Summary Report of Benefit-Risk Assessment

YUPELRI INHALATION SOLUTION 175MCG/3ML

NEW DRUG APPLICATION

Active Ingredient(s)	Revefenacin
Product Registrant	Mylan Pharmaceuticals Pte. Ltd.
Product Registration Number	SIN16336P
Application Route	Abridged Evaluation
Date of Approval	28 September 2021

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A INTRODUCTION

Yupelri inhalation solution is indicated for the maintenance treatment of patients with chronic obstructive pulmonary disease (COPD).

The active substance, revefenacin, is a long-acting muscarinic antagonist. In the airways, it exhibits pharmacological effects through inhibition of M3 receptor at the smooth muscle leading to bronchodilation.

Yupelri is available as unit-dose vials. Each vial contains 175 mcg of revefenacin in 3 mL of aqueous solution. Other ingredients in the solution are sodium chloride, citric acid, sodium citrate and water for injection.

B ASSESSMENT OF PRODUCT QUALITY

The drug substance, revefenacin, is manufactured at Finorga SAS (Novasep), Chasse-sur-Rhône, France. The drug product, Yupelri Inhalation Solution 175mcg/3ml, is manufactured at The Ritedose Corporation, SC, USA.

Drug substance:

Adequate controls have been presented for the starting materials, intermediates and reagents. The in-process control tests and acceptance criteria applied during the manufacturing of the drug substance are considered appropriate.

The characterisation of the drug substance and its impurities are in accordance with ICH guidelines. Potential and actual impurities are adequately controlled.

The drug substance specifications are established in accordance with ICH Q6A and the impurity limits are considered appropriately qualified. The analytical methods used are adequately described and non-compendial methods were validated in accordance with ICH guidelines. Information on the reference standards used for identity, assay and impurities testing is presented.

The stability data presented for Finorga SAS was adequate to support the approved storage condition and shelf life. The packaging comprised double low density polyethylene (LDPE) bags sealed inside a high density polyethylene (HDPE) drum with a secure fitting lid and a tamper evident seal. The drug substance is approved for storage at USP controlled room temperature with a re-test period of 36 months.

Drug product:

The manufacturing process utilises aseptic processing.

All manufacturing sites involved are compliant with Good Manufacturing Practice (GMP). Proper development and validation studies were conducted. It has been demonstrated that the manufacturing process is reproducible and consistent. Adequate in-process controls are in place.

The specifications are established in accordance with ICH Q6A and impurity limits are considered adequately qualified. The analytical methods used are adequately described and non-compendial methods were validated in accordance with ICH guidelines. Information on the reference standards used for identity, assay and impurities testing is presented.

The stability data submitted was adequate to support the approved shelf-life of 36 months when stored at or below 30 ºC. The container closure system is a low-density polyethylene (LDPE) unit-dose vial in an aluminium foil laminate pouch. The vial should only be removed from the foil pouch and opened immediately before use.

C ASSESSMENT OF CLINICAL EFFICACY

The clinical efficacy of revefenacin in the treatment of COPD was based on two pivotal Phase 3 studies (Studies 0126 and 0127) and a supportive Phase 3 safety study (Study 0128).

Study 0126/0127

Studies 0126 and 0127 were identical in design. Both were Phase 3, randomised, double-blind, placebo-controlled studies in patients with moderate to very severe COPD. Patients were randomised 1:1:1 to receive 1 of 2 doses of revefenacin (88 mcg or 175 mcg) or matching placebo, administered daily in the morning by a standard jet nebulizer for 12 weeks.

The primary efficacy endpoint was the change from baseline in the trough force expiratory volume in 1 second (FEV_1) on Day 85. The secondary efficacy endpoints were (i) trough FEV_1 overall treatment effect (OTE), (ii) Peak FEV_1 on Day 1, (iii) rescue medication use (incidence of albuterol use), (iv) percentage of albuterol rescue-free 24-hour periods, and (v) patient health status as measured by Saint George's Respiratory Questionnaire (SGRQ) proportion of responders on Day 85. Due to the testing of multiple efficacy endpoints in the studies, the type I error was controlled at the 0.05 significance level using a truncated Hochberg procedure. Hierarchical testing of both doses of revefenacin (88 mcg and 175 mcg) was sequentially performed against placebo in a parallel manner for the primary endpoint and each of the secondary endpoint in the order described above.

