.7-fold increase of maximum plasma concentrations and AUC was observed [*see Clinical Pharmacology ~~Pharmacokinetics~~ (12.3)*]. STRIVERDI RESPIMAT was evaluated in clinical trials for up to one year at doses up to twice the recommended therapeutic dose. No dose adjustment is necessary.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Teratogenic Effects: Pregnancy Category C.

There are no adequate and well-controlled studies with STRIVERDI RESPIMAT in pregnant women. STRIVERDI RESPIMAT should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

STRIVERDI RESPIMAT was not teratogenic in rats at inhalation doses approximately 2,731 times the maximum recommended human daily inhalation dose (MRHDID) on an AUC basis (at a rat maternal inhalation dose of 1,054 mcg/kg/day). Placental transfer of STRIVERDI RESPIMAT was observed in pregnant rats.

STRIVERDI RESPIMAT has been shown to be teratogenic in New Zealand rabbits at inhalation doses approximately 7,130 times the MRHDID in adults on an AUC basis (at a rabbit maternal inhalation dose of 2,489 mcg/kg/day). STRIVERDI RESPIMAT exhibited the following fetal toxicities: enlarged or small heart atria or ventricles, eye abnormalities, and split or distorted sternum. No significant effects occurred at an inhalation dose approximately 1,353 times the MRHDID in adults on an AUC basis (at a rabbit maternal inhalation dose of 974 mcg/kg/day).

8.2 Labor and Delivery

There are no adequate and well-controlled human studies that have investigated the effects of STRIVERDI RESPIMAT on preterm labor or labor at term. Because of the potential for beta-agonist interference with uterine contractility, use of STRIVERDI RESPIMAT during labor should be restricted to those patients in whom the benefits clearly outweigh the risks.

8.3 Nursing Mothers

Olodaterol, the active component of STRIVERDI RESPIMAT, and/or its metabolites are excreted into the milk of lactating rats. Excretion of olodaterol and/or its metabolites into human milk is probable. There are no human studies that have investigated the effects of STRIVERDI RESPIMAT on nursing infants. Caution should be exercised when STRIVERDI RESPIMAT is administered to nursing women.

8.4 Pediatric Use

STRIVERDI RESPIMAT is not indicated for use in children. The safety and effectiveness of STRIVERDI RESPIMAT in the pediatric population have not been established.

8.5 Geriatric Use

Based on available data, no adjustment of STRIVERDI RESPIMAT dosage in geriatric patients is necessary.

Of the 876 patients who received STRIVERDI RESPIMAT at the recommended dose of 5 mcg once-daily in the clinical studies from the pooled 1-year database, 485 were less than or equal to 65 years of age and 391 (44.6%) were greater than 65 years of age.

No overall differences in effectiveness were observed, and in the 1-year pooled data, the adverse drug reaction profiles were similar in the older population compared to the patient population overall.

8.6 Hepatic Impairment

Subjects with mild and moderate hepatic impairment showed no changes in C_{max} or AUC, nor did protein binding differ between mild and moderate hepatically impaired subjects and their healthy controls. A study in subjects with severe hepatic impairment was not performed.

8.7 Renal Impairment

Subjects with severe renal impairment showed no clinically relevant changes in C_{max} or AUC compared to their healthy controls.

10 OVERDOSAGE

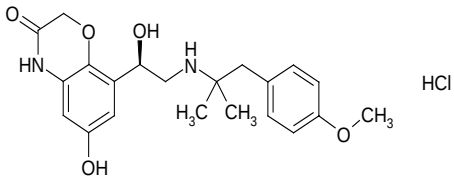
The expected signs and symptoms with overdosage of STRIVERDI RESPIMAT are those of excessive beta-adrenergic stimulation and occurrence or exaggeration of any of the signs and symptoms, e.g., myocardial ischemia, angina pectoris, hypertension or hypotension, tachycardia, arrhythmias, palpitations, dizziness, nervousness, insomnia, anxiety, headache, tremor, dry mouth, muscle spasms, nausea, fatigue, malaise, hypokalemia, hyperglycemia, and metabolic acidosis. As with all inhaled sympathomimetic medications, cardiac arrest and even death may be associated with an overdose of STRIVERDI RESPIMAT.

Treatment of overdosage consists of discontinuation of STRIVERDI RESPIMAT together with institution of appropriate symptomatic and 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 STRIVERDI RESPIMAT. Cardiac monitoring is recommended in cases of overdosage.

11 DESCRIPTION

The active moiety olodaterol is a selective beta$_2$-adrenergic bronchodilator. The drug substance, olodaterol hydrochloride, is chemically described as 2H-1,4-Benzoxazin-3H(4H)-one, 6-hydroxy-8-[(1R)-1-hydroxy-2-[[2-(4-methoxyphenyl)-1,1-dimethylethyl]-amino]ethyl]-, monohydrochloride. Olodaterol hydrochloride is a white to off-white powder that is sparingly-slightly soluble in water and slightly soluble in ethanol. The molecular weight is 422.9 g/mole (salt): 386.5 g/mole (base), and the molecular formula is $C_{21}H_{26}N_2O_5$ x HCl as a hydrochloride. The conversion factor from salt to free base is 1.094.

The structural formula is:



The drug product, STRIVERDI RESPIMAT, is composed of a sterile, aqueous solution of olodaterol hydrochloride filled into a 4.5 mL plastic container crimped into an aluminum cylinder (STRIVERDI RESPIMAT cartridge) for use with the STRIVERDI RESPIMAT inhaler.

