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Olodaterol (Striverdi® Respimat®): A New Once-Daily Long-Acting β-Agonist for the Treatment of COPD

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Chronic obstructive pulmonary disease (COPD) is characterized by irreversible and usually progressive airflow limitation exacerbated and caused most often by exposure to lung irritants, with cigarettes and other smoked tobacco products being the leading source.[1] This disease is the third leading cause of death among American adults and contributed to at least 3 million deaths worldwide in 2012.[2,3] In 2010, COPD cost the U.S. roughly $49.9 billion, $29.5 billion of which come from direct health care expenditures.[2]

At present, no curative treatments have been developed for COPD; thus, current approaches to COPD include prevention and treatment, the latter of which is focused on symptomatic control and reducing the risk of hospitalization. According to the most recent GOLD guidelines published in 2015, short-acting bronchodilators are recommended for essentially all patients, for use as an as-needed rescue inhaler.[4] A long-acting β-agonist (LABA) or long-acting muscarinic antagonist (LAMA) is considered the next step for the maintenance of mild-to-moderate COPD that is uncontrolled with a short-acting inhaler alone.[4]

Commonly used LABAs, salmeterol and formoterol, are indicated for twice-daily use only. However, previous research has demonstrated that COPD treatment with drugs administered once-daily are associated with significantly greater adherence and reduced use of resources and costs compared to other dosing frequencies.[5] Thus, manufactures have recently focused their attention towards developing once-daily COPD inhalers and combination products. Two once-daily LABAs, indacaterol and vilanterol, have received FDA-approved indications for treatment of COPD in recent years, but only indacaterol is available as a single drug product, whereas vilanterol is only available in combination with either an inhaled corticosteroid (fluticasone) or a LAMA (umeclidinium).

Olodaterol (Striverdi® Respimat®; Boehringer Ingelheim Pharmaceuticals; Ridgefield, CT) is a new once-daily LABA that was granted an FDA-approved indication, in July 2014, for the treatment of COPD, including chronic bronchitis and emphysema.[6] The purpose of this article is to review the pharmacological profile of olodaterol including its efficacy, safety, dosing, and administration.

Pharmacology and Pharmacokinetics

Mechanism of Action

Olodaterol acts as an agonist at the β_2-adrenergic receptors located along the smooth muscle of the lung. β-receptors are coupled to a stimulatory G-protein of the enzyme adenylyl cyclase which produces the second messenger cyclic adenosine monophosphate (cAMP).[7] Elevated cAMP is believed to decrease intracellular calcium and increase membrane potassium conductance to produce smooth muscle relaxation and bronchodilation.[7]

In vitro studies demonstrate that olodaterol has a higher β_2 selectivity than formoterol and salmeterol with a 241-fold greater selectivity for β_2 receptors than β_1.[8] Greater β_2 selectivity is associated with fewer β_1 mediated tachycardia and cardiac effects, although the clinical relevance of this β_2 selectivity in affecting cardiac tissue is minimized for drugs which are not significantly absorbed into systemic circulation (e.g., most inhaled medications). The pharmacokinetic properties of olodaterol are summarized in Table 1.

Drug Interactions

Concomitant use of olodaterol with other β-adrenergic drugs may potentiate the effects of olodaterol. Administration of olodat-

Table 1 | Pharmacokinetics of olodaterol.[9]

Absorption	
C_{max}	10-20 minutes following inhalation
C_{ss}	8 days
Bioavailability	30% (inhaled); <1% (orally)
Distribution	
Protein Binding	60% (concentration independent)
V_d	1110 L; high tissue distribution
Metabolism	
Glucuronidation	UGT2B7, UGT1A1, UGT1A7, UGT1A9
O-demethylation	CYP2C9, 2C8 (negligible 3A4)
Elimination	
Excretion	5%-7% excreted unchanged in the urine after inhalation
Half-life	45 hours

C_{max} = maximum concentration; **C_{ss}** = steady state concentration; **V_d** = volume of distribution.

