Tiotropium Bromide/Olodaterol (Stiolo Respimat) Once-Daily Combination Therapy for the Maintenance of COPD

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INTRODUCTION

Chronic obstructive pulmonary disease (COPD), a relatively common respiratory disorder in the U.S., is the third leading cause of death in this country.1 It has been estimated that 15 million Americans have COPD.1 Since the disorder is so common, effective treatment regimens are a prominent research topic in pharmacology. Still, the development of pharmacological treatments for COPD has been a struggle. Only recently has sufficient progress been made in understanding the molecular and cell biology of COPD to allow the identification of new therapeutic targets.2 Currently, no drugs can reverse the progression of COPD.2 Hence, the development of new monotherapies or combination therapies is pivotal in providing relief to these patients.

Several drug classes are used to treat COPD, including anticholinergic agents, short- and long-acting beta2 agonists (LABAs), inhaled corticosteroids, and phosphodiesterase 4 (PDE4) inhibitors.3 Since COPD is most commonly caused by smoking and by exposure to second-hand smoke, the predominant nonpharmacological treatment is smoking cessation. Patients are also advised to avoid other triggers that may worsen respiration, such as air pollution, pet dander, and noxious chemicals.3 Because COPD is a progressive, debilitating disorder, patients commonly rely on combination therapies for relief.2 Of the available combination products, anticholinergic agents plus LABAs are often used for maintenance treatment.

Anticholinergics work primarily by inhibiting the action of acetylcholine and by reducing cyclic-adenosine monophosphate (cAMP) in bronchial smooth muscles, thereby triggering bronchodilation. LABAs bind to beta-adrenergic receptors, resulting in the relaxation of bronchial smooth muscles.5 When drugs from these two classes are used in combination, they have a synergistic effect on bronchodilation and improve airflow throughout the lungs during the first second of a forced exhalation.

The Fredericca corrections of QT (QTcF)—alternative formula used to correct the observed QT interval in an electrocardiogram based on cardiac rate. The Fredericca formula is: QT = QT/(-0.33).

FVC—forced vital capacity, the total volume of air that can be forcefully expelled after a full, deep inhalation.

GLOSSARY

Actuation—in an inhaler, the process by which a single dose is released for patient use.

Acute exacerbation COPD—a sustained worsening of the patient’s condition, from stable state and beyond normal day-to-day variations, that is sudden in onset and may warrant additional treatment; also called an exacerbation.

Bazett corrections of QT (QTcB)—standard formula used to correct the observed QT interval in an electrocardiogram based on cardiac rate. The Bazett formula is: QT = QTcB/√RR sec.

Bronchodilation—expansion of the air passages to the lungs (bronchioles and bronchi) to provide better air flow.

Cardiac electrophysiology—process that records electrical transmissions through the heart; used mainly to diagnose cardiac arrhythmias such as QT-interval prolongation.

Chronic bronchitis—inflammation of mucous membranes leading to excess mucus production and development of a chronic, productive cough; associated with vulnerability to lung infections.

Chronic obstructive pulmonary disease (COPD)—group of respiratory diseases characterized by the chronic obstruction of airflow to the lungs and not fully reversible; chronic bronchitis and emphysema are major forms of COPD.

Emphysema—abnormal enlargement of air sacs (alveoli) in the lungs that can progressively damage tissue; characterized by breathlessness.

FEV1—forced expiratory volume in one second, the volume of air that can be forcefully expired in that time after a full, deep inhalation.

FEV1/FVC ratio—percentage of the total FVC that is expelled from the lungs during the first second of a forced exhalation.

Fredericca corrections of QT (QTcF)—alternative formula used to correct the observed QT interval in an electrocardiogram based on cardiac rate. The Fredericca formula is: QT = QT/(-0.33).

FVC—forced vital capacity, the total volume of air that can be forcefully expelled after a full, deep inhalation.

Millisecond (msec)—one-thousandth of a second.

Priming (an inhaler)—spraying one or more puffs into the air prior to using the inhaler initially or after an extended period of disuse to ensure proper dose delivery.

Respimat Soft Mist inhaler—new-generation, propellant-free inhaler that allows a patient to inhale normally and still achieve increased lung penetration.

