This article was sponsored by Boehringer Ingelheim Pharmaceuticals, Inc.

Improving Lung Function (FEV_1) in COPD Through Appropriate Counseling on Use of Inhaled Medications

Chronic obstructive pulmonary disease (COPD) is a progressive, but treatable, disease characterized by airflow limitation and inflammation.[1] Although COPD affects people of all ages, it is primarily a disease of older adults, with approximately three-fourths (74.2%) of all patients with COPD older than 55 years.[2] Pharmacists have a pivotal role to help ensure that treatments for COPD deliver on patients' expectations to help them manage their disease effectively. Part of this is accomplished through understanding the role of guideline-recommended pharmacotherapy, such as the use of multiple bronchodilator classes and long-acting drug options.[1] Additionally, instruction on the proper use of drug products and delivery devices is key to efficacy and experience with prescribed medications. This article reviews this information, as well as a treatment option for management of COPD.

MECHANISM OF ACTION

One chronic management treatment is the combination of 2 bronchodilatory medications: muscarinic antagonists and long-acting $beta_2$-agonists (LABAs).[1] STIOLTO® RESPIMAT® (tiotropium bromide and olodaterol) inhalation spray is one such combination product. Both medications in STIOLTO RESPIMAT exert bronchodilatory effects. The muscarinic antagonist tiotropium inhibits M_3 receptors of the smooth muscle in the lung, resulting in bronchodilation, while olodaterol binds to and activates $beta_2$-adrenoceptors in the airways, resulting in cyclic adenosine monophosphate-mediated bronchodilation.[3]

INDICATION

STIOLTO RESPIMAT is a combination of tiotropium, an anticholingeric, and olodaterol, a long-acting $beta_2$ adrenergic agonist (LABA), indicated for long-term, once-daily maintenance treatment of airflow obstruction in patients with COPD, including chronic bronchitis and/or emphysema.[3]

IMPORTANT LIMITATIONS OF USE

STIOLTO RESPIMAT is not indicated to treat acute deteriorations of COPD. STIOLTO RESPIMAT is not indicated to treat asthma. The safety and effectiveness of STIOLTO RESPIMAT in asthma have not been established.[3]

IMPORTANT SAFETY INFORMATION

As STIOLTO RESPIMAT contains the LABA olodaterol, the medication carries a boxed warning for an increased risk of asthma-related death.[3]

WARNING: ASTHMA-RELATED DEATH

Long-acting $beta_2$-adrenergic agonists (LABA) such as olodaterol, one of the active ingredients in STIOLTO RESPIMAT, 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) with 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 all LABA, including olodaterol, one of the active ingredients in STIOLTO RESPIMAT. The safety and efficacy of STIOLTO RESPIMAT in patients with asthma have not been established. STIOLTO RESPIMAT is not indicated for the treatment of asthma.

EFFICACY DATA

In two 52-week randomized, double-blind, parallel group studies, patients received STIOLTO RESPIMAT, tiotropium alone, or olodaterol alone through the RESPIMAT inhaler. Enrolled patients were 40 years or older with a clinical diagnosis of COPD, a smoking history longer than 10 pack-years, severe pulmonary impairment, and a forced expiratory volume in 1 second (FEV_1)/forced vital capacity ratio after receiving a bronchodilator of less than 70%. Treatments were administered at the same time of day every morning.[3]

Please see additional Important Safety Information throughout this article and Brief Summary of full Prescribing Information adjacent to this article, including boxed WARNING.

