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Yupelri® (Revefenacin): The Only Nebulized Once-Daily Long-Acting Muscarinic Antagonist for Chronic Obstructive Pulmonary Disease

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Chronic obstructive pulmonary disease (COPD) is a progressive respiratory disease marked by persistent airflow limitation. It is a public health issue and is currently the third leading cause of death in the United States and the fourth leading cause of death in the world.[1,2] The morbidity and mortality caused by COPD is projected to increase in the coming years due to exposure to risk factors and the continually aging world population.[3] The goal of treatment for COPD is to reduce symptoms such as dyspnea and cough, reduce exacerbations and hospitalizations, improve exercise tolerance, improve quality of life, and prevent complications. Complications like chronic bronchitis and emphysema can be prevented and managed but may arise due to inadequate COPD therapy.[2] According to the most recent Global Initiative for Chronic Obstructive Lung Disease (GOLD) guidelines, a long-acting muscarinic antagonist (LAMA) may be used as initial monotherapy in all groups of COPD patients (Group A, Group B, Group C, and Group D).[4]

LAMAs are the mainstay of therapy for patients with COPD, and several LAMAs with varying dosage forms and dosing schedules are currently on the market. For example, tiotropium is supplied as a dry powder inhaler (DPI) or soft mist inhaler (SMI) inhaled once-daily. Aclidinium is supplied as a metered dose inhaler (MDI) or DPI inhaled twice-daily. Umeclidinium is a once-daily DPI. Glycopyrrolate is a twice daily nebulized LAMA.[4]

In November 2018, the FDA granted approval for revefenacin (Yupelri®) as a once-daily nebulized bronchodilator for maintenance therapy of bronchospasm associated with COPD, including chronic bronchitis and emphysema. Revefenacin attempts to fill a gap in therapy to improve patient convenience as the first and only once-daily, nebulized LAMA for the treatment of COPD.[5] Revefenacin is not indicated to treat asthma or acute deterioration of COPD.[6] The purpose of this article is to review the pharmacologic profile, clinical trials, adverse effects, drug interactions, dosing, and costs associated with revefenacin therapy.

Pharmacology

Revefenacin is a LAMA which binds to muscarinic receptor subtypes M1, M2, M3, M4, and M5, with similar affinity for all subtypes. It exhibits its pharmacological effects via inhibition of the M3 receptor at the smooth muscle, which leads to bronchodilation. The bronchodilatory effects of revefenacin is dose-dependent and last over 24 hours based on sustained improvements in FEV1.[6] Revefenacin has similar selectivity and potency for M3 receptors when compared to tiotropium. However, it is less selective than tiotropium for salivary glands in animal studies which may cause less anticholinergic dry mouth side effects than tiotropium, although no comparison studies have been conducted.[7]

Revefenacin has minimal systemic absorption with a

Table 1 | Select Revefenacin Pharmacokinetics[6,7,8]

Property	Revefenacin	THRX-195518
Absorption		
Cmax[a] (ng/mL)	0.114	0.178
Tmax[b] (h)	0.23	0.48
AUC_{0-24c} (ng*h/L)	0.143	0.559
Bioavailability (%)	< 3%	-
Distribution		
Transport	P-gp[d] & BCRP[e] substrate	OATP1B1[f] & OATP1B3 substrate
Vd (L)	218	
Metabolism		
Reaction	Hydrolysis of primary amide to carboxylic acid to form THRX-195518	
Enzymes	CYP-2D6	
Elimination		
Half life (h)	22-70 hours	
Route	Feces: Majority Urine: < 1%	

[a] Maximum serum concentration; [b] Time to peak serum concentration; [c] Area under the curve from time zero to 24 hours post-dose; [d] P-glycoprotein; [e] Breast cancer resistance protein; [f] Organic-anion-transporting polypeptide

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bioavailability of <3% after inhalation, which may lead to less systemic adverse effects, discussed later. Additionally, revefenacin has a major active metabolite, THRX-195518, formed rapidly by hepatic metabolism via CYP2D6. The active metabolite has pharmacologic activity at muscarinic receptors that is approximately one-third to one-tenth that of revefenacin.[6] Plasma exposure of the active metabolite is 4 to 6 times greater than the exposure to the parent drug.[6] Revefenacin's active metabolite is a substrate of both OATP1B1 and OATP1B3, which leads to multiple drug interactions, discussed later.[6] Excretion is mostly fecal with <1% being excreted in the urine. The pharmacokinetic properties of revefenacin are summarized in **TABLE 1**.

