Brand Name: Stiolto Respimat

Generic Name: tiotropium bromide and olodaterol

Manufacturer[1]: Boehringer Ingelheim

Drug Class[1,2,3,4]: long-acting anticholinergic (tiotropium bromide) and long-acting $beta_2$-adrenergic agonist (olodaterol)

Uses:

Labeled Uses[1,2,3,4]: Maintenance treatment of chronic obstructive pulmonary disease (COPD), including chronic bronchitis and/or emphysema

Unlabeled Uses[1,2]: None

Mechanism of Action[1,2,3,4]:

Tiotropium: Tiotropium is a long-acting anticholinergic that inhibits M_3 receptors at the airway smooth muscle, leading to bronchodilation.

Olodaterol: Olodaterol is a long-acting $beta_2$-adrenergic agonist (LABA) that binds and activates $beta_2$ receptors. Activation of these receptors in the airways causes stimulation of intracellular adenyl cyclase, an enzyme that mediates the synthesis of cyclic-3',5' adenosine monophosphate (cAMP). Elevated levels of intracellular cAMP result in bronchodilation by relaxation of the airway smooth muscles.

Pharmacokinetics[1,2,3,4]:

	Tiotropium	Olodaterol
Tmax	5-7 minutes	10-20 minutes
Bioavailability	33%	30%
Vd	32 L/kg	1,110 L
Protein binding	72%	60%
Clearance (total)	880 mL/min	872 mL/min
t1/2	25 hours	45 hours

Metabolism:

Tiotropium: 25% of Tiotropium is metabolized by the liver via CYP2D6 and CYP3A4.

Olodaterol: Olodaterol is metabolized substantially in the liver by direct glucoronidation and O-demethylation. CYP2C9 and CYP2C8 are involved in the O-demethylation.

Elimination:

Tiotropium: Tiotropium is mainly excreted via the feces with 18.6% of the dose being excreted unchanged in the urine.

Olodaterol: Olodaterol is mainly excreted in the feces. After inhalation, 5-7% of the dose is excreted unchanged in the urine.

Efficacy:

ZuWallack R, Allen L, Hernandex G, Ting N, Abrahams R. Efficacy and safety of combining olodaterol Respimat and tiotropium HandiHaler in patients with COPD: results of two randomized, double-blind, active-controlled studies. International Journal of COPD. 2014: 9; 1133-1144.[5]

Study Design: Two replicate, randomized, double-blind, parallel group, multicenter, active-controlled trials

Description of Study: *Methods:* A total of 2,271 patients were randomized to receive 12 weeks of once daily coadministration of tiotropium 18 mcg (via HandiHaler) and placebo olodaterol (via Respimat inhaler) or tiotropium 18 mcg (via HandiHaler) and olodaterol 5 mcg (via Respimat inhaler). The patients were to take two inhalations from the Respimat inhaler followed by two inhalations of one capsule of tiotropium via the HandiHaler at the same time each morning between 7 am and 10 am. Inhaled, oral, and injected corticosteroids, cromolyn sodium/nedocromil sodium, antihistamines, antileukotrienes, methylxanthines, mucolytics, and theophyllines were permitted. Albuterol was provided as rescue medication only. The primary efficacy end points were FEV_1 AUC_{0-3} and trough FEV_1 responses at 12 weeks. A key secondary end point was St. George's Respiratory Questionnaire (SGRQ) total score at week 12. The safety end points included adverse events, serious adverse events, vital signs, blood chemistry, and electrocardiogram. *Outcome Results:* Improvements in FEV_1 AUC_{0-3} and trough FEV_1 responses were greater with tiotropium + olodaterol than tiotropium + placebo olodaterol at week 12 in each study ($p < 0.01$). The mean difference in SGRQ total score at week 12 between groups was -1.85 (95% CI: -2.8 to -1.0) ($p < 0.0001$), in favor of the tiotropium + olodaterol group. The most frequent adverse events across the two studies were worsening of COPD (10.7%) and dry mouth (2.7%). Most events were mild to moderate in intensity and not considered related to the study treatment.