Researchers evaluated the primary end points of a change in baseline FEV_1 area under the curve $(AUC)_{0\text{-}3h}$ and trough FEV_1 levels after 24 weeks of treatment. Patients receiving STIOLTO RESPIMAT experienced a 256-mL improvement in FEV_1 $AUC_{0\text{-}3h}$, which was significantly greater (P <.0001) than improvements on the same measure with tiotropium alone (139 mL) or olodaterol alone (133 mL). Increases in trough FEV_1 after 24 weeks with STIOLTO RESPIMAT averaged 136 mL, significantly greater (P <.0001) than the mean 65-mL improvement with tiotropium or the mean 54-mL increase with olodaterol.[3]

SAFETY CONSIDERATIONS

STIOLTO® RESPIMAT® (tiotropium bromide and olodaterol) inhalation spray has been used by 1988 patients across two 52-week active-controlled trials, a 12-week placebo-controlled trial, three 6-week placebo-controlled crossover trials, and several other smaller studies. Common adverse events were nasopharyngitis, cough, and back pain, each of which occurred with STIOLTO RESPIMAT more often than with active control medications, at an incidence greater than 3%.[3]

DOSAGE AND ADMINISTRATION

STIOLTO RESPIMAT is administered using the RESPIMAT inhaler, which is designed to deliver medication in a slow-moving mist independent of inspiratory effort.[4] As with all inhaled drugs, the actual amount of medication delivered to the lungs 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).[3] Upon actuation, a specially engineered nozzle propels 2 fine jets of liquid at a precise angle to form a slow-moving mist of approximately 1.5 seconds.[4]

STIOLTO RESPIMAT is administered as 2 inhalations once daily at the same time each day. No more than 2 inhalations should be used in a given 24-hour period. Before the first use or after 21 days of nonuse, patients should actuate the inhaler toward the ground until an aerosol cloud is visible and should then repeat the actuation 3 times. Additionally, if the medication is not used for 3 days, the inhaler must be actuated once before use.[3]

PREPARING AND USING THE STIOLTO RESPIMAT INHALER

Patients should be instructed on proper inhaler preparation methods for STIOLTO RESPIMAT before the first use. To start, with the cap closed, instruct patients to press the safety catch, pull to remove the clear base, and write the "discard by" date on the label (3 months from the date the cartridge is inserted). Then, instruct patients to place the narrow end of the cartridge into the inhaler (leaving about an eighth of an inch of the cartridge visible when the cartridge is fully inserted) and, finally, to replace the clear base.[3]

To prime the inhaler, instruct patients to hold it upright with the cap closed and turn the clear base one-half turn in the direction of the black arrows on the label until the inhaler clicks. Then, patients should flip the green cap, point the inhaler toward the ground,

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ADDITIONAL IMPORTANT SAFETY INFORMATION

CONTRAINDICATION

All LABA are contraindicated in patients with asthma without use of a long-term asthma control medication. STIOLTO is contraindicated in patients with hypersensitivity to tiotropium, ipratropium (atropine derivatives), olodaterol, or any component of this product.

In clinical trials and postmarketing experience with tiotropium, immediate hypersensitivity reactions, including angioedema (including swelling of the lips, tongue, or throat), itching, or rash have been reported. Hypersensitivity reactions were also reported in clinical trials with STIOLTO.

WARNINGS AND PRECAUTIONS

STIOLTO should not be initiated in patients with acutely deteriorating COPD, which may be a life-threatening condition, or used as rescue therapy for acute symptoms. Acute symptoms should be treated with an inhaled short-acting $beta_2$-agonist. Patients who have been taking inhaled, short-acting $beta_2$-agonists on a regular basis should discontinue the regular use of these drugs and use them only for acute respiratory symptoms.

STIOLTO should not be used more often or at higher doses than recommended, or in conjunction with other LABA as an overdose may result.

Immediate hypersensitivity reactions, including urticaria, angioedema, rash, bronchospasm, anaphylaxis, or itching may occur after administration of STIOLTO. If such a reaction occurs, discontinue therapy with STIOLTO and consider alternative treatments. Patients with a history of hypersensitivity reactions to atropine or its derivatives should be closely monitored for similar hypersensitivity reactions to STIOLTO.

