Olodaterol (Striverdi Respimat)
National Drug Monograph
VA Pharmacy Benefits Management Services, Medical Advisory Panel, and VISN Pharmacist Executives

The purpose of VA PBM Services drug monographs is to provide a comprehensive drug review for making formulary decisions. Updates will be made when new clinical data warrant additional formulary discussion. Documents will be placed in the Archive section when the information is deemed to be no longer current.

FDA Approval Information

Description/Mechanism of Action	Olodaterol is a long-acting beta2-adrenergic agonist (LABA). Binding to and activating beta2-adrenoceptors in the airways results in 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.
Indication(s) Under Review	Long-term once daily maintenance bronchodilator treatment of airflow obstruction in patients with COPD including chronic bronchitis and/or emphysema
Dosage Form(s) Under Review	Inhalation spray for oral inhalation via Respimat (a soft-mist inhaler) The soft-mist inhalers (SMI) provide multi-dose medication using liquid formulations similar to that used in nebulizers and are propellant-free. Presently, Respimat is the only SMI commercially available for clinical use. The soft mist is released at a slower velocity and has more prolonged spray duration than the mist produced from pressurized metered dose inhalers (pMDIs). Pressurized MDIs require coordination of actuation with inhalation which may be difficult for some patients partly due to the rapid speed at which the drug is delivered and the short duration of the mist. Because of the slower spray velocity and longer spray duration, use of Respimat is less dependent on inhalation technique. A spacer is not needed with Respimat. In addition, Respimat does not require generation of high inspiratory flow rates required for some dry powder inhalers. Each actuation from the inhaler delivers 2.5mcg of olodaterol. Two actuations equal one dose.
REMS	☐ REMS ☒ No REMS *See Other Considerations for additional REMS information* There are no Post Marketing Study requirements for olodaterol
Pregnancy Rating	Category C

Executive Summary	
Efficacy	The improvement in the co-primary endpoints $FEV1_{0\text{-}3h}$ and trough FEV1 was significantly greater with olodaterol and formoterol than placebo. Studies were not designed to compare olodaterol and formoterol.
Safety	Safety considerations are consistent with those of the LABA class. Two 48-week clinical trials appear to indicate a similar safety profile between olodaterol and formoterol.
Other Considerations	First inhaler within the LABA class (excluding fixed-dose combinations and nebulized solutions) that offers an alternative to dry powder delivery systems.
Potential Impact	Olodaterol is a once daily option for those unable to use a dry powder formulation.

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 olodaterol for possible addition to the VA National Formulary.

Other Therapeutic Options

Formulary Alternatives	Other Considerations
Formoterol	Twice daily dosing, dry-powder inhaler (capsule); store 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**
Salmeterol	Twice daily dosing; dry-powder inhaler (doses pre-loaded)
Indacaterol	Once daily dosing; dry powder inhaler (capsule)

Efficacy (FDA Approved Indications)

Literature Search Summary

A literature search was performed on PubMed/Medline (1966 to January 2015) using the search term olodaterol. The search was limited to studies performed in humans and published in the English language. Trials ≤ 6 weeks were excluded from the efficacy review as were studies evaluating single device combination therapy with tiotropium. These excluded trials primarily evaluated lung function which was assessed in the pivotal 48 week trials.

Results for olodaterol 10mcg are not included as this dose did not receive FDA approval. In the clinical trials, there was no separation between the 5mcg and 10mcg doses. Because of the dose-related concerns with LABAs in patients with asthma, it was determined not to market the higher dose (noting that these risks have not been demonstrated in patients with COPD).

Review of Efficacy

The FDA approval of olodaterol was based on 4 pivotal Phase 3 randomized controlled trials.

These trials were randomized, double-blind, double-dummy, and placebo-controlled. The trials by Koch et al. also included formoterol as an active comparator. Patients were allowed to continue background medications (anticholinergics, inhaled steroids, and methylxanthines). Randomization was stratified according to background tiotropium use.

Patients were eligible for the trial if they were ≥40 years old, had moderate to very severe COPD (GOLD 2-4), post-bronchodilator FEV1 <80% predicted, FEV1/FVC <70%, and current/ex-smokers with 10 pack-years history. Patients were excluded from the trial if they had a history of asthma, MI or hospitalization for heart failure within 1 year, clinically relevant cardiac arrhythmia, known active TB, cystic fibrosis or life-threatening pulmonary obstruction, bronchiectasis, thyrotoxicosis, paroxysmal tachycardia, previous thoracotomy with pulmonary resection, regular use of daytime O2 if unable to abstain during clinic visits, currently enrolled in pulmonary rehabilitation (or completed within 6 weeks of screening).

