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

Boehringer Ingelheim Pharmaceuticals Inc.

**HIGHLIGHTS OF PRESCRIBING INFORMATION**

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

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

**Indication and Usage**

STIOLTO RESPIMAT is a combination of tiotropium, an anticholinergic and olodaterol, a long-acting beta₂-adrenergic agonist (LABA) indicated for the long-term, once-daily maintenance treatment of patients with chronic obstructive pulmonary disease (COPD). (1.1)

**Contraindications, revised**

- Hypersensitivity to tiotropium, ipratropium, olodaterol, or any component of this product. (1.1)

**Warnings and Precautions, revised**

- Do not exceed the recommended dose. Excessive use of STIOLTO RESPIMAT, or use in conjunction with other long-acting beta₂-adrenergic drugs may potentiate effect on cardiovascular system. (2.2)

**Drug Interactions**

- Anticholinergics: May interact additively with concomitantly used anticholinergic medications. Avoid administration of anticholinergic-containing drugs. (5.1)

**Adverse Reactions**

The most common adverse reactions (>3% incidence and more than an active control) were nasopharyngitis, cough, and back pain. (7.1)

**Use in Specific Populations**

- Pregnancy. (8.1)

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* Revised: 5/2019
Deterioration of Disease and Acute Episodes

Serious Asthma-Related Events – Hospitalizations, Intubations, Death

Use of a LABA, including STIOLTO RESPIMAT, without an inhaled corticosteroid is contraindicated in patients with asthma (see Warnings and Precautions (5.1)). 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 (5.4)).

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

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

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 (5.1)).

Use of long-acting beta-2 adrenergic agonist (LABA) as monotherapy (without inhaled corticosteroids (ICS)) for asthma is associated with an increased risk of asthma-related death. Available data from controlled clinical trials also suggest that use of LABA as monotherapy increases the risk of asthma-related hospitalization in pediatric and adolescent patients. These findings are considered a class effect of LABA monotherapy. When LABA are used in fixed dose combination with ICS, data from large clinical trials do not show a significant increase in the risk of serious asthma-related events (hospitalizations, intubations, death) compared with ICS alone.

A 28-week, placebo-controlled US study comparing the safety of another LABA (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 LABA, 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.

Available data do not suggest an increased risk of death with use of LABA in patients with COPD.

5.2 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-agonist.

When beginning STIOLTO RESPIMAT, patients who have been taking inhaled, short-acting beta-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-agonist and instruct the patient on how it should be used. Increasing inhaled beta-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-agonist becomes less effective or the patient needs more inhalation of short-acting beta-agonist than usual, these may be markers of deterioration in 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.

5.3 Excessive Use of STIOLTO RESPIMAT and Use With Other Long-Acting Beta-Agonists

As with other inhaled drugs containing beta-adrenergic agonists, 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-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 Immediate Hypersensitivity Reactions

Immediate hypersensitivity reactions, including urticaria, angioedema (including swelling of the lips, tongue or throat), rash, bronchospasm, anaphylaxis, or anaphasia 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.

5.5 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.

5.6 Cardiovascular Effects

Olopatadine, like other beta-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 tachycardia. 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-adrenergic agonists should be administered with caution in patients with cardiovascular disorders, especially coronary insufficiency, cardiac arrhythmias, hypertrophic obstructive cardiomyopathy, and hypertension.

5.7 Coexisting Conditions

Olopatadine, like other sympathomimetic amines, should be used with caution in patients with coexisting disorders or diseases, in patients who have a history of bronchospasm, or 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-agonist albuterol, when administered intravenously, have been reported to aggravate pre-existing diabetes mellitus and hyperglycemia.

5.8 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.

5.9 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 prostate 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.

5.10 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 (8.7) and Clinical Pharmacology (12.3)].

5.11 Hypokalemia and Hyperglycemia

Beta-adrenergic agonist 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-adrenergic agonists may produce increases in plasma glucose.

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 ololudexam with the rates similar to those for placebo controls. Olopatadine has not been investigated in patients whose diabetes mellitus is not well controlled.

6 ADVERSE REACTIONS

LABA, such as olodaterol, one of the active components in STIOLTO RESPIMAT, as monotherapy (without an inhaled corticosteroid) for asthma, increase the risk of asthma-related events. STIOLTO RESPIMAT is not indicated for the treatment of asthma [see Warnings and Precautions (5.1)].

The following adverse reactions are described, or described in greater detail, in other sections:

- Immediate hypersensitivity reactions [see Warnings and Precautions (5.4)]
- Paradoxical bronchospasm [see Warnings and Precautions (5.8)]
- Worsening of narrow-angle glaucoma [see Warnings and Precautions (5.8)]
- Worsening of urinary retention [see Warnings and Precautions (5.9)]

6.1 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 crossover trials, and four additional trials of shorter duration. A total of 1988 subjects received at least 1
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 olodaterol, one component of STIOLTO RESPIMAT, may be potentiated [see Warnings and Precautions (5.3, 5.6, 5.11)].

7.2 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 hypotensive effect of olodaterol [see Warnings and Precautions (5.11)].

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. If additional adrenergic drugs are to be administered by any route, they should be used with caution in the co-administration of STIOLTO RESPIMAT with non-potassium sparing diuretics.

7.4 Monoamine Oxidase Inhibitors, Tricyclic Antidepressants, QTc Prolonging Drugs
STIOLTO RESPIMAT, as with other drugs containing beta-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 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.

7.6 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 (5.8, 5.9) and Adverse Reactions (6)].

