Drug Use Research & Management Program
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New Drug Evaluation: Olodaterol oral inhalation solution (Striverdi Respimat)

Month/Year of Review: January 2015
Generic Name: olodaterol
PDL Class: Long-acting Bronchodilators

End Date of Literature Search: November 2014
Brand Name (Manufacturer): Striverdi® Respimat
Dossier Received: Yes

FDA Approved Indication: For the long-term, once-daily maintenance bronchodilator treatment of airflow obstruction in patients with COPD, including chronic bronchitis and/or emphysema.

Research Questions:

- Is there any evidence that olodaterol is more effective or safer than other long acting bronchodilators in adults with COPD?
- Are there subgroups of patients in which olodaterol is more effective or safer than other available treatments for the treatment of COPD in adults?

Conclusions:

- There is low quality evidence of no difference in mean change in lung function from baseline to 24 weeks, as measured by trough forced expiratory volume in the first second (FEV1), between olodaterol 5 mcg daily via Respimat inhaler and formoterol 12 mcg twice daily.[1]
- There is low quality evidence that once daily olodaterol improves lung function from baseline to 24 weeks in patients with moderate to severe COPD compared to placebo, as measured by FEV1 and FEV1 area under the curve from 0 to 3 hours (AUC_{0-3}). This improvement in lung function is not considered clinically meaningful but may be explained in the context that use of other COPD medications were permitted during the study periods.
- There is insufficient evidence that olodaterol decreases COPD exacerbations, hospitalizations, mortality or health-related quality of life.[1,2] There is low quality evidence that olodaterol does not improve dypsnea compared to placebo.[1,3]
- Serious adverse events were similar among olodaterol groups and placebo. The most common adverse events were nasopharyngitis, upper respiratory tract infection, bronchitis, cough, and back pain.
- There is insufficient evidence of olodaterol in specific subpopulations in which the drug may be more or less effective or less safe.

Recommendations:

- Designate olodaterol as non-preferred due to lack of quality evidence demonstrating clinical effectiveness.

Background:

Chronic Obstructive Pulmonary Disease (COPD) is a leading cause of morbidity and mortality worldwide and results in an economic and social burden that is both substantial and increasing.[4] COPD is characterized by persistent airflow limitation that is usually progressive and associated with an enhanced chronic inflammatory response in the airways and the lung to noxious particles or gases.[5] The chronic airflow limitation characteristic of COPD is caused by a mixture of small airways disease (obstructive bronchiolitis) and parenchymal destruction (emphysema); the degree to which each type of structural changes contributes to disease varies in each individual. Chronic inflammation causes structural changes and narrowing of the small airways.[4] COPD is the result of cumulative exposures over decades. The most common risk factor for COPD is tobacco smoking. Other risk factors include indoor air pollution, occupational dusts and chemicals, outdoor air pollution, and factors that affect lung growth during gestation and childhood. COPD results from a gene-environment interaction. The genetic risk factor that is best documented is a severe hereditary deficiency of alpha-1 antitrypsin, a circulating inhibitor of serine proteases. COPD has a higher prevalence among men and prevalence increases with age.[5]

COPD is defined as a ratio of FEV1 and forced vital capacity (FEV1/FVC) less than 0.70 based on a post-bronchodilator FEV1. Patients are stratified into groups (A-D) based on their symptoms and future risk of exacerbations.[5] Many trials for COPD use a surrogate endpoint of change in FEV1 because it is highly reproducible in a majority of patients. However, FEV1 measurements do not always correlate with clinically relevant outcomes such as dyspnea, health status, exercise capacity, quality of life or exacerbations and hospitalization, and changes in lung volume can occur without concomitant changes in FEV1.[6] A change of 5-10% from baseline FEV1 values is considered to be clinically important to regulators. [7] The American Thoracic Society/European Respiratory Society (ATS/ERS) recommends the change in FEV1 should be ≥20% in short-term trials and ≥15% in long-term trials (≥1 year) to be confident that a clinically meaningful change has occurred. [7] A minimal clinically important difference in trough FEV1 in COPD of 100 mL is generally accepted.[8]