If paradoxical bronchospasm occurs, STIOLTO should be dis-

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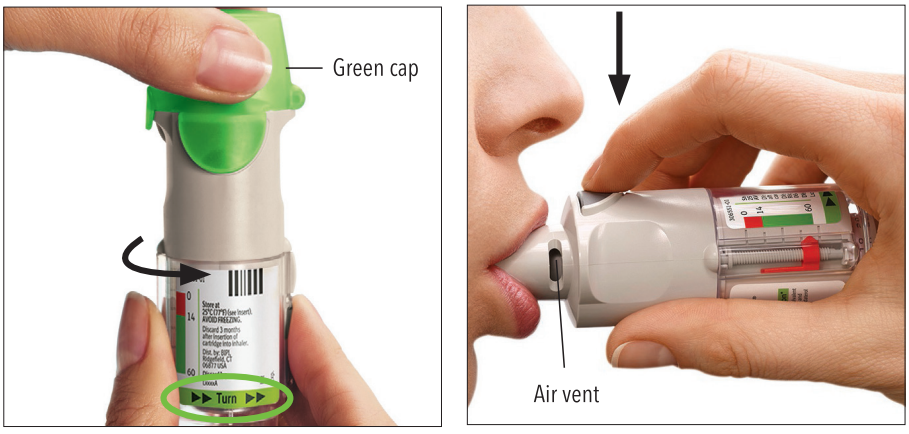
and press the dose-release button. This action of closing and opening the green cap and pressing the dose-release button while aiming the inhaler at the ground should be repeated until a fine mist is visible, and then 3 additional times after the first visible mist forms. At this point, the inhaler is ready to deliver the labeled number of doses (30).[3]

To administer the inhaler on a daily basis, patients should remember the acronym **TOP**: (1) **T**urn the clear base in the direction of the black arrows one-half turn until it clicks; (2) **O**pen the green cap, exhale completely, and close your lips around the mouthpiece, being careful not to cover the inhaler air vents; and (3) **P**ress the dose-release button to inhale medication. Each daily dose consists of 2 inhalations, with both inhalations administered on a daily basis at the same time of day (see FIGURE).[3]

FIGURE. DAILY ADMINISTRATION OF STIOLTO® RESPIMAT® (TIOTROPIUM BROMIDE AND OLODATEROL) INHALATION SPRAY[3]



Turn the clear base in the direction of the black arrows one-half turn until it clicks.
Open the green cap, exhale completely, and close lips around the mouthpiece, being careful not to cover the inhaler's air vents.
Press the dose-release button to inhale medication.

These steps should be repeated 2 times to deliver the correct daily dose of STIOLTO RESPIMAT.

STIOLTO RESPIMAT must be prepared and primed before first use. Please see full Instructions for Use for additional details on preparing and priming the inhaler, and how to use the inhaler for daily dosing.

IMPORTANT SAFETY INFORMATION

continued immediately.

STIOLTO 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, STIOLTO may need to be discontinued.

Use caution in patients with convulsive disorders, thyrotoxicosis, diabetes mellitus, ketoacidosis, in patients with known or suspected prolongation of the QT interval, and in patients who are unusually responsive to sympathomimetic amines.

Use with caution in patients with narrow-angle glaucoma. Instruct patients to contact a physician immediately if signs or symptoms of acute narrow-angle glaucoma develop (e.g., eye pain or discomfort, blurred vision, visual halos or colored images in association with red eyes from conjunctival congestion and corneal edema).

Use with caution in patients with urinary retention, which can be associated with symptoms like difficulty passing urine and painful urination in patients with prostatic hyperplasia or bladder-neck obstruction. Instruct patients to consult a physician immediately should any of these signs or symptoms develop.

Patients with moderate to severe renal impairment (creatinine clearance of ≤60 mL/min) treated with STIOLTO should be monitored closely for anticholinergic side effects.

Be alert to hypokalemia, which has the potential to produce adverse cardiovascular effects. Be alert to hyperglycemia.

ADVERSE REACTIONS

The most common adverse reactions with STIOLTO (>3% incidence and higher incidence than any of the comparators—tiotropium and/or olodaterol) were: nasopharyngitis, 12.4% (11.7%/12.6%), cough, 3.9% (4.4%/3.0%), and back pain, 3.6% (1.8%/3.4%).