Spirometry—test of the lungs’ air capacity in terms of the volumes of air inspired and expired. Spirometric criteria are used by the COPD GOLD guidelines to classify the severity of the illness: mild disease, FEV1 > 80%; moderate disease, FEV1 > 50% but < 80%; severe disease, FEV1 > 30% but < 50%; very severe disease, FEV1 < 30%.

St. George’s Respiratory Questionnaire (SGRQ)—50-item survey for patients with chronic respiratory illnesses to assess the impact of obstructive airway diseases on overall health, daily life, and perceived well-being. Scores range from 0 to 100; higher numbers equate to more limitations.

Thyrotoxicosis—overproduction of thyroid hormones in the body; hyperthyroidism is a type of thyrotoxicosis.

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the respiratory system. Tiotropium bromide/olodaterol inhalation spray (Sti- olto Respimat, Boehringer Ingelheim), approved in May 2015 by the Food and Drug Administration, is a new fixed-dose anticholinergic/LABA combination medica tion for patients with COPD.

INDICATION AND USAGE

Tiotropium bromide/olodaterol is indicated for the long-term, once-daily maintenance therapy of airflow obstruction in patients with COPD. It is not indicated to treat asthma or acute deterioration of COPD.

MECHANISM OF ACTION

As an anticholinergic agent, tiotropium bromide antagonizes the effect of acetylcholine in the bronchioles to prevent bronchoconstriction and to trigger bronchodilation. In preclinical in vitro investigations as well as in vivo studies, the prevention of methacholine-induced bronchoconstriction was dose-dependent and lasted longer than 24 hours. The bronchodilation following inhalation of tiotropium is predominantly a site-specific effect. After topical administration by inhalation, the LABA olodaterol binds to beta2-adrenergic receptors in the bronchioles and triggers smooth-muscle relaxation, resulting in bronchodilation.

EFFECT ON CARDIAC ELECTROPHYSIOLOGY

In two 52-week, randomized, double-blind trials of fixed-dose tiotropium/olodaterol, electrocardiograph (ECG) assessments were performed after dosing on days 1, 85, 169, and 365 in a total of 5,162 patients with COPD. In this study, the number of subjects with changes from the baseline-corrected QT interval of greater than 30 msec was higher in the tiotropium group than in the placebo group. This between-group difference was established using both QTcB (20 patients [20%] versus 12 patients [12%]) and QTcF (16 patients [16%] versus one patient [1%]). None of the patients in either group had either a QTcB or QTcF of greater than 500 msec. Other clinical studies did not detect an effect of tiotropium on QTc intervals.

Olodaterol Hydrochloride

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

The effects of 5 mcg and 10 mcg of olodaterol on heart rate and rhythm were assessed using continuous 24-hour ECG recording (Holter monitoring) in 772 patients. No dose- or time-related trends or patterns were 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 clinically meaningful differences among olodaterol 5 mcg, olodaterol 10 mcg, and placebo.

PHARMACOKINETICS

When tiotropium/olodaterol was administered by inhalation, the pharmacokinetic parameters for the two components were similar to those observed when each substance was administered separately. Some of the pharmacokinetic data described below were obtained with dosages that were higher than the recommended dosage of two inhalations per day.

Absorption and Distribution Tiotropium

After inhalation of a tiotropium solution by young, healthy volunteers, urinary excretion data indicated 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.

Maximum tiotropium plasma concentrations are observed five to seven minutes after inhalation.

Tiotropium is 72% plasma protein-bound and has a volume of distribution of 32 L/kg. Lung concentrations are unknown, but the mode of administration suggests substantially higher concentrations in the lung. In rats, tiotropium did not cross the blood–brain barrier.

Olodaterol

Olodaterol generally reaches maximum plasma concentrations within 10 to 20 minutes after inhalation. In healthy volunteers, the absolute bioavailability of olodaterol after inhalation was estimated to be approximately 30%, whereas the absolute bioavailability was less than 1% when the drug was given as an oral solution. Thus, the systemic availability of olodaterol after inhalation is primarily determined by lung absorption.

Olodaterol exhibits multicompartmental disposition kinetics after both inhalation and intravenous (IV) administration. The volume of distribution is high (1,110 L/kg), suggesting extensive distribution into tissues. In vitro binding of [14C] olodaterol to human plasma proteins is approximately 60% and is independent of drug concentration.