Demographic and mean baseline information was as follows: 77% male, 66% Caucasian, 64 years old, post-bronchodilator FEV1 1.38L, 50% GOLD II, 40% GOLD III, and 10% GOLD IV. Background therapy included tiotropium 24%, ipratropium 25%, inhaled steroids 45%, and methylxanthines 16%.

The co-primary outcomes were the change from baseline for FEV1 $AUC_{0\text{-}3h}$ and trough FEV1 at week 12 for studies by Ferguson et al. and at week 24 for studies by Koch et al. Other outcomes included change in FEV1 $AUC_{0\text{-}3h}$ and trough FEV1 at other time points throughout the study, FVC, and use of rescue albuterol. Koch et al. also evaluated dyspnea and quality of life. The 4 primary trials were not designed to evaluate COPD exacerbations. However, COPD exacerbation data were collected as part of the routine adverse event analysis (see safety section).

Primary Outcomes

The improvement in $FEV1_{0-3h}$ and trough FEV1 was significantly greater with olodaterol and formoterol than placebo with the exception of formoterol trough FEV1 in study 14 at week 48 (**Table 1**).

Table 1: Pulmonary Function Outcomes at Weeks 12, 24, and 48

Treatment		FEV1 AUC $_{0-3h}$ (mL)			Trough FEV1 (mL)		
		12	24	48	12	24	48
Ferguson 2014 Study 11	OLO 5mcg QD (n=208)	165*	156*	130*	50*	36*	19*
	PBO (n=209)	-7	-18	-43	-41*	-50	-74
Ferguson 2014 Study 12	OLO 5cmg QD (n=209)	159*	155*	132*	44*	33*	11*
	PBO (n=216)	8	-10	-30	-3	-36	-57
Koch 2014 Study 13	OLO 5cmg QD (n=227)	176*	142*	122*	56*	21*	3*
	FOR 12mcg BID (n=227)	182*	168*	149*	33*	-2	-6*
	PBO (n=225)	-3	-9	-23	-27	-56	-65
Koch 2014 Study 14	OLO 5mcg QD (n=232)	138*	116*	93*	18*	-3*	-16*
	FOR 12mcg BID (n=233)	163*	137*	104*	24*	-13*	-24
	PBO (n=235)	-8	-13	-25	-41	-55	-60

*Significant vs. placebo

Secondary Outcomes

Compared to placebo, olodaterol and formoterol significantly improved FVC_{0-3h} at weeks 12, 24, and 48. Trough FVC was significantly improved with olodaterol versus placebo in study 11; there was no significant difference versus placebo in the other studies.

The transitional dyspnea index (TDI) was used to assess relief of dyspnea. An improvement from baseline of ≥ 1 is considered to be clinically meaningful. The combined results for the studies by Koch et al. showed the mean change in score at week 24 was 1.9, 1.8, and 1.5 for olodaterol, formoterol, and placebo respectively. The percentage of patient considered responders (improvement ≥ 1) was 55.4%, 54.7% and 52.3% respectively.

Health-related quality of life was measured using the St George's Respiratory Questionnaire (SGRQ). An improvement in score of ≥4 units is considered to be clinically meaningful. The difference from placebo for the combined study results was -2.8 and -1.2 for olodaterol and formoterol respectively. The improvement in score for olodaterol versus placebo was statistically significant; however, the change in score is not considered as clinically meaningful. The percentage of patient considered responders (improvement ≥ 4) was 50.1, 39.1, and 36.4% for olodaterol, formoterol, and placebo respectively. Compared to placebo, the percentage of olodaterol responders was statistically significant.

Olodaterol and formoterol significantly reduced the need for daytime and nighttime rescue albuterol use. In Ferguson et al., the difference from placebo for mean daytime and nighttime reduction for olodaterol at week 48 was 0.46 and 0.5 actuations/day respectively. Koch et al. showed mean reduction from placebo in daytime use over 48 weeks ranging between 0.01-0.57 actuations/day; nighttime reduction over 48 weeks ranged between 0.13- 0.85 actuations/day. Values for formoterol were not shown, but were said to be significantly improved compared to placebo.

Overall Quality of Evidence: High (Refer to Appendix A)

Potential Off-Label Use

Asthma: There are no published data at this time. There are several completed and ongoing trials in asthma.