Excipients include water for injection, benzalkonium chloride, edetate disodium, and anhydrous citric acid. The STRIVERDI RESPIMAT cartridge is only intended for use with the STRIVERDI RESPIMAT inhaler. The STRIVERDI RESPIMAT inhaler is a hand held, pocket sized oral inhalation device that uses mechanical energy to generate a slow-moving aerosol cloud of medication from a metered volume of the drug solution. The STRIVERDI RESPIMAT inhaler has a yellow-colored cap.

When used with the STRIVERDI RESPIMAT inhaler, each cartridge containing a minimum of 4 grams of a sterile aqueous solution, delivers 60 (or 28) metered actuations after preparation for use, the equivalent of 30 days' or 14 days' medication when used as two actuations once a day. Each dose (1 dose equals 2 actuations) from the STRIVERDI RESPIMAT inhaler delivers 5 mcg olodaterol in 22.1 mcL of solution from the mouthpiece. As with all inhaled drugs, the actual amount of drug delivered to the lung may depend on patient factors, such as the coordination between the actuation of the inhaler and inspiration through the delivery system. The duration of inspiration should be at least as long as the spray duration (1.5 seconds).

Prior to first use, the STRIVERDI RESPIMAT cartridge is inserted into the STRIVERDI RESPIMAT inhaler and the unit is primed. When using for the first time, patients are to actuate the inhaler toward the ground until an aerosol cloud is visible and then repeat the process three more times. The unit is then considered primed and ready for use. If not used for more than 3 days, patients are to actuate the inhaler once to prepare the inhaler for use. If not used for more than 21 days, patients are to actuate the inhaler until an aerosol cloud is visible and then repeat the process three more times to prepare the inhaler for use [*see Patient Counseling Information (17.2)*].

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

Olodaterol is a long-acting beta$_2$-adrenergic agonist (LABA). The compound exerts its pharmacological effects by binding and activation of beta$_2$-adrenoceptors after topical administration by inhalation. Activation of these receptors in the airways results in a stimulation of intracellular adenyl cyclase, an enzyme that mediates the synthesis of cyclic-3', 5' adenosine monophosphate (cAMP). Elevated levels of cAMP induce bronchodilation by relaxation of airway smooth muscle cells. *In vitro* studies have shown that olodaterol has 241-fold greater agonist activity at beta$_2$-adrenoceptors compared to beta$_1$-adrenoceptors and 2,299-fold greater agonist activity compared to beta$_3$-adrenoceptors. The clinical significance of these findings is unknown.

Beta-adrenoceptors are divided into three subtypes: beta$_1$-adrenoceptors predominantly expressed on cardiac smooth muscle, beta$_2$-adrenoceptors predominantly expressed on airway smooth muscle, and beta$_3$-adrenoceptors predominantly expressed on adipose tissue. Beta$_2$-agonists cause bronchodilation. Although the beta$_2$-adrenoceptor is the predominant adrenergic receptor in the airway smooth muscle, it is also present on the surface of a variety of other cells, including lung epithelial and endothelial cells and in the heart. The precise function of beta$_2$-receptors in the heart is not known, but their presence raises the possibility that even highly selective beta$_2$-agonists may have cardiac effects.

12.2 Pharmacodynamics

Systemic Safety

The major adverse effects of inhaled beta$_2$-adrenergic agonists occur as a result of excessive activation of systemic beta-adrenergic receptors. The most common adverse effects in adults include skeletal muscle tremor and cramps, insomnia, tachycardia, decreases in serum potassium, and increases in plasma glucose.

Changes in serum potassium were evaluated in COPD patients in double-blind phase 3 studies. In pooled data, at the recommended 5 mcg dose there was no clinically relevant change compared to placebo in serum potassium.

Electrophysiology

The effect of STRIVERDI RESPIMAT on the QT/QTc interval of the ECG was investigated in 24 healthy male and female volunteers in a double-blind, randomized, placebo- and active (moxifloxacin)- controlled study at single doses of 10, 20, 30, and 50 mcg. Dose-dependent QTcI (individual subject corrected QT interval) prolongation was observed. The maximum mean (one-sided 95% upper confidence bound) difference in QTcI from placebo after baseline correction was 2.5 (5.6) ms, 6.1 (9.2) ms, 7.5 (10.7) ms and 8.5 (11.6) ms following doses of 10, 20, 30 and 50 mcg, respectively.

The effect of 5 mcg and 10 mcg STRIVERDI RESPIMAT on heart rate and rhythm was assessed using continuous 24-hour ECG recording (Holter monitoring) in a subset of 772 patients in the 48-week, placebo-controlled phase 3 trials. There were no dose- or time-related trends or patterns observed for the magnitudes of mean changes in heart rate or premature beats. Shifts from baseline to the end of treatment in premature beats did not indicate meaningful differences between STRIVERDI RESPIMAT 5 mcg, 10 mcg, and placebo.

12.3 Pharmacokinetics

Olodaterol showed linear pharmacokinetics. On repeated once-daily inhalation steady-state of olodaterol plasma concentrations was achieved after 8 days, and the extent of exposure was increased up to 1.8-fold as compared to a single dose.

Absorption

Olodaterol reaches maximum plasma concentrations generally within 10 to 20 minutes following drug inhalation. In healthy volunteers, the absolute bioavailability of olodaterol following inhalation was estimated to be approximately 30%, whereas the absolute bioavailability was below 1% when given as an oral solution. Thus, the systemic availability of olodaterol after inhalation is mainly determined by lung absorption, while any swallowed portion of the dose only negligibly contributes to systemic exposure.

Distribution

Olodaterol exhibits multi-compartmental disposition kinetics after inhalation as well as after intravenous administration. The volume of distribution is high (1110 L), suggesting extensive distribution into tissue. *In vitro* binding of [^{14}C] olodaterol to human plasma proteins is independent of concentration and is approximately 60%.