Limitations: Several authors are employees of and this study was supported by Boehringer Ingelheim Pharmaceuticals Inc. When discussing the means of the end point results, the study reported standard error of the mean instead of standard deviation

Conclusion: These studies demonstrated that adding olodaterol to tiotropium did provide greater bronchodilation and an improved health-related quality of life than that of tiotropium alone. The incidence of COPD exacerbations was similar between treatment groups. This study was relatively short and not powered for statistical comparison of exacerbations between groups. Therefore, a clinical trial of longer duration would be needed to determine if a further reduction in exacerbations occurs with the combination of tiotropium and olodaterol versus tiotropium alone.

Aalbers R, Maleki-Yazdi MR, Hamilton A, Waitere-Wijker S, Zhao Y, Amatto VC, et al. Randomized, Double-Blind, Dose-Finding Study for Tiotropium when Added to Olodaterol, Administered via the Respimat Inhaler in Patients with Chronic Obstructive Pulmonary Disease. Adv Ther. 2015; 32: 809-822.[6]

Study Design: Randomized, double-blind, phase IIb, incomplete crossover trial.

Description of Study: *Methods:* 233 patients were randomized to receive four out of eight combinations: olodaterol (5 or 10 mcg) in combination with tiotropium (1.25, 2.5, or 5 mcg) or placebo (in place of tiotropium) for 4 weeks each in a randomized order. Patients continued to take inhaled corticosteroids (ICS) throughout the trial if used prior to study entry. During run-in, washout, and post-treatment follow-up periods, long-acting beta-agonists (LABAs) and short-acting muscarinic antagonists were permitted, with a 48 hour washout for LABAs and an 8 hour washout for short-acting muscarinic antagonists before pulmonary function testing. Long-acting muscarinic antagonists (LAMAs) other than study drug were only permitted during the follow-up period. The short-acting $beta_2$-agonist, salbutamol, was provided as rescue therapy throughout the trial. The primary end point was trough FEV_1 response after 4 weeks of treatment. *Outcome Results:* Trough FEV_1 responses with olodaterol 5 and 10 mcg were 0.071 and 0.083, respectively, after 4 weeks of treatment. Compared to olodaterol 5 mcg monotherapy, the addition of tiotropium 1.25, 2.5, and 5 mcg increased trough FEV_1 response by 0.054, 0.065, and 0.084 L, respectively. Compared to olodaterol 10 mcg monotherapy, the addition of tiotropium 1.25, 2.5, and 5 mcg increased trough FEV_1 by 0.051, 0.083, and 0.080 L, respectively. The most common adverse effects were nasopharyngitis and COPD exacerbation. The incidence of AEs across treatment groups was similar.

Limitations: One limitation this study had was that because the lower dose of tiotropium was not available in a fixed dose combination, the tiotropium + olodaterol doses were administered as free-dose combinations in separate inhalers. Another limitation is the lack of a placebo group, so only improvement differences between monotherapy versus combination are known and not from combination versus no therapy. The study also did not include patients with GOLD 4 COPD, so the results cannot be extrapolated to that group. The study reported standard error of the mean instead of standard deviation in their results, which could lead the reader to believe that there was less variation between patients. There were also some conflicts of interest, with many authors employed or otherwise affiliated with the manufacturer. The study was also funded by Boehringer Ingelheim.

Conclusion: The addition of tiotropium to olodaterol did improve lung function overall. After 4 weeks of treatment, the FEV_1 profiles showed a definite improvement with tiotropium + olodaterol compared to olodaterol monotherapy, and increasing improvements of trough FEV_1 with an increase of tiotropium added to olodaterol 5 mcg or 10 mcg. The combination of tiotropium + olodaterol was well tolerated and had similar AE to olodaterol alone.