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

Boxed Warning	• Long-acting beta2-adrenergic agonists (LABA) increase the risk of asthma-related death • A placebo-controlled study with another long-acting beta2adrenergic agonist (salmeterol) showed an increase in asthma-related deaths in patients receiving salmeterol • This finding of an increased risk of asthma-related death with salmeterol is considered a class effect of LABA, including olodaterol. The safety and efficacy of olodaterol in patients with asthma have not been established. Olodaterol is not indicated for the treatment of asthma.
Contraindications	All LABA are contraindicated in patients with asthma without use of long-term asthma control mediation. Olodaterol is not indicated for the treatment of asthma.
Warnings/Precautions	• Do not initiate in patients with acutely deteriorating COPD • Do not use for relief of acute symptoms (e.g., rescue therapy) <u>Warnings/precautions common to the LABA class:</u> • Paradoxical bronchospasm • Cardiovascular Effects such as increase in pulse rate, blood pressure, ECG changes (such as flattening T wave, prolongation of QTc interval, ST segment depression) • Use with caution in patients with convulsive disorders, thyrotoxicosis, known or suspected prolongation of QT interval, or who are unusually responsive to sympathomimetic amines • Hypokalemia and hyperglycemia • Hypersensitivity reactions including angioedema
Safety Considerations	<u>Adjudicated Analysis of Major Adverse Cardiovascular Events (MACE)</u>: Fatal MACE events occurred in 3 (0.3%), 6 (1.3%), and 8 (0.9%) of patients in the olodaterol 5 mcg, formoterol, and placebo groups respectively. No imbalances were noted in the MACE analysis (fatal and non-fatal events)' <u>Electrophysiology</u>: A dedicated QT/QTc interval study (n=24) showed dose-dependent QTc prolongation. The difference from placebo 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. In the 48-week trials, ECGs were obtained on all patients. There were no significant changes from baseline in heart rate, PR interval, and QRS interval. Changes in QTcF were similar between groups 24h Holter monitoring was performed in a subset of patients from the 48 week trials (n=772). There were no dose- or time-related trends or patterns for the magnitudes of mean changes in HR or premature beasts. Shifts from baseline to end of treatment in premature beats showed no meaningful differences between olodaterol and placebo (same for formoterol). <u>Cardiac Standard MedDRA Queries</u>: There was an imbalance noted between olodaterol and placebo for cardiac arrhythmias and ventricular arrhythmias (**<u>Table 2</u>**). The rates for the 10mcg dose were similar to or slightly lower than the 5mcg dose; therefore, the FDA concluded that due to a lack of a dose response, it is less likely that the imbalances were entirely due to drug exposure and that there does not appear to be a cardiac safety signal with olodaterol. There will be continued monitoring in the post-market period.

Table 2: Cardiac Standard MedDRA Queries (%)

	Olodaterol 5	Olodaterol 10	Formoterol	Placebo
Total	71	72.7	69.1	70.8
Cardiac arrhythmia	5.6	4.4	4.3	4.2
• Tachyarrhythmia	3.5	2.9	3.3	3.4
• Ventricular tachyarrhythmia	1.9	1.4	2.0	1.0
Myocardial Infarction	0.5	1.4	0.9	1.0
Cardiac Failure	1.3	0.8	0.2	0.6
Torsades de pointes/QT prolongation	1.3	0.5	1.1	0.7

Data obtained from FDA transcripts

COPD exacerbations: The 4 primary trials were not designed to evaluate COPD exacerbations. However, COPD exacerbation data were collected as part of the routine adverse event analysis. COPD exacerbations occurred in 25.9% (olodaterol 5), 28.5% (formoterol), and 28.8% (placebo) of patients.

Lung cancer: Lung cancers were reported in 3 (0.3%), 6 (0.7%), and 2 (0.2%) of patients receiving olodaterol 5mcg, olodaterol 10mcg, and placebo respectively.

Adverse Reactions

Common adverse reactions

		Olodaterol 5	Formoterol	Placebo
Reactions occurring in > 2% of olodaterol patients (and higher than placebo and formoterol)	Nasopharyngitis	11.3	10.0	7.7
	URI	8.2	7.0	7.5
	Bronchitis	4.7	2.8	3.6
	UTI	2.5	1.1	1.0
	Dizziness	2.3	1.5	2.1
	Diarrhea	2.9	2.4	2.5
	Arthralgia	2.1	1.3	0.8
Reactions occurring in > 2% of formoterol patients (and higher than olodaterol and placebo)	Pneumonia	2.5	3.0	2.7
	Influenza	1.8	2.4	1.8
	Gastroenteritis	1.1	2.2	1.2
	Cough	4.2	5.9	4.0
	Dyspnea	4.0	5.4	4.2
	Back pain	3.5	3.9	2.7
	Chest pain	1.3	2.8	1.8
	Pyrexia	1.4	2.6	1.9

Pivotal 48 week trials
Data obtained from FDA review transcripts

Death/Serious adverse reactions

There were a total of 53 on-treatment adjudicated deaths; 13 (1.5%), 17 (1.9%), 10 (2.2%), and 13 (1.5%) for olodaterol 5mcg, olodaterol 10mcg, formoterol, and placebo respectively.