Metabolism

Olodaterol is substantially metabolized by direct glucuronidation and by O-demethylation at the methoxy moiety followed by conjugation. Of the six metabolites identified, only the unconjugated demethylation product binds to beta$_2$-receptors. This metabolite, however, is not detectable in plasma after chronic inhalation of the recommended therapeutic dose.

Cytochrome P450 isozymes CYP2C9 and CYP2C8, with negligible contribution of CYP3A4, are involved in the O-demethylation of olodaterol, while uridine diphosphate glycosyl transferase isoforms UGT2B7, UGT1A1, 1A7, and 1A9 were shown to be involved in the formation of olodaterol glucuronides.

Elimination

Total clearance of olodaterol in healthy volunteers is 872 mL/min, and renal clearance is 173 mL/min. The terminal half-life following intravenous administration is 22 hours. The terminal half-life following inhalation in contrast is about 45 hours, indicating that the latter is determined by absorption rather than by elimination processes. However, the effective half-life at daily dose of 5 µg calculated from C_{max} from COPD patients is 7.5 hours.

Following intravenous administration of [^{14}C]-labeled olodaterol, 38% of the radioactive dose was recovered in the urine and 53% was recovered in feces. The amount of unchanged olodaterol recovered in the urine after intravenous administration was 19%. Following oral administration, only 9% of olodaterol and/or its metabolites was recovered in urine, while the major portion was recovered in feces (84%). More than 90% of the dose was excreted within 6 and 5 days following intravenous and oral administration, respectively. Following inhalation, excretion of unchanged olodaterol in urine within the dosing interval in healthy volunteers at steady state accounted for 5% to 7% of the dose.

Special Populations

A pharmacokinetic meta-analysis showed that no dose adjustment is necessary based on the effect of age, gender, and weight on systemic exposure in COPD patients after inhalation of STRIVERDI RESPIMAT.

Renal Impairment

Olodaterol levels were increased by approximately 40% in subjects with severe renal impairment. A study in subjects with mild and moderate renal impairment was not performed.

Hepatic Impairment
Subjects with mild and moderate hepatic impairment showed no changes in C_{max} or AUC, nor did protein binding differ between mild and moderate hepatically impaired subjects and their healthy controls. A study in subjects with severe hepatic impairment was not performed.

Drug-Drug Interactions
Drug-drug interaction studies were carried out using fluconazole as a model inhibitor of CYP 2C9 and ketoconazole as a potent P-gp (and CYP3A4, 2C8, 2C9) inhibitor.

Fluconazole: Co-administration of 400 mg fluconazole once a day for 14 days had no relevant effect on systemic exposure to olodaterol.

Ketoconazole: Co-administration of 400 mg ketoconazole once a day for 14 days increased olodaterol C_{max} by 66% and AUC_{0-1} by 68%.

Tiotropium: Co-administration of tiotropium bromide, delivered as fixed-dose combination with olodaterol, for 21 days had no relevant effect on systemic exposure to olodaterol, and vice versa.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Two-year inhalation studies were conducted in rats and mice to assess the carcinogenic potential of olodaterol. Lifetime treatment of female rats induced leiomyomas of the mesovarium at doses of 25.8 and 270 mcg/kg/day (approximately 18- and 198-fold, respectively, the MRHDID on an AUC basis). No tumor findings were observed in male rats at doses up to 270 mcg/kg/day (approximately 230-fold the MRHDID on an AUC basis). Lifetime treatment of female mice induced leiomyomas and leiomyosarcomas of the uterus at doses ≥76.9 mcg/kg/day (approximately 106-fold the MRHDID on an AUC basis). No tumor findings were observed in male mice at doses up to 255 mcg/kg/day (approximately 455-fold the MRHDID on an AUC basis). Increases in leiomyomas and leiomyosarcomas of the female rodent reproductive tract have been similarly demonstrated with other β_2-adrenergic agonist drugs. The relevance of these findings to human use is unknown.

Olodaterol was not mutagenic in the *in vitro* Ames test or in the *in vitro* mouse lymphoma assay. Olodaterol produced increased frequency of micronuclei in rats after intravenous doses. The increased frequency of micronuclei was likely related to drug enhanced (compensatory) erythropoiesis. The mechanism for induction of micronuclei formation is likely not relevant at clinical exposures.

Olodaterol did not impair male or female fertility in rats at inhalation doses up to 3,068 mcg/kg/day (approximately 2,322 times the MRHDID on an AUC basis).

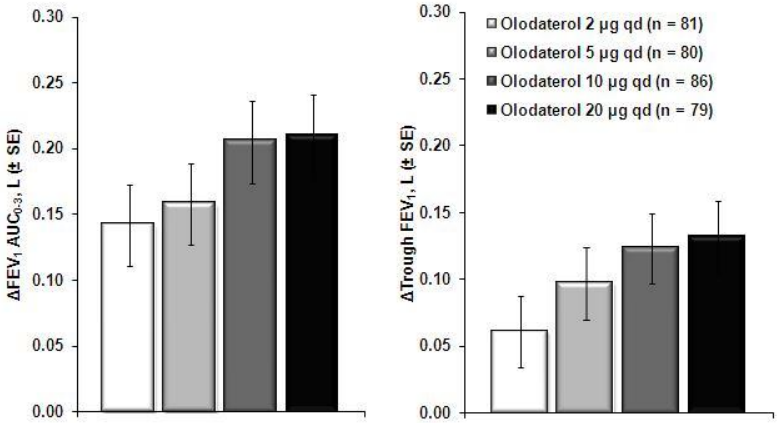
14 CLINICAL STUDIES

The STRIVERDI RESPIMAT clinical development program included three dose-ranging trials in COPD patients, four dose-ranging trials in asthma patients, and eight confirmatory trials in patients with COPD.