Buhl R, Maltais F, Abrahams R, Bjermer L, Derom E, Ferguson G, et al. Tiotropium and olodaterol fixed-dose combination versus mono-components in COPD (Gold 2-4). Eur Respir J. 2015; 45: 969-979.[7]

Study Design: Two replicate, multinational, phase III, randomized, double-blind, parallel group, active-controlled trials

Description of Study: *Methods:* 5162 patients were randomized and treated with olodaterol 5 mcg, tiotropium 2.5 mcg, tiotropium 5 mcg, tiotropium + olodaterol 2.5/5 mcg, or tiotropium + olodaterol 5/5 mcg. Patients continued to receive treatment with inhaled corticosteroids as required and were provided with salbutamol/albuterol MDI rescue inhalers to use as needed throughout the trial. Primary efficacy end points were FEV_1 AUC_{0-3} response, trough FEV_1 response, and St George's Respiratory Questionnaire (SGRQ) total score at 24 weeks. *Outcome Results:* Improvements in adjusted mean FEV_1 AUC_{0-3} with tiotropium + olodaterol FDC 5/5 mcg and 2.5/5 mcg over the monocomponents in the individual studies and the combined analysis were statistically significant ($p<0.0001$ for all comparisons). Improvements in the adjusted mean trough FEV_1 with tiotropium + olodaterol FDC 5/5 mcg and 2.5/5 mcg over the corresponding monocomponents in both the individual studies and the combined data were statistically significant ($p<0.05$ for all comparisons). After 24 weeks, the pre-specified analysis of the adjusted mean SGRQ total score showed statistically significant improvements for tiotropium + olodaterol FDC 5/5 mcg over corresponding individual components, but did not for tiotropium + olodaterol FDC 2.5/5 mcg versus the individual components. The increase in responder rate for tiotropium + olodaterol FDC 5/5 mcg over its monocomponents were statistically significant ($p < 0.05$). For tiotropium + olodaterol 2.5/5 mcg, there was a significant improvement in responder rate versus olodaterol 5 mcg ($p < 0.05$) and tiotropium 5 mcg ($p < 0.05$) but not tiotropium 2.5 mcg ($p=0.107$).

Limitations: There was no placebo group, so further analysis of the relevance of the improvements shown in the results is limited. The impact of tiotropium + olodaterol on COPD exacerbations was not assessed. There was nothing done to determine whether or not the patients were consistently adherent to the study drugs. A few of the authors were affiliated with the manufacturer. This study was also supported by Boehringer Ingelheim Pharmaceuticals.

Conclusion: Both of the replicate studies in this trial confirmed the safety and efficacy of once-daily tiotropium + olodaterol as maintenance therapy in patients with COPD (GOLD stage 2-4). The tiotropium + olodaterol 5/5 mcg dose seems to be the optimal combination, since it provided improvement in the three endpoints (FEV_1 AUC_{0-3}, trough FEV_1, and SGRQ score) compared to tiotropium or olodaterol alone.

Contraindications[1,2,3]:

Asthma: All LABAs are contraindicated in patients with asthma without long-term asthma control medication, due to increased risk of asthma-related death

Hypersensitivity to tiotropium, ipratropium, olodaterol or any component of this product: Immediate hypersensitivity reactions, including angioedema (swelling of lips, tongue, or throat), itching, or rash have been reported.

Precautions[1,2,3,4]:

Asthma-Related Death [Black Box Warning]: Long-acting beta$_2$-agonists (LABAs) increase the risk of asthma-related deaths. A large, 28 week, placebo-controlled study comparing the safety of a LABA (salmeterol) with placebo, when added to asthma therapy, showed an increase in asthma-related deaths in patients receiving salmeterol. This increased risk of asthma-related death is considered a class effect of LABAs, including olodaterol. LABAs are not indicated for the treatment of asthma.