TABLE 2 | Summary of phase II olodaterol dose-ranging trials in COPD.[11]

Trial #	Design/ Duration	Treatments	Primary Endpoint(s) (Secondary)	Results	Authors Conclusions
1222.3[12]	DB, PC, CO 1 dose (n=36)	• olodaterol 2 mcg x 1 dose • olodaterol 5 mcg x 1 dose • olodaterol 10 mcg x 1 dose • olodaterol 20 mcg x 1 dose • placebo x 1 dose	Trough FEV_1	• FEV_1 with 1 dose of olodaterol > placebo	• Promising QD LABA for COPD
1222.5[13]	DB, PC, PG 4 weeks (n=405)	• olodaterol 2 mcg QD • olodaterol 5 mcg QD • olodaterol 10 mcg QD • olodaterol 20 mcg QD • placebo QD	Trough FEV_1	• All doses ↑ FEV_1; order of efficacy: 2<5<10=20 mcg	• QD olodaterol has a 24-hour duration of action that is maintained over 4 weeks in patients with COPD; dose-response curve level above 10 mcg/ day
1222.26[14]	DB, CO 3 weeks (n=47)	• olodaterol 5 mcg QD • olodaterol 10 mcg QD • olodaterol 2 mcg BID • olodaterol 5 mcg BID	FEV_1 AUC_{0-12} FEV_1 AUC_{12-24} (FEV_1 AUC_{0-24})	• Significant ↑ FEV_1 AUC_{12-24} with BID dosing verses QD dosing • BID verses QD treatment difference was small and not significant for FEV_1 AUC_{0-12} and FEV_1 AUC_{0-24}	• QD ≈ BID dosing based on non– significant difference in FEV_1 AUC_{0-24} and FEV_1 AUC_{0-12} • 5 mcg QD ≈10 mcg QD efficacy

AUC = area under the curve; **QD** = once daily; **BID** = twice daily; **CO** = cross-over; **COPD** = chronic obstructive pulmonary disease; **DB** = double blind; **FEV_1** = forced expiratory volume in 1 second; **PC** = placebo controlled; **PG** = parallel group.

erol together with theophylline, steroids, or non-potassium sparing diuretics (e.g., loop or thiazide diuretics) may cause or potentiate hypokalemia and corresponding adverse cardiovascular effects.[9] Monoamine oxidase (MAO) inhibitors, tricyclic antidepressants, ketoconazole, and other medications that prolong the QT interval should be combined very cautiously with olodaterol due to an increased risk of QTc prolongation.[9] If a β-blocking agent is combined with olodaterol, a selective β_1-antagonist may be preferred over non-selective agents; however, non-selective β-blockers are not contraindicated for concomitant use with a LABA.[10]

The olodaterol clinical development program was composed of three dose-ranging trials and eight confirmatory trials in patients with COPD. Four additional dose-ranging trials were conducted in patients with asthma,[11] but olodaterol is not currently indicated for asthma and a review of these studies is outside the scope of this manuscript and will not be discussed further.

CLINICAL STUDIES

Phase II Trials

All three phase II dose-ranging trials for COPD demonstrated that olodaterol, at any of the studied doses, significantly improved forced expiratory volume in 1 second (FEV_1) from baseline (**Table 2**). Based upon the results of the dose-ranging trials, 5 -mcg and 10-mcg doses were further evaluated in the phase III COPD trials.

Phase III trials

The olodaterol phase III studies were designed to include patients with concomitant medications, very severe COPD (10% of patients in trials, on average), and comorbidities (about 80% of patients) as would typically occur in clinical practice.[11] Only 5-mcg and 10-mcg doses of olodaterol were assessed in these phase III trials. The ten randomized, double-blind confirmatory trials in the olodaterol clinical development program are summarized in **Table 3**.

All ten trials only enrolled patients who were 40 years of age or older with a clinical diagnosis of COPD according to a FEV_1 to forced vital capacity (FEV_1/FVC) ratio of <70%.[15] Other inclusion criteria were a FEV_1 <80% of predicted normal (GOLD categories II – IV) and a smoking history of ≥10 pack-years.[15] Patients were excluded if they had a history of asthma, history of myocardial infarction within 1 year of the screening visit, and unstable or life-threatening cardiac arrhythmia within the past year.[15] With the exception of other LABAs, all pulmonary medications were allowed as concomitant therapy; for the 48 week trials patient enrollment was stratified by tiotropium use.