Metabolism and Elimination Tiotropium

In vitro experiments with human liver microsomes and human hepatocytes suggest that a fraction of the administered
dose of tiotropium is metabolized by cytochrome P450 (CYP450)-dependent oxidation and subsequent glutathione conjugation to a variety of phase 2 metabolites. Tiotropium, an ester, is nonenzymatically cleaved to the alcohol N-methylscopine and to dihydroxyglycolic acid, neither of which binds to muscarinic receptors. This enzymatic pathway can be inhibited by CYP2D6 and 3A4 inhibitors, such as quinidine, ketoconazole, and gestodene.4

**Olopataderol**

Olopataderol is substantially metabolized by direct glucuronidation and by O-demethylation at the methoxy moiety, followed by conjugation. Of the six metabolites currently identified, only the unconjugated demethylating product binds to β2 receptors. This metabolite, however, is not detectable in plasma after chronic inhalation of the recommended therapeutic dose of tiotropium/olodaterol. CYP2C8, 2C9, and 3A4 are involved in the O-demethylation of olodaterol, whereas the uridine diphosphate glucosyl transferase (UGT) isoforms UGT1A1, 1A7, 1A9, and 2B7 are involved in the formation of olodaterol glucuronides.8

**Excretion**

**Tiotropium**

The terminal half-life of tiotropium in COPD patients after once-daily inhalation of 5 mcg is approximately 25 hours. Total clearance was 880 mL/min after an IV dose in young, healthy volunteers. IV tiotropium bromide is mainly excreted unchanged in urine (74%). After inhalation of the solution, urinary excretion is 19% of the dose; the remainder is mainly nonabsorbed drug in the gut, which 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.4

**Olopataderol**

Total clearance of olodaterol in healthy volunteers is 872 mL/min, and renal clearance is 173 mL/min. The terminal half-life after IV administration is 22 hours. In contrast, the terminal half-life after inhalation is approximately 45 hours, indicating that the latter is determined by absorption rather than by elimination. The effective

half-life of olodaterol at a daily dose of 5 mcg, calculated from the Cmax in COPD patients, is 7.5 hours.4

After IV administration of [14C]-labeled olodaterol, 38% of the radioactive dose was recovered in urine and 53% was recovered in feces. The amount of unchanged olodaterol recovered in urine after IV administration was 19%. After oral administration, only 9% of olodaterol and/or its metabolites was recovered in urine, while the major portion (84%) was recovered in feces. More than 90% of the dose was excreted within five and six days after oral and IV administration, respectively. After inhalation, the excretion of unchanged olodaterol in urine within the dosing interval in healthy volunteers at steady state accounted for 5% to 7% of the dose.4

**CLINICAL STUDIES**

The efficacy of fixed-dose tiotropium/olodaterol combinations is based primarily on two four-week dose-ranging trials in a total of 592 COPD patients and on two confirmatory, active-controlled, 52-week trials in a total of 5,162 COPD patients.4

**Dose-Ranging Studies**

Aalbers and colleagues conducted a four-week, randomized, double-blind, incomplete-crossover study to determine the optimum once-daily dose of olodaterol (5 and 10 mcg) and tiotropium (1.25, 2.5, and 5 mcg) in combination when delivered via the Respimat Soft Mist inhaler in patients with COPD. The study’s primary efficacy endpoint was the trough forced expiratory volume in one second (FEV1) response (the change from baseline) after four weeks of treatment (day 29). Secondary efficacy endpoints included the FEV1 area under the curve from zero to six hours (AUC0–6 hrs) response after four weeks of treatment; the trough forced vital capacity (FVC) response, the FVC AUC0–6 hrs response after four weeks of treatment; and the incidence and severity of adverse events.9

The study included male and female patients 40 years of age and older with a diagnosis of COPD confirmed by spirometric criteria. The patients were required to have a post-bronchodilator FEV1 equal to or greater than 30% and less than 80% as well as a post-bronchodilator FEV1/FVC ratio of less than 70%. Current and former smokers with a smoking history of more than 10 pack-years were also enrolled.