A total of 1,229 patients were included in the studies (N = 619 Study 0126 and N = 610 in Study 0127). In both studies, the majority of the patients (90.2%) were white. Patients ranged in age from 41 to 88 years, with a mean age of 63.7 years. Nearly half (47.8%) of the total patients were current smokers and the remaining 52.2% were former smokers. At screening, the mean post-bronchodilator percent predicted FEV_1 was 54.6%. The patient demographics and baseline disease characteristics were generally well-balanced between the treatment arms.

Treatment with both revefenacin doses of 88 mcg and 175 mcg resulted in statistically significant improvement in the primary efficacy endpoint of change from baseline trough FEV_1 on Day 85. In Study 0126, the difference in least squares (LS) mean trough FEV_1 was 79.2 mL and 146.3 mL for revefenacin 88 mcg and 175 mcg, respectively, compared to placebo. In Study 0127, the differences in LS mean trough FEV_1 from revefenacin doses of 88 mcg and 175 mcg compared with placebo were 160.5 mL and 147.0 mL, respectively.

Summary of primary efficacy endpoint (Studies 0126 and 0127)

	Study 0126			Study 0127		
	Placebo (n=209)	**Revefenacin 88 mcg (n=212)**	**Revefenacin 175 mcg (n=198)**	**Placebo (n=208)**	**Revefenacin 88 mcg (n=205)**	**Revefenacin 175 mcg (n=197)**
Change from baseline trough FEV_1 on Day 85						
LS Mean (SE)	-19.4 (16.1)	59.8 (15.1)	126.9 (15.4)	-44.9 (18.8)	115.6 (18.6)	102.1 (18.5)
LS Mean Difference vs Placebo (SE)	-	79.2 (21.3)	146.3 (21.6)	-	160.5 (25.5)	147.0 (25.5)
95% CI for LS Mean Difference	-	37.3, 121.1	103.7,188.8	-	110.5, 210.5	97.0, 197.1
P value vs Placebo	-	0.0002	<0.0001	-	< 0.0001	< 0.0001

In both studies, all the secondary spirometric endpoints (trough FEV_1 OTE and peak FEV_1 on Day 1) were statistically improved compared to placebo. As testing of the rescue medication use endpoint failed to achieve statistical significance, all subsequent secondary endpoints (percentage of rescue medication-free 24-hour periods and SGRQ proportion of responders) were considered to have not reached statistical significance within the framework of the hierarchical testing. Nonetheless, there were numerical improvements in favour of revefenacin in terms of rescue medicine use and health status as measured by the SGRQ.

Summary of secondary efficacy endpoints (Studies 0126 and 0127)*

	Study 0126			Study 0127		
	Placebo (n=209)	**Revefenacin 88 mcg (n=212)**	**Revefenacin 175 mcg (n=198)**	**Placebo (n=208)**	**Revefenacin 88 mcg (n=205)**	**Revefenacin 175 mcg (n=197)**
Trough FEV_1 OTE						
LS Mean (SE)	-30.8 (3.2)	73.1 (3.1)	124.8 (3.2)	-39.9 (3.2)	83.9 (3.1)	87.1 (3.2)
LS Mean Difference (SE) vs Placebo	-	103.8 (4.4)	155.6 (4.6)	-	123.7 (4.5)	127.0 (4.5)
95% CI for LS Mean Difference	-	95.1, 112.5	146.8, 164.5	-	115.0, 132.4	118.2, 135.8
P value vs Placebo	-	0.0003	<0.0001	-	<0.0001	<0.0001
Peak FEV_1 Day 1						
LS Mean (SE)	91.8 (10.0)	218.1 (9.4)	224.4 (9.7)	88.2 (10.1)	218.7 (10.3)	216.8 (10.2)
LS Mean Difference (SE) vs Placebo	-	126.3 (12.8)	132.7 (13.1)	-	130.4 (13.3)	128.6 (13.4)