Please see additional Important Safety Information throughout this article and Brief Summary of full Prescribing Information adjacent to this article, including boxed WARNING.

ROLE OF THE PHARMACIST

Understanding the role of pharmacologic management in COPD and being familiar with current guidelines, such as combination therapy and long-acting medications, is important. This knowledge can be used as pharmacists work with prescribers in identifying appropriate options for patients, including product selection that aligns with treatment guidelines.

Patients with COPD can be informed of the value of pharmacologic treatment and instructed on how to use inhaled medications, such as STIOLTO RESPIMAT. Counseling patients on the inhaler is a key point; with the patient's permission, pharmacists can prime the inhaler before dispensing the medication. Expressing the importance of the **TOP** acronym is important because it will remind patients of the proper use of the STIOLTO® RESPIMAT® (tiotropium bromide and olodaterol) inhalation spray inhaler.

IMPORTANT SAFETY INFORMATION

DRUG INTERACTIONS

- Use caution if administering adrenergic drugs because sympathetic effects of olodaterol may be potentiated.
- Concomitant treatment with xanthine derivatives, steroids, or diuretics may potentiate any hypokalemic effect of olodaterol.
- Beta agonists, such as olodaterol, can acutely worsen the ECG changes and/or hypokalemia that may result from administration of non-potassium sparing diuretics. The action of adrenergic agents on the cardiovascular system may be potentiated by monoamine oxidase inhibitors or tricyclic antidepressants or other drugs known to prolong the QTc interval. Therefore beta-agonists should be used with extreme caution in patients being treated with these drugs. Drugs that prolong the QTc interval may be associated with an increased risk of ventricular arrhythmias.
- Beta-blockers should be used with caution as they can inhibit the therapeutic effect of beta agonists which may produce severe bronchospasms in patients with COPD. 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, cardio selective beta-blockers could be considered, although they should be administered with caution.
- Avoid co-administration of STIOLTO with other anticholinergic-containing drugs as this may lead to an increase in anticholinergic adverse effects.

STIOLTO is for oral inhalation only. The STIOLTO cartridge is only intended for use with the STIOLTO RESPIMAT inhaler.

Inform patients not to spray STIOLTO into the eyes.

REFERENCES

1. Decramer M, Agusti AG, Bourbeau J, et al. Global strategy for the diagnosis, management, and prevention of chronic obstructive pulmonary disease. Global Initiative for Chronic Obstructive Lung Disease website. www.goldcopd.org. Updated 2016. Accessed April 8, 2016.

2. Centers for Disease Control and Prevention. Chronic obstructive pulmonary disease among adults—United States, 2011. *MMWR Morb Mortal Wkly Rep*. 2012;61(46):938-943.

3. Stiolto Respimat [prescribing information]. Ridgefield, CT: Boehringer Ingelheim Pharmaceuticals, Inc; 2016.

4. Dalby R, Spallek M, Voshaar T. A review of the development of Respimat Soft Mist Inhaler. *Int J Pharmaceutics*. 2004;283(1-2):1-9.

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STIOLTO® RESPIMAT® (tiotropium bromide and olodaterol) inhalation spray, for oral inhalation use

BRIEF SUMMARY OF PRESCRIBING INFORMATION

Please see package insert for full Prescribing Information

WARNING: ASTHMA-RELATED DEATH

Long-acting beta$_2$-adrenergic agonists (LABA) such as olodaterol, one of the active ingredients in STIOLTO RESPIMAT, 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) with 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 all LABA, including olodaterol, one of the active ingredients in STIOLTO RESPIMAT. The safety and efficacy of STIOLTO RESPIMAT in patients with asthma have not been established. STIOLTO RESPIMAT is not indicated for the treatment of asthma *[see Contraindications, Warnings and Precautions]*.

INDICATIONS AND USAGE: Maintenance Treatment of COPD: STIOLTO RESPIMAT is a combination of tiotropium and olodaterol indicated for long-term, once-daily maintenance treatment of airflow obstruction in patients with chronic obstructive pulmonary disease (COPD), including chronic bronchitis and/or emphysema. Important Limitations of Use: STIOLTO RESPIMAT is not indicated to treat acute deteriorations of COPD *[See Warnings and Precautions];* STIOLTO RESPIMAT is not indicated to treat asthma. The safety and effectiveness of STIOLTO RESPIMAT in asthma have not been established.