Forty-Eight-Week Trials

The 48-week trials were conducted to establish the long-term efficacy and safety of olodaterol. Results from the two pairs of 48-week trails concluded that olodaterol 5 mcg once-daily and olodaterol 10 mcg once-daily provided statistically significant improvements in the primary endpoints of FEV_1 AUC_{0-3} response and

TABLE 3 | Summary of phase III trials of olodaterol in COPD.[11]

	Pivotal Studies: Long-Term Efficacy and Safety[15,16]		24-Hour Bronchodilating Profile[17,18]		Exercise Endurance[19]
Trials	• 1222.11 (n=624) • 1222.12 (n=642)	• 1222.13 (n=904) • 1222.14 (n=934)	• 1222.24 (n=99) • 1222.25 (n=100)	• 1222.39 (n=108) • 1222.40 (n=122)	• 1222.37 (n=151) • 1222.38 (n=157)
Design:	Parallel-Group/ 48-week		Cross-Over/ 6-week		
Treatment	olodaterol 5 mcg or 10 mcg once-daily				
Comparator (s)	• placebo	• placebo • formoterol 12 mcg BID	• placebo • formoterol 12 mcg BID	• placebo • tiotropium 18 mcg QD	• placebo
Primary End-points (Secondary)	After 12 weeks: • FEV_1 AUC_{0-3} • Trough FEV_1	After 24 weeks: • FEV_1 AUC_{0-3} • Trough FEV_1 • (TDI + SGRQ)	• FEV_1 AUC_{0-12} • FEV_1 AUC_{12-24} • (FEV_1 AUC_{0-24})	• FEV_1 AUC_{0-12} • FEV_1 AUC_{12-24} • (FEV_1 AUC_{0-24})	• ET • (IC)
Results	Combined Mean Trough FEV_1 difference from placebo: • olodaterol 5 mcg: 0.076 L (p<0.0001) • olodaterol 10 mcg: 0.083 L (p<0.0001) Combined Mean FEV_1 AUC_{0-3} difference from placebo: • olodaterol 5 mcg: 0.176 L (p<0.0001) • olodaterol 10 mcg: 0.173 L (p<0.0001)	Combined Mean Trough FEV_1 difference from placebo: • olodaterol 5 mcg: 0.059 L (p=0.0003) • olodaterol 10 mcg: 0.083 L (p<0.0001) • formoterol: 0.053 L (p=0.0011) Combined Mean FEV_1 AUC_{0-3} difference from placebo: • olodaterol 5 mcg: 0.134 L (p<0.0001) • olodaterol 10 mcg: 0.171 L (p<0.0001) • formoterol: 0.172 L (p<0.0001) Treatment difference between olodaterol 5 mcg and formoterol: • FEV_1 AUC_{0-3} (p<0.1014) • Trough FEV_1 (p<0.2230)	1222.25 Mean FEV_1 AUC_{0-12} difference from placebo: • olodaterol 5 mcg: 0.172 L (p<0.0001) • olodaterol 10 mcg: 0.174 L (p<0.0001) • formoterol: 0.158 L(p<0.0001) 1222.25 Mean FEV_1 AUC_{12-24} difference from placebo: • olodaterol 5 mcg: 0.118 L (p<0.0001) • olodaterol 10 mcg: 0.120 L (p<0.0001) • formoterol: 0.155 L (p<0.0001) Treatment difference between olodaterol 5 mcg and formoterol: • FEV_1 AUC_{0-12} (p<0.3876) • FEV_1 AUC_{12-24} (p<0.0001) • FEV_1 AUC_{0-24} • (p<0.0944)	1222.40 Mean FEV_1 AUC_{0-12} difference from placebo: • olodaterol 5 mcg: 0.197 L (p<0.0001) • olodaterol 10 mcg: 0.221 L (p<0.0001) • tiotropium: 0.221 L (p<0.0001) 1222.40 Mean FEV_1 AUC_{12-24} difference from placebo: • olodaterol 5 mcg: 0.153 L (p<0.0001) • olodaterol 10 mcg: 0.170 L (p<0.0001) • tiotropium: 0.164 L (p<0.0001) Treatment difference between olodaterol 5 mcg and tiotropium: • FEV_1 AUC_{0-12} (p<0.5900) • FEV_1 AUC_{12-24} (p<0.9093) • FEV_1 AUC_{0-24} (p<0.7382)	1222.37 Mean ET ratio to placebo: • olodaterol 5 mcg: 1.140 (p=0.040) • olodaterol 10 mcg: 1.138 L (p=0.040) 1222.38 Mean ET ratio to placebo: • olodaterol 5 mcg: 1.118 (p=0.040) • olodaterol 10 mcg: 1.105 (p=0.039) 1222.37 Mean IC difference from placebo: • olodaterol 5 mcg: 0.182 L (p<0.0001) • olodaterol 10 mcg: 0.174 L (p<0.0001) 1222.38 Mean IC difference from placebo: • olodaterol 5 mcg: 0.84 L (p=0.0155) • olodaterol 10 mcg: 0.166 L (p<0.0001)
Conclusions	• olodaterol 5 mcg and 10 mcg ↑ FEV_1 AUC_{0-3} & trough FEV_1 compared to placebo	• olodaterol 5 & 10 mcg and formoterol ↑ FEV_1 compared to placebo • No differences in FEV_1 were observed between olodaterol 5 mcg QD and formoterol 12 mcg BID after 24 weeks	• Significant ↑ in FEV_1 AUC_{12-24} with formoterol BID dosing vs. olodaterol QD dosing but no difference in FEV_1 AUC_{0-12} or AUC_{0-24}. • olodaterol 5 & 10 mcg, formoterol ↑ FEV_1 compared to placebo	• No significant FEV_1 difference between tiotropium QD and olodaterol QD • olodaterol, 5 & 10 mcg and tiotropium ↑ FEV_1 compared to placebo	• Both studies showed significant ↑ in mean EC and mean IC for olodaterol 5 mcg and 10 mcg compared with placebo.