Both pharmacological and non-pharmacological treatment options exist for COPD. Smoking cessation is one of the most effective interventions. Other non-pharmacological options are modification of occupational exposure, reducing or avoiding indoor air pollution, and participating in physical exercise. There are several drug classes available for the relief of airflow obstruction in patients with COPD and to reduce the frequency and severity of COPD exacerbations. These include short- and long-acting beta-2 adrenergic agonists (SABAs and LABAs), short- and long-acting anticholinergic agents (SAMAs and LAMAs), combination products containing beta-2 adrenergic agonists and anticholinergic agents (both short-acting and long-acting), combination of LABAs and ICS, as well as methylxanthines and phosphodiesterase-4 (PDE4) inhibitors. There are a small number of drug classes available for reducing COPD exacerbations. These include LAMAs, combination products containing LABA and ICS, and PDE inhibitors. With the exception of methylxanthines and PDE4 inhibitors, all products are inhaled. Adjunctive therapies include systemic corticosteroids, vaccines, alpha-1 antitrypsin augmentation therapy, antibiotics, mucolytic agents, antitussives and vasodilators. Optimal therapy must factor in the severity of disease, comorbidities, frequency and severity of exacerbations, cost, and general health status.[5,9]

Combination therapy with ICS and long acting agents appears to reduce the risk of exacerbation and improve lung function and health status in patients with moderate to severe COPD. Based on the Global Initiative for Chronic Obstructive Lung Disease (GOLD) guidelines, patients who are in Group A (and low risk of exacerbation) should be managed by SABAs and/or SAMAs, patients in Group B should be on a long acting agent (LABA or LAMA), and patients in Group C and D should be on an ICS and a long acting agent. Drug therapy can be escalated based on patient response and deterioration in lung capacity.[5] The NICE guidelines recommend adding therapy based on an algorithm of breathless ness and FEV1. If patients have intermittent breathlessness, they should use a short-acting agent. Patients with exacerbations or persistent breathlessness should be on a long-acting agent. These guidelines recommend adding an ICS to a long acting

agent when a patient's FEV1 is less than 50% predicted or in patients with an FEV1 greater than 50% predicted who remain breathless or have exacerbations despite maintenance therapy with a LABA.[6]

Olodaterol is a new LABA and joins short-acting LAMA ipratropium/albuterol (Combivent) as drugs available in the Respimat inhaler, a delivery device aerosolizes the drug into a mist. Olodaterol is not approved for use in patients with asthma, although it may be used off-label, and carries a safety warning in patients with asthma, as LABAs increase the risk of asthma-related death.[10]

Clinical Efficacy:

The approval of olodaterol was based on two pairs of replicate, poor to fair-quality, 48-week phase 3 studies enrolling 3,104 total patients. All four studies were randomized, double-blind, and placebo-controlled with similar inclusion and exclusion criteria and study design. The co-primary endpoints in the first two studies was the change in trough FEV1 and change in FEV1 AUC_{0-3} after 12 weeks, and the co-primary endpoints for the second two studies were after 24 weeks of therapy. The second set of studies also had an additional co-primary endpoint of rating change in severity of dyspnea. These studies included patients who had a diagnosis of moderate-to-severe COPD. Patients were assigned to 5 mcg or 10 mcg daily doses of olodaterol or placebo. With the exception of other LABAs, all pulmonary medications were allowed as concomitant therapy and enrollment was stratified by tiotropium use. Despite the long follow-up period, these studies did not report data on COPD exacerbations as a studied outcome and instead focused on surrogate analyses. **Table 1** details the efficacy and safety data for olodaterol.

Results from these four trials showed a statistically significant improvement in lung function for olodaterol 5 mcg daily versus placebo, as measured by change from baseline in trough FEV1 and FEV1 AUC_{0-3} after week 12 or week 24. There was no incremental benefit for olodaterol 10 mcg when compared with 5 mcg, but there was an increase in safety concerns with the 10 mcg dose. Therefore, the FDA only approved the 5 mcg daily dose.

The first pair of studies (1222.11 and 1222.12) included 1,266 patients randomized to once daily olodaterol 5 mcg, olodaterol 10 mcg or placebo. The statistical analyses were amended for studies 1222.11 and 1222.12 after unblinding of the data.[2,3] The FDA considered the amendment a post-hoc analyses, which are not reasonable to use as the basis for efficacy conclusions. The treatment effect of olodaterol with the amended analyses was of a higher magnitude, making all co-primary endpoint comparisons of olodaterol 5 mcg versus placebo statistically significant.[3,11] However, the pre-specified analysis of the trough FEV1 response with olodaterol after 12 weeks was not statistically significant from placebo.[3] Using the pre-specified data analysis, olodaterol 5 mcg daily increased trough FEV1 after 12 weeks from baseline by 84 mL relative to placebo in study 1222.11 and 33 mL in study 1222.12. The difference was statistically significant in study 1222.11 but not in study 1222.12. For the second co-primary endpoint, olodaterol 5 mcg daily increased trough FEV1 AUC_{0-3} after 12 weeks from baseline by 164 mL relative to placebo in study 1222.11 and 134 mL in study 1222.12. The differences were statistically significant in both studies.[3]