CONTRAINDICATIONS: All LABAs are contraindicated in patients with asthma without use of a long-term asthma control medication *[see Warnings and Precautions]*. STIOLTO RESPIMAT is not indicated for the treatment of asthma. STIOLTO RESPIMAT is contraindicated in patients with a hypersensitivity to tiotropium, ipratropium, olodaterol, or any component of this product *[see Warnings and Precautions]*. In clinical trials and postmarketing experience with tiotropium, immediate hypersensitivity reactions, including angioedema (including swelling of the lips, tongue, or throat), itching, or rash have been reported. Hypersensitivity reactions were also reported in clinical trials with STIOLTO RESPIMAT.

WARNINGS AND PRECAUTIONS: 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 olodaterol, one of the active ingredients in STIOLTO RESPIMAT. No study adequate to determine whether the rate of asthma-related death is increased in patients treated with STIOLTO RESPIMAT has been conducted. The safety and efficacy of STIOLTO RESPIMAT in patients with asthma have not been established. STIOLTO RESPIMAT is not indicated for the treatment of asthma. *[See Contraindications].* **Deterioration of Disease and Acute Episodes:** STIOLTO RESPIMAT should not be initiated in patients with acutely deteriorating COPD, which may be a life-threatening condition. STIOLTO RESPIMAT has not been studied in patients with acutely deteriorating COPD. The use of STIOLTO RESPIMAT in this setting is inappropriate. STIOLTO RESPIMAT should not be used for the relief of acute symptoms, i.e., as rescue therapy for the treatment of acute episodes of bronchospasm. STIOLTO 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 STIOLTO 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 STIOLTO 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 STIOLTO 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 STIOLTO RESPIMAT beyond the recommended dose is not appropriate in this situation. **Excessive Use of STIOLTO RESPIMAT and Use With Other Long-Acting Beta$_2$-Agonists:** As with other inhaled drugs containing beta$_2$-adrenergic agents, STIOLTO 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. **Immediate Hypersensitivity Reactions:** Immediate hypersensitivity reactions, including urticaria, angioedema (including swelling of the lips, tongue or throat), rash, bronchospasm, anaphylaxis, or itching may occur after administration of STIOLTO RESPIMAT. If such a reaction occurs, therapy with STIOLTO RESPIMAT should be stopped at once and alternative treatments should be considered. Given the similar structural formula of atropine to tiotropium, patients with a history of hypersensitivity reactions to atropine or its derivatives should be closely monitored for similar hypersensitivity reactions to STIOLTO RESPIMAT. **Paradoxical Bronchospasm:** As with other inhaled medicines, STIOLTO RESPIMAT may cause paradoxical bronchospasm that may be life-threatening. If paradoxical bronchospasm occurs, STIOLTO RESPIMAT should be stopped immediately and alternative therapy instituted. **Cardiovascular Effects:** Olodaterol, 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, STIOLTO 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. **Coexisting Conditions:** Olodaterol, 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. **Worsening of Narrow-Angle Glaucoma:** STIOLTO RESPIMAT should be used with caution in patients with narrow-angle glaucoma. Prescribers and patients should be alert for signs and symptoms of acute narrow-angle glaucoma (e.g., eye pain or discomfort, blurred vision, visual halos or colored images in association with red eyes from conjunctival congestion and corneal edema). Instruct patients to consult a physician immediately should any of these signs or symptoms develop. **Worsening of Urinary Retention:** STIOLTO RESPIMAT should be used with caution in patients with urinary retention. Prescribers and patients should be alert for signs and symptoms of prostatic hyperplasia or bladder-neck obstruction (e.g., difficulty passing urine, painful urination), especially in patients with prostatic hyperplasia or bladder neck obstruction. Instruct patients to consult a physician immediately should any of these signs or symptoms develop. **Renal Impairment:** Because tiotropium is a predominantly renally excreted drug, patients with moderate to severe renal impairment (creatinine clearance of ≤60 mL/min) treated with STIOLTO RESPIMAT should be monitored closely for anticholinergic side effects *[see Use in Specific Populations]*. **Hypokalemia and Hyperglycemia:** Beta-adrenergic agonists may produce significant hypokalemia in some patients, which has the potential to produce adverse cardiovascular effects. 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]*, 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 olodaterol with the rates similar to those for placebo controls. Olodaterol has not been investigated in patients whose diabetes mellitus is not well controlled.