The US Food and Drug Administration (FDA) approved revefenacin for the maintenance treatment of COPD based on the results of three phase III clinical trials. The phase III trials have yet to be formally published at the time of this manuscript writing. However, there are abstracts that detail these studies. Additionally, a phase IIb dose-finding study will also be discussed as it helped establish efficacy. **TABLE 2** provides a summary of the clinical trial data.

Clinical Trials

Pudi et al:

A 28-day phase IIb, randomized, double-blind, placebo-controlled, parallel group study was conducted by Pudi et al as a dose-finding study to determine the optimal safe and effective dose of revefenacin in patients with COPD.[8] In this study, patients were randomly allocated in a 1:1:1:1:1 ratio to receive revefenacin 44 mcg (n=68), 88 mcg (n=71), 175 mcg (n=71), 350 mcg (n=74) or placebo (n=70) once-daily via nebulization. Before treatment allocation and randomization, patients were stratified based on their responsiveness to ipratropium during screening. Patients were either labeled as responsive to ipratropium (defined as a ≥12% change and ≥200 mL change in forced expiratory volume in 1 second (FEV1) 45 minutes after completion of ipratropium bromide nebulization) or non-responsive to ipratropium. Inclusion criteria were age ≥40 years, a post-bronchodilator FEV1/forced vital capacity (FVC) ratio <0.7, moderate to severe COPD (GOLD Stage 2 or 3), post-bronchodilator FEV1 ≥30% and <80% of predicted normal, and a current or past smoking history of at least 10 pack-years. Participants were excluded if they had significant respiratory disease other than COPD, hospitalized for COPD or pneumonia within last 12 weeks, required long-term oxygen therapy (longer 15 hours a day), or were pregnant, lactating, breast-feeding, or planning to become pregnant during the study. The primary endpoint measured was change from baseline in trough FEV1 at day 28. Secondary endpoints included weighted mean FEV1 over 0 to 24 hours and rescue inhaler usage. A clinically meaningful difference was considered >100 mL improvement in FEV1. Safety endpoints included adverse events, laboratory results, and electrocardiograms.

Baseline characteristics were similar between groups. Patients were 50% male, 92% white, 54% current smokers, mean age of 62 years, and a mean FEV1 of 44%. For the primary endpoint of change in trough FEV1 at day 28, revefenacin dose groups of 88 mcg, 175 mcg, and 350 mcg significantly improved trough FEV1 over placebo by 155.0 mL, 134.2 mL, and 138.2 mL for all analyses, respectively (p<0.001 for all). However, revefenacin 44 mcg produced a sub-therapeutic response of 19.4 mL (placebo produced a response of −32.4 mL). Doses of 88 mcg or greater, more than 80% of patients achieved at least a 100 mL increase from baseline FEV1 in the first 4 hours after revefenacin administration compared with 33% of placebo patients. Revefenacin doses ≥88 mcg sustained bronchodilation for ≥24 hours and reduced rescue inhaler use by ≥1 puff per day (p<0.005 for doses greater than 88 mcg). Higher revefenacin doses led to less rescue inhaler usage in a dose-dependent relationship, with the revefenacin 350 mcg dose producing the least rescue medication usage. While the 350 mcg dose of revefenacin demonstrated additional efficacy over the 175 mcg dose with regards to the primary endpoint, it did not demonstrate a clinically meaningful difference therefore the following phase III trials used a max dose of 175 mcg. Revefenacin was generally well tolerated, with minimal reports of systemic anticholinergic effects.[8] Adverse events are discussed in detail in a later section.

Ferguson et al.

