

Brand Name: Yupelri
Generic Name: revefenacin
Manufacturer: Mylan
Drug Class: Anticholinergic
Uses:

Labeled Uses: inhalation solution for maintenance treatment of COPD¹
Unlabeled Uses: no off-label indications have been reported²

Mechanism of Action:^{1,2}

long-acting muscarinic antagonist (anticholinergic); binds to receptors M1 and M5, and inhibits M3

Pharmacokinetics:^{1,2}

Absorption:

T _{max}	14 – 41 minutes
V _d	218
t _{1/2}	22 to 70
Clearance	22 – 70 hours
Protein Binding	71%, active metabolite 42%
Bioavailability	3%

Metabolism:^{1,2} Rapid conversion via hepatic metabolism to an active metabolite occurs quickly after inhalation. Exposure to the active metabolite exceeds that of revefenacin by 4-6 times revefenacin's AUC.

Elimination:^{1,2} IV doses of revefenacin showed 54% excretion in the feces and 27% in the urine. 19% was recovered in the feces as the active metabolite. Taken orally, 88% was recovered in the feces, and 5% in the urine. Minimal (<1%) renal excretion of revefenacin and the active metabolite was recovered.

Efficacy:

DeLaCruz, Luis et al Trial in Progress: A 52-Week, Randomized, Double-Blind, Placebo-Controlled, Parallel-Group Phase 3 Trial to Evaluate the Safety and Tolerability of a Nebulized Long-Acting Muscarinic Antagonist (Revefenacin) in Study Participants with COPD. Chest. 150(4):866A

Study Design: 52 week, randomized, active-control, double-blind

Description of Study: 52 week open-label active control versus tiotropium 18mcg QD, partial-blind, parallel-group with three groups (revefenacin via jet nebulizer, tiotropium via jet nebulizer, tiotropium via Handihaler®) 1055 patients with moderate to severe COPD randomized to revefenacin (364 for 88mcg, 335 for 175mcg) and tiotropium 18mcg (356) for 52 weeks. Long term safety and tolerability evaluated by measuring adverse events, exacerbations, trough FEV₁, use of rescue inhaler, and patient-reported outcomes. Patients in this study are allowed to use ICS and LABA. The final results of this study are currently unpublished, but the trial has been completed.

Limitations: 43% of patients received concomitant ICS +/- LABA combination therapy without restrictions. The study was funded by Theravance Biopharma.

Conclusion: Preliminary results tout that safety and adverse reaction profile is consistent with observations from other studies. Revefenacin may be an important treatment option for patients who prefer nebulization therapy, and another advantage is its once daily administration.

Pudi K, Pendyala S, Barnes C, Moran E, Haumann B, Kerwin E. Two 12-Week, Randomized, Double-Blind, Placebo-Controlled, Parallel-Group Phase 3 Trials of a Nebulized Long-Acting Muscarinic Antagonist (Revefenacin) in Study Participants With Moderate to Very Severe COPD. Chest Journal. 2016;150(4):825A

Study Design: Multicenter, double-blind, randomized, placebo-controlled, parallel group study

Description of Study: 355 patients with COPD with mean FEV₁ of 44% were randomized to placebo or revefenacin. ICS and SABA use were permitted. Primary endpoint was mean change in FEV₁ from baseline on day 85 of dosing. Doses of 44mcg, 88mcg, 175mcg, or 350mcg and matching placebo were administered via jet nebulizer for 28 days. The change in baseline in trough FEV on day 85 of revefenacin compared to placebo. The first twelve week trial showed a an increase in the least square mean FEV₁ change from baseline and standard error was 59.81 (15.095) for the 88mcg dose of revefenacin, 126.85 (15.389) for the 175mcg dose of revefenacin, and -19.41 (16.108) for placebo. In the second twelve week trial, the least square mean FEV change from baseline and standard error was 115.58 (18.637) for the 88mcg revefenacin group, 102.90 (18.542) for the 175mcg, and -44.92 (18.841) in the placebo group.