Dose-ranging trials

The first COPD dose-ranging trial was a randomized, double-blind, placebo-controlled, single-dose, 5-way cross-over trial in 36 patients. Results demonstrated dose-related improvements in forced expiratory volume in one second (FEV_1) compared to placebo. The difference in trough FEV_1 from placebo for the 2, 5, 10, and 20 mcg doses were 0.07L (95% CI 0.03, 0.11), 0.10L (0.06, 0.14), 0.11L (0.07, 0.15), and 0.12L (0.08, 0.16), respectively. The second COPD dose-ranging trial was a 4-week, randomized, double-blind, placebo-controlled, parallel group trial in 405 patients. Dose-related improvements in lung function were also seen, with no added benefit of the 20 mcg dose over the 10 mcg dose (Figure 1). The third COPD dose-ranging trial was a randomized, double-blind, 4-way cross-over, dose-regimen trial in 47 patients. Treatment arms included 2 mcg twice-daily, 5 mcg once-daily, 5 mcg twice-daily, and 10 mcg once-daily. There was no clear difference in treatment effect when comparing twice-daily dosing to once-daily dosing.

Figure 1. Difference from placebo for STRIVERDI RESPIMAT for FEV_1 AUC_{0-3hr} and trough FEV_1 after 4 weeks



Four randomized, double-blind, placebo-controlled dose-ranging trials were performed in patients with asthma, evaluating doses from 2 to 20 mcg. Results from patients with asthma were consistent with results from dose-ranging trials in patients with COPD. **STRIVERDI RESPIMAT is not indicated for asthma.**

Based upon the results of the dose-ranging trials, 5 and 10 mcg doses were further evaluated in the confirmatory COPD trials.

Confirmatory Trials

The eight confirmatory trials in the STRIVERDI RESPIMAT clinical development program were four pairs of replicate, randomized, double-blind, placebo-controlled trials in 3533 COPD patients (1281 received the 5 mcg dose, 1284 received the 10 mcg dose):
(i) two replicate, placebo-controlled, parallel group, 48 week trials (Trials 1 and 2)
(ii) two replicate, placebo- and active- [formoterol 12 mcg twice-daily] controlled, parallel group, 48-week trials (Trials 3 and 4)
(iii) two replicate, placebo- and active- [formoterol 12 mcg twice-daily] controlled, 6-week cross-over trials (Trials 5 and 6)
(iv) two replicate, placebo- and active- [tiotropium bromide 18 mcg once-daily] controlled, 6-week cross-over trials (Trials 7 and 8).

These eight trials enrolled patients who were 40 years of age or older with a clinical diagnosis of COPD, a smoking history of at least 10 pack-years, and moderate to very severe pulmonary impairment (post-bronchodilator FEV_1 less than 80% predicted normal [GOLD II – IV] and a post-bronchodilator FEV_1 to FVC ratio of less than 70%).

The majority of the 3104 patients in the 48-week trials (Trials 1 and 2, Trials 3 and 4) were male (77%), white (66%) or Asian (32%), with a mean age of 64 years. Mean post-bronchodilator FEV_1 was 1.38 L (GOLD II [50%], GOLD III [40%], GOLD IV [10%]). Mean $beta_2$-agonist responsiveness was 15% of baseline (0.16 L). With the exception of other LABAs, all pulmonary medications were allowed as concomitant therapy (e.g., tiotropium [24%], ipratropium [25%], inhaled corticosteroids [45%], xanthines [16%]); patient enrollment was stratified by tiotropium use. In all four trials, the primary efficacy endpoints were change from pre-treatment baseline in FEV_1 AUC_{0-3} and trough (pre-dose) FEV_1 (after 12 weeks in Trials 1 and 2; after 24 weeks in Trials 3 and 4).

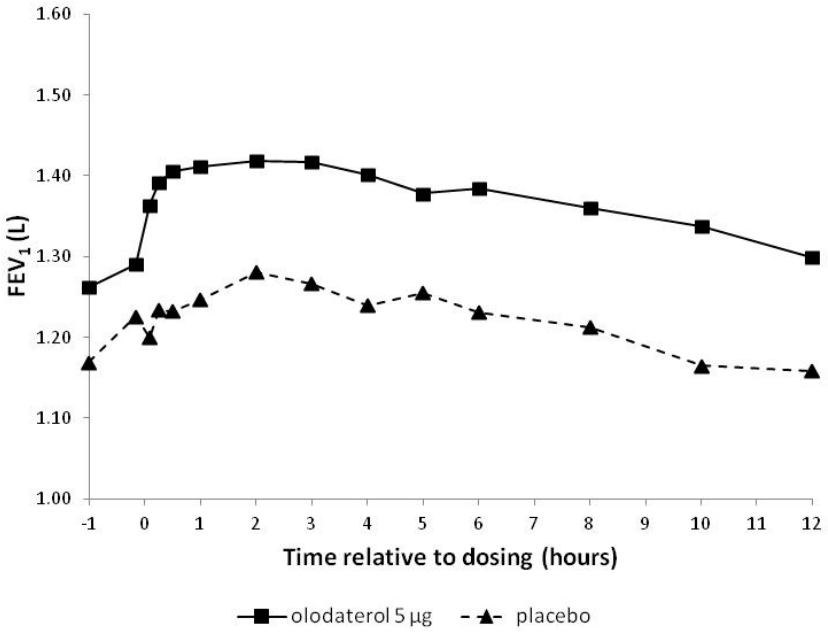
In all four 48-week trials, STRIVERDI RESPIMAT 5 mcg demonstrated significant improvements in FEV_1 AUC_{0-3hr} compared to placebo at week 12 (Table 2) and at week 24. In the four 48-week trials, STRIVERDI RESPIMAT 5 mcg demonstrated significant improvements in trough FEV_1 compared to placebo at week 12 (Table 2; 3 of 4 trials) and at week 24 (4 trials). STRIVERDI RESPIMAT 5 mcg demonstrated a bronchodilatory treatment effect at 5 minutes after the first dose with a mean increase in FEV_1 compared to placebo of 0.11L (range: 0.10L to 0.12L). The 10 mcg dose demonstrated no additional benefit over the 5 mcg dose (data not shown). Patients treated with STRIVERDI RESPIMAT 5 mcg used less rescue albuterol compared to patients treated with placebo.