7.7 Inhibitors of Cytochrome P450 and P-gp Efflux Transporter

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Table 1: Number and frequency of adverse drug reactions greater than 3% (and higher than any of the comparators tiotropium and 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

<table>
<thead>
<tr>
<th>Body system (adverse drug reaction)</th>
<th>STIOLTO RESPIMAT (once daily)</th>
<th>Tiotropium (5 mcg once daily)</th>
<th>Olodaterol (5 mcg once daily)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Infections and infestations</td>
<td>1029 (9.9)</td>
<td>1033 (10.0)</td>
<td>1038 (10.1)</td>
</tr>
<tr>
<td>Noninfectious</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nasopharyngitis</td>
<td>128 (12.4)</td>
<td>121 (11.7)</td>
<td>131 (12.6)</td>
</tr>
<tr>
<td>Respiratory, thoracic, and mediastinal disorders</td>
<td>40 (3.9)</td>
<td>45 (4.4)</td>
<td>31 (3.0)</td>
</tr>
<tr>
<td>Cough</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Musculoskeletal and connective tissue disorders</td>
<td>37 (3.6)</td>
<td>19 (1.8)</td>
<td>35 (3.4)</td>
</tr>
</tbody>
</table>
| 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 Cardiovascular disorders: atrial fibrillation, palpitation, 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, angioedema, 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 COPD Exacerbation Reduction Trial In a one year trial (Trial 5) of 7888 patients to compare rates of COPD exacerbations, 3939 patients were treated with STIOLTO RESPIMAT and 3941 patients were treated with tiotropium 5 mcg inhalation spray. The safety profile of STIOLTO RESPIMAT was similar to that of tiotropium 5 mcg inhalation spray and consistent with that documented in the STIOLTO RESPIMAT primary safety database.
High doses of tiotropium may lead to anticholinergic signs and symptoms. However, there were no
Tiotropium should be monitored closely for anticholinergic side effects. No dose adjustment is required for patients with renal impairment. However, patients with moderate to severe renal impairment (creatinine clearance of <40 mL/min) treated with STIOLTO RESPIMAT should be monitored closely for anticholinergic side effects (see Dosage and Administration (2), Warnings and Precautions (5.10), and Clinical Pharmacology (12.3)).

8.2 Lactation
Risk Summary
There are no data on the presence of tiotropium or olodaterol in human milk, the effects on the breastfed infant, or the effects on milk production. Tiotropium, olodaterol, and/or their metabolites are present in the milk of lactating rats; however, due to species-specific differences in lactation physiology, the clinical relevance of these data are not clear (see Data). The developmental and health benefits of breastfeeding should be considered along with the mother’s clinical need for STIOLTO RESPIMAT and any potential adverse effects on the breastfed child from STIOLTO RESPIMAT or from the components of STIOLTO RESPIMAT, tiotropium bromide and olodaterol.

Data
Animal Data
Animal reproduction studies with the combination of tiotropium and olodaterol are not available; however, studies are available with the individual components.

Tiotropium
In 2 separate embryo-fetal development studies, pregnant rats and rabbits received tiotropium during the period of organogenesis at doses up to approximately 790 and 8 times the MRHDID, respectively (on a mg/m² basis at inhalation doses of 1471 and 7 mcg/kg/day in rats and rabbits, respectively). No evidence of structural abnormalities was observed in rats or rabbits. However, in rat, 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 tiotropium doses of approximately 40 times the MRHDID (on a mg/m² basis at a maternal inhalation dose of 78 mcg/kg/day). In rabbits, tiotropium caused an increase in post-implantation loss at a tiotropium dose of approximately 430 times the MRHDID (on a mg/m² basis at a maternal inhalation dose of 400 mcg/kg/day). Such effects were not observed at approximately 5 and 95 times the MRHDID, respectively (on a mg/m² basis at inhalation doses of 9 and 85 mcg/kg/day in rats and rabbits, respectively).

Olodaterol
Olodaterol was not teratogenic in rats at inhalation doses approximately 2371 times the MRHDID (on an AUC basis at a maternal inhalation dose of 1054 mcg/kg/day). No significant effects occurred in rabbits at inhalation doses approximately 1353 times the MRHDID in adults (on an AUC basis at a maternal inhalation dose of 78 mcg/kg/day). Placental transfer of olodaterol was observed in pregnant rats.

Olodaterol has been shown to be teratogenic in New Zealand rabbits at inhalation doses approximately 7130 times the MRHDID 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 uremum.

8.4 Pediatric Use
COPD does not normally occur in children. The safety and effectiveness of STIOLTO RESPIMAT in the pediatric population has not been established.

8.5 Geriatric Use
Based on available data, no adjustment of STIOLTO RESPIMAT dosage in geriatric patients is warranted (see Clinical Pharmacology (12.3)). 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.

8.6 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 (see Clinical Pharmacology (12.3)).

8.7 Renal Impairment
No dose adjustment is required for patients with renal impairment. However, patients with moderate to severe renal impairment (creatinine clearance of <40 mL/min) treated with STIOLTO RESPIMAT should be monitored closely for anticholinergic side effects (see Dosage and Administration (2), Warnings and Precautions (5.10), and Clinical Pharmacology (12.3)).

10. OVERDOSAGE
STIOLTO RESPIMAT contains both tiotropium bromide and olodaterol; therefore, the risks associated with overdose 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
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, hypotension or hypertension, tachycardia, arrhythmias, palpitation, dizziness, nervousness, insomnia, anxiety, headache, tremor, dry mouth, muscle spasm, 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 bronchoconstriction. There is insufficient evidence to determine if dialysis is beneficial for overdosage of STIOLTO RESPIMAT. Cardiac monitoring is recommended in cases of overdosage.

11 DESCRIPTION
STIOLTO RESPIMAT is a combination of tiotropium, an anticholinergic, and olodaterol, a long-acting beta-adrenergic agonist (LABA).