AUC = area under the curve; **QD =** once daily; **BID =** twice daily; **COPD =** chronic obstructive pulmonary disease; **FEV_1 =** forced expiratory volume in 1 second; **TDI =** transition dyspnea index; **ET =** exercise endurance time; **IC =** inspiratory capacity; **SGRQ =** St. George's Respiratory Questionnaire.

trough FEV_1 response after 12 weeks (studies 1222.11/1222.12) and after 24 weeks in (studies 1222.13/1222.14) compared with placebo (**Table 3**).[15,16]

Trough FEV_1 is a measure of the extent of bronchodilation at the end of the 24-hour dosing interval. FEV_1 AUC_{0-3} characterizes the peak bronchodilating efficacy of olodaterol from time 0 to 3 hours within the 24-hour dosing interval. In studies 1222.13/1222.14, improvements in FEV_1 AUC_{0-3} and trough FEV_1 were additionally found to be comparable to a well-established active comparator, formoterol 12 mcg twice daily (**Table 3**).[16] Trough FVC difference from placebo was 0.066 L for olodaterol 5 mcg and 0.063 L for olodaterol 10 mcg ($p<0.0001$ for both), thus both doses of olodaterol produced significant improvements in FVC.[11] The FVC response mirrored the FEV_1 results and was significantly improved compared with placebo.

The secondary endpoint of each 48-week trial included rescue medication use. Statistically significant reductions in weekly mean daytime and night-time rescue medication use were observed in patients taking formoterol 12 mcg twice-daily (trials 1222.13 and 1222.14), olodaterol 5 mcg once-daily (reduced by 0.46 actuations/day and 0.50 actuations/night), and olodaterol 10 mcg once-daily (reduced by 0.57 actuations/day and 0.78 actuations/night) relative to placebo.[15] Another secondary endpoint for trials 1222.13 and 1222.14 was the St. George's Respiratory Questionnaire (SGRQ), a validated measure of symptomatic benefit. Using combined data from studies 1222.13 and 1222.14, the total SGRQ score difference, compared to placebo, was -2.8 for olodaterol 5 mcg once daily ($p=0.0034$ for comparison to placebo), -3.4 for olodaterol 10 mcg once daily ($p=0.0004$), and -1.2 for formoterol 12 mcg twice daily ($p=0.20$).[11,16] However, these differences in the olodaterol groups did not meet the minimum clinically important difference of 4-units. The authors attributed these results to the patient population being maintained on concomitant COPD therapies in all phase 3 studies.

The Mahler transition dyspnea index (TDI) focal score was included in studies 1222.13 and 1222.14 as a third measure of symptomatic benefit.[16] After 24 weeks, no significant difference was observed between placebo and olodaterol-treated patients. Interestingly an unexpected improvement occurred in the placebo group of study 1222.13 that was almost double that seen in study 1222.14.[11] Due to the unexplained placebo response, it cannot be concluded that dyspnea improved with olodaterol 5 mcg and 10 mcg, solely based on the TDI focal scores gathered after 24 weeks.