Table 2. Differences from placebo for STRIVERDI RESPIMAT 5 mcg for FEV_1 AUC_{0-3hr} and trough FEV_1 at week 12

	Difference from placebo [L] (95% CI)	
	FEV_1 AUC_{0-3hr}	**Trough FEV_1**
Trial 1	0.16 (0.12, 0.21)	0.08 (0.04, 0.13)
Trial 2	0.13 (0.09, 0.18)	0.03 (-0.01, 0.08)
Trial 3	0.18 (0.14, 0.22)	0.08 (0.04, 0.12)
Trial 4	0.15 (0.11, 0.18)	0.06 (0.02, 0.10)

In Trials 1 and 2, serial spirometric evaluations were performed pre-dose and up to 12 hours after dosing in a sub-group of 562 patients (201 patients receiving STRIVERDI RESPIMAT 5 mcg, 192 patients receiving 10 mcg, and 169 patients receiving placebo) after 12 weeks of treatment. Dosing occurred at approximately the same time of the day in the morning. The spirometric curves from Trial 1 are displayed in Figure 2.

Figure 2 **FEV_1 profile for STRIVERDI RESPIMAT 5 mcg and placebo at week 12 (pre-dose and up to 12 hrs post-dose) (Trial 1)**



The bronchodilatory profile of STRIVERDI RESPIMAT 5 mcg over the 24 hour dosing interval was evaluated in two pairs of replicate, placebo- and active-controlled, 6 week cross-over trials in 199 patients (Trials 5 and 6) and 230 patients (Trials 7 and 8) with moderate to very severe COPD. Mean $beta_2$-agonist responsiveness ranged from 14% -21% of baseline (0.18 to 0.22 L). All pulmonary medications were allowed as concomitant therapy with the exception of other LABAs (all trials) and anti-cholinergics (Trials 7 and 8). In all four trials, the primary endpoints were change from pre-treatment baseline in FEV_1 $AUC_{0\text{-}12hr}$ and FEV_1 $AUC_{12\text{-}24hr}$ after 6 weeks; although not a primary endpoint, trough FEV_1 was also measured after 6 weeks. Results are shown in Table 3.

Table 3: Differences from placebo for STRIVERDI RESPIMAT 5 mcg after 6 weeks in cross-over spirometry trials

	Difference from placebo [L] (95% CI)		
	FEV_1 $AUC_{0\text{-}12hr}$	**FEV_1 $AUC_{12\text{-}24\ hr}$**	**Trough FEV_1**
Trial 5	0.15 (0.11, 0.18)	0.11 (0.07, 0.15)	0.11 (0.06, 0.15)
Trial 6	0.17 (0.14, 0.21)	0.12 (0.08, 0.15)	0.10 (0.05, 0.15)
Trial 7	0.19 (0.15, 0.23)	0.13 (0.09, 0.17)	0.13 (0.10, 0.17)
Trial 8	0.20 (0.16, 0.23)	0.15 (0.12, 0.19)	0.13 (0.10, 0.17)

16 HOW SUPPLIED/STORAGE AND HANDLING

STRIVERDI RESPIMAT Inhalation Spray is supplied in a labeled carton containing one STRIVERDI RESPIMAT cartridge and one STRIVERDI RESPIMAT inhaler.

The STRIVERDI RESPIMAT cartridge is an aluminum cylinder with a tamper protection seal on the cap. The STRIVERDI RESPIMAT cartridge is only intended for use with the STRIVERDI RESPIMAT inhaler.

The STRIVERDI RESPIMAT inhaler is a cylindrical-shaped plastic inhalation device with a gray-colored body and a clear base. The clear base is removed to insert the cartridge. The inhaler contains a dose indicator. The yellow colored cap and the written information on the label of the gray inhaler body indicates that it is labeled for use with the STRIVERDI RESPIMAT cartridge.

STRIVERDI RESPIMAT Inhalation Spray is available as:
STRIVERDI RESPIMAT Inhalation Spray: 60 metered actuations (NDC 0597-0192-61)
STRIVERDI RESPIMAT Inhalation Spray: 28 metered actuations (NDC 0597-0192-31) (institutional pack)

The STRIVERDI RESPIMAT cartridge has a net fill weight of at least 4 grams and when used with the STRIVERDI RESPIMAT inhaler, is designed to deliver the labeled number of metered actuations (60 or 28) after preparation for use; which is respectively equivalent to 30 or 14 days of medication when used according to the directions for use (one dose equals two actuations).

When the labeled number of metered actuations (60 or 28) has been dispensed from the inhaler, the STRIVERDI RESPIMAT locking mechanism will be engaged and no more actuations can be dispensed.

After assembly, the STRIVERDI RESPIMAT inhaler should be discarded at the latest 3 months after first use or when the locking mechanism is engaged , whichever comes first.