To establish the efficacy and safety of revefenacin 88 mcg and 175 mcg for the treatment of COPD, revefenacin was studied in two replicate 12-week randomized, double-blind, placebo-controlled trials by Ferguson et al.[9,10] In pooled data, participants were randomly allocated in a 1:1:1 ratio to receive revefenacin 88 mcg (n=425), revefenacin 175 mcg (n=402), or matching placebo (n=429) once-daily via nebulization for 12 weeks. Participants were eligible for study inclusion if they were over 40 years of age, had a post-bronchodilator FEV1/FVC ratio <0.7, had moderate to severe COPD (GOLD Stage 2 or 3), had post-bronchodilator FEV1 ≥30% and <80% of predicted normal, and had a current or past smoking history of at least 10 pack-years.[6] Participants were excluded if they were pregnant, lactating, breast-feeding, or planning to become pregnant during the study. Additional exclusion criteria were narrow-angle glaucoma, unstable cardiac disease or symptomatic prostatic hypertrophy or bladder outlet obstruction.[6] The primary endpoint is the 24-hour change from baseline in trough FEV1 at day 85. Safety endpoints included monitoring adverse events, laboratory results, and electrocardiograms. An additional endpoint studied include changes in health status using the St. George's Respiratory Questionnaire (SGRQ). The SGRQ measures patient quality of life with diseases of obstructed airways. Scores range from 0 to 100, with higher scores indicating more limitations.

None of the baseline characteristics were significantly different across treatment groups. Patients had a mean age of 64 years, 50% male, 49% of patients were current smokers, and patients had a mean predicted FEV1 of 54%. At baseline, 35% of study participants were categorized as GOLD category D, and 37% of participants received concomitant ICS (inhaled corticosteroid) therapy.[10] Concomitant therapies were handled in the following way. LABA and LAMA bronchodilators were prohibited. Combination steroid/LABA therapy was discontinued and replaced with equivalent strength ICS monotherapy. Albuterol was allowed as needed but was held for 6 hours before each study visit and during study visits unless medically necessary. The 24-hour change from baseline in trough FEV1 on day 85, the primary

Table 2 | *Revefenacin Clinical Trials*[8,10,17]

Trial	Primary Endpoint	Intervention	Result	Difference (95% CI[a])
***Pudi et al*[8]** **Phase IIb**	Change in trough FEV_1[b] at day 28	Placebo (n=70)	-32.4 mL	-
		Revefenacin 44 mcg (n=68)	19.4 mL	51.8 mL (-17.2 to 121.0)
		Revefenacin 88 mcg (n=71)	155.0 mL	187.4 mL (118.8 to 256.1)
		Revefenacin 175 mcg (n=71)	134.2 mL	166.6 mL (97.3 to 236.0)
		Revefenacin 350 mcg (n=74)	138.2 mL	170.6 mL (101.9 to 293.3)
***Ferguson et al*[10]** **Phase III**	Change in trough FEV_1 at day 85	Placebo (n=209)	-19.4 mL	-
		Revefenacin 88 mcg (n=212)	59.8 mL	79.2 mL (37.3 to 121.1)
		Revefenacin 175 mcg (n=198)	126.8 mL	146.3 mL (103.7 to 188.8)
		Placebo (n=209)	-44.9 mL	-
		Revefenacin 88 mcg (n=205)	115.6 mL	160.5 mL (110.5 to 210.5)
		Revefenacin 175 mcg (n=197	102.9 mL	147.0 mL (97.0 to 197.1)
***Mahler et al*[17]** **Phase IIIb**	Change in trough FEV_1 at day 28	Revefenacin 175 mcg (n=103)	63.0 vs 47.3 mL	15.7 mL (p=0.4811)*
		Tiotropium 18 mcg (n=104)		

[a] Confidence interval; [b] Forced expiratory volume in one second; * Confidence interval not reported

outcome, was significantly improved for both revefenacin 88 mcg (86.7 mL) and 175 mcg (115.0 mL) dose groups compared to placebo (-33.2 mL). The least squares mean difference from placebo was significant for both doses of revefenacin 88 mcg (119.8 mL) and 175 mcg (148.1 mL) compared to placebo (p<0.0001 for both comparisons).[10] The revefenacin 88 mcg and 175 mcg failed to achieve a significant difference in the number of COPD exacerbations.[11] Additionally, significant improvements in SGRQ scores were only shown in only one of the two replicate trials for either revefenacin doses. The study with significant improvement in SGRQ, the odds ratio (OR) for revefenacin 88 mcg was 2.06 (p=0.0203) and revefenacin 175 mcg was 2.11 (p=0.0183) compared to placebo.[12] No differences were reported in laboratory results including hematology and electrocardiograms among the placebo and treatment arms across both replicate studies.[13] The adverse events will be discussed in more detail in a later section.