Six-Week Trials

A total of six 6-week double-blind, double-dummy, randomized, crossover studies were performed: 4 studies assessed 24-hour bronchodilation profiles comparing olodaterol to placebo and formoterol (studies 1222.24 and 1222.25) or tiotropium (studies 1222.39 and 1222.40); the remaining 2 studies (1222.37 and 1222.38) assessed exercise endurance, comparing olodaterol with placebo. These studies are summarized in **Table 3**.

The first four 6-week trials assessed the 24-h bronchodilator efficacy of olodaterol as a once-daily maintenance inhaler for COPD patients. Studies 1222.24 and 1222.25 allowed tiotropium as a concomitant medication. FEV_1 was measured 72 hours after the last dose of tiotropium and a wash out period of at least 48 hours was required.[17] Studies 1222.39 and 1222.40 did not allow use of a LAMA, since tiotropium was used as an active comparator in these studies.[18] FEV_1 AUC_{0-12} and FEV_1 AUC_{12-24} were the primary endpoints of all 4 studies.[18]

Patients treated with formoterol 12 mcg twice-daily and both doses of daily olodaterol demonstrated significant increases in mean FEV_1 AUC_{0-12} and mean FEV_1 AUC_{12-24} after 6 weeks compared with placebo (studies 1222.24 and 1222.25).[17] Compared to formoterol twice-daily, olodaterol once-daily did not significantly increase mean FEV_1 AUC_{12-24} or FEV_1 AUC_{0-24}.[11] These results are consistent with the FEV_1 AUC_{12-24} effects seen during Phase II studies when twice-daily and once-daily formulations were compared. In studies 1222.39 and 1222.40, tiotropium 18 mcg daily and both doses of daily olodaterol demonstrated significant increases in mean FEV_1 AUC_{0-12} and mean FEV_1 AUC_{12-24} after 6 weeks compared with placebo.[11] No significant difference was seen between olodaterol and tiotropium on FEV_1.

In the remaining two exercise endurance trials, after 6 weeks of treatment, mean endurance time increased significantly for both olodaterol doses versus placebo.[11] In study 1222.37, endurance time increased by 14% for olodaterol 5 mcg once-daily and 13.8% for olodaterol 10 mcg once-daily ($p<0.001$ for both olodaterol groups) compared to placebo.[11] In study 1222.38 endurance time increased by 11.8% for olodaterol 5 mcg once-daily and 10.5% for olodaterol 10 mcg once-daily compared to placebo.[11] Increases versus placebo in mean inspiratory capacity for patients treated with olodaterol 5 mcg and 10 mcg also were significant: 0.182 L and 0.174 L, respectively (both $p<0.0001$ comparing olodaterol groups to placebo; study 1222.37) and 0.084 L and 0.166 L, respectively (both $p\leq0.02$ comparing olodaterol groups to placebo; study 1222.38).[19]

Adverse Events

Adverse events observed in the dose-ranging trials and four 6-week cross-over trials were consistent with those observed in the 48-week parallel group trials.[9] **Table 4** summarizes adverse drug reactions that occurred in olodaterol 5 mcg treated patients ≥2% placebo**.** Nasopharyngitis was the most common adverse event seen in clinical trials with olodaterol use. Other frequently reported adverse reactions were upper respiratory tract infections, bronchitis, back pain, cough, urinary tract infection, diarrhea, dizziness, skin rashes, and arthralgia.[9] Pneumonia, constipation, and fever were reported in patients exposed to 10mcg doses of olodaterol (i.e., a higher dose than is currently recommended).[15] The most common serious adverse event with olodaterol use was further exacerbation of COPD which occurred in study 1222.12 at a rate of 25.5%, with placebo, 22.0% with olodaterol 5 mcg, and 27.2% with olodaterol 10 mcg; however, COPD exacerbation rarely led to a life-threatening bronchospasm in phase III studies.[15] Patients should be educated to seek help if signs or symptoms of angioedema (<1% incidence in olodaterol-treated patients) or a cardiac event are present such as chest tightness, swelling of the face, lips, tongue, or throat.[20] Also of concern, malignant neoplasm of the lung was reported in 0.3% of patients who received olodaterol 5 mcg compared with 0.2% using placebo.[9] In any such case of a serious complication, olodaterol should be discontinued and another medication should be initiated in its place for maintenance treatment of COPD.