Concomitant respiratory medications included inhaled corticosteroids, inhaled short-acting beta-adrenergics, LABAs, and short-acting anticholinergics.9

A total of 232 patients with COPD (133 men and 99 women) were enrolled and received treatment with study medication. At day 29, the adjusted mean trough FEV1 and FEV1 AUC0–6 hrs were increased from baseline with olodaterol 5-mcg and 10-mcg monotherapy. The trough FEV1 response and FEV1 AUC0–6 hrs responses were similar for olodaterol 5-mcg and 10-mcg monotherapy (0.071 L and 0.083 L, respectively, for trough FEV1 response, and 0.188 L and 0.198 L, respectively, for FEV1 AUC0–6 hrs response).9

All of the tiotropium/olodaterol combinations (0/5, 1.25/5, 2.5/5, 5/5, 0/10, 1.25/10, 2.5/10, and 5/10 mcg) resulted in larger trough FEV1 and FEV1 AUC0–6 hrs responses and higher FVC values compared with the respective olodaterol monotherapies.9 The mean differences in trough FEV1 for the tiotropium/olodaterol doses of 1.25/5, 2.5/5, and 5/5 mcg once daily from olodaterol 5 mcg were 0.54 L, 0.065 L, and 0.084 L, respectively.4

The authors concluded that the addition of tiotropium to olodaterol resulted in improvements in lung function parameters compared with olodaterol monotherapy in this four-week study.9

In another dose-ranging trial, Maltais and associates investigated the bronchodilator efficacy of a fixed-dose combination of tiotropium and olodaterol in comparison with tiotropium monotherapy, both administered using the Respimat Soft Mist inhaler, in 360 patients (196 men and 164 women; mean age, 63 years) with COPD. FEV1 was measured pre-dose (trough) and for up to six hours post-dose.10

At the end of this randomized, double-blind, parallel-group study, the peak FEV1 response from baseline was significantly increased for all doses of the tiotropium/olodaterol combination (5/2, 5/5, and 10/5 mcg) compared with tiotropium (5 mcg) alone.12 The mean differences in trough FEV1 for the tiotropium/olodaterol doses of 5/2, 5/5, and 5/10 mcg compared with tiotropium (5 mcg) alone.12 The mean differences in trough FEV1 for the tiotropium/olodaterol doses of 5/2, 5/5, and 5/10 mcg compared with tiotropium (5 mcg) alone.12 The mean differences in trough FEV1 for the tiotropium/olodaterol doses of 5/2, 5/5, and 5/10 mcg compared with tiotropium (5 mcg) alone.12 The mean differences in trough FEV1 for the tiotropium/olodaterol doses of 5/2, 5/5, and 5/10 mcg compared with tiotropium (5 mcg) alone.12 The mean differences in trough FEV1 for the tiotropium/olodaterol doses of 5/2, 5/5, and 5/10 mcg compared with tiotropium (5 mcg) alone.12 The mean differences in trough FEV1 for the tiotropium/olodaterol doses of 5/2, 5/5, and 5/10 mcg compared with tiotropium (5 mcg) alone.12

**Confirmatory Studies**

The positive results from the dose-ranging studies of fixed-dose tiotropium/olodaterol combinations were confirmed in a confirmatory study in 232 patients with COPD. The study included 133 men and 99 women; mean age, 63 years; and mean FEV1, 0.24 L, 0.033 L, and 0.057 L, respectively.4

The study included male and female patients 40 years of age and older with a diagnosis of COPD confirmed by spirometric criteria. The patients were required to have a post-bronchodilator FEV1 equal to or greater than 30% and less than 80% as well as a post-bronchodilator FEV1/FVC ratio of less than 70%. Current and former smokers with a smoking history of more than 10 pack-years were also enrolled.

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olodaterol combinations supported the evaluation of once-daily doses of tiotropium/olodaterol 2.5/5 mcg and 5/5 mcg in two 52-week, phase 3 confirmatory trials. These replicate, randomized, double-blind, active-controlled, parallel-group studies evaluated a total of 5,162 COPD patients (1,029 receiving tiotropium/olodaterol 2.5/5 mcg or 5/5 mcg, 1,033 receiving tiotropium 2.5 mcg or 5 mcg, and 1,038 receiving olodaterol 5 mcg). All of the products were administered using the Respimat inhaler. The primary endpoints of both studies were the change from baseline in FEV\textsubscript{1} AUC\textsubscript{0–3 hrs} and trough FEV\textsubscript{1} after 24 weeks of treatment. Most of the 5,162 patients were men (73%) and were either white (71%) or Asian (25%), with a mean age of 64 years. The mean post-bronchodilator FEV\textsubscript{1} was 1.37 L, and the mean beta\textsubscript{2}-agonist responsiveness was 16.6% of baseline (0.171 L). Pulmonary medications, such as inhaled steroids (47%) and xanthines (10%), were allowed as concomitant therapy.