Deterioration of Disease and Acute Episodes:

Stiolto Respimat should not be used as rescue therapy for the treatment of acute episodes of bronchospasm. Acute symptoms should only be treated with short-acting beta$_2$-agonists (SABAs).

When starting Stiolto Respimat, patients who have been taking SABAs on a regular basis (four times a day) should be instructed to discontinue regular use of this drug and to only use it for symptomatic relief of acute respiratory symptoms. The healthcare provider should prescribe a SABA for rescue therapy along with initiation of Stiolto Respimat.

Stiolto Respimat should not be initiated in patients with acutely deteriorating COPD, which may be a life-threatening condition. COPD may deteriorate acutely over hours or chronically over several days or longer. If Stiolto Respimat no longer controls symptoms of bronchoconstriction, the patient's SABA becomes less effective, or the patient needs to use the SABA more 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 done.

Excessive Use of Stiolto Respimat and Use with Other Long-Acting Beta$_2$ Agonists: Stiolto Respimat should not be used more often than recommended, at a higher dose than recommended, or with other medications containing LABAs, which could result in an overdose. Cardiovascular effects and fatalities have been reported with excessive use of inhaled sympathomimetic drugs.

Immediate Hypersensitivity Reactions: Immediate hypersensitivity reactions, such as urticarial, angioedema (swelling of the lips, tongue, or throat), rash, bronchospasm, anaphylaxis, or itching have been reported after administration. If such reactions occur, treatment should be discontinued immediately. Because of the similar structural formula of atropine to tiotropium, patients with a history of hypersensitivity reactions to atropine or its derivatives should be monitored for similar reactions to Stiolto Respimat.

Paradoxical Bronchospasm: Stiolto Respimat may cause life-threatening paradoxical bronchospasm. If this occurs, discontinue treatment and initiate alternative therapy.

Cardiovascular Effects: Beta$_2$ agonists can produce significant cardiovascular effects of increased pulse rate and systolic or diastolic blood pressure. They have also been reported to produce ECG changes, such as flattening of the T wave, prolongation of the QTc interval, and ST segment depression. LABAs should be administered with caution in patients with cardiovascular disorders, especially coronary insufficiency, cardiac arrhythmias, hypertrophic obstructive cardiomyopathy, and hypertension.

Coexisting Conditions: Olodaterol should be used with caution in patients with convulsive disorders, hyperthyroidism (thyrotoxicosis), patients suspected of QT interval prolongation, and patients who are unusually responsive to sympathomimetic amines.

Worsening of Narrow-Angle Glaucoma: Stiolto Respimat should be used with caution in patients with narrow-angle glaucoma, since it can worsen symptoms. Prescribers and patients should be alert for signs and symptoms, such as eye pain or discomfort, blurred vision, visual halos or colored images.

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, such as difficulty passing urine and painful urination.

Renal Impairment: Stiolto Respimat should be used with caution in patients with moderate to severe renal impairment (creatinine clearance of ≤ 60 mL/min). Patients should be monitored closely for anticholinergic side effects.

Hypokalemia and Hyperglycemia: Beta-agonists may produce significant hypokalemia in some patients, which could produce adverse cardiovascular effects. The decrease in potassium usually does not require supplementation. In patients with severe COPD, hypokalemia may be potentiated by hypoxia and concomitant treatment, increasing the risk for cardiac arrhythmias. High doses of beta$_2$ agonists may produce increases in plasma glucose.