A pre-specified subgroup analysis of the Ferguson et al. studies was conducted to examine specific subsets of patients who may be at higher risk of COPD exacerbation. This subgroup analysis examined multiple populations including the elderly (defined as patients >65 years old), patients receiving concomitant therapy with a LABA or an ICS, and patients with COPD classified as GOLD category D. Treatment benefits as evidenced by improvements in FEV1 from both dosages of revefenacin 88 mcg or 175 mcg one time daily were seen in all of the four subgroups studied, but treatment favored the 175 mcg dose (p values not reported).[14] This analysis suggests that these higher risk COPD patient populations benefit from maintenance treatment with revefenacin; however further studies may be warranted to confirm this treatment effect and the potential benefits in patients in a lower GOLD category.

Kerwin et al.

The safety and efficacy of revefenacin for the treatment of COPD compared to tiotropium was studied in a 52-week randomized, parallel group, partially blind, active-controlled phase III trial by Kerwin et al.[15,16] In this trial, participants were randomly allocated in a 1:1:1 ratio to receive either revefenacin 88 mcg via nebulization (n=364), revefenacin 175 mcg via nebulization (n=335), or tiotropium 18 mcg via Handihaler® inhalation (n=356) administered once-daily. Participants were eligible for study inclusion if they were over 40 years old. Exclusion criteria were pregnancy, lactating, breast-feeding, or planning to become pregnant during the study. The primary outcome was to determine the safety and tolerability of revefenacin over 1 year of treatment as determined by the frequency and severity of treatment-emergent adverse events. Other endpoints examined were adverse cardiac events and COPD exacerbations.

None of the baseline characteristics were significantly different across treatment groups.[11] Patients had a mean age of 64 years, 58% male, 93% white, 46% of patients were current smokers, and patients had a mean predicted FEV1 of 54%.16 Concurrent long-acting beta agonists (LABA) or LABA/ICS therapy was used in 50% of patients. Fewer patients had COPD exacerbations in the revefenacin 175 mcg group (21.8%) than in the revefenacin 88 mcg (29.4%) group or active-control group with tiotropium 18 mcg (28.1%) (p values not reported).[11] There was a lower incidence of dry mouth in the revefenacin groups (≤0.9%) compared to tiotropium (2.8%). Instances of major adverse cardiac events and mortality were similar between all treatment arms with one death per treatment arm. The adverse reactions encountered in this trial were consistent with those observed in previous studies.[16] The authors concluded that over 1 year of treatment, revefenacin was a well-tolerated therapy, and can be used as a long-term once-daily nebulized bronchodilator in COPD patients.[16]

Similar to the previous study Ferguson et al., a pre-specified subgroup analysis in the Kerwin et al. study was conducted to examine subsets of patients who may be at higher risk

of COPD exacerbation.[14] This subgroup analysis examined multiple populations including the elderly (defined as patients > 65 years old), patients receiving concomitant therapy with a LABA or ICS, and patients with COPD classified as GOLD category D. In the LABA subgroup, revefenacin 175 mcg once-daily had greater improvements in trough FEV1 than revefenacin 88 mcg. Both doses of revefenacin were equally effective at improving trough FEV1 in the ICS and elderly subgroups.[14] This analysis suggests that these higher risk COPD patient populations benefit from maintenance treatment with revefenacin; however further studies may be warranted to confirm this treatment effect.

Mahler et al.

In a randomized, double-blind, double-dummy, parallel group phase IIIb study by Mahler et al, participants with COPD were randomized 1:1 to receive revefenacin 175 mcg once-daily via a nebulizer (n=103) or tiotropium 18 mcg once-daily via HandiHaler® (n=104) for 28 days.[17] The primary endpoint measured was change from baseline in trough FEV1 at day 28. A secondary endpoint measured was trough FVC. All patients enrolled had moderate to very severe COPD and suboptimal peak inspiratory flow rate (PIFR) defined as < 60 L/min. Most patients enrolled (80%) had severe to very severe COPD (defined as FEV1 < 50% of predicted). At study conclusion, revefenacin was not able to achieve statistically significant improvements over tiotropium for trough FEV1 (p=0.481) or FVC (p=0.104).[17] In a prespecified subgroup analysis of patients with severe to very severe COPD, revefenacin significantly improved trough FEV1 (p=0.0302) as well as FVC (p=0.0407) from baseline compared with tiotropium.[17]