Dosing and Administration

Olodaterol hydrochloride is packaged in an aluminum cylinder cartridge together with a separate Striverdi® Respimat® inhaler. Each actuation from the inhaler delivers 2.7 mcg of olodaterol hydrochloride, which is equivalent to 2.5 mcg olodaterol per

TABLE 4 | Adverse events occurring in >2% of patients in phase III clinical trials of olodaterol 5 mcg for COPD.[9]

Adverse Event	Olodaterol 5 mcg once-daily (n=876)	Placebo (n=885)
Infections and infestations		
Nasopharyngitis	99 (11.3%)	68 (7.7%)
Upper Respiratory Tract Infection	72 (8.2%)	66 (7.5%)
Bronchitis	41 (4.7%)	32 (3.6%)
Urinary Tract Infection	22 (2.5%)	9 (1.0%)
Respiratory and thoracic disorders		
Cough	37 (4.2%)	35 (4.0%)
Nervous system disorders		
Dizziness	20 (2.3%)	19 (2.1%)
Skin and subcutaneous tissue disorders		
Rash (plus group of similar terms)	19 (2.2%)	10 (1.1%)
Gastrointestinal disorders		
Diarrhea	25 (2.9%)	22 (2.5%)
Musculoskeletal and connective tissue disorders		
Back Pain	31 (3.5%)	24 (2.7%)
Arthralgia	18 (2.1%)	7 (0.8%)

puff.[9]

Olodaterol is indicated for oral inhalation only. The recommended dose of olodaterol is two actuations (5 mcg) once-daily, at the same time each day; 5 mcg per day is considered the maximum dose per 24-hours.[9] Olodaterol is available in 30-day (60 puffs) or 14-day (28 puffs) packaging.[9] In contradistinction to the indacaterol Neohaler® or tiotropium HandiHaler®, the Respimat® doesn't need a capsule loaded for each dose.

Patients should be counseled on how to use and actuate the inhaler. Prior to first use, patients must load the cartridge into the inhaler and prime it. To prime the inhaler for the first time (or after more than 21 days without use), patients should be instructed to actuate the inhaler toward the ground until an aerosol cloud is visible. This process must be repeated three more times until the inhaler is ready for use.[9] If the inhaler is not used for more than three days, patients are to actuate the inhaler once before use. Patients should be instructed to discard the inhaler three months after the cartridge is loaded.[9]

Monitoring

Increased use of short-acting β_2-agonist inhalers may be marker of a deteriorating condition and signal a need to add an additional agent to olodaterol. FEV_1, FVC, and/or other pulmonary function tests can help determine COPD progression. Serum potassium, serum glucose, blood pressure, CNS stimulation, and heart rate may be monitored for evidence of olodaterol toxicity.[20]

Precautions

Olodaterol should be cautiously given to patients that are unusually responsive to sympathomimetic amines, those with convulsive disorders, or those with hyperthyroidism.[21] Long-acting β-agonists should also be administered with caution in patients with cardiovascular disorders, including known or suspected prolongation of the QT interval, coronary insufficiency, cardiac arrhythmias, hypertrophic obstructive cardiomyopathy, or hypertension.[9] If increases in pulse or blood pressure occur, olodaterol may need to be discontinued. Although changes in blood glucose were infrequent during clinical studies with long-term administration, caution should be exercised in patients with diabetes since β_2-agonists may increase serum glucose.[20] Olodaterol has not been studied in patients with uncontrolled diabetes.

Olodaterol could have fatal cardiovascular repercussions if given in excessive doses or together with another LABA.[9] Also, olodaterol is not intended to be used as a rescue inhaler, nor is it indicated for acutely deteriorating COPD.[9] Olodaterol should be stopped at once if an immediate hypersensitivity reaction, including angioedema, occurs after administration.[21]

Special Populations

A pharmacokinetic meta-analysis showed that no dose adjustment is necessary for olodaterol based on sex, weight, and age (including geriatric patients).[9] Olodaterol has not been studied in patients with mild or moderate renal impairment. In subjects with severe renal impairment, olodaterol concentration is increased by approximately 40%, but no dose adjustment is recommended at this time for renally-impaired patients.[21] Furthermore, no dose adjustment is required for patients with mild or moderate hepatic impairment.[9] Olodaterol has not been studied in patients with severe hepatic impairment.[9]

Olodaterol should not be used in children due to lack of safety and efficacy studies. Olodaterol is pregnancy category C due to lacking human studies and teratogenicity seen in New Zealand

TABLE 5 | Average cash price in 2015 for a 30-day supply in Gainesville, FL.[24]