The second pair of studies (1222.13 and 1222.14) included 1,838 patients randomized to once daily olodaterol 5 mcg, olodaterol 10 mcg, twice daily formoterol 12 mcg or placebo. Results from both trials showed a statistically significant increase in mean change from baseline in pre-dose trough FEV1 for olodaterol 5 mcg versus placebo by 78 mL and 53 mL, respectively. Data from the FDA indicated there was not a significant difference in either co-primary endpoint between either dose of olodaterol relative to formoterol in both studies.[1,3] These studies had an additional co-primary endpoint of the Transitional Dyspnea Index (TDI), a measurement of shortness of breath. There was no statistically significant difference between the olodaterol arms and placebo for total or individual

components of the TDI score when data from these two trials were pooled for analysis by the FDA.[3] Based on this analysis, there is low quality evidence that olodaterol does not significantly improve dypsnea.

Despite the statistical significance for most of the trough FEV1 response data, the treatment effect was modest and not clinically significant.[8] This may be explained by the concomitant pulmonary medications permitted for all patients. Nearly half of all participants were on inhaled corticosteroids (ICS), 25% were taking ipratropium, 24% also used tiotropium, and 16% used methylxanthines, which were relatively equal between groups. Clinically, LABAs are not used alone or as first-line therapy in patients with moderate-to-severe COPD.

Numerous secondary endpoints were also studied. These endpoints largely showed a sustained improvement in lung function to 48 weeks with less need for rescue medications but no difference in COPD exacerbations or hospitalizations.[3] These results may be a reflection of the majority of patients enrolled in these studies having moderate COPD (GOLD 2) compared to more severe cases.

Clinical Safety:

Overall, the most common adverse events seen in trials were nasopharyngitis, upper respiratory tract infection, bronchitis, cough and dyspnea. The total incidence of adverse events was comparable across treatment groups and respiratory events were the most commonly reported. Rates of discontinuation due to adverse events were comparable across treatment groups. The proportion on serious adverse events (SAEs) was balanced across treatment groups with COPD exacerbation and pneumonia being the most common SAEs. There is low quality evidence of no statistically significant difference in rates of mortality.

Because this is a LABA, the FDA has issued a safety warning for its use in patients with asthma, as LABAs have been shown to increase asthma exacerbation and asthma-related death.[12] Olodaterol has not been specifically studied in the pediatric population, and as such no safety data for this population is available.[10]

COMPARATIVE CLINICAL EFFICACY

Relevant Endpoints:

1) Mortality
2) Rate of COPD exacerbations
3) Hospitalizations
4) Health-related quality of life

Primary Study Endpoint:

1) Mean change from baseline in pre-dose trough FEV1
2) Dyspnea

Table 1. Phase 3 Trial Efficacy and Safety Data for Olodaterol Administered with Respimat Inhaler.

