

Tiotropium-Olodaterol (Stiolto) Respimat Abbreviated Review

VA Pharmacy Benefits Management Services,
Medical Advisory Panel, and VISN Pharmacist Executives

The PBM prepares abbreviated reviews to compile information relevant to making formulary decisions. VA clinical experts may provide input on the content. Wider field review is not sought. Documents no longer current will be placed in the Archive section.

FDA Approval Information

Description	Fixed-dose combination of tiotropium, a long-acting anticholinergic (LAMA) and olodaterol, a long-acting beta-agonist (LABA)
Indication(s) Under Review	Maintenance treatment of airflow obstruction in patients with COPD
Dosage Form(s) Under Review	Tiotropium 2.5mg/olodaterol 2.5mg per actuation in the Respimat inhaler
REMS	<input type="checkbox"/> REMS <input checked="" type="checkbox"/> No REMS <i>See Other Considerations for additional REMS information</i>
Pregnancy Rating	Category C

Executive Summary	
Efficacy	Two 52-week trials showed significantly greater improvement in FEV1 AUC _{0-3h} and trough FEV1, SGRQ, and dyspnea with TIO/OLO 5/5mcg compared to the individual components. There was a trend in improving moderate-severe exacerbations with the combination versus individual components
Safety	There was no significant difference in major adverse cardiovascular events or any cardiac event between TIO/OLO and the individual components. In other studies of olodaterol as a single agent in COPD, there was a slightly higher risk of CV adverse events compared to formoterol or placebo
Projected Place in Therapy	May be an option for patients require both a LABA and LAMA for management of COPD.

Background

Purpose for Review

The purpose of this monograph is to evaluate the available evidence of safety, tolerability, efficacy, cost, and other pharmaceutical issues that would be relevant to evaluating tiotropium/olodaterol (TIO/OLO) inhaler for possible addition to the VA National Formulary

Other Therapeutic Options

Formulary Alternatives	Other Considerations
Tiotropium Olodaterol Formoterol	LABA and LAMA be administered as separate inhalers Formoterol: twice daily dosing; requires storage in refrigerator prior to dispensing (CMOP mails in cold pack). After dispensing to patient, may be stored at room temperature
Non-formulary Alternatives	Other Considerations
Combo: Umeclidinium/vilanterol LABA: Salmeterol, indacaterol LAMA: aclidinium, umeclidinium	Combo: Once daily administration; high cost LABA: salmeterol twice daily, indacaterol once daily; high cost LAMA: aclidinium twice daily, umeclidinium once daily; high cost

Efficacy (FDA Approved Indications)

Literature Search Summary

A literature search was performed on PubMed/Medline (1966 to September 2015) using the search terms tiotropium and olodaterol. The search was limited to studies performed in humans and published in the English language.

Review of Efficacy

There are 10 trials in the Phase 3 Program for TIO/OLO. Three have been published and the others are in various stages of patient recruitment or completion ([Appendix 1](#)). The efficacy review is limited to published trials/abstracts.

TOnado 1 and 2 are replicate randomized, double-blind, active-controlled 52-week trials. Patients (n=5162) were randomized to TIO/OLO 5/5mcg, TIO/OLO 2.5/5mcg, TIO 5mcg, TIO 2.5mcg, or OLO 5mcg administered once daily. Inhaled corticosteroids were continued as appropriate for those receiving them at baseline. There were 3 primary outcomes after 24 weeks of treatment; FEV1 AUC_{0-3h}, trough FEV1, and St. George's Respiratory Questionnaire (SGRQ) total score.

General inclusion criteria: ≥40 years old, moderate-very severe COPD (GOLD stage 2-4), current or ex-smokers with >10pack-year history, post-bronchodilator FEV1 <80% predicted normal, post-bronchodilator FEV1/FVC <70%.

General exclusion criteria: History of asthma, myocardial infarction within 1 year of screening, unstable or life-threatening arrhythmias, hospitalized for heart failure in the past year, thyrotoxicosis, paroxysmal tachycardia, regular daytime use of oxygen if unable to abstain during clinic visits, clinically evident bronchiectasis, cystic fibrosis, life-threatening pulmonary obstruction, previous pulmonary resection, currently enrolled in pulmonary rehabilitation program (or completed in 6 weeks prior to screening), other clinically significant disease or clinically relevant abnormal baseline lab parameters.