The drug substance tiotropium bromide monohydrate is chemically described as 1α, 2β, 4β, 5α, 7β-[(Hydroxydi-2-thienylacetyl)oxy]-9,9-dimethyl-3-oxa-9-azoniatricyclo[3.3.1.02,6]nonane bromide monohydrate. It is a synthetic, non-chiral, quaternary ammonium compound. Tiotropium bromide is a white or yellowish white powder. It is sparingly soluble in water and soluble in methanol. The structural formula is:

\[
\text{Tiotropium bromide (monohydrate)} \quad \text{has a molecular mass of 490.4 and a molecular formula of C}_{28}\text{H}_{42}\text{N}_{2}\text{O}_{5}\text{Br} \cdot \text{H}_{2}\text{O}.
\]

The drug substance olodaterol hydrochloride is chemically described as 1H-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_{26}H_{27}N_{2}O_{3} • HCl as a hydrochloride. The conversion factor from salt to free base is 1.094.

The structural formula is:

\[
\text{The drug product, STIOLTO RESPIMAT, is composed of a sterile aqueous solution of tiotropium bromide and olodaterol hydrochloride filled into a 4.5 mL plastic container crimped into an aluminum cylinder (STIOLTO RESPIMAT cartridge) for use with the STIOLTO RESPIMAT inhaler.}
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Excipients include water for injection, benzoic acid, edetate disodium, and hydrochloric acid.

The STIOLTO RESPIMAT cartridge is only intended for use with the STIOLTO RESPIMAT inhaler. The STIOLTO 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 STIOLTO RESPIMAT inhaler has a light green-colored cap.

When used with the STIOLTO RESPIMAT inhaler each cartridge, containing 4 grams of sterile aqueous solution, delivers the labeled number of metered actuations after preparation for use. Each dose (one dose equals two actuations) from the STIOLTO RESPIMAT inhaler delivers 5 mcg tiotropium and 5 mcg olodaterol in 22.1 mL 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).

12 CLINICAL PHARMACOLOGY
12.1 Mechanism of Action
STIOLTO RESPIMAT contains both tiotropium and olodaterol. The properties described below for the individual components apply to STIOLTO RESPIMAT. These drugs represent 2 different classes of medication (an anticholinergic and a beta-agonist) that have different effects on clinical and physiological indices.

Tiotropium
Tiotropium is a long-acting, muscarinic antagonist which is often referred to as an anticholinergic. It has similar affinity to the subtypes of muscarinic receptors, M5 to M1. In the airways, it exhibits pharmacological effects through inhibition of M2 receptors at the smooth muscle leading to bronchodilation. The competitive and reversible nature of antagonism was shown with human and animal origin receptors and isolated organ preparations. In preclinical in vitro as well as in vivo studies, prevention of methacholine-induced bronchoconstriction effects were dose-dependent and lasted longer than 24 hours. The bronchodilation following inhalation of tiotropium is predominantly a site-specific effect.

Olodaterol
Olodaterol is a long-acting beta2-adrenergic agonist (LABA). The compound exerts its pharmacological effects by binding and activation of beta2-adrenergceptors 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 beta2-adrenoceptors compared to beta2-adrenoceptors and 2299-fold greater agonist activity compared to beta2-adrenoceptors. The clinical significance of these findings is unknown.

Beta2-adrenoceptors are divided into three subtypes: beta2-adrenoceptors predominantly expressed on cardiac muscle, beta2-adrenoceptors predominantly expressed on airway smooth muscle, and beta2-adrenoceptors predominantly expressed on adipose tissue. Beta2-receptors cause bronchodilation. Although the beta2-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 beta2-receptors in the heart is not known, but their presence raises the possibility that even highly selective beta2-agonists may have cardiac effects.

12.2 Pharmacodynamics

Cardiac Electrophysiology

STILOTTO RESPIMAT
In two 52-week randomized, double-blind trials using STILOTTO RESPIMAT that enrolled 5662 patients with COPD, ECG assessments were performed post-dose on days 1, 85, 169, and 365. In a pooled analysis the number of subjects with changes from baseline-corrected QT interval of >30 msec using both the Bazet (QTcB) and Fredericia (QTcF) corrections for QT for heart rate were not different for the STILOTTO RESPIMAT group compared to olodaterol 5 mcg and tiotropium 5 mcg across the assessments conducted.

Tiotropium
The effect of tiotropium dry powder for inhalation on QT interval was also evaluated in a randomized, placebo- and positive-controlled crossover study in 53 healthy volunteers. Subjects received tiotropium inhalation powder 18 mcg, 54 mcg (3 times the recommended dose), or placebo for 12 days. ECG assessments were performed at baseline and throughout the dosing interval following the first and last dose of study medication. Relative to placebo, the maximum mean change from baseline in study-specific QTcF was 0.9 (95% CI: 0.4, 1.3) and 0.6 (95% CI: 0.2, 1.0) msec for tiotropium inhalation powder 18 mcg and 54 mcg, respectively. No subject showed a new onset of QTc >500 msec or QTc changes from baseline of >60 msec.

In a multicenter, randomized, double-blind trial using tiotropium dry powder for inhalation that enrolled 198 patients with COPD, the number of subjects with changes from baseline-corrected QT interval of >30–60 mcg was higher in the tiotropium group as compared with placebo. This difference was apparent using both the Bazet (QTcB) and Fredericia (QTcF) [16% (16%) vs. 2% (2%) patients] and Fredericia (QTcF) [16% (16%) vs. 1% (1%) patients] correction for QT of heart rate. No patients in either group had either QTcB or QTcF of >500 msec. Other clinical trials with tiotropium did not detect an effect of the drug on QT intervals.

Olodaterol
The effect of olodateron on the QTcF 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 (45%) (individual subject corrected QT interval) prolongation was observed. The maximum mean (one-sided 95% upper confidence bound) difference in QTcF 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 olodateron 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 pattern 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 olodaterol 5 mcg, 10 mcg, and placebo.

12.3 Pharmacokinetics

STILOTTO RESPIMAT
When STILOTTO RESPIMAT was administered by the inhalation route, the pharmacokinetic parameters for tiotropium and for olodaterol were similar to those observed when each active substance was administered separately.