The most frequent causes of death were COPD (n=20), sudden cardiac death (n=7), unknown (n=6), and lung cancer (n=6). Death due to COPD occurred more often in the olodaterol 5mcg group 9 (1.0%), followed by formoterol 3 (0.7%), and 0.5% each for olodaterol 10mcg and placebo. Sudden cardiac death occurred more often with formoterol 3(0.65%); there were 2 (0.23%) cases each for olodaterol 5mcg and placebo, and none with olodaterol 10mg.

Serious adverse events occurred in 15.8%, 15%, and 16.4% of patients randomized to olodaterol 5mcg, formoterol, and placebo respectively. The most common SAE reported were COPD exacerbation (5.8%) and pneumonia (1.8%) and were similar across treatment groups

Discontinuations due to adverse

Discontinuations due to AEs occurred in 6.7%, 7.8%, and 8.8% of patients randomized to olodaterol 5mcg, formoterol, and placebo respectively. In the overall group, the most

reactions	common reasons were COPD exacerbation (2.2%), dyspnea (0.4%) and pneumonia (0.3%) and were relatively balanced among treatment groups.

Drug Interactions

Drug-drug interactions	Common amongst LABA class: • Other adrenergic drugs may potentiate effect: Use with caution • Xanthine derivatives, steroids, diuretics or non-potassium sparing diuretics may potentiate hypokalemia or ECG changes. Use with caution. • MAO inhibitors, tricyclic antidepressants, and drugs that prolong QTc interval may potentiate effect on cardiovascular system. Use with extreme caution. • Beta-blockers may decrease effectiveness: Use with caution and only when medically necessary. Unique to olodaterol (and indacaterol): Co-administration with a strong dual CYP and P-gp inhibitor ketoconazole resulted in a 1.7-fold increase of maximum plasma concentration and AUC. No dose adjustment is necessary
Drug-food interactions	None
Drug-lab interactions	None

Risk Evaluation

As of October 2014

Sentinel event advisories	None Sources: ISMP, FDA, TJC
Look-alike/sound-alike error potentials	

NME Drug Name	Lexi-Comp	First DataBank	ISMP	Clinical Judgment
Olodaterol Inhaler	None	None	None	Indacaterol Olopatadine Optipranolol
Striverdi Respimat	None	None	None	Spiriva Respimat Combivent Respimat Stribild

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

Patient Satisfaction:

Patient satisfaction with the Respimat device has been evaluated using other drugs. The Patient Satisfaction and Preference Questionnaire (PASAPQ) is a validated tool for evaluating inhaler satisfaction. The questionnaire is comprised of 3 sections; total PASAPQ score, preference, and willingness to continue. The total PASAPQ score has 2 domains; performance and convenience. There are 2 comparative studies that used PASAPQ to evaluate inhaler satisfaction with Respimat versus other delivery devices (i.e., HFA pMDI, and Turbuhaler) in patients with COPD or asthma. A 10-point difference in the total PASAPQ score between devices is considered to be the minimum important difference (MID). The PASAPQ scores were higher for Respimat (MID met in Schurmann study) and more patients preferred and were willing to continue treatment with Respimat.

Table 3: Patient Satisfaction

Design	Disease	Treatment Arms	Duration	n	Total PASAPQ score	Preference	Willingness to continue[§]
Schurmann 2005 CO, OL	Asthma/ COPD	IPR+FEN via Respimat IPR+FEN via HFA-MDI	7 weeks per arm	224	83.7±14.6 (Respimat) 72.9±15.7 (HFA-MDI)	80.6% (Respimat) 19.4% (HFA-MDI)	85% (Respimat) 50% (HFA-MDI)
Hodder 2009 R, DB, DD	Asthma	BUD via Respimat BUD via Tubuhaler	12 weeks	153	85.5(Respimat) 76.9 (Turbuhaler)	73.7% (Respimat) 17.1% (Turbuhaler) 9.2% (no preference)	80 (Respimat) 62(Turbuhaler)

BUD=budesonide; CO=cross-over; DB=double-blind; DD=double-dummy; IPR+FEN=ipratropium + fenoterol; OL=open-label; R=randomized
[§]For Schurmann, % of patients willing to continue on each device is shown; for Hodder, a score for willingness to continue is shown

A small study conducted in Japanese patients with COPD evaluated switching from tiotropium HandiHaler to tiotropium Respimat (n=34). Four patients dropped after the switch; 2 because of difficulty handling Respimat and 1 each for cough and feeling of discomfort. The majority (73%) found Respimat easier to use. When asked how they felt about switching from HandiHaler to Respimat, 53% favored Respimat; the remainder felt both were the same. There was no significant difference in FEV1, quality of life, or dyspnea. More patients reported cough initially after switching; however, this improved as patients became accustomed to the different inhalation technique.