Select demographic information: males 72.9%, approximately 1/3 current smokers, 50% GOLD 2, 38.5% GOLD 3, 11.3% GOLD 4, FEV1 50% predicted, inhaled corticosteroid (ICS) use 47.4%, 21.4% had cardiac disorders, and 48.1% had vascular disorders.

Pulmonary Function

There was significantly greater improvement in FEV1 AUC_{0-3h} and trough FEV1 with TIO/OLO 5/5mcg compared to the individual components. The difference in FEV1 AUC_{0-3h} between TIO/OLO 5/5mcg and TIO/OLO 2.5/5mcg was not significant except for trough FEV1 ([Table 1](#)).

Table 1: Select Efficacy Measures at Week 24 (Combined Analysis TOnado 1 and 2 Trials)**

	TIO/OLO 5/5 vs. OLO 5	TIO/OLO 5/5 vs. TIO 5	TIO/OLO 5/5 vs. TIO/OLO 2.5/5
FEV1 AUC 0-3h (L)	0.128 [0.111, 0.144]	0.110 [0.093, 0.127]	0.013 [-0.004, 0.030]
Trough FEV1 (L)	0.085 [0.067, 0.102]	0.060 [0.43, 0.077]	0.022 [0.005, 0.039]
SGRQ total score	-1.693 [-2.778, -0.608]	-1.233 [-2.313, -0.153]	-0.662 [-1.73, 0.407]
TDI focal score	0.420 [0.155, 0.684]	0.356 [0.092, 0.619]	0.003 [-0.259, 0.266]
Exacerbations (Risk ratio)	0.834 [0.706, 0.986]	0.925 [0.781, 1.095]	Not shown

**Exacerbation data are over 52-weeks

Data shown as treatment differences

When analyzed according to disease severity, there was less improvement in those with more severe disease (data not shown in this review). There was significantly greater improvement in pulmonary function with the combination compared to individual components regardless of whether patients were using concomitant ICS or not.

A 6-week randomized, double-blind, placebo-controlled, incomplete cross-over design study (n=259) further supports the pulmonary function findings of the 52-week trials. For the primary analysis of FEV1 AUC_{0-24h}, the fixed-dose combinations significantly improved pulmonary function compared to placebo and the individual drug components ([Table 2](#)).

Table 2: Pulmonary Function (6-Week Trial)

	TIO/OLO 5/5 vs. OLO 5	TIO/OLO 5/5 vs. TIO 5	TIO/OLO 5/5 vs. TIO/OLO 2.5/5	TIO/OLO 5/5 vs. PBO
FEV1 AUC 0-24h (L)	0.11 [0.087, 0.143]	0.110 [0.082, 0.139]	0.003 [-0.025, 0.031]	0.280 [0.252, 0.309]

Data shown as treatment differences

Health Status

The percentage of patients having a clinically meaningful improvement in SGRQ total score (≥ 4.0 unit improvement from baseline) was 57.5%, 44.8%, and 48.7% for TIO/OLO 5/5, OLO5, and TIO5 respectively. The difference in score with TIO/OLO was statistically significantly greater than the individual components. There was no significant difference between the two TIO/OLO doses (**Table 1**).

Transitional Dyspnea Index

The transitional dyspnea index (TDI) was used to assess relief of dyspnea. The differences between the combination and individual components were considered to be statistically significant; there was no significant difference between the two TIO/OLO doses (**Table 1**).

Exacerbations

These studies were not designed to assess exacerbations; however, such data were included as part of the safety analysis. There was a trend in improving moderate-severe exacerbations with the combination versus individual components (**Table 1**). A dedicated 52-week exacerbation trial (planned enrollment 7800 patients) is currently recruiting patients.

Rescue Medication

The combination reduced the weekly mean daily rescue medication use compared to the individual components (shown graphically in publication).

Exercise endurance

A 12-week randomized, double-blind trial (n=404) compared exercise endurance using TIO/OLO 5/5, TIO/OLO 2.5/5, and placebo in patients with GOLD 2-3 COPD. Mean baseline post-bronchodilator FEV1 was 58.6% predicted. The primary endpoint was endurance time during constant work-rate cycle ergometry to symptom limitation. A subset of 165 patients was also assessed for endurance time during endurance shuttle walking to symptom limitation.