Tiotropium
Tiotropium is administered as an inhalation spray. Some of the pharmacokinetic data described below were obtained with higher doses than recommended for therapy.

Olodaterol
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
Tiotropium
Following inhalation of the solution by young healthy volunteers, urinary excretion data suggest that approximately 33% of the inhaled dose reaches the systemic circulation. Oral solutions of tiotropium have an absolute bioavailability of 2% to 3%. Food is not expected to influence the absorption of tiotropium for the same reason. Maximum tiotropium plasma concentrations were observed 5 to 7 minutes after inhalation.

Olodaterol
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
Tiotropium
The drug has a plasma protein binding of 72% and shows a volume of distribution of 32 L/kg. Local concentrations in the lung are not known, but the mode of administration suggests substantially higher concentrations in the lung. Studies in rats have shown that tiotropium does not penetrate the blood-brain barrier.

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

Elimination
Metabolism
Tiotropium
The extent of metabolism is small. This is evident from a urinary excretion of 74% of unchanged substance after an intravenous dose to young healthy volunteers. Tiotropium, an ester, is hydrolyzed to its free base, tiotropium bromide, in human plasma within 24 hours following a single dose. In vitro experiments with human liver microsomes and human hepatocytes suggest that a fraction of the administered dose (74% of an intravenous dose is excreted unchanged in the urine, leaving 25% for metabolism) is metabolized by cytochrome P450-dependent oxidation and subsequent glutathione conjugation to a variety of Phase 2 metabolites. This enzymatic pathway can be inhibited by CYP3A4 and 3A4 inhibitors, such as quinidine, ketoconazole, and gestodene. Thus, CYP3A4 is involved in the metabolic pathway that is responsible for the elimination of a small part of the administered dose. In vitro studies using human liver microsomes showed that tiotropium in supra-therapeutic concentrations does not inhibit CYP3A4 1A1, 1A2, 2B6, 2C9, 2C19, 2D6, 2E1, or 3A4.

Olodaterol
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-receptors. This metabolite, however, is not detectable in plasma after chronic inhalation of the recommended therapeutic dose.

Cytochrome P450 isozymes CYP2C9 and CYP3A4, with negligible contribution of CYP3A4, are involved in the O-dealkylation of olodaterol, while uridine diphosphoglucuron transferase isoforms UGT1A7, UGT1A1, 1A7, and 1A9 were shown to be involved in the formation of olodaterol glucuronides.

Excretion

**Tiotropium**
The terminal half-life of tiotropium in COPD patients following once-daily inhalation of 5 mcg tiotropium was approximately 25 hours. Total clearance was 880 mL/min after an intravenous dose in young healthy volunteers. Intravenously administered tiotropium bromide is mainly excreted unchanged in urine (74%). After inhalation of the solution by patients with COPD, urinary excretion is 18.6% (0.932 mcg) of the dose, the remainder being mainly non-absorbed drug in the gut that is eliminated via the feces. The renal clearance of tiotropium exceeds the creatinine clearance, indicating secretion into the urine. After chronic once-daily inhalation by COPD patients, pharmacokinetic steady state was reached by day 7 with no accumulation thereafter.

**Olodaterol**
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 mcg calculated from Cmax from COPD patients is 7.5 hours.

Following intravenous administration of [14C]-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.

**Drug Interactions**

**STIOLTO RESPIMAT**
Pharmacokinetic drug interaction studies with STIOLTO RESPIMAT have not been performed; however, such studies have been conducted with individual components tiotropium and olodaterol.

When tiotropium and olodaterol were administered in combination by the inhaled route, the pharmacokinetic parameters for each component were similar to those observed when each active substance was administered separately.

**Tiotropium**
An interaction study with tiotropium (14.4 mcg intravenous infusion over 15 minutes) and cimetidine 400 mg three times daily or ranitidine 300 mg once-daily was conducted. Concomitant administration of cimetidine with tiotropium resulted in a 20% increase in the AUC\(_{\text{max}}\), a 28% decrease in the renal clearance of tiotropium and no significant change in the C\(_{\text{max}}\) and amount excreted in urine over 96 hours. Co-administration of tiotropium with ranitidine did not affect the pharmacokinetics of tiotropium.

Common concomitant medications (long-acting beta(u) agonists (LABA), inhaled corticosteroids (ICS)) used by patients with COPD were not found to alter the exposure to tiotropium.

**Olodaterol**
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\(_{\text{max}}\) by 66% and AUC\(_{\text{max}}\) by 68%.

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

**Specific Populations**

**Olodaterol**
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 olodaterol.

**Geriatric Patients**

**Tiotropium**
As expected for all predominantly renally excreted drugs, advancing age was associated with a decrease of tiotropium renal clearance (347 mL/min in COPD patients ≥65 years to 275 mL/min in COPD patients ≥65 years). This did not result in a corresponding increase in AUC\(_{0-1}\) and C\(_{\text{max},0-1}\) values.

**Renal Impairment**

**Tiotropium**
Following intravenous administration of therapeutic doses of tiotropium to steady-state in patients with COPD, mild renal impairment (creatinine clearance 60 - <90 mL/min) resulted in 23% higher AUC\(_{0-1}\) and 17% higher C\(_{\text{max},0-1}\) Values. Moderate renal impairment (creatinine clearance 30 - <60 mL/min) resulted in 55% higher AUC\(_{0-1}\) and 33% higher C\(_{\text{max},0-1}\) values compared to COPD patients with normal renal function (creatinine clearance ≥90 mL/min). In COPD patients with severe renal impairment (CL\(_{\text{CR}}\) = 30 mL/min), a single intravenous administration of tiotropium bromide resulted in 54% higher AUC\(_{0-1}\) and 52% higher C\(_{\text{max}}\) compared to COPD patients with normal renal function.