Adverse effects[1,2,3,4]:

Occurring in > 10% of patients

Respiratory
Nasopharyngitis (12.4%)

Occurring in > 3% to < 10% of patients

Neuromuscular & skeletal
Back pain (3.6%)

Respiratory
Cough (3.9%)

Occurring in ≤ 3% of patients

Metabolism and nutrition disorders
Dehydration

Nervous system disorders
Dizziness
Insomnia

Eye disorders
Glaucoma
Increased intraocular pressure
Blurred vision

Cardiovascular disorders
Atrial fibrillation
Palpitations
Supraventricular tachycardia
Tachycardia
Hypertension

Respiratory, thoracic, and mediastinal disorders
Epistaxis
Pharyngitis
Dysphonia
Gastroesophageal reflux disease
Gingivitis
Glossitis
Stomatitis
Intestinal obstruction

Skin and subcutaneous disorders
Rash
Pruritus
Angioneurotic edema
Urticaria
Skin infection
Skin ulcer
Dry skin
Hypersensitivity

Musculoskeletal disorders
Arthralgia
Joint swelling

Renal and urinary disorders
Urinary retention
Dysuria
Urinary tract infection

Drug Interactions[1,2,3,4]:

Adrenergic Drugs

Concomitant administration of additional adrenergic drugs should be used with caution because they can potentiate the sympathetic effects of olodaterol.

Sympathomimetics, Xanthine Derivatives, Steroids, or Diuretics

Concomitant treatment with xanthine derivatives, steroids, or diuretics may potentiate any hypokalemic effect of olodaterol. Concomitant use of sympathomimetics may enhance the adverse effects of other sympathomimetics.

Non-Potassium Sparing Diuretics

Co-administration with non-potassium sparing diuretics should be used with caution. Beta agonist side effects of ECG changes and/or hypokalemia can be worsened by non-potassium sparing diuretics, such as thiazide or loop diuretics.

Monoamine Oxidase Inhibitors, Tricyclic Antidepressants, QTc Prolonging Drugs

Caution should be used with concomitant administration of monoamine oxidase inhibitors, tricyclic antidepressants, or other QTc prolonging drugs because these agents may potentiate the effect of the $beta_2$ agonist on the cardiovascular system. Drugs known to prolong the QTc interval may be associated with increased risk of ventricular arrhythmias. Because of the potential for Torsades de pointes, the use of the following drugs in products containing olodaterol is contraindicated: astemizole, bepridil, bretylium, cisapride, dofetilide, dronedarone, grepafloxacin, halofantrine, levomethadyl, mesoridazine, pimozide, probucol, sparfloxacin, terfenadine, thioridazine, and ziprasidone.

Beta-Blockers

Concurrent administration of beta-blockers along with $beta_2$-agonists, like olodaterol, may interfere with the effect of each other. This is of particular concern with the nonselective beta-blockers or with higher doses of the $beta_1$ selective beta-blockers. Beta-blockers will not only block the therapeutic effect of the beta-agonist, but causes severe bronchospasm in COPD patients. COPD patients should not be treated with beta-blockers, except under certain circumstances, like prophylaxis after an MI, where a cardioselective beta-blocker should be considered and administered with caution.

Anticholinergics

Avoid co-administration of other anticholinergic agents with Stiolto Respimat, which can cause an increase of anticholinergic adverse effects.

Analgesics (Opioid)

Concomitant use of opioid analgesics with an anticholinergic agent may cause increased risk of constipation and urinary retention. It also may result in additive respiratory and CNS depression.

Inhibitors of Cytochrome P450 and P-gp Efflux Transporter

In a drug-drug interaction study with ketoconazole, a P-gp, CYP 3A4, 2C8, 2C9 inhibitor, co-administration of 400 mg ketoconazole daily with olodaterol for 14 days increased olodaterol C_{max} by 66% and AUC_{0-1} by 68%. Olodaterol was evaluated up to one year for doses up to twice the recommended therapeutic dose. No dose adjustment of Stiolto Respimat is necessary.

Dosing/Administration[1,2,3,4]:

Adult Dose: 2 inhalations once daily at the same time of the day

Geriatric Dose: No dosage adjustment is necessary in geriatric patients

Renal Impairment Dose:

CrCl > 60 mL/min: No dosage adjustment is necessary
CrCl ≤ 60 mL/min: No dosage adjustment is necessary. Monitor for anticholinergic side effects

Hepatic Impairment Dose: No dosage adjustment is necessary in patients with mild to moderate hepatic impairment

Use in special circumstances[1,2,3,4]:

Pregnancy: *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 have been done with the individual components. Stiolto Respimat should be used during pregnancy only if the potential benefit outweighs the potential risk to the fetus.