Limitations: This study included a small number of patients and had a very short treatment period. Three of the main authors are employed by Theravance Biopharma, the sole source of funding for the study. One author is both a consultant for Theravance Biopharma and many other pharmaceutical companies. Additionally, the study reports their data in a somewhat misleading way, giving the standard error of the mean as a measure of variability. This may be due to a potential conflict of interest.

Conclusion: FEV₁ significantly improved with revefenacin compared to placebo. However, the variability of the data is greater than what is expressed using the standard error of the mean. Larger trials with more people would have to be conducted in order to better narrow the true variability in response in the population. It is evident from this study that revefenacin has some positive effect on patients with COPD.

Pudi K, Barnes C, Moran E, Haumann B, Kerwin E. A 28-day, randomized, double-blind, placebo-controlled, parallel group study of nebulized revefenacin in patients with chronic obstructive pulmonary disease.

Study Design: randomized, double-blind, placebo-controlled, parallel group

Description of Study: 355 patients with COPD with mean FEV₁ of 44% were randomized to placebo or revefenacin. ICS and SABA use were permitted, but LABA medications were discontinued in both arms prior to enrollment. Primary endpoint was mean change in FEV₁ from baseline in a 24 hour time period and at day 29. Doses of 44mcg, 88mcg, 175mcg, or 350mcg and matching placebo were administered via jet

nebulizer for 28 days. A significant change in baseline trough FEV₁ was achieved for all doses of revefenacin in the first six hours after a dose compared to placebo (P <0.001). From hours 0-12, a significant change was achieved in the highest three doses of revefenacin (p < 0.001). The 24 hour change was significant for all doses of revefenacin (p < 0.02 for 88mcg, p < 0.001 for all other doses). On day 29, a significant change from baseline was detected for the highest three doses of revefenacin.

Limitations: This was a short trial with a small amount of subjects. A potential conflict of interest may exist as three of the main authors are employed by Theravance Biopharma, the sole source of funding for the study. One author is both a consultant for Theravance Biopharma and many other pharmaceutical companies including Mylan, which funded the writing. Similar to the two twelve week parallel trials, the reporting of variability uses the standard error. Variability in mL is much greater than what appears to be present when reading the SE values.

Conclusion: FEV₁ significantly improved with revefenacin compared to placebo. The optimal dose of revefenacin is 88mcg or 175mcg. However, larger trials with more subjects and longer treatment periods will be better equipped to conclude clinical efficacy. Safety can be concluded from this study.

Contraindications:^{1,2} hypersensitivity to revefenacin or any component in the medication.

Precautions:^{1,2}

Hypersensitivity

If hypersensitivity reactions occur, discontinue therapy immediately.

Overdose

Anticholinergic effects such as nausea, vomiting, dizziness, lightheadedness, blurred vision, increased intraocular pressure, obstipation and difficulties voiding. Doses as high as 700 mcg inhaled once daily for 7 days were well tolerated in patients with COPD.

Ocular exposure

Use caution to avoid ocular exposure to revefenacin during administration; aggravation of closed-angle glaucoma can occur. Signs and symptoms include eye pain or discomfort, blurred vision, halos or colored images in association with red eyes from conjunctival congestion and corneal edema. Seek emergency care right away if these symptoms develop.

Rescue Therapy

Revefenacin is not intended to be used as rescue therapy during acute exacerbations.

Paradoxical Bronchospasm

Treat immediately with a short-acting beta-adrenergic agonist.

Urinary Retention

Can exacerbate urinary retention in patients who have prior conditions such as bladder neck obstructions, or prostate hypertrophy.

Hepatic Disease

Revefenacin is not recommended for use in hepatic impairment or disease. Its safety has not been evaluated in patients with mild to severe impairment.

Blurred vision

Revefenacin may cause blurred vision. Use caution operating machinery or driving until the effects of the drug are predictable.

Geriatric Use

Anticholinergic effects may be more pronounced in geriatric patients.