Ref./Study Design	Drug Regimens	Patient Population	N	Efficacy Outcomes	ARR/ NNT	Safety Outcomes	ARR/ NNH	Quality Rating; Internal Validity Risk of Bias/ Applicability Concerns
1. 1222.11[2,3] R, DB, PC, MC, PG Phase 3 48 weeks	O5: olodaterol 5 mcg INH daily w/ Respimat inhaler O10: olodaterol 10 mcg INH daily w/ Respimat inhaler P: placebo daily Background SABA, LAMA, SAMA, PO/INH corticosteroid, methylxanthine permitted	Demographics: Males: 73% Mean age: 65 years Current smokers: 38.6% Mean Pack Year: 49 years GOLD 2: 45-48% GOLD 3: 40-45% Mean FEV1 predicted: 41-43% Key Inclusion Criteria: COPD GOLD stage 2-4, age ≥40 years, ≥10 pack-year smoking history, post-bronchodilator FEV1 <80% predicted, or post-bronchodilator FEV1/FVC <70% predicted Key Exclusion Criteria: Regular oxygen use; significant disease other than COPD, h/o asthma, MI in past year, unstable or life-threatening cardiac arrhythmia, or heart failure hospitalization in past year.	mITT: O5: 206 (99%) O10: 206 (99.5%) P: 208 (99.5%) Per-protocol: O5: 202 (97.1%) O10: 200 (96.6%) P: 207 (99%) Attrition: O5: 35 (16.8%) O10: 35 (16.9%) P: 50 (23.2%)	**Primary Outcomes:*** **1. Mean ΔFEV1 trough after 12 weeks (SE)** O5: 0.052 L O10: 0.048 L P: -0.032 L O5 vs. P: 0.084 L (0.023) p<0.0001 O10 vs. P: 0.080 L (0.022) p<0.0001 **2. Mean ΔFEV1 AUC_{0-3} after 12 weeks (SE)** O5: 0.167 L (0.016) O10: 0.157 L (0.016) P: 0.002 L (0.016) O5 vs. P: 0.164 L (0.023) p<0.0001 O10 vs. P: 0.155 L (0.022) p<0.0001 *Pre-specified analysis reported. Statistical analysis amended after un-blinding of data, which the FDA considered a post-hoc analysis and not reasonable to use as the basis for efficacy conclusions	NA	SAE: O5: 39 (18.8%) O10: 43 (20.8%) P: 34 (16.3%) p-value = NS Withdrawals due to AE: O5: 15 (7.2%) O10: 16 (7.7%) P: 20 (9.6%) p-value = NS Deaths: O5: 3 (1.4%) O10: 1 (0.5%) P: 1 (0.5%) p-value = NS	NA	**Quality Rating: Poor** **Internal Validity:** Selection: randomization not described Performance: blinding not described Detection: planned statistical stratification based on tiotropium use was changed after unblinding of results, unclear what this means for subsequent statistical testing. Imputed random missing data w/ LOCF. Attrition: high for all groups; similar to other COPD trials. Attrition higher for placebo due to lack of efficacy and worsening COPD. **Applicability:** Recruitment: Not described Patient Characteristics: Baseline characteristics were similar across all groups. Most aged mid-60s, male, GOLD stage 2/3, and about 40% used ICS Setting: USA, Germany, Australia, New Zealand, China and Taiwan. Outcomes: The accepted surrogate outcome of FEV1 was used for efficacy measure. No clinically important primary outcomes measured, including mortality, COPD exacerbations, hospitalizations, or quality of life. **Analysis:** No evidence of a dose response with O5 vs. O10. Response with olodaterol is smaller than with other LABA studies, likely due to background use of other COPD inhalers in these studies. Twenty secondary endpoints studies did not have pre-specified hierarchical analysis plan and are not reported here - see references for details. Adherence similar across groups.

2. 1222.12[2,3] R, DB, PC, MC, PG Phase 3 48 weeks	Same as 1222.11	<u>Demographics</u>: Males: 71% Mean age: 65 years Current smokers: 43.8% Mean Pack Year: 50 years GOLD 2: 43-49% GOLD 3: 33-45% Mean FEV1: 43% <u>Key Inclusion/Exclusion Criteria</u>: Same as 1222.11	<u>mITT</u>: O5: 207 (99%) O10: 215 (99.1%) P: 215 (99.5%) <u>Per Protocol</u>: O5: 206 (98.6%) O10: 211 (97.2%) P: 210 (97.2%) <u>Attrition</u>: O5: 24 (11.5%) O10: 36 (16.6%) P: 41 (19%)	**<u>Primary Outcomes</u>:*** **1. Mean ΔFEV1 trough after 12 weeks (SE)** O5: 0.038 L O10: 0.049 L P: 0.005 L <u>O5 vs P:</u> 0.033 L (0.024) p=0.16 (NS) <u>O10 vs P:</u> 0.045 L (0.023) p=0.056 (NS) **2. Mean ΔFEV1 AUC_{0-3} after 12 weeks (SE)** O5: 0.155 L O10: 0.151 L P: 0.021 L <u>O5 vs. P</u>: 0.134 L (0.022) p<0.0001 <u>O10 vs. P</u>: 0.130 L (0.022) p<0.0001 *Pre-specified analysis reported. Statistical analysis amended after un-blinding of data, which the FDA considered a post-hoc analysis and not reasonable to use as the basis for efficacy conclusions	NA	<u>SAE:</u> O5: 32 (15.3%) O10: 37 (17.1%) P: 32 (14.8%) p-value = NS Withdrawals due to AE: O5: 9 (4.3%) O10: 19 (8.8%) P: 19 (8.8%) p-value = NS Deaths: O5: 0 (0%) O10: 4 (1.8%) P: 1 (0.5%) p-value = NS	NA	Same as 1222.11