Prescribing Information

Adverse Effects

The majority of the adverse effects associated with revefenacin are localized reactions. Revefenacin has the potential to cause systemic side effects related to the drug's anticholinergic properties (e.g., dry eyes, blurred vision, urinary retention, mydriasis, ocular hypertension) if large doses are systemically absorbed. However, due to the low bioavailability of revefenacin after inhalation, the incidence of antimuscarinic systemic side effects is low.[6,13]

TABLE 3 summarizes the treatment-emergent adverse effects with an incidence of 1% or more and which are reported more commonly than placebo in the Ferguson et al. trials. Other studies confirm similar rates however specifics are not available entirely. According to the Ferguson et al. trials, none of the adverse events reported were significantly different across treatment groups.[13] With 53.4% of patients reported adverse events in the revefenacin 88 mcg group, 50.7% of patients in the revefenacin 175 mcg group, and 48.3% patients in the placebo group. Adverse events causing treatment discontinuation occurred in 13% of patients treated with revefenacin and 19% of patients treated with placebo. Adverse events observed in the Ferguson *et al.* trials are similar in frequency and severity as with those seen in other clinical trials.[8,9,10,16]

Table 3 | Adverse Effects of Revefenacin[13]

Adverse Event	Revefenacin 88 mcg	Revefenacin 175 mcg
Cough	4.0%	4.2%
Nasopharyngitis	3.3%	3.7%
Headache	4.9%	4.0%
URTI	4.7%	2.7%
Back Pain	1.4%	2.2%
HTN	1.9%	1.7%
UTI	2.1%	1.0%
Oropharyngeal Pain	2.1%	1.5%
Bronchitis	0.2%	1.5%
Dizziness	1.4%	1.5%

[a] Upper respiratory tract infection; [b] Hypertension; [c] Urinary tract infection

Drug Interactions

The use of revefenacin is not recommended in patients taking other anticholinergic medications as this combination may increase the potential for anticholinergic adverse effects such as dry mouth, constipation, and urinary retention. Additionally, co-administration of revefenacin with OATP1B1 and OATP1B3 inhibitors is not recommended because it could lead to an increase in systemic exposure of the active revefenacin metabolite and an increased potential for anticholinergic adverse effects.[6] Some pertinent OATP1B1 and OATP1B3 inhibitors that lead to major drug interactions include atazanavir, clarithromycin, cobicistat, cyclosporine, daclatasvir, erythromycin, gemfibrozil, leflunomide, rifampicin, simeprevir, and velpatasvir. It would be prudent to use alternative agents to avoid combining revefenacin with OATP1B1 or OATP1B3 inhibitors. Though revefenacin is metabolized via cytochrome P450 2D6 to an active metabolite, it does not appear to be an inducer or inhibitor of the enzyme nor have any drug interactions related to the cytochrome P450 metabolism.

Precautions

Revefenacin has an FDA-approved indication for maintenance treatment of COPD, and should not be used as a rescue inhaler for due to a relatively slow onset of action compared to alternative agents. Currently revefenacin does not have any contraindications for use. However, revefenacin is not recommended in patients with any degree of hepatic disease or hepatic impairment due to higher systemic exposure of its active metabolite. Specifically, the systemic exposure of the active metabolite of revefenacin is increased in patients with moderate hepatic impairment (Child-Pugh score of 7 to 9).[6] While not specifically observed in clinical trials, revefenacin has the potential to cause paradoxical bronchospasm similar to other LAMAs; if paradoxical bronchospasm occurs, discontinue revefenacin therapy and treat with a SABA. Other precautions include patients with urinary retention or closed-angle glaucoma due to the potential for exacerbation of these disease states. Revefenacin clinical trial use was excluded for patients with unstable cardiac disease or in

patients who are pregnant, lactating, breast-feeding, or planning to become pregnant; therefore, caution in these populations is warranted.[6]