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

Breastfeeding: Clinical data from nursing women or infants exposed to Stiolto Respimat or its individual components are not available. It is not known whether these compounds are excreted in human milk. Tiotropium, olodaterol, and metabolites of olodaterol are excreted into the milk of lactating rats. Caution should be exercised if Stiolto Respimat is administered to a nursing woman.

Overdosage:

Tiotropium: High doses of tiotropium may lead to anticholinergic signs and symptoms, such as bilateral conjunctivitis, dry mouth, dry throat, and dry nasal mucosa. However, there were no systemic anticholinergic adverse effects following a single inhaled dose of up to 282 mcg tiotropium in 6 healthy volunteers.

Olodaterol: The signs and symptoms of olodaterol overdosage is expected to be consistent with that of excessive beta-adrenergic stimulation, such as 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. Cardiac arrest and even death may be associated with an olodaterol overdose.

Treatment of an overdose consists of discontinuation of Stiolto Respimat along with appropriate symptomatic and supportive therapy. Cardiac monitoring is recommended in cases of overdosage. Use of cardioselective beta-blockers may be considered, but keeping in mind it can also cause bronchospasms. There is insufficient evidence to determine if dialysis is beneficial for overdosage of Stiolto Respimat.

Conclusion:

Stiolto Respimat (tiotropium bromide/olodaterol) has shown to be an effective therapy for patients with GOLD 2-4 COPD. The combination of the long-acting anticholinergic and long-acting beta$_2$-agonist has a greater improvement on lung function than either tiotropium or olodaterol monotherapy. The adverse effects are minimal, with the most common being nasopharyngitis and the most common serious adverse reaction being COPD exacerbation. Further studies do need to be done to assess whether there are less COPD exacerbations with this combination therapy than in monotherapy. With Stiolto Respimat being well tolerated in the study groups, this is an excellent addition to the available treatments for COPD, especially in situations where monotherapy has been ineffective for patients.

Recommended References:

1. Stiolto Respimat [package insert]. Ridgefield, CT: Boehringer Ingelheim Pharmaceuticals, Inc.; 2015.
2. Stiolto Respimat. In: DRUGDEX System [Internet database]. Greenwood Village, Colo: Thomson Micromedex. Updated periodically. Accessed January 26, 2016.
3. Tiotropium and Olodaterol. Lexi-Drugs [database online]. Lexi-Comp, Inc; January 26, 2016.
4. Stiolto Respimat. Clinical Pharmacology [Internet database]. Gold Standard, Inc., 2007. Available at: http://www.clinicalpharmacology.com. Accessed: January 29, 2016.
5. ZuWallack R, Allen L, Hernandex G, Ting N, Abrahams R. Efficacy and safety of combining olodaterol Respimat and tiotropium HandiHaler in patients with COPD:

results of two randomized, double-blind, active-controlled studies. International Journal of COPD. 2014: 9; 1133-1144.
6. Aalbers R, Maleki-Yazdi MR, Hamilton A, Waitere-Wijker S, Zhao Y, Amatto VC, et al. Randomized, Double-Blind, Dose-Finding Study for Tiotropium when Added to Olodaterol, Administered via the Respimat Inhaler in Patients with Chronic Obstructive Pulmonary Disease. Adv Ther. 2015; 32: 809-822.
7. Buhl R, Maltais F, Abrahams R, Bjermer L, Derom E, Ferguson G, et al. Tiotropium and olodaterol fixed-dose combination versus mono-components in COPD (Gold 2-4). Eur Respir J. 2015; 45: 969-979.

Prepared by: Kristen Sayre, Doctor of Pharmacy Candidate