**Olodaterol**
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**

**Tiotropium**
The effects of hepatic impairment on the pharmacokinetics of tiotropium were not studied.

**Olodaterol**
Subjects with mild and moderate hepatic impairment showed no changes in C\(_{\text{max}}\) 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.

13.1 NONCLINICAL TOXICOLOGY

**STIOLTO RESPIMAT**
No studies of the carcinogenicity, in vitro mutagenicity, or impairment of fertility were conducted with STIOLTO RESPIMAT, however, studies are available for the individual components, tiotropium and olodaterol.

**Tiotropium**
No evidence of tumorigenicity was observed in a 104-week inhalation study in rats at tiotropium doses up to 59 mcg/kg/day, in an 83-week inhalation study in female mice at doses up to 145 mcg/kg/day, and in a 101-week inhalation study in male mice at doses up to 2 mg/kg/day. These doses correspond to approximately 30, 40, and 0.5 times the recommended human daily inhalation dose (RHIDID) on a mcg/m² basis, respectively.

Tiotropium bromide demonstrated no evidence of mutagenicity or clastogenicity in the following assays: the bacterial gene mutation assay, the V79 Chinese hamster cell mutagenesis assay, the chromosomal aberration assay in human lymphocytes in vitro, the mouse micronucleus assay in vivo, and the unscheduled DNA synthesis assay in primary rat hepatocytes in vitro.
In rats, decreases in the number of corpora lutea and the percentage of implants were noted at inhalation doses of tiotropium bromide and olodaterol of 78 mcg/kg/day or greater (approximately 35 times the RHDID on an AUC basis). No such effects were observed at 9 mcg/kg/day (approximately 4 times the RHDID on a mcg.m² basis).

Tiotropium 5 mcg and olodaterol 5 mcg were maintained throughout the 52-week treatment period. The difference in trough FEV₁ for the tiotropium bromide/olodaterol doses of 1.25/5, 2.5/5, and 5/5 mcg once daily from olodaterol 5 mcg were 0.054 L (95% CI -0.029, 0.076), 0.033 L (-0.019, 0.085), and 0.057 L (0.004, 0.110), respectively. Results of these trials supported the evaluation of once-daily doses of tiotropium bromide/olodaterol 2.5/5 mcg and 5/5 mcg in the confirmatory trials.

Confirmatory Trials
A trial of 5162 COPD patients (1029 receiving STIOLTO RESPIMAT, 1038 receiving olodaterol 5 mcg, and 1031 receiving tiotropium bromide 5 mcg) were studied in two confirmatory trials of STIOLTO RESPIMAT. Trials 1 and 2 were 52-week, replicate, randomized, double-blind, active-controlled trials that included three dose ranging trials, two active- and placebo-controlled trials, and one placebo-controlled trial. The efficacy of STIOLTO RESPIMAT is based primarily on two 4-week dose-ranging trials in 592 COPD patients and two confirmatory active-controlled 52-week trials (Trials 1 and 2) in 5162 COPD patients.

Dose-Ranging Trials
Dose selection for STIOLTO RESPIMAT was primarily based on trials for the individual components, tiotropium bromide and olodaterol. Dose selection was also supported by two randomized, double-blind, active-controlled, 4-week trials. In one trial in 232 patients with COPD, three tiotropium doses (1.25, 2.5, and 5 mcg) were given in combination with olodaterol 5 or 10 mcg and were evaluated compared to olodaterol monotherapy. Results demonstrated improvement in trough FEV₁ for the combination when compared to olodaterol alone. The difference in trough FEV₁ for the tiotropium bromide/olodaterol doses of 1.25%, 2.5%, and 5/5 mcg once daily from olodaterol 5 mcg were 0.054 L (95% CI 0.016, 0.092), 0.065 L (0.027, 0.103), and 0.117 L (0.078, 0.157), respectively. In the second trial in 369 patients with COPD, three olodaterol doses (2, 5, and 10 mcg) were given in combination with tiotropium 5 mcg and were evaluated compared to tiotropium monotherapy. The difference in trough FEV₁ for the tiotropium/olodaterol doses of 5, 5/10 mcg once daily from tiotropium 5 mcg were 0.024 L (95% CI -0.029, 0.076), 0.033 L (-0.019, 0.085), and 0.057 L (0.004, 0.110), respectively. Results of these trials supported the evaluation of once-daily doses of tiotropium bromide/olodaterol 2.5/5 mcg and 5/5 mcg in the confirmatory trials.

Table 2 FEV₁ AUC₀₋₃hr and Trough FEV₁ response for STIOLTO RESPIMAT compared to tiotropium 5 mcg and olodaterol 5 mcg after 24 weeks (primary endpoints; Trials 1 and 2)

<table>
<thead>
<tr>
<th></th>
<th>Trial 1</th>
<th></th>
<th>Trial 2</th>
<th></th>
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<tbody>
<tr>
<td></td>
<td>n</td>
<td>Mean (L)</td>
<td>Difference (L) (85% CI)</td>
<td>n</td>
</tr>
<tr>
<td><strong>STIOLTO RESPIMAT</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Tiotropium 5 mcg</td>
<td>522</td>
<td>0.256</td>
<td>-</td>
<td>500</td>
</tr>
<tr>
<td>Olodaterol 5 mcg</td>
<td>525</td>
<td>0.133</td>
<td>0.117 (0.094, 0.140)</td>
<td>500</td>
</tr>
<tr>
<td><strong>Trough FEV₁ response</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>STIOLTO RESPIMAT</td>
<td>521</td>
<td>0.136</td>
<td>-</td>
<td>497</td>
</tr>
<tr>
<td>Tiotropium 5 mcg</td>
<td>520</td>
<td>0.065</td>
<td>0.071 (0.047, 0.094)</td>
<td>498</td>
</tr>
<tr>
<td>Olodaterol 5 mcg</td>
<td>519</td>
<td>0.054</td>
<td>0.082 (0.059, 0.106)</td>
<td>501</td>
</tr>
</tbody>
</table>

For the subset of patients (n=522) who completed extended lung function measurements up to 12 hours post-dose, STIOLTO RESPIMAT showed a significantly greater FEV₁ response compared to tiotropium 5 mcg and olodaterol 5 mcg over the full 24-hour dosing interval. Results from Trial 2 are shown in Figure 1.
inhaled corticosteroid], increase the risk of serious asthma-related events, including asthma-related
Serious Asthma-Related Events

Use).