Dosing and Administration

Yupelri® is supplied as a 175 mcg/3 mL nebulized solution for inhalation. Efficacy has been established for the use of revefenacin 175 mcg over the 88 mcg dose due to a more consistent treatment effect size.[8,10] Additionally, revefenacin 175 mcg is not significantly different compared to the 88 mcg dose when it comes to adverse drug reactions.[8,9,10,13,16] The recommended dose of revefenacin for adults is to inhale 175 mcg (the contents of 1 vial) once-daily by nebulizer over 8 minutes using a mouthpiece for oral inhalation.[6] Revefenacin should not be mixed with any other medications in the nebulizer since the compatibility with other drugs has not been established. Do not administer more than 1 dose every 24 hours. The unit-dose vial should be stored in the foil pouch and should only be removed immediately before use.[6] Revefenacin should be colorless, and the vial should be discarded if the solution is not colorless. No dosage adjustment is required for patients with renal impairment or in geriatric patients, but patients will need to be monitored for anticholinergic adverse effects due to an increased susceptibility for adverse effects.[6]

Pricing

Currently, revefenacin is only available as brand name Yupelri®. Cost data from March 2019 for revefenacin compared to other similar COPD agents is summarized in **TABLE 4**. Mylan, the manufacturer of Yupelri®, offers a copay assistance program with savings up to $550 per prescription according to the Yupelri® product website. This can reduce a patient's out-of-pocket costs to as little as $0 per month for eligible patients with commercial insurance.

Table 4 | 30-Day Supply Cost Comparison[18,19]

Medication	Price
Yupelri® (revefenacin)	$1,021.46
Spiriva® (tiotropium)	$451.71
Incruse Ellipta® (umeclidinium)	$339.60
Tudorza Pressair® (aclidinium)	$322.61
Lonhala Magnair® (glycopyrrolate)	$1,129.88

CLINICAL IMPLICATIONS

LAMAs are the mainstay of treatment in COPD patients and may be used as initial monotherapy in all groups of COPD patients (Group A, Group B, Group C, and Group D).[4] While the GOLD guidelines do not specifically make mention of revefenacin as an option for a LAMA, it is a new agent and may have a specific place in therapy with some considerations in mind. LAMAs are often delivered via hand-held inhalers, either a MDI, SMI, or DPI. However, for many patients, typical inhalers may be difficult to use, causing poor adherence and inaccurate dosing, which can ultimately lead to poor clinical outcomes.[14] According to a systematic literature review which analyzed inhaler use (e.g., MDIs and DPIs) in patients with asthma or COPD, the majority of patients use their inhalers inaccurately. Studies report incorrect inhaler usage in up to 94% of patients, with common problems being failure to continue inhale slowly after activation of the canister or failure to exhale before the inhalation.[20]

Currently options for long-acting nebulized bronchodilator therapy are limited. Glycopyrrolate (Lonhala Magnair®) is a twice daily nebulized LAMA; however, the twice daily administration may be inconvenient for patients. Revefenacin helps to fill the gap in therapy as the only nebulized once-daily LAMA approved for COPD. It provides similar efficacy to other hand-held inhalers, as evidenced by significant improvements in FEV_1.[14] Revefenacin's nebulized delivery may have a unique place in therapy for patients who have suboptimal peak inspiratory flow rates or patients who are cognitively impaired or have physical limitations such as a tracheostomy collar or endotracheal tube which may prevent the proper use of a typical inhaler. Revefenacin may have a place in therapy as an alternative agent for patients who may be struggling with traditional inhaled delivery methods.

Revefenacin may have an additional place in therapy for patients at high COPD exacerbation risk. There is evidence to suggest that patients with more severe COPD may benefit more from treatment with revefenacin than patients with less severe disease. In the subgroup analysis of both the Ferguson *et al.* and Mahler *et al.* trials, these higher risk patients (e.g., elderly, patients receiving concomitant therapy with a LABA or ICS, and patients with COPD classified as GOLD category D), benefited from revefenacin treatment. Further studies are warranted to confirm this treatment effect.

CONCLUSION

Revefenacin (Yupelri®) is a once-daily nebulized LAMA approved for the maintenance treatment of COPD. Studies have demonstrated that revefenacin 175 mcg inhaled once-daily is an effective therapy for the treatment of COPD as evidenced by significant improvement in FEV_1.[8] Though its exact place in therapy has not been elucidated, revefenacin fills a current gap in the market for a once-daily, nebulized LAMA. However, due to cost and the 8-minute nebulizer treatment duration, revefenacin is likely to be reserved for patients who have difficulty with soft mist or dry powder formulations of the other LAMAs.

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