Keep out of reach of children. Do not spray into eyes.

Storage
Store at 25°C (77°F); excursions permitted to 15°C–30°C (59°F–86°F) [see USP Controlled Room Temperature]. Avoid freezing.

17 PATIENT COUNSELING INFORMATION

See FDA-Approved Patient Labeling (Medication Guide and Instructions for Use).

17.1 Asthma-Related Death

Inform patients that LABA, such as STRIVERDI RESPIMAT, increase the risk of asthma-related death. STRIVERDI RESPIMAT is not indicated for the treatment of asthma.

17.2 Preparation for Use and Priming

Instruct patients that priming STRIVERDI RESPIMAT is essential to ensure appropriate content of the medication in each actuation.

When using the unit for the first time, the STRIVERDI RESPIMAT cartridge is inserted into the STRIVERDI RESPIMAT inhaler and the unit is primed. STRIVERDI RESPIMAT patients are to actuate the inhaler toward the ground until an aerosol cloud is visible and then repeat the process three more times. The unit is then considered primed and ready for use. If not used for more than 3 days, patients are to actuate the inhaler once to prepare the inhaler for use. If not used for more than 21 days, patients are to actuate the inhaler until an aerosol cloud is visible and then repeat the process three more times to prepare the inhaler for use.

17.3 Not for Acute Symptoms

STRIVERDI RESPIMAT is not meant to relieve acute asthma symptoms or exacerbations of COPD and extra doses should not be used for that purpose. Acute symptoms should be treated with an inhaled, short-acting beta$_2$-agonist such as albuterol. (The healthcare provider should provide the patient with such medication and instruct the patient in how it should be used.)

Instruct patients to notify their physician immediately if they experience any of the following:

- Worsening of symptoms
- Decreasing effectiveness of inhaled, short-acting beta$_2$-agonists
- Need for more inhalations than usual of inhaled, short-acting beta$_2$-agonists
- Significant decrease in lung function as outlined by the physician

Instruct patients not to stop therapy with STRIVERDI RESPIMAT without physician/provider guidance since symptoms may recur after discontinuation.

17.4 Do Not Use Additional Long-Acting Beta$_2$-Agonists

Patients who have been taking inhaled, short-acting beta$_2$-agonists on a regular basis should be instructed to discontinue the regular use of these products and use them only for the symptomatic relief of acute symptoms.

When patients are prescribed STRIVERDI RESPIMAT, other inhaled medications containing long-acting beta$_2$-agonists should not be used. Patients should not use more than the recommended once-daily dose of STRIVERDI RESPIMAT. Excessive use of sympathomimetics may cause significant cardiovascular effects, and may be fatal.

17.5 Risks Associated with Beta$_2$-Agonist Therapy

Inform patients of adverse effects associated with beta$_2$-agonists, such as palpitations, chest pain, rapid heart rate, tremor, or nervousness.

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Ridgefield, CT 06877 USA

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Medication Guide
STRIVERDI® RESPIMAT® (STRIH ver dee– RES peh mat)
(olodaterol) inhalation spray

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

What is the most important information I should know about STRIVERDI RESPIMAT?

STRIVERDI RESPIMAT has been approved for chronic obstructive pulmonary disease (COPD) only. STRIVERDI RESPIMAT is NOT to be used in asthma.

STRIVERDI RESPIMAT can cause serious side effects, including:

- **People with asthma who take long-acting beta$_2$-adrenergic agonist (LABA) medicines, such as STRIVERDI RESPIMAT, have an increased risk of death from asthma problems.**
- **It is not known if LABA medicines, such as STRIVERDI RESPIMAT, increase the risk of death in people with COPD.**
- Get emergency medical care if:
  - breathing problems worsen quickly
  - you use your rescue inhaler medicine, but it does not relieve your breathing problems

What is STRIVERDI RESPIMAT?

STRIVERDI RESPIMAT is used long term, 1 time each day, in controlling symptoms of COPD in adults with COPD.

LABA medicines such as STRIVERDI RESPIMAT help the muscles around the airways in your lungs stay relaxed to prevent symptoms, such as wheezing, cough, chest tightness, and shortness of breath.

STRIVERDI RESPIMAT is not for use to treat sudden symptoms of COPD. Always have a rescue medicine with you to treat sudden symptoms. If you do not have a rescue inhaler, contact your healthcare provider to have one prescribed for you.

It is not known if STRIVERDI RESPIMAT is safe and effective in people with asthma.

STRIVERDI RESPIMAT should not be used in children. It is not known if STRIVERDI RESPIMAT is safe and effective in children.

Who should not use STRIVERDI RESPIMAT?

Do not use STRIVERDI RESPIMAT if you have asthma.

What should I tell my healthcare provider before using STRIVERDI RESPIMAT?

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 STRIVERDI RESPIMAT can harm your unborn baby.
- are breastfeeding. It is not known if STRIVERDI RESPIMAT passes into your breast milk and if it can harm your baby.
- are allergic to STRIVERDI RESPIMAT or any of its ingredients, any other medicines, or food products.

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

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

How should I use STRIVERDI RESPIMAT?

- The STRIVERDI RESPIMAT inhaler has a slow-moving mist that helps you inhale the medicine.
- **Read the step-by-step instructions for using STRIVERDI RESPIMAT at the end of this Medication Guide.**
- Use STRIVERDI RESPIMAT exactly as your healthcare provider tells you to use it.
- **Use 1 dose (2 puffs) of STRIVERDI RESPIMAT, 1 time each day, at the same time of the day.**
- If you miss a dose of STRIVERDI RESPIMAT, take it as soon as you remember. Do not take more than 1 dose (2 puffs) in 24 hours.
- **Do not spray STRIVERDI RESPIMAT in your eyes.**
- Always use the new STRIVERDI RESPIMAT inhaler that is provided with each new prescription.
- **STRIVERDI RESPIMAT does not relieve sudden symptoms of COPD.** Always have a rescue inhaler medicine with you to treat sudden

symptoms. If you do not have a rescue inhaler medicine, call your healthcare provider to have one prescribed for you.