3. 1222.13[1,3] R, DB, PC, MC, PG Phase 3 48 weeks	O5: olodaterol 5 mcg INH daily w/ Respimat inhaler O10: olodaterol 10 mcg INH daily w/ Respimat inhaler F: Formoterol 12 mcg INH BID P: Placebo	Demographics: Males: 78% Mean age: 64 years Current smokers: 35% Mean Pack Year: 45 years GOLD 2: 54% GOLD 3: 39% Mean FEV1: 45.3% Key Inclusion/Exclusion Criteria: Same as 1222.11	mITT: O5: 222 (97.8%) O10: 223 (99.1%) F: 223 (98.2%) P: 217 (96.4%) Per Protocol: O5: 213 (93.8%) O10: 215 (95.6%) F: 215 (94.7%) P: 211 (93.8%) Attrition: O5: 36 (15.9%) O10: 39 (17.3%) F: 43 (18.9%) P: 57 (25.3%)	**Primary Outcomes:** **1. Mean ΔFEV1 trough after 24 weeks (SE)** O5: 0.021 L (0.015) O10: 0.028 L (0.015) F: -0.002 L (0.015) P: -0.056 L (0.015) O5 vs P: 0.078 L (0.021); p=0.0002 O10 vs P: 0.085 L (0.021); P<0.0001 F vs P: 0.054 L (0.021); P=0.0088 **2. Mean ΔFEV1 AUC_{0-3} after 24 weeks (SE)** O5: 0.142 L (0.015) O10: 0.156 L (0.015) F: 0.168 L (0.015) P: -0.009 L (0.016) O5 vs P: 0.151 L (0.021); p<0.0001 O10 vs P: 0.165 L (0.021); p<0.0001 F vs P: 0.177 L (0.021); p<0.0001 **3. TDI score after 24 weeks** No statistically significant difference between treatment groups and placebo for total and individual component scores	NA	SAE: O5: 33 (14.5%) O10: 26 (11.6%) P: 31 (13.8%) F: 33 (14.5%) p-value = NS Withdrawals due to AE: O5: 15 (6.6%) O10: 15 (6.7%) P: 16 (7.1%) F: 19 (8.4%) p-value = NS Deaths: O5: 3 (1.3%) O10: 6 (2.7%) P: 4 (1.8%) F: 4 (1.8%) p-value = NS	NA	**Quality Rating: Poor-Fair** **Internal Validity:** Selection: Randomization not described Performance: Double-dummy, but no details given Detection: Spirometry read centrally by one center Attrition: High; withdrawals similar to other COPD trials **Applicability:** Recruitment: Not described Patient Characteristics: Baseline characteristics similar across all groups. Most aged between 50-60 years, male, GOLD stage II or III, and about 45% used ICS Setting: No sites in US. Multiple sites in Europe, Asia and Africa. Outcomes: The accepted surrogate outcome of FEV1 was used for efficacy measure. No clinically important primary outcomes measured, such as mortality, COPD exacerbations, hospitalizations, or quality of life. **Analysis:** Adherence was high across all groups, ranging from 97-98%. Patients were randomized by tiotropium use; tiotropium non-users generally responded better relative to placebo. No evidence of a dose response with O5 vs. O10. Response with olodaterol is smaller than with other LABA studies, likely due to background use of other COPD inhalers in these studies. There were no statistically significant differences between olodaterol and formoterol in the co-primary endpoints. Several secondary endpoints studied but not reported here – see references for details.