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

Storage

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

After assembly, the STIOLTO RESPIMAT inhaler should be discarded at the latest 3 months after first
mechanism will be engaged and no more actuations can be dispensed.

When the labeled number of actuations has been dispensed from the inhaler, the RESPIMAT locking
preparation for use.

The STIOLTO RESPIMAT cartridge is provided as an aluminum cylinder with a tamper protection seal
RESPIMAT cartridge and one STIOLTO RESPIMAT inhaler.

The STIOLTO RESPIMAT cartridge is designed to deliver the labeled number of metered actuations after
preparation for use.

When the labeled number of actuations has been dispensed from the inhaler, the RESPIMAT locking
mechanism will be engaged and no more actuations can be dispensed.

After assembly, the STIOLTO 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 to 30°C (59°F to 86°F) [see USP Controlled Room Temperature]. Avoid freezing.

17. PATIENT COUNSELING INFORMATION

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

Serious Asthma-Related Events

Inform patients that LABA, such as STIOLTO RESPIMAT, when used as monotherapy [without an
inhaled corticosteroid], increase the risk of serious asthma-related events, including asthma-related
What is STIOLTO RESPIMAT? 
STIOLTO RESPIMAT is a prescription medicine used to control the symptoms of COPD in adults with COPD. COPD is a chronic lung disease that includes chronic bronchitis, emphysema, or both. STIOLTO RESPIMAT is for long-term use and should be taken as 2 puffs 1 time each day, to improve the symptoms of COPD for better breathing.

Do not use STIOLTO RESPIMAT if you:
- have asthma.
- are allergic to tiotropium, ipratropium, olodaterol, or any of the ingredients in STIOLTO RESPIMAT. See the end of this Patient Information leaflet for a complete list of ingredients in STIOLTO RESPIMAT.

Before you use STIOLTO RESPIMAT, tell your healthcare provider about all of your medical conditions, including if you:

Instructions for Administering STIOLTO RESPIMAT
It is important for patients to understand how to correctly administer STIOLTO RESPIMAT inhalation spray using the STIOLTO RESPIMAT inhaler. Instruct patients that STIOLTO RESPIMAT inhalation spray should only be administered via the STIOLTO RESPIMAT inhaler and the STIOLTO RESPIMAT inhaler should not be used for administering other medications.

Instruct patients that priming STIOLTO RESPIMAT is essential to ensure appropriate content of the medication in each actuation. When using the unit for the first time, the STIOLTO RESPIMAT cartridge is inserted into the STIOLTO RESPIMAT inhaler and the unit is primed. STIOLTO RESPIMAT patients are to actuate the inhaler toward the ground until an aerosol cloud is visible and then to 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 three more times. The unit is then considered primed and ready for use.
STIOLTO RESPIMAT can cause serious side effects, including:

- Have heart problem.
- Have high blood pressure.
- Have seizures.
- Have thyroid problem.
- Have diabetes.
- Have eye problem, such as glaucoma. STIOLTO RESPIMAT can make your glaucoma worse.
- Have prostate or bladder problems, or problem passing urine. STIOLTO RESPIMAT can make these problems worse.
- Have kidney problem.
- Are pregnant or plan to become pregnant. It is not known if the medicines tiotropium or olodaterol in STIOLTO RESPIMAT can harm your unborn baby.
- Are breastfeeding or plan to breastfeed. It is not known if the medicines tiotropium or olodaterol in STIOLTO RESPIMAT passes into your breast milk and if it can harm your baby. You and your healthcare provider should decide if you will take STIOLTO RESPIMAT while breastfeeding.

Tell your healthcare provider about all the medicines you take, including prescription and over-the-counter medicines, eye drops, vitamins, and herbal supplements. STIOLTO RESPIMAT and certain other medicines may affect each other. This may cause serious side effects. Especially tell your healthcare provider if you take:

- Anticholinergics (including ipratropium, aclidinium, umeclidinium or another tiotropium-containing product such as SPIRIVA RESPIMAT or SPIRIVA HANDIHALER)
- Atropine

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 STIOLTO RESPIMAT?

Read the step-by-step instructions for using STIOLTO RESPIMAT at the end of this Patient Information Leaflet.

- Do not use STIOLTO RESPIMAT unless your healthcare provider has taught you how to use the inhaler and you understand how to use it correctly. Ask your healthcare provider or pharmacist if you have any questions.
- STIOLTO RESPIMAT inhaler has a slow-moving mist that helps you inhale the medicine.
- Use STIOLTO RESPIMAT exactly as your healthcare provider tells you to use it. Do not use STIOLTO RESPIMAT more often than prescribed.
- Use 1 dose (2 puffs) of STIOLTO RESPIMAT, 1 time each day, at the same time of the day.
- If you miss a dose of STIOLTO RESPIMAT, take it as soon as you remember. Do not take more than 1 dose (2 puffs) in 24 hours.
- If you take too much STIOLTO RESPIMAT, call your healthcare provider or go to the nearest hospital emergency room right away.
- Do not spray STIOLTO RESPIMAT in your eyes. Your vision may become blurred and your pupils may become larger (dilated).
- STIOLTO RESPIMAT Inhalation Spray should only be given using the STIOLTO RESPIMAT inhaler. The STIOLTO RESPIMAT inhaler should not be used to give other medicines.
- Always use the new STIOLTO RESPIMAT inhaler that is provided with each new prescription.
- STIOLTO RESPIMAT does not relieve sudden symptoms of COPD. You should not take extra doses of STIOLTO RESPIMAT to 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.
- If your COPD symptoms worsen over time, do not increase your dose of STIOLTO RESPIMAT, instead call your healthcare provider.
- Do not stop using STIOLTO 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 STIOLTO RESPIMAT:
  - More often than prescribed for you
  - At a higher dose than prescribed for you, or
  - With other medicines that contain LABA or an anticholinergic for any reason. Ask your healthcare provider or pharmacist if any of your other medicines are LABA or anticholinergic medicines.
- Call your healthcare provider or get emergency medical care right away if your breathing problems worsen with STIOLTO RESPIMAT, you need to use your rescue inhaler medicine more often than usual, or your rescue inhaler medicine does not work as well for you at relieving your symptoms.