- Do not stop using STRIVERDI RESPIMAT or other medicines to control or treat your COPD unless told to do so by your healthcare provider because your symptoms might get worse. Your healthcare provider will change your medicines as needed.
- **Do not use STRIVERDI RESPIMAT:**
  - more often than prescribed for you, or
  - with other LABA medicines
- **Call your healthcare provider or get emergency medical care right away if:**
  - your breathing problems worsen with STRIVERDI RESPIMAT
  - you need to use your rescue medicine more often than usual
  - your rescue inhaler medicine does not work as well for you at relieving your symptoms

What are the possible side effects with STRIVERDI RESPIMAT?

STRIVERDI RESPIMAT can cause serious side effects, including:

- **See "What is the most important information I should know about STRIVERDI RESPIMAT?"**
- If your COPD symptoms worsen over time do not increase your dose of STRIVERDI RESPIMAT, instead call your healthcare provider.
- sudden shortness of breath that may be life-threatening
- fast or irregular heartbeat, palpitations
- chest pain
- increased blood pressure
- low blood potassium (which may cause symptoms of muscle spasm, muscle weakness or abnormal heart rhythm)
- high blood sugar
- 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.

Common side effects of STRIVERDI RESPIMAT include:

- runny nose
- upper respiratory infection
- bronchitis
- urinary tract infection
- cough
- dizziness
- rash
- diarrhea
- back pain
- joint pain

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 STRIVERDI RESPIMAT. 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 should I store STRIVERDI RESPIMAT?

- Store STRIVERDI RESPIMAT at room temperature between 59°F to 86°F (15°C to 30°C).
- Do not freeze your STRIVERDI cartridge or RESPIMAT inhaler.
- **Keep your STRIVERDI RESPIMAT and all medicines out of the reach of children.**

General Information about safe and effective use of STRIVERDI RESPIMAT

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

This Medication Guide summarizes the most important information about STRIVERDI RESPIMAT. If you would like more information, talk with your healthcare provider. You can ask your healthcare provider or pharmacist for information about STRIVERDI RESPIMAT that was written for healthcare professionals.

For more information about STRIVERDI RESPIMAT or a video demonstration on how to use STRIVERDI RESPIMAT, go to www.STRIVERDI.com, or scan the code below. You may also call 1-800-542-6257 or (TTY) 1-800-459-9906 for further information about STRIVERDI RESPIMAT.

What are the ingredients in STRIVERDI RESPIMAT?

Active ingredient: Olodaterol

Inactive ingredients: water, benzalkonium chloride, edetate disodium, and anhydrous citric acid

Instructions for Use

STRIVERDI® RESPIMAT® (STRIH ver dee- RES peh mat)

(olodaterol) inhalation spray

For Oral Inhalation Only
Do not spray STRIVERDI RESPIMAT into your eyes.

Read these Instructions for Use before you start using STRIVERDI RESPIMAT and each time you get a refill. There may be new information. This leaflet does not take the place of talking to your healthcare provider about your medical condition or your treatment.

Your STRIVERDI RESPIMAT cartridge contains either 60 puffs (equal to 30 doses of medicine) or 28 puffs (equal to 14 doses of medicine) after you prepare your inhaler for the first use. There is enough medicine for 30 days or 14 days when it is used as 2 puffs 1 time each day.

Before your STRIVERDI RESPIMAT inhaler is used for the first time, the STRIVERDI RESPIMAT cartridge must be inserted into the STRIVERDI RESPIMAT inhaler and then primed. The instructions below show you how to prepare and prime the inhaler for first time use and how to use the inhaler for daily dosing.

Do not turn the clear base before inserting the cartridge.

The STRIVERDI RESPIMAT inhaler

Prepare For First Time Use

Figure 1

Step 1. With the yellow cap closed, press the safety catch while pulling off the clear base. See Figure 1.

Be careful not to touch the piercing element located inside the bottom of the clear base.


Figure 2

Step 2. Write the **discard by** date on the label of the STRIVERDI RESPIMAT inhaler. The **discard by** date is 3 months from the date the cartridge is inserted into the inhaler. See Figure 2.

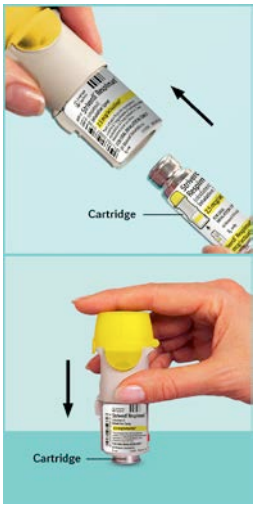

Figure 3

Step 3. Take the STRIVERDI RESPIMAT cartridge out of the box. Push the ***narrow*** end of the cartridge into the inhaler. The base of the cartridge will not sit flush with the inhaler. **About 1/8 of an inch will remain visible** when the cartridge is correctly inserted. See Figure 3.

The cartridge can be pushed against a firm surface to ensure that it is correctly inserted. See Figure 3.

Do not remove the cartridge once it has been inserted into the inhaler.

Step 4. Put the clear base back into place. See Figure 4.

Do not remove the clear base again.

Your STRIVERDI RESPIMAT inhaler should not be taken apart after you have inserted the cartridge and put the clear base back.