ADVERSE REACTIONS: LABA, such as olodaterol, one of the active components in STIOLTO RESPIMAT, increase the risk of asthma-related death. STIOLTO RESPIMAT is not indicated for the treatment of asthma *[see Boxed Warning and Warning and Precautions]*. The following adverse reactions are described, or described in greater detail, in other sections: Immediate hypersensitivity reactions *[see Warnings and Precautions]*; Paradoxical bronchospasm *[see Warnings and Precautions]*; Worsening of narrow-angle glaucoma *[see Warnings and Precautions]*; Worsening of urinary retention *[see Warnings and Precautions]*. **Clinical Trials Experience in Chronic Obstructive Pulmonary Disease:** Because clinical trials are conducted under widely varying conditions, the incidence of adverse reactions observed in the clinical trials of a drug cannot be directly compared to the incidences in the clinical trials of another drug and may not reflect the incidences observed in practice. The clinical program for STIOLTO RESPIMAT included 7151 subjects with COPD in two 52-week active-controlled trials, one 12-week placebo-controlled trial, three 6-week placebo-controlled cross-over trials, and four additional trials of shorter duration. A total of 1988 subjects received at least 1 dose of STIOLTO RESPIMAT. Adverse reactions observed in the ≤12-week trials were consistent with those observed in the 52-week trials, which formed the primary safety database. The primary safety database consisted of pooled data from the two 52-week double-blind, active-controlled, parallel group confirmatory clinical trials. These trials included 5162 adult COPD patients (72.9% males and 27.1% females) 40 years of age and older. Of these patients, 1029 were treated with STIOLTO RESPIMAT once daily. The STIOLTO RESPIMAT group was composed of mostly Caucasians (71.1%) with a mean age of 63.8 years and a mean percent predicted FEV_1 at baseline of 43.2%. In these two trials, tiotropium 5 mcg and olodaterol 5 mcg were included as active control arms and no placebo was used. In these two clinical trials, 74% of patients exposed to STIOLTO RESPIMAT reported an adverse reaction compared to 76.6% and 73.3% in the olodaterol 5 mcg and tiotropium 5 mcg groups, respectively. The proportion of patients who discontinued due to an adverse reaction was 7.4% for STIOLTO RESPIMAT treated patients compared to 9.9% and 9.0% for olodaterol 5 mcg and tiotropium 5 mcg treated patients. The adverse reaction most commonly leading to discontinuation was worsening COPD. The most common serious adverse reactions were COPD exacerbation and pneumonia. Table 1 shows all adverse drug reactions that occurred with an incidence of >3% in the STIOLTO RESPIMAT treatment

group and a higher incidence rate than the active comparator groups listed.

Table 1: Number and frequency of adverse drug reactions greater than 3% (and higher than any of the comparators tiotropium and/or olodaterol) in COPD patients exposed to STIOLTO RESPIMAT: Pooled data from the two 52-week, double-blind, active-controlled clinical trials in COPD patients 40 years of age and older

Treatment	STIOLTO RESPIMAT (once daily)	Tiotropium (5 mcg once daily)	Olodaterol (5 mcg once daily)
Body system (adverse drug reaction)	**n=1029 n (%)**	**n=1033 n (%)**	**n=1038 n (%)**
Infections and infestations			
Nasopharyngitis	128 (12.4)	121 (11.7)	131 (12.6)
Respiratory, thoracic, and mediastinal disorders			
Cough	40 (3.9)	45 (4.4)	31 (3.0)
Musculoskeletal and connective tissue disorders			
Back Pain	37 (3.6)	19 (1.8)	35 (3.4)