95% CI for LS Mean Difference	-	101.1, 151.6	106.9, 158.5	-	104.3, 156.5	102.3, 155.0
P value vs Placebo	-	0.0003	0.0002	-	<0.0001	<0.0001
Rescue medication use (incidence of albuterol use, puffs per day) Day 1-85						
LS Mean (SE)	2.7 (0.2)	2.3 (0.2)	2.3 (0.2)	2.5 (0.2)	2.0 (0.2)	2.4 (0.2)
LS Mean Difference (SE) vs Placebo	-	-0.5 (0.3)	-0.5 (0.3)	-	-0.5 (0.3)	-0.2 (0.3)
95% CI for LS Mean Difference	-	-1.1, 0.2	-1.1, 0.2	-	-1.1, -0.0	-0.7, 0.4
P value vs Placebo	-	0.2251	0.2251	-	0.0911	0.7346
Percentage of albuterol rescue-free 24-hour periods Day 1-85						
LS Mean (SE)	45.2 (2.9)	48.4 (2.8)	43.6 (2.8)	37.2 (2.8)	44.8 (2.8)	43.3 (2.8)
LS Mean Difference (SE) vs Placebo	-	3.1 (3.7)	-1.6 (3.8)	-	7.6 (3.6)	6.0 (3.7)
95% CI for LS Mean Difference	-	-4.2, 10.5	-9.2, 5.9	-	0.4, 17.7	-1.2, 13.3
P value vs Placebo	-	0.8045	0.8904		0.1542	0.7346
SGRQ Responder (Decrease of ≥ 4 points) Day 85						
Responders (%)	33.8	47.3	48.9	38.6	46.2	45.0
Odds Ratio (Revefenacin /Placebo)	-	2.1	2.1	-	1.4	1.3
P value vs Placebo	-	0.8045	0.8045	-	0.7346	0.7346