What are the possible side effects with STIOLTO RESPIMAT?

STIOLTO RESPIMAT can cause serious side effects, including:

- Serious problems from asthma. People with asthma who take long-acting beta-2-adrenergic agonists (LABA) medicines, such as olodaterol (one of the medicines in STIOLTO RESPIMAT), without also using a medicine called an inhaled corticosteroid, have an increased risk of serious problems from asthma, including being hospitalized, needing a tube placed in their airway to help them breathe, or death.
- Call your healthcare provider if breathing problems worsen over time while using STIOLTO RESPIMAT. You may need a different treatment.

Get emergency medical care if:

- Your breathing problems worsen quickly
- You use your rescue inhaler medicine, but it does not relieve your breathing problem
- Using too much of a LABA medicine (one of the medicines in STIOLTO RESPIMAT) may cause:
  - Increased blood pressure
  - Headache
  - Nervousness
- COPD symptoms can get worse over time. If your COPD symptoms worsen over time, do not increase your dose of STIOLTO RESPIMAT, instead call your healthcare provider.
- Serious allergic reactions including rash, hives, itching, swelling of the face, lips, tongue, throat, difficulty in breathing or swallowing. Stop taking STIOLTO RESPIMAT and get emergency medical help right away if you get any symptoms of a serious allergic reaction after using STIOLTO RESPIMAT.
- Sudden shortness of breath can happen immediately after using STIOLTO RESPIMAT. Sudden shortness of breath may be life-threatening. Stop taking STIOLTO RESPIMAT and call your healthcare provider or get emergency medical help right away if you get sudden shortness of breath after using STIOLTO RESPIMAT.
- Effects on your heart, including fast or irregular heartbeat, palpitations, chest pain, and increased blood pressure.
- New or worsening eye problems including acute narrow-angle glaucoma. Symptoms of acute narrow-angle glaucoma include eye pain or discomfort, blurred vision, seeing halos or colored images around lights, and red eyes. Call your healthcare provider right away if you have any of these symptoms. Use caution as some of these eye problems can affect your ability to drive and operate appliances and machinery.
- New or worsening urinary retention. Symptoms of urinary retention may include difficulty urinating, painful urination, urinating frequently, or urinating in a weak stream or drips. Call your healthcare provider right away if you have any of these symptoms.
- Changes in laboratory blood levels including high blood sugar (hyperglycemia) and low levels of potassium (hypokalemia), which may cause symptoms of muscle weakness or abnormal heart rhythm.
Common side effects of STIOLTO RESPIMAT include: runny nose, cough, and back pain. These are not all the side effects of STIOLTO RESPIMAT. 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 STIOLTO RESPIMAT?
- Store STIOLTO RESPIMAT at room temperature, between 68°F to 77°F (20°C to 25°C).
- Do not freeze your STIOLTO cartridge or RESPIMAT inhaler.
- Keep your STIOLTO RESPIMAT inhaler, cartridge, and all medicines out of the reach of children.

General information about the safe and effective use of STIOLTO RESPIMAT
Medicines are sometimes prescribed for purposes other than those listed in a Patient Information leaflet. Do not use STIOLTO RESPIMAT for a condition for which it was not prescribed. Do not give STIOLTO RESPIMAT to other people, even if they have the same symptoms that you have. It may harm them.

You can ask your healthcare provider or pharmacist for information about STIOLTO RESPIMAT that is written for health professionals.

Active ingredients:
- Tiotropium bromide and olodaterol

Inactive ingredients:
- Water for injection, benzalkonium chloride, edetate disodium, and hydrochloric acid

Distributed by:
Boehringer Ingelheim Pharmaceuticals, Inc.
Ridgefield, CT 06877 USA

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

Instructions for Use
STIOLTO RESPIMAT® (sti-OL-to- RES peh mat)
(tiotropium bromide and olodaterol)
inhalation spray, for oral inhalation use

For Oral Inhalation Only
Do not spray STIOLTO RESPIMAT into your eyes.
Read these Instructions for Use before you start using STIOLTO RESPIMAT and each time you get a refill. There may be new information. This leaflet does not take the place of talking to your doctor about your medical condition or your treatment.

You will need to use this inhaler 1 time each day, at the same time each day. Each time you use it take 2 puffs.

Do not turn the clear base before inserting the cartridge.

How to store your STIOLTO RESPIMAT inhaler
- Store STIOLTO RESPIMAT at room temperature between 68°F to 77°F (20°C to 25°C).
- Do not freeze your STIOLTO RESPIMAT cartridge and inhaler.
- If STIOLTO RESPIMAT has not been used for more than 3 days, release 1 puff towards the ground.
- If STIOLTO RESPIMAT has not been used for more than 21 days, repeat steps 4 to 6 under the “Prepare for first use” until a mist is visible. Then repeat steps 4 to 6 three more times.
- Keep your STIOLTO RESPIMAT cartridge, inhaler, and all medicines out of the reach of children.