Other adverse drug reactions in patients receiving STIOLTO RESPIMAT that occurred in ≤3% of patients in clinical studies are listed below: *Metabolism and nutrition disorders:* dehydration; *Nervous system disorders:* dizziness, insomnia; *Eye disorders:* glaucoma, intraocular pressure increased, vision blurred; *Cardiac/vascular disorders:* atrial fibrillation, palpitations, supraventricular tachycardia, tachycardia, hypertension; *Respiratory, thoracic, and mediastinal disorders:* epistaxis, pharyngitis, dysphonia, bronchospasm, laryngitis, sinusitis; *Gastrointestinal disorders:* dry mouth, constipation, oropharyngeal candidiasis, dysphagia, gastroesophageal reflux disease, gingivitis, glossitis, stomatitis, intestinal obstruction including ileus paralytic; *Skin and subcutaneous disorders:* rash, pruritus, angioneurotic edema, urticaria, skin infection, and skin ulcer, dry skin, hypersensitivity (including immediate reactions); *Musculoskeletal and connective tissue disorders:* arthralgia, joint swelling; *Renal and urinary disorders:* urinary retention, dysuria, and urinary tract infection.

DRUG INTERACTIONS: Adrenergic Drugs: If additional adrenergic drugs are to be administered by any route, they should be used with caution because the sympathetic effects of olodaterol, one component of STIOLTO RESPIMAT may be potentiated *[see Warnings and Precautions]*. **Sympathomimetics, Xanthine Derivatives, Steroids, or Diuretics:** Tiotropium has been used concomitantly with short-acting and long-acting sympathomimetic (beta-agonists) bronchodilators, methylxanthines, and oral and inhaled steroids, without increases in adverse reactions. Concomitant treatment with xanthine derivatives, steroids, or diuretics may potentiate any hypokalemic effect of olodaterol *[see Warnings and Precautions]*. **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 STIOLTO RESPIMAT with non-potassium sparing diuretics. **Monoamine Oxidase Inhibitors, Tricyclic Antidepressants, QTc Prolonging Drugs:** STIOLTO RESPIMAT, as with other drugs containing 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. **Beta-Blockers:** Beta-adrenergic receptor antagonists (beta-blockers) and the olodaterol component of STIOLTO 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. **Anticholinergics:** There is potential for an additive interaction with concomitantly used anticholinergic medications. Therefore, avoid co-administration of STIOLTO RESPIMAT with other anticholinergic-containing drugs as this may lead to an increase in anticholinergic adverse effects *[see Warnings and Precautions and Adverse Reactions]*. **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 olodaterol maximum plasma concentrations and AUC was observed *[see Pharmacokinetics]*. Olodaterol was evaluated in clinical trials for up to one year at doses up to twice the recommended therapeutic dose. No dose adjustment of STIOLTO RESPIMAT is necessary.