In both studies, the two fixed-dose combinations of tiotropium/olodaterol (2.5/5 mcg and 5/5 mcg) significantly improved FEV\textsubscript{1} AUC\textsubscript{0–3 hrs} and trough FEV\textsubscript{1} compared with the individual components.

FEV\textsubscript{1} AUC\textsubscript{0–3 hrs} responses for tiotropium/olodaterol (2.5/5 mcg and 5/5 mcg), for tiotropium (2.5 mcg and 5 mcg), and for olodaterol (5 mcg) were 241, 256, 148, 139, and 133 mL, respectively, in the first study, and 256, 268, 125, 165, and 136 mL, respectively, in the second study. In both trials, the improvements in the adjusted mean FEV\textsubscript{1} AUC\textsubscript{0–3 hrs} with tiotropium/olodaterol (2.5/5 mcg and 5/5 mcg) versus those with the corresponding individual components were statistically significant (P < 0.0001) for all comparisons.

Similarly, trough FEV\textsubscript{1} responses after 24 weeks for tiotropium/olodaterol (2.5/5 mcg and 5/5 mcg), for tiotropium (2.5 mcg and 5 mcg), and for olodaterol (5 mcg) were 111, 136, 83, 65, and 54 mL, respectively, in the first study, and 125, 145, 62, 96, and 57 mL, respectively, in the second study. The improvements with tiotropium/olodaterol 2.5/5 mcg and 5/5 mcg over the corresponding individual components were statistically significant (P < 0.05) in both studies.

**SAFETY PROFILE**

**Adverse Events in COPD Trials**

The primary safety database for tiotropium/olodaterol consists of pooled data from the two 52-week confirmatory studies described previously. These studies included a total of 1,029 patients who were treated with tiotropium/olodaterol once daily. Tiotropium 5 mcg and olodaterol 5 mcg were included as active control arms in both studies; no placebo treatments were used.

In these two clinical studies, 74.0% of the patients treated with tiotropium/olodaterol reported an adverse event, compared with 76.6% and 73.3% of the olodaterol and tiotropium groups, respectively. The most common adverse events were nasopharyngitis (12.4% for tiotropium/olodaterol), 11.7% for tiotropium, and 12.6% for olodaterol, cough (3.9%, 4.4%, and 3.0%), and back pain (3.6%, 1.8%, and 3.4%). In both studies, the most common serious adverse events were COPD exacerbation and pneumonia.

The proportions of patients who discontinued treatment because of an adverse event were 7.4% for the tiotropium/olodaterol group, 9.9% for the olodaterol group, and 9.0% for the tiotropium group. The adverse event most commonly leading to discontinuation was worsening COPD.

**Drug–Drug Interactions**

Several drugs, including adrenergic agents, sympathomimetics, and non–potassium-sparing diuretics, should be used with caution with fixed-dose tiotropium/olodaterol because of the potential for adverse drug–drug interactions. These medications are listed in Table 1.

**Contraindications**

All LABAs, including olodaterol, increase the risk of asthma-related death and are contraindicated in patients with asthma without the use of a long-term asthma-control medication. Fixed-dose tiotropium/olodaterol is not indicated for the treatment of asthma. Further, fixed-dose tiotropium/olodaterol is contraindicated in patients with a hypersensitiv-

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**Table 1** Drugs With a Potential to Interact With Fixed-Dose Tiotropium/Olodaterol