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

When to get a new STIOLTO RESPIMAT inhaler
- The scale on your inhaler will show the number of puffs you have, if used as indicated (2 puffs 1 time each day).
- The dose indicator will show you approximately how much medicine is left.
- When the dose indicator enters the red area of the scale, it will show you approximately how many puffs are left before you need a refill or new prescription.
- When the dose indicator reaches the end of the red scale, your STIOLTO RESPIMAT is empty and automatically locks. At this point, the clear base cannot be turned any further.

Prepare for first use

- Three months after insertion of cartridge, throw away the STIOLTO RESPIMAT even if it has not been used, or when the inhaler is locked, or when it expires, whichever comes first.
3. Remove clear base
   - Keep the cap closed.
   - Press the safety catch while firmly pulling off the clear base with your other hand. Be careful not to touch the piercing element.
   - Write the discard by date on the label (3 months from the date the cartridge is inserted).

2. Insert cartridge
   - Insert the narrow end of the cartridge into the inhaler.
   - Place the inhaler on a firm surface and push down firmly until it clicks into place.

3. Replace clear base
   - Put the clear base back into place until it clicks.
   - Do not remove the clear base or the cartridge after it has been put together.

4. Turn
   - Keep the cap closed.
   - Turn the clear base in the direction of the arrows on the label until it clicks (half a turn).

5. Open
   - Open the cap until it snaps fully open.

6. Press
   - Point the inhaler toward the ground.
   - Press the dose-release button.
   - Close the cap.
   - If you do not see a mist, repeat steps 4 to 6 until a mist is seen.
   - After a mist is seen, repeat steps 4 to 6 three more times.
   - After complete preparation of your inhaler, it will be ready to deliver the number of puffs on the label.

Daily use (TOP)

Turn
   - Keep the cap closed.
   - Turn the clear base in the direction of the arrows on the label until it clicks (half a turn).

Open
   - Open the cap until it snaps fully open.
Press
• Breathe out slowly and fully.
• Close your lips around the mouthpiece without covering the air vents.
• Point the inhaler to the back of your throat.
• While taking a slow, deep breath through your mouth, press the dose-release button and continue to breathe in.
• Hold your breath for 10 seconds or for as long as comfortable.
• Repeat Turn, Open, Press (TOP) for a total of 2 puffs.
• Close the cap until you use your inhaler again.

Answers to Common Questions

Is it difficult to insert the cartridge deep enough?
Did you accidentally turn the clear base before inserting the cartridge? Open the cap, press the dose-release button, then insert the cartridge.

Did you insert the cartridge with the wide end first?
Insert the cartridge with the narrow end first.

Is the dose indicator on the STIOLTO RESPIMAT pointing to 0 (zero)?
If the dose indicator on the STIOLTO RESPIMAT is locked after the labeled number of puffs have been used, prepare and use your new STIOLTO RESPIMAT inhaler.

I cannot press the dose-release button:
Did you turn the clear base? If not, turn the clear base in a continuous movement until it clicks (half a turn).

Is the dose indicator on the STIOLTO RESPIMAT pointing to 0 (zero)?
Prepare and use your new STIOLTO RESPIMAT inhaler.

I cannot turn the clear base:
Did you turn the clear base already? If the clear base has already been turned, follow steps “Open” and “Press” under “Daily use” to get your medicine.

Is the dose indicator on the STIOLTO RESPIMAT pointing to 0 (zero)?
The STIOLTO RESPIMAT inhaler is locked after the labeled number of puffs have been used. Prepare and use your new STIOLTO RESPIMAT inhaler.

The dose indicator on the STIOLTO RESPIMAT reaches 0 (zero) too soon:
Did you use STIOLTO RESPIMAT as indicated (2 puffs 1 time each day)? STIOLTO RESPIMAT will deliver the labeled number of puffs if used at 2 puffs 1 time each day.

Did you turn the clear base before you inserted the cartridge?
The dose indicator counts each turn of the clear base regardless of whether a cartridge has been inserted or not.

Did you spray in the air to check whether the STIOLTO RESPIMAT is working?
After you have prepared STIOLTO RESPIMAT, no test-spraying is required if used daily.

Did you insert the cartridge into a used STIOLTO RESPIMAT?
The dose indicator counts each turn of the clear base regardless of whether a cartridge has been inserted or not.

My STIOLTO RESPIMAT sprays automatically:
Was the cap open when you turned the clear base? Close the cap, then turn the clear base.

Did you press the dose-release button when turning the clear base?
Close the cap, so the dose-release button is covered, then turn the clear base.

Did you stop when turning the clear base before it clicked?
Turn the clear base in a continuous movement until it clicks (half a turn).

My STIOLTO RESPIMAT does not spray:
Did you insert a cartridge?
If not, insert a cartridge.

Did you repeat Turn, Open, Press (TOP) less than 3 times after inserting the cartridge?
Repeat Turn, Open, Press (TOP) 3 times after inserting the cartridge as shown in steps 4 to 6 under “Prepare for first use”.

Is the dose indicator on the STIOLTO RESPIMAT pointing to 0 (zero)?
You have used up all your medicine and the inhaler is locked.

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

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

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IT6053SM042019
Stiolto Respimat
NDC 0597-0155-70
STIOLTO RESPIMAT
tiotropium bromide and olodaterol spray, metered

**Product Information**
- **Product Type**: HUMAN PRESCRIPTION DRUG
- **Item Code (Source)**: NDC:0597-0155

**Route of Administration**
- RESPIRATORY (INHALATION)

**Active Ingredient/Active Moiety**

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<th>Ingredient Name</th>
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**Packaging**

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### Marketing Information

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**Labeler** - Boehringer Ingelheim Pharmaceuticals Inc. (603175944)

**Registrant** - Boehringer Ingelheim Pharmaceuticals Inc. (603175944)

### Establishment

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