Preparing and priming olodaterol Respimat may be difficult for some patients. Because this is a relatively new delivery device (Combivent and tiotropium are other medication that use the Respimat delivery system), patient education will be needed.

Storage:
Olodaterol may be stored at room temperature.

Dosing and Administration

Two inhalations of olodaterol once-daily at the same time of day

Prior to first use, the olodaterol cartridge is inserted into the olodaterol RESPIMAT inhaler and the unit is primed. When using the unit for the first time, patients are to 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 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 until an aerosol cloud is visible and then repeat the process three more times to prepare the inhaler for use. The discard date is 3 months from the date the cartridge is inserted into the inhaler.

No dosage adjustment is required for geriatric patients, patients with mild and moderate hepatic impairment, or renally-impaired patients. There are no data available for use of olodaterol in severe hepatic impairment.

Special Populations (Adults)

	Comments
Elderly	44.6% of patients who received olodaterol 5mcg from the four 48-week trials were ≥ 65 years old. There was no difference in effectiveness and adverse reaction profiles between the older population and the overall population.
Pregnancy	• No adequate well-controlled studies in pregnant women. Use during pregnancy if potential benefits outweigh potential risks to the fetus. • Olodaterol shown to be teratogenic in New Zealand rabbits at inhalation doses ≈7130 times maximum recommended human daily inhalation dose (MRHDID) in adults on an AUC basis. The following fetal toxicities were noted: enlarged or small heart atria or ventricles, eye abnormalities, and split or distorted sternum. No teratogenic effects

	were noted at ≈1353 times the MRHDID • No teratogenic effects were shown in rats at inhalation doses ≈2731 times MRHDID in adults on an AUC basis. • There is potential for beta-agonists to interfere with uterine contractility. Use of olodaterol during labor should be restricted to those in whom benefits clearly outweigh risks.
Lactation	Olodaterol and metabolites are excreted into the milk of lactating rats; excretion into human milk is probable. There are no human studies investigating the effects of olodaterol on nursing infants. Use with caution in nursing women.
Renal Impairment	No clinically relevant changes in olodaterol Cmax or AUC compared to healthy controls
Hepatic Impairment	No changes in olodaterol Cmax, AUC, and protein binding in patients with mild-moderate hepatic impairment versus healthy controls. There are no studies in patients with severe hepatic impairment.
Pharmacogenetics/ genomics	No data identified

Projected Place in Therapy

Long-acting beta-agonists have an established role in maintenance treatment of COPD. The current LABAs are available as a dry-powder inhaler. Olodaterol is the first LABA available as a soft-mist inhaler and is the second LABA that is administered on a once daily basis. Olodaterol is an option for patients unable to use dry-powder inhalers.

References

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FDA Advisory Committee Briefing Document for OLODATEROL RESPIMAT
http://www.accessdata.fda.gov/drugsatfda_docs/nda/2014/203108Orig1s000MedR.pdf

Product Package Insert for olodaterol (STRIVERDI) Respimat (7/2014).

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Appendix A: GRADEing the Evidence

Designations of Quality

Quality of evidence designation	Description
High	Evidence includes consistent results from well-designed, well-conducted studies in representative populations that directly assess effects on health outcomes (2 consistent, higher-quality randomized controlled trials or multiple, consistent observational studies with no significant methodological flaws showing large effects).
Moderate	Evidence is sufficient to determine effects on health outcomes, but the number, quality, size, or consistency of included studies; generalizability to routine practice; or indirect nature of the evidence on health outcomes (1 higher-quality trial with > 100 participants; 2 higher-quality trials with some inconsistency; 2 consistent, lower-quality trials; or multiple, consistent observational studies with no significant methodological flaws showing at least moderate effects) limits the strength of the evidence.
Low	Evidence is insufficient to assess effects on health outcomes because of limited number or power of studies, large and unexplained inconsistency between higher-quality studies, important flaws in study design or conduct, gaps in the chain of evidence, or lack of information on important health outcomes.