<table>
<thead>
<tr>
<th>Agent</th>
<th>Potential Interactions</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adrenergic drugs</td>
<td>Coadministration with tiotropium/olodaterol may potentiate sympathetic effects of olodaterol.</td>
</tr>
<tr>
<td>Anticholinergic drugs</td>
<td>Coadministration with tiotropium/olodaterol may increase anticholinergic adverse effects.</td>
</tr>
<tr>
<td>Beta-adrenergic receptor antagonists</td>
<td>Beta blockers and olodaterol (a beta-adrenergic receptor agonist) may interfere with each other’s effects when administered concurrently. Beta blockers inhibit therapeutic effects of beta agonists and may produce severe bronchospasm in COPD patients.</td>
</tr>
<tr>
<td>Diuretics</td>
<td>Coadministration with tiotropium/olodaterol may potentiate hypokalemic effects of olodaterol.</td>
</tr>
<tr>
<td>Non–potassium-sparing diuretics</td>
<td>ECG changes and/or hypokalemia may result from coadministration of non–potassium-sparing diuretics and beta agonists, such as olodaterol.</td>
</tr>
<tr>
<td>QTc-prolonging agents</td>
<td>Action of adrenergic agonists, such as olodaterol, may be potentiated by QTc-prolonging agents, such as monoamine oxidase inhibitors and tricyclic antidepressants. Drugs that prolong QTc interval may increase risk of ventricular arrhythmias.</td>
</tr>
<tr>
<td>Steroids</td>
<td>Coadministration with tiotropium/olodaterol may potentiate hypokalemic effects of olodaterol.</td>
</tr>
<tr>
<td>Sympathomimetic drugs</td>
<td>Coadministration with tiotropium/olodaterol may potentiate hypokalemic effects of olodaterol.</td>
</tr>
<tr>
<td>Xanthine derivatives</td>
<td>Coadministration with tiotropium/olodaterol may potentiate hypokalemic effects of olodaterol.</td>
</tr>
</tbody>
</table>

COPD = chronic obstructive pulmonary disease; ECG = electrocardiogram
ity to tiotropium, ipratropium, olodaterol, or any component of the product.

Immediate hypersensitivity reactions, including angioedema, itching, and rash, have been reported in both clinical trials and post-marketing experience with tiotropium monotherapy. Hypersensitivity reactions were also reported in clinical studies of fixed-dose tiotropium/olodaterol.

**Key Warnings and Precautions**

**Asthma-Related Death**

Data from a large placebo-controlled study in asthma patients showed that long-acting beta2-adrenergic agonists may increase the risk of asthma-related death. The increased risk of asthma-related death is considered a class effect of these agents, including olodaterol. No studies have been conducted to determine whether the rate of asthma-related death is increased in patients treated with tiotropium/olodaterol. As noted above, tiotropium/olodaterol is contraindicated in asthma patients.

**Deterioration of COPD and Acute Episodes**

Treatment with tiotropium/olodaterol should not be initiated in patients with acutely deteriorating COPD because the drug has not been studied in this population. Moreover, tiotropium/olodaterol should not be used to relieve acute symptoms of COPD, i.e., as rescue therapy for the treatment of acute episodes of bronchospasm. When prescribing tiotropium/olodaterol, health care providers should also prescribe an inhaled, short-acting beta2 agonist in case rescue therapy is needed, and they should instruct patients on how and when to use it.

**Paradoxical Bronchospasm**

As with other inhaled drugs containing beta2-adrenergic agents, tiotropium/olodaterol may cause paradoxical bronchospasm, which may be life-threatening. If paradoxical bronchospasm occurs, tiotropium/olodaterol should be stopped immediately and an alternative therapy instituted.

**Cardiovascular Effects**

Olodaterol, like other beta2 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 other cardiovascular symptoms. If such effects occur, tiotropium/olodaterol may need to be discontinued. In addition, beta agonists have been reported to produce ECG changes, such as prolongation of the QTc interval, but the clinical significance of these findings is unknown. LABAs should be administered with caution in patients with cardiovascular disorders, especially coronary insufficiency, cardiac arrhythmias, hypertrophic obstructive cardiomyopathy, and hypertension.

**Worsening of Urinary Retention**

Tiotropium/olodaterol should be used with caution in patients with urinary retention. Prescribers and patients should be alert for signs and symptoms of acute narrow-angle glaucoma. If any of these signs or symptoms develop, the patient should consult a physician immediately.