Adverse Effects:

Occurring in >10%

No side effects occurred with greater than 10% frequency (2)

Occurring in >1% - 10% (1)

Respiratory, Thoracic, and Mediastinal Disorders

Cough (4%)

Infections and Infestations

Nasopharyngitis (4%)

Upper respiratory tract infection (3%)

Nervous System Disorders

Headache (4%)

Musculoskeletal and Connective Tissue Disorders

Back pain (2%)

Drug Interactions:²

Revefenacin is a P-gp and BCRP substrate. It does not inhibit these transporters. Additionally, it is a substrate of OATP1B1 and OATP1B3, but does not inhibit the uptake of these transporters. It is not an inhibitor or inducer of any major P450 isoforms (CYP1A2, 2B6, 2C8, 2C9, 2C19, 2D6, 3A4/5, and 1A2, 2B6, 3A4/5 respectively). Consequently, no metabolic drug interactions involving CYP450 enzymes exist. (1) Coadministration with drugs that inhibit *OATP1B1* and *OATP1B3*, such as clarithromycin, daclatasvir, cyclosporine, paritaprevir, eltrombopag, erythromycin, gemfibrozil, pibrentasvir, rifampin, leflunomide, letermovir, lopinavir, obeticholic acid, simeprevir, velpatasvir, telithromycin, teriflunomide, atazanavir, and cobicistat, is not recommended due to the risk of increased anticholinergic adverse effects from prolonged exposure to revefenacin's active metabolite. Additionally, coadministration with other anticholinergics may have an additive effect on the anticholinergic effects of the small amount of revefenacin that is absorbed systemically.

Dosing/Administration:^{1,2}

Adult

175 mcg inhaled via jet nebulizer once daily

Peds

No studies conducted, not indicated for children.

Elderly

No dose adjustments needed.

Renal

No dose adjustments necessary. Monitor for systemic anticholinergic effects in poor renal function.

Hepatic

Active metabolite exposure is increased in patients with hepatic dysfunction. Safety has not been evaluated. It is not recommended in patients with any degree of hepatic impairment.

Use in special circumstances:^{1,2}

Pregnancy

No well-controlled studies including pregnant women. No evidence of fetal harm observed in animal studies of pregnant rats and rabbits.

Lactation

No information for effects on milk production or effects on breastfed infant. Revefenacin was present in milk of lactating rats.

Conclusion: Revefenacin is a safe option for patients who prefer a once daily nebulized long-acting muscarinic antagonist. Before wide distribution, head to head trials with the current standard of care must be evaluated. Currently, results of a 52 week trial against tiotropium seem to be pending. While it is clear that revefenacin has a positive impact on the surrogate markers used to evaluate the severity of COPD, the variability in data reported in the above-mentioned trials makes it difficult to accurately predict the response of patients today. Additionally, trials comparing revefenacin to placebo have stripped away the use of long-acting beta agonists. This may cause an elongated gap between the trough FEV₁ values reported by the placebo and revefenacin groups. There is likely a market for revefenacin in patients who report difficulty using standard LAMA delivery devices such as MDIs or DPIs, as nebulizers may be an easier way to deliver the drug in this subset of patients.

Recommended References:

1. Revefenacin [package insert] Morgantown, WV. Mylan Specialty L.P.; 1993.
2. Revefenacin. Clinical Pharmacology. [Internet database]. Gold Standard, Inc., 2007. Available at: <http://www.clinicalpharmacology.com> Accessed: February 3rd, 2019.
3. DeLaCruz L, Pendyala S, Barnes C, Moran E, Haumann B, Fledman G. A 52-week randomized, double-blind, placebo-controlled, parallel-group phase 3 trial to evaluate the safety and tolerability of a nebulized long-acting muscarinic antagonist (revefenacin) in study participants with COPD. *Chest Journal*. 2016;150(4):866A.
4. Pudi K, Pendyala S, Barnes C, Moran E, Haumann B, Kerwin E. Two 12-Week, Randomized, Double-Blind, Placebo-Controlled, Parallel-Group Phase 3 Trials of a Nebulized Long-Acting Muscarinic Antagonist (Revefenacin) in Study Participants With Moderate to Very Severe COPD. *Chest Journal*. 2016;150(4):825A
5. Pudi K, Barnes C, Moran E, Haumann B, Kerwin E. A 28-day, randomized, double-blind, placebo-controlled, parallel group study of nebulized revefenacin in patients with chronic obstructive pulmonary disease.

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