Drug	Striverdi® (olodaterol)	Arcapta® (indacaterol)	Spiriva® (tiotropium)
Price	$168.00	$215.00	$320.00

rabbits; thus olodaterol should only be used if the potential benefit justifies the potential risk to the fetus.[9] Although no human studies have been done, the approved labeling recommends prescribing an alternative well-studied COPD agent in nursing mothers since excretion of olodaterol's metabolites into breast-milk is probable as evidenced during animal studies.[9]

COST

Cost data for olodaterol and select other once-daily COPD inhalers are summarized in **Table 5**. Boehringer Ingelheim offers two cost saving options for olodaterol. The first alternative is a manufacturer savings card that allows most eligible patients to get their first prescription of olodaterol at no cost, depending on their insurance provider.[22] The Boehringer Ingelheim Cares Foundation is another option for low income patients. Patients can call 1-800-556-8317 to see if they qualify for monthly olodaterol free of charge.[23]

SUMMARY

Olodaterol (Striverdi® Respimat®) is a newly-approved alternative for the once-daily treatment of COPD. Clinical trials have shown that olodaterol is non-inferior to formoterol and superior to placebo for the treatment of COPD. The recommended dose of olodaterol is 5 mcg (two inhalations) once-daily. Dose adjustments are not necessary; however, olodaterol should not be used in children, or patients with uncontrolled diabetes, or severe hepatic impairment due to lack of safety and efficacy studies.

Olodaterol carries a black-box warning contraindicating its use for the treatment of asthma. Furthermore, olodaterol is not intended to be used as a rescue inhaler, nor is it indicated for acutely deteriorating COPD. Olodaterol should be used cautiously in pregnant women and nursing mothers, and in patients with diabetes, cardiovascular comorbidities, convulsive disorders, or hyperthyroidism. The most commonly reported adverse drug events seen in clinical trials with olodaterol use were COPD exacerbations, pharyngitis, respiratory tract infections, bronchitis, back pain, cough, UTI, diarrhea, dizziness, skin rashes, and arthralgia. Additional research is needed to better define the precise role for olodaterol among the currently-available LABAs for the treatment of COPD.

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Editor's Corner

Perioperative Bridging Anticoagulation in Patients with Atrial Fibrillation

A recent study published in the *New England Journal of Medicine* investigated whether bridging with low molecular weight heparin (LMWH) is necessary during interruption of warfarin therapy for an elective procedure.[1]

The study included adult patients with chronic atrial fibrillation or flutter with at least one $CHADS_2$ risk score and were on therapy with warfarin for at least three months. The patients included in the study were undergoing an elective procedure that required temporary interruption of warfarin therapy. Patients with a mechanical heart valve, recent thromboembolism, or recent major bleed were excluded from the study. One-thousand eight-hundred and eighty-four patients were randomized to receive bridging with dalteparin sodium (100 IU/kg administered subcutaneously twice daily) or no bridging therapy with matching placebo starting three days prior to the procedure. Dalteparin or placebo was continued until 24 hours before the procedure and then for 5 to 10 days after the procedure. Primary efficacy endpoint and safety outcome were arterial thromboembolism and major bleeding, respectively, at 30 days.

At study end, the incidence of arterial thromboembolism was similar between the two groups (0.4% in the placebo group vs. 0.3% in the dalteparin group; p=0.01 for noninferiority). Significantly less major bleeding occurred in the no-bridging group compared to patients receiving bridging therapy (1.3% in the placebo group vs. 3.2% in the dalteparin group; p=0.005 for superiority). None of the major bleeding occurrences were fatal.

The results of the study are consistent from previous observational comparisons of the two strategies; however, several considerations should be kept in mind with regards to this study.[2,3] First, several important patient groups were underrepresented in the study. About 3% of the patients included in the study had $CHADS_2$ score of 5 or 6. Patients with mechanical heart valves or who were undergoing procedures associated with high risk for arterial thromboembolism were excluded. Generalization of the results is difficult to these patient populations. Second, the overall rate of thromboembolism was lower than expected and may potentially indicate that the occurrence of these events during short-term warfarin interruption is uncommon.

The most recent AHA/ACC guidelines for the management of atrial fibrillation were updated prior to the publication of this study. The guidelines favor bridging therapy in patients with a mechanical heart valve and highlight the importance of balancing between the benefits and risks in patients without a mechanical heart valve.[4] The current study indicates that bridging therapy may not be necessary during interruption of warfarin therapy to prevent thromboembolism in select low to medium risk patients with atrial fibrillation.

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