USE IN SPECIFIC POPULATIONS: Pregnancy: *Teratogenic Effects: Pregnancy Category C.:* There are no adequate and well-controlled studies with STIOLTO RESPIMAT or its individual components, tiotropium bromide and olodaterol, in pregnant women. Animal reproduction studies were conducted with the individual components of STIOLTO RESPIMAT, tiotropium bromide and olodaterol. STIOLTO RESPIMAT should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus. Tiotropium: No evidence of structural alterations was observed in rats and rabbits at approximately 790 and 8 times the recommended human daily inhalation dose (RHDID; on a mcg/m^2 basis at maternal inhalation doses of 1471 and 7 mcg/kg/day in rats and rabbits, respectively). However, in rats, tiotropium caused fetal resorption, litter loss, decreases in the number of live pups at birth and the mean pup weights, and a delay in pup sexual maturation at approximately 40 times the RHDID (on a mcg/m^2 basis at a maternal inhalation dose of 78 mcg/kg/day). In rabbits, tiotropium caused an increase in post-implantation loss at approximately 430 times the RHDID (on a mcg/m^2 basis at a maternal inhalation dose of 400 mcg/kg/day). Such effects were not observed at approximately 5 and 95 times the RHDID (on a mcg/m^2 basis at maternal inhalation doses of 9 and 88 mcg/kg/day in rats and rabbits, respectively). Olodaterol: Olodaterol was not teratogenic in rats at approximately 2731 times the RHDID (on an AUC basis at a maternal inhalation dose of 1054 mcg/kg/day). Placental transfer of olodaterol was observed in pregnant rats. Olodaterol has been shown to be teratogenic in New Zealand rabbits at approximately 7130 times the RHDID in adults (on an AUC basis at a maternal inhalation dose of 2489 mcg/kg/day). Olodaterol exhibited the following fetal toxicities: enlarged or small heart atria or ventricles, eye abnormalities, and split or distorted sternum. No significant effects occurred at approximately 1353 times the RHDID in adults (on an AUC basis at a maternal inhalation dose of 974 mcg/kg/day). **Labor and Delivery:** There are no adequate and well-controlled human studies that have investigated the effects of STIOLTO RESPIMAT on preterm labor or labor at term. Because of the potential for beta-agonist interference with uterine contractility, use of STIOLTO RESPIMAT during labor should be restricted to those patients in whom the benefits clearly outweigh the risks. **Nursing Mothers:** Clinical data from nursing women or infants exposed to STIOLTO RESPIMAT or its individual active components are not available. Tiotropium, olodaterol, and metabolites of olodaterol are excreted into the milk of lactating rats. It is not known whether these compounds are excreted in human milk, but because many drugs are excreted in human milk and given these findings in rats, caution should be exercised if STIOLTO RESPIMAT is administered to a nursing woman. **Pediatric Use:** COPD does not normally occur in children. The safety and effectiveness of STIOLTO RESPIMAT in the pediatric population has not been established. **Geriatric Use:** Based on available data, no adjustment of STIOLTO RESPIMAT dosage in geriatric patients is warranted. Of the 1029 patients who received STIOLTO RESPIMAT at the recommended dose once daily in the clinical studies from the pooled 1-year database, 525 (51.0%) were <65 years of age, 407 (39.6%) were 65 to <75, 96 (9.3%) were 75 to <85, and 1 (0.1%) was ≥85. 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. **Hepatic Impairment:** No dose adjustment is needed in patients with mild and moderate hepatic impairment. A study in subjects with severe hepatic impairment was not performed. **Renal Impairment:** No dose adjustment is required for patients with renal impairment. However, patients with moderate to severe renal impairment (creatinine clearance of ≤60 mL/min) treated with STIOLTO RESPIMAT should be monitored closely for anticholinergic side effects *[see Warnings and Precautions]*.

OVERDOSAGE: STIOLTO RESPIMAT contains both tiotropium bromide and olodaterol; therefore, the risks associated with overdosage for the individual components described below apply to STIOLTO RESPIMAT. Tiotropium: High doses of tiotropium may lead to anticholinergic signs and symptoms. However, there were no systemic anticholinergic adverse effects following a single inhaled dose of up to 282 mcg tiotropium in 6 healthy volunteers. In a study of 12 healthy volunteers, bilateral conjunctivitis and dry mouth were seen following repeated once-daily inhalation of 141 mcg of tiotropium. Dry mouth/throat and dry nasal mucosa occurred in a dose-dependent [10-40 mcg daily] manner, were observed following 14-day dosing of up to 40 mcg tiotropium bromide inhalation solution in healthy subjects. Olodaterol: The expected signs and symptoms with overdosage of olodaterol 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 olodaterol. Treatment of overdosage consists of discontinuation of STIOLTO 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 STIOLTO RESPIMAT. Cardiac monitoring is recommended in cases of overdosage.

STO-BS-5/16 IT6053FC232016 305630-03

PC-STO-0502-PROF

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