At week 12, endurance time during cycle ergometry increased by 14% in the TIO/OLO 5/5 group compared to placebo ($p < 0.05$). Increase in endurance time in the TIO/OLO 2.5/5 group was 9% compared to placebo and was not considered significant. In the subgroup of patients who underwent endurance shuttle walking, both doses increased endurance time by 21% compared to placebo; however, the change was not considered significant ($p = 0.06$).

Potential Off-Label Use

In asthma

Safety

(for more detailed information refer to the product package insert)

	Comments
Boxed Warning	LABAs such as olodaterol increase the risk of asthma-related death
Contraindications	All LABAs: In patients with asthma without the use of a long-term asthma control medication Hypersensitivity to tiotropium, olodaterol, ipratropium or any component of this product
Warnings/ Precautions	The warnings and precautions are the same as those listed for the individual components. There were no warnings and precautions listed unique to the fixed-dose combination product
Safety Considerations	<u>Cardiovascular</u> There was no significant difference in major adverse cardiovascular events or any cardiac event between TIO/OLO and the individual components (Table 3).

Table 3: Rate Ratio [95%CI] of MACE and Cardiac Adverse Events from TOnado 1 and 2

	TIO/OLO 5/5 vs. TIO 5	TIO/OLO 5/5 vs. OLO 5	TIO/OLO 2.5/5 vs. TIO 2.5	TIO/OLO 2.5/5 vs. OLO 5
Any MACE	1.11 [0.68, 1.80]	1.07 [0.66, 1.73]	1.00 [0.60, 1.68]	0.87[0.53, 1.44]
Any cardiac event	0.81 [0.55, 1.20]	0.75 [0.51, 1.10]	0.97 [0.68, 1.38]	0.98 [0.68, 1.40]

In the 52-week TOnado trials, ECGs were assessed post-dose at days 1, 85, 169, and 365. In a pooled analysis, there was no difference in the number of patients with changes from baseline-corrected QT interval >30msec (Bazett and Fredericia corrections of QT for heart rate) in the TIO/OLO 5/5, TIO 5, and OLO 5 groups.

The incidence of overall adverse events in the subset of patients with a cardiac history was 78.1%, 75.8%, 80.6, and 79.7% for TIO/OLO 5/5, TIO/OLO 2.5/5, TIO 5, and OLO 5 respectively.

Adverse Reactions

Common adverse reactions The majority of adverse reactions were considered to be mild to moderate in severity.

Table 5: Adverse reactions occurring in a frequency of ≥3% and more often with TIO/OLO than TIO or OLO

	TIO/OLO 5/5 (n=1029)	TIO 5 (n=1033)	OLO 5 (n=1038)
COPD (%)	32.3	32.9	35.6
Nasopharyngitis (%)	12.4	11.7	12.6
Cough (%)	3.9	4.4	3.0
Dyspnea (%)	3.8	4.9	3.7
Back pain (%)	3.6	1.8	3.4
Pneumonia (%)	3.3	2.5	3.5
Bronchitis (%)	3.0	2.2	3.2

Death/Serious adverse reactions (SAE) The most common SAEs were COPD exacerbation and pneumonia.

Table 6: Serious Adverse Events and Deaths from TOnado 1 and 2

	TIO/OLO 5/5	TIO/OLO 2.5/5	TIO 5	OLO 5
SAEs (%)	16.4	16.3	16.7	17.4
Deaths (%)	1.7	1.4	1.6	1.3

Discontinuations due to adverse reactions **Table 7: Discontinuations due to Adverse Reactions from TOnado 1 and 2**

	TIO/OLO 5/5	TIO/OLO 2.5/5	TIO 5	OLO 5
	7.4	5.5	9.0	9.9

Drug Interactions

Drug-drug interactions Strong dual Inhibitor of CYP P450 and P-gp inhibitor (ketoconazole) resulted in a 1.7 fold increase of olodaterol maximum plasma concentration and AUC. No dosage adjustment is necessary.

Refer to product package insert for other drug-interactions common to the LABA and anticholinergic class.