4. 1222.14[1,3] R, DB, PC, MC, PG Phase 3 48 weeks	Same as 1222.13	<u>Demographics:</u> Males: 81% Mean age: 64 years Current smokers: 33% Mean Pack Year: 42.5 years GOLD 2: 52% GOLD 3: 39% Mean FEV1: 46% <u>Key Inclusion/Exclusion Criteria</u>: Same as 1222.11	<u>mITT</u>: O5: 230 (99.1%) O10: 233 (99.6%) F: 232 (99.6%) P: 233 (99.1%) <u>Per Protocol</u>: O5: 223 (96.1%) O10: 228 (97.4%) F: 218 (93.6%) P: 220 (93.6%) <u>Attrition</u>: O5: 37 (16.0%) O10: 36 (15.4%) P: 51 (21.7%) F: 40 (17.2%)	**<u>Primary Outcomes</u>:** **1. Mean ΔFEV1 trough after 24 weeks (SE)** O5: -0.003 L (0.014) O10: 0.014 L (0.014) F: -0.13 L (0.014) P: -0.055 L (0.014) <u>O5 vs P:</u> 0.053 L (0.019); p=0.0055 <u>O10 vs P:</u> 0.069 L (0.019); p=0.0003 <u>F vs P</u>: 0.042 L (0.019); p=0.027 **2. Mean ΔFEV1 AUC_{0-3} after 24 weeks (SE)** O5: 0.116 L (0.014) O10: 0.140 L (0.014) F: 0.137 L (0.014) P: -0.013 L (0.014) <u>O5 vs P:</u> 0.129 L (0.019); p<0.0001 <u>O10 vs P:</u> 0.154 L (0.019); p<0.0001 <u>F vs P</u>: 0.150 L (0.019); p<0.0001 **3. TDI score after 24 weeks** No statistically significant difference between treatment groups and placebo for total and individual component scores	NA	<u>SAE:</u> O5: 34 (14.7%) O10: 41 (17.5%) P: 48 (20.4%) F: 36 (15.5%) p-value = NS Withdrawals due to AE: O5: 15 (6.5%) O10: 16 (6.8%) P: 19 (8.1%) F: 17 (7.3%) p-value = NS Deaths: O5: 7 (3.0%) O10: 6 (2.6%) P: 6 (2.6%) F: 6 (2.6%) p-value = NS	NA	Same as 1222.13

Key: AE= adverse events; ARR = absolute risk reduction; AUC_{0-3} = area under the curve from 0 to 3 hours; BID=twice daily; DB = double-blind; DD=double-dummy; FEV1=forced expletory volume in 1 second; FVC=forced volume capacity; GOLD = Global Obstructive Lung Disease; h/o = history of; ICS=inhaled corticosteroid; INH = inhaled; ITT=intention-to-treat; L = Liters; LAMA = long-acting muscarinic antagonist; LOCF = last observation carried forward; MC =multicenter; mITT = modified intention to treat; NA=not applicable; NNH = number needed to harm; NNT = number needed to treat; NS = not significant; PC = placebo-controlled, PG = parallel group; RRR = relative risk reduction; SABA = short-acting beta-agonist; SAE = serious adverse events; SAMA = short-acting muscarinic antagonist; SE = standard error; TDI = Transitional Dyspnea Index.

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Author: Amanda Meeker Date: January 2015

Appendix 1: Specific Drug Information

CLINICAL PHARMACOLOGY

PHARMACOKINETICS [12]

Parameter	Result
Bioavailability	30% (inhaled)
Protein Binding	60%
Half-Life	7.5 hours
Metabolism	Glucoronidation and CYP 2C9, 2C8, 1A7 and 1A9
Bioavailability	30% (inhaled)

DOSE & AVAILABILITY [12]

STRENGTH	ROUTE	FREQUENCY	DOSAGE:	RENAL ADJ	HEPATIC ADJ	Pediatric Dose	Elderly Dose	OTHER DOSING CONSIDERATIONS
2.5 mcg/ actuation	INH	Once daily	2 actuations (5 mcg)	None	None	None	Same as adult	None

DRUG SAFETY [12]

Serious (REMS, Black Box Warnings, Contraindications):

Black Boxed Warning: May cause an increase in asthma-related death, which is considered a class effect of LABA. No study adequate to determine whether the rate of asthma-related death is increased in subjects treated with olodaterol has been conducted.

Warnings and Precautions:

- Should not be initiated in patients during rapidly deteriorating exacerbations.
- Should not be used as a rescue inhaler
- Should not use with any other LABA-containing medication
- May produce a clinically significant cardiovascular effect in some patients as measured by increases in pulse rate, systolic or diastolic blood pressure, and cardiac arrhythmias

Unanswered Safety Questions:
Pediatric efficacy/safety
Safety and efficacy in asthma

Look-alike / Sound-alike (LA/SA) Error Risk Potential:
Olodaterol may be confused with indacaterol
Striverdi may be confused with Stribild

Adverse Reactions Table [12]

Adverse Reaction	Placebo (n=876)	Olodaterol 5 mcg (n=885)
Nasopharyngitis	7.7%	11.3%
Upper Respiratory Tract Infection	7.5%	8.2%
Bronchitis	3.6%	4.7%
Cough	4.0%	4.2%
Back Pain	2.7%	3.5%