Figure 4

Prime For First Time Use

The following steps are needed to fill the dosing system the first time you use it and will not affect the number of doses available. After preparation and initial priming, your STRIVERDI RESPIMAT inhaler will be able to deliver the labeled number of doses (30 or 14).

Proper priming of the inhaler is important to make sure the correct amount of medicine is delivered.

Figure 5

Step 5. Hold the STRIVERDI RESPIMAT inhaler upright, with the yellow cap closed, to avoid accidental release of the dose.

Turn the clear base in the direction of the black arrows on the label until it clicks (half a turn). See Figure 5.


Figure 6

Step 6. Flip the yellow cap until it snaps fully open. See Figure 6.

Figure 7

Step 7. Point the STRIVERDI RESPIMAT inhaler toward the ground (away from your face).

Press the dose release button. See Figure 7. Close the yellow cap.

Repeat Steps 5, 6, and 7 until a spray is visible.

Once the spray is visible, you must repeat Steps 5, 6, and 7 three more times to make sure the inhaler is prepared for

use.

Your STRIVERDI RESPIMAT inhaler is now ready to use.

These steps will not affect the number of doses available. After preparation and initial priming, your STRIVERDI RESPIMAT inhaler will be able to deliver the labeled number of doses (30 or 14).

Daily Dosing

Figure A

Step A. Hold the STRIVERDI RESPIMAT inhaler upright with the yellow cap closed, so you do not accidentally release a dose of medicine.

Turn the clear base in the direction of the black arrows on the label until it clicks (half a turn). See Figure A.

Figure B

Step B. Flip the yellow cap until it snaps fully open.

Breathe out slowly and fully, and then close your lips around the end of the mouthpiece without covering the air vents. See Figure B.

Point your STRIVERDI RESPIMAT inhaler to the back of your throat.

While taking in a slow, deep breath through your mouth, press the dose release button and continue to breathe in slowly for as long as you can.

Hold your breath for 10 seconds or for as long as comfortable. Repeat Step A and Step B so that you get the full dose.

Close the yellow cap until you use your STRIVERDI RESPIMAT inhaler again.

Helpful Hints for Daily Dosing:

Using the STRIVERDI RESPIMAT inhaler requires 3 simple steps. A helpful way to remember the steps for Daily Dosing is to remember **TOP**:

Turn the clear base
Open the cap and close your lips around the mouthpiece
Press the dose-release button and inhale

These steps should be performed two times to receive the proper dose of medicine.

If your STRIVERDI RESPIMAT inhaler has not been used for more than 3 days, spray 1 puff toward the ground to prepare the inhaler for use.

If your STRIVERDI RESPIMAT inhaler has not been used for more than 21 days, repeat Steps 5, 6, and 7 until a spray is visible. Then repeat Steps 5, 6, and 7 three more times to prepare the inhaler for use.

For more information about STRIVERDI RESPIMAT or a video demonstration on how to use STRIVERDI RESPIMAT, go to www.STRIVERDI.com, or scan the code below. You may also call 1-800-542-6257 or (TTY) 1-800-459-9906 for further information about STRIVERDI RESPIMAT.

When should I get a new STRIVERDI RESPIMAT inhaler?

30 dose product

STRIVERDI RESPIMAT is available with 30 or 14 doses of medicine. Two puffs from STRIVERDI RESPIMAT equals one dose of medicine. The dose indicator shows approximately how much medicine is left. When the pointer enters the red area of the scale, there is enough medicine for 7 days (30 dose product) or 3 days (14 dose product). This is when you need to refill your prescription or ask your doctor if you need another prescription for STRIVERDI RESPIMAT Inhalation Spray.

Once the dose indicator has reached the end of the scale, all puffs have been used and the STRIVERDI RESPIMAT inhaler locks automatically. At this point, the base cannot be turned any further.

Throw away the STRIVERDI RESPIMAT inhaler 3 months after insertion of cartridge into inhaler, even if all the medicine has not

14 dose product

been used, or when the inhaler is locked, whichever comes first.

Questions and Answers about your STRIVERDI RESPIMAT inhaler

What if...	Reason	What to do
I can not turn the base easily?	The STRIVERDI RESPIMAT inhaler is already prepared and ready to use. The STRIVERDI RESPIMAT inhaler is locked and all the medicine has been used.	The STRIVERDI RESPIMAT inhaler can be used as it is. Prepare and use a new STRIVERDI RESPIMAT inhaler.
I can not press the dose release button?	The clear base has not been turned.	Turn the clear base until it clicks (half a turn).
The clear base springs back after I have turned it and a small amount of moisture is released?	The clear base was not turned far enough.	Prepare the STRIVERDI RESPIMAT inhaler for use by turning the clear base until it clicks (half a turn).

I can turn the clear base past the point where it clicks?	Either the dose release button has been pressed, or the clear base has been turned too far.	With the yellow cap closed, turn the clear base until it clicks (half a turn).

How should I care for my STRIVERDI RESPIMAT inhaler?
Clean the mouthpiece, including the metal part inside the mouthpiece, with a damp cloth or tissue only, at least 1 time a week. Any minor discoloration in the mouthpiece does not affect your STRIVERDI RESPIMAT inhaler.

If the outside of your STRIVERDI RESPIMAT inhaler gets dirty, wipe it with a damp cloth.

How should I store my STRIVERDI RESPIMAT inhaler?
- Store STRIVERDI RESPIMAT at Room Temperature between 59°F to 86°F (15°C to 30°C).
- Do not freeze your STRIVERDI RESPIMAT cartridge and inhaler

Keep your STRIVERDI RESPIMAT cartridge and inhaler out of the reach of children.

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

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