**Worsening of Narrow-Angle Glaucoma**

Tiotropium/olodaterol 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. If any of these signs or symptoms develop, the patient should consult a physician immediately.

**Renal Impairment**

Because tiotropium is mainly excreted via the kidneys, patients with moderate-to-severe renal impairment (i.e., those with a creatinine clearance of 60 mL/min or less) treated with tiotropium/olodaterol should be monitored closely for anticholinergic effects.

**Hypokalemia and Hyperglycemia**

Beta-adrenergic agonists may produce significant hypokalemia in some patients, which can result in adverse cardiovascular effects. This decrease in serum potassium is usually transient and does not require supplementation. The inhalation of high doses of beta2-adrenergic agonists may increase plasma glucose levels.

Clinically relevant decreases in serum potassium or changes in blood glucose occurred infrequently during clinical trials involving the long-term administration of olodaterol, with rates similar to those of placebo-treated controls. Olodaterol has not been investigated in patients whose diabetes mellitus is not well controlled.

**DOSAGE AND ADMINISTRATION**

The recommended dose of tiotropium/olodaterol is two inhalations once daily at the same time of the day. Tiotropium/olodaterol should not be used at more than two inhalations every 24 hours.

Before the first use, the tiotropium/olodaterol cartridge is inserted into the Stiolo Respimat inhaler and the unit is primed. When using the unit for the first time, patients should actuate the inhaler toward the ground until an aerosol cloud is visible, and then repeat the process three more times. The unit is then considered primed and ready to use. If it is not used for more than three days, patients should actuate the inhaler once to prepare the inhaler for use. If it is not used for more than 21 days, patients should actuate the inhaler until an aerosol cloud is visible and then repeat the process three more times to prepare the inhaler for use.

No dosage adjustment is required for geriatric, hepatically impaired, or renally impaired patients. However, patients with moderate-to-severe renal impairment treated with tiotropium/olodaterol should be monitored closely for anticholinergic effects.

**COST**

The average wholesale price (AWP) of one tiotropium/olodaterol inhalation device is $379. Each device supplies 60 metered inhalations of 2.5/2.5 mg per actuation, meaning it should last 30 days using the recommended regimen of two inhalations per day.

**P&T COMMITTEE CONSIDERATIONS**

Because several drug classes are available for the treatment of COPD, many hospital pharmacies are questioning which of these agents should be on their institutions’ formularies for inpatient use. Of the many drug classes used for COPD, LABAs and anticholinergics are the mainstays of current treatment protocols. Both of these drug classes promote bronchodilation and improve airflow in COPD patients.

Fixed-dose tiotropium/olodaterol offers a long-acting beta2 agonist in combination with a long-acting anticholinergic. Because of their extended activity, the two agents have an additive effect in maintaining airflow dilation. Since the approval of tiotropium bromide inhalation powder (Spiriva HandiHaler) and olodat-
Another anticholinergic/LABA combination is similar to umeclidinium/velanterol; therefore, this medication cannot be used in patients who are allergic to milk. Further, umeclidinium/velanterol, which uses a dry-powder inhaler, requires patients to inhale with a long, steady, deep breath, which may be difficult for elderly patients. Tiotropium/olodaterol allows patients to inhale normally.14,15

CONCLUSION

The anticholinergic and LABA drug classes have been shown to decrease exacerbations and to improve respiration in patients with COPD. Tiotropium/olodaterol (Stiolo Respimat) is the newest combination drug product indicated for the maintenance of COPD.16 Recent studies have demonstrated that the combination of tiotropium bromide and olodaterol hydrochloride is more effective at improving FEV1 AUC0–3 hrs than either of the two agents used alone.11 Tiotropium/olodaterol is also one of the few combination products that includes a LABA and a long-acting anticholinergic. Like olodaterol alone, the fixed-dose combination of tiotropium and olodaterol improves airflow in children five minutes after the first dose.16 While the fixed-dose product has been associated with various adverse events, including nasopharyngitis, pneumonia, cough, and back pain, the proportions of patients who withdrew from clinical trials because of such events were significantly lower for the tiotropium/olodaterol combination than for tiotropium or olodaterol alone.9 With these considerations in mind, fixed-dose tiotropium/olodaterol appears to offer an attractive option for the maintenance treatment of patients with COPD.

REFERENCES


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