Drug-food interactions None

Drug-lab interactions None

Risk Evaluation

As of September 2015

Sentinel event advisories

None

Sources: ISMP, FDA, TJC

Look-alike/sound-alike error potentials

NME Drug Name	Lexi-Comp	First DataBank	ISMP	Clinical Judgment
Tiotropium/olodaterol Inhaled solution	None	None	None	Tiotropium Olodaterol Ipratropium/albuterol
Stiolto Respimat	None	None	None	Spiriva Respimat Striverdi Respimat Sirturo

Sources: Based on clinical judgment and an evaluation of LASA information from three data sources (Lexi-Comp, First Databank, and ISMP Confused Drug Name List)

Other Considerations

Store at 25°C (77°F); excursions permitted to 15°C-30°C (59°F-86°F)

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

Dosing and Administration

- Two inhalations once-daily at the same time of day
- Do not use more than two inhalations every 24 hours

Special Populations (Adults)

	Comments
Elderly	<p>Among the patients who received TIO/OLO at the recommended dose, 39.6% were 65 to <75, 9.3% were 75 to <85 and 0.1% was ≥ 85 years of age.</p> <p>Overall efficacy and adverse drug reaction profiles were similar in the older population and the overall population. No dosage adjustment is recommended for geriatric patients.</p>

Projected Place in Therapy

TIO/OLO may be an option for patients require both a LABA and LAMA for management of COPD.

References

Product package insert for tiotropium bromide and olodaterol (STIOLTO RESPIMAT) inhalation spray. June 2015

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Beeh, K-M, Westerman J, Kirsten AM, et al. The 24-h lung-function profile of once-daily tiotropium and olodaterol fixed-dose combination in chronic obstructive pulmonary disease. *Pulm Pharmacol Ther* 2015; 32: 53-59.

Maltais F, Bautista J, Iturri G, et al. Effects of 12 weeks of once-daily tiotropium and olodaterol fixed-dose combination on exercise endurance in patients with COPD. *Eur Resp J* 2014; 44 Suppl 58 P283

McGarvey L, Niewoehner D, Magder S, et al. One-year safety of olodaterol once daily via respimat in patients with GOLD 2-4 chronic obstructive pulmonary disease: results of a pre-specified pooled analysis. *COPD* 2015 Feb 18 [epub ahead of print] DOI:10.3109/15412555.2014.991864

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October 2015**

Appendix 1: TOviTO Phase 3 Program

Studies	Duration	Treatment Arms	Outcomes	Status
Buhl 2015 TONado 1 TONado 2	52 weeks	TIO/OLO 5/5, TIO/OLO 2.5/5, TIO 5, TIO 2.5, OLO 5	Lung function, SGRQ, dyspnea, exacerbation, safety	Published
Beeh 2015 VIVACITO	Crossover; 6 week periods	TIO/OLO 2.5/5, TIO/OLO 5/5, individual components, PBO	Lung function	Published
ENERGITO	4-week crossover; 6- week periods	TIO/OLO 1.25/2.5, TIO/OLO 2.5, 2.5, FP/SAL 250/50, FP/SAL 500/50	Lung function	Recruitment complete
OTEMTO 1	12 weeks	2 doses of FDC	Efficacy: pulmonary function, SGRQ	Recruiting has not started
OTEMTO 2	12 weeks	2 doses of FDC	Efficacy: pulmonary function, SGRQ	Recruiting has not started
Maltais 2014 TORRACTO	12 weeks	TIO/OLO 2.5/5, TIO/OLO 5/5, PBO	Exercise endurance	Abstract available
MORACTO 1	6 weeks	TIO/OLO 5/5, TIO/OLO 2.5/5, TIO5, OLO5, PBO	Endurance time, lung hyperinflation	Trial complete; awaiting results
MORACTO 2	6 weeks	TIOLO 5/5, TIO/OLO 2.5/5, TIO5, OLO5, PBO	Endurance time, lung hyperinflation	Trial complete; awaiting results
PHYSACTO	12 week	TIO/OLO 5/5mcg, TIO5, OLO5, PBO	Exercise capacity, physical activity	Recruiting patients
DYNAGITO	52 weeks	TIO/OLO 5/5mcg, TIO5	Exacerbations, survival	Recruiting patients

Abbreviations: FDC=fixed-dose combination; FP/SAL=fluticasone propionate/salmeterol; OLO=olodaterol; PBO=placebo; SGRQ=St. George's Respiratory Questionnaire; TIO=tiotropium