*presented in the sequence of statistical hierarchical testing

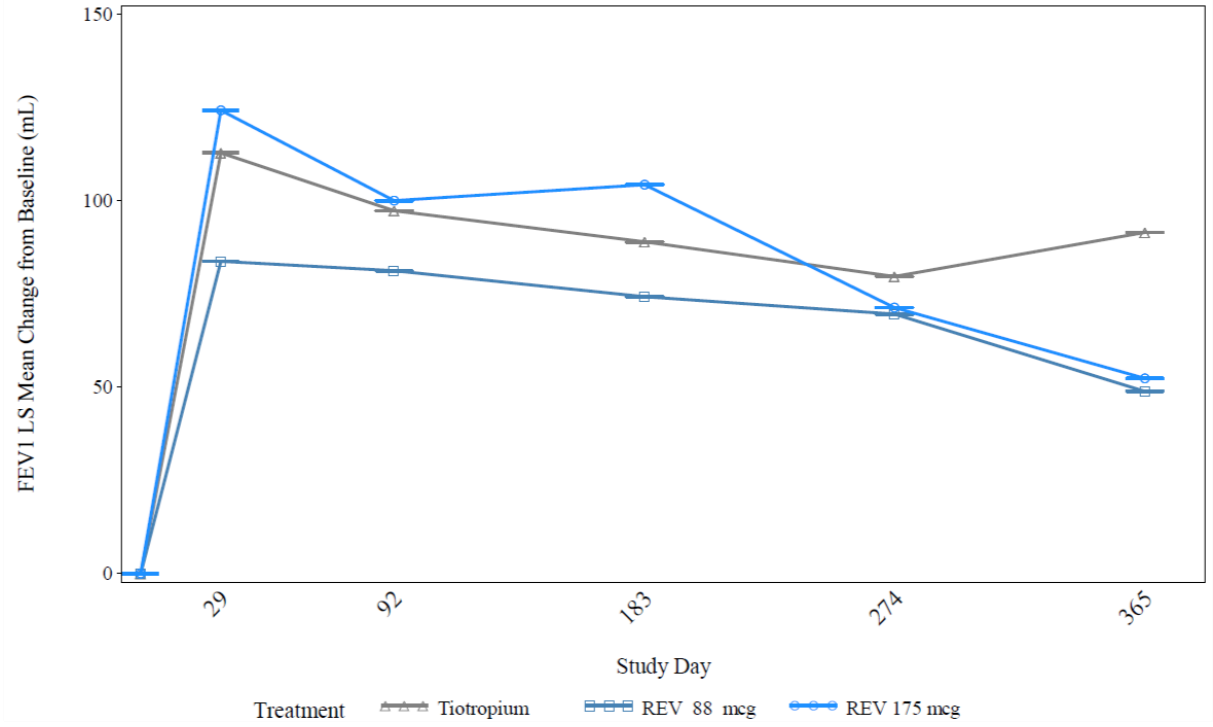
Study 0128

Study 0128 was a Phase 3 randomised, active-controlled, 52-week study in patients with moderate to severe COPD. Each patient received one of two doses of revefenacin (88 mcg or 175 mg) or tiotropium (18 mcg) daily for a total of 52 weeks. Tiotropium is a long-acting muscarinic antagonist registered for the treatment of COPD.

The primary objective of the study was to characterise the safety of revefenacin and the efficacy assessment was considered exploratory. A total of 1020 patents were analysed for efficacy. The change in trough FEV_1 from baseline for all 3 treatment arms was studied on Days 29, 92, 183, 274 and 365, i.e., up to Week 52. Nominally statistically significant differences from baseline in trough FEV_1 were observed for both revefenacin 88 mcg and 175 mcg groups, as well as for tiotropium, over the entire treatment period of 52 weeks. The overall

changes from baseline in trough FEV_1 were numerically greater for the revefenacin 175 mcg group relative to the revefenacin 88 mcg group and were generally comparable to tiotropium.

LS Mean change from baseline: Trough FEV_1 Days 1-365 (mL) (Study 0128)



Overall, the pivotal studies each met their primary efficacy endpoints and demonstrated an improvement in lung function, FEV_1 for both revefenacin doses when compared with placebo. Efficacy in favour of revefenacin were also demonstrated for the spirometric secondary endpoints. The magnitude of FEV_1 response following the 88 mcg dose was noted to be variable across the studies, whereas that with the 175mcg was relatively consistent in the two pivotal studies with generally larger treatment effect compared to the 88 mcg dose. Additionally, in the supportive long-term study, revefenacin treatment resulted in improvements in lung function, with the 175 mcg dose conferring greater numerical benefits compared to the 88 mcg dose. Overall, the clinical efficacy of revefenacin for the maintenance treatment of patients with COPD was demonstrated.

D ASSESSMENT OF CLINICAL SAFETY

The clinical safety of revefenacin was based primarily on the placebo-controlled studies (Study 0126 and 0127) and from the long-term active-controlled safety study (Study 0128). Overall, there were 781 subjects received revefenacin 88 mcg and 730 subjects received revefenacin 175 mcg. In the placebo-controlled studies, the median study duration ranged from 84 days to 85 days, while in the long-term active-controlled study, the median duration ranged from 362 days to 364 days.

Overview of safety profile (Studies 0126 and 0127, pooled)

	Placebo (N=418) n (%)	Revefenacin 88 mcg (N=417) n (%)	Revefenacin 175 mcg (N=395) n (%)
Treatment-emergent adverse event (TEAE)	206 (49.3)	226 (54.2)	203 (51.4)
TEAE related to study drug	39 (9.3)	33 (7.9)	41 (10.4)
SAE	21 (5.0)	21 (5.0)	15 (3.8)
SAE related to study drug	0	0	2 (0.5)
AE leading to study drug discontinuation	59 (14.1)	50 (12.0)	43 (10.9)

SAE: serious adverse event; TEAE: treatment-emergent adverse event

Overview of safety profile (Study 0128)

	Tiotropium (N=356) n (%)	Revefenacin 88 mcg (N=364) n (%)	Revefenacin 175 mcg (N=335) n (%)
Treatment-emergent adverse event (TEAE)	275 (77.2)	272 (74.7)	242 (72.2)
TEAE related to study drug	42 (11.8)	53 (14.6)	45 (13.4)
SAE	58 (16.3)	58 (15.9)	43 (12.8)
SAE related to study drug	1 (0.3)	2 (0.5)	1 (0.3)
AE leading to study drug discontinuation	33 (9.3)	47 (12.9)	41 (12.2)

SAE: serious adverse event; TEAE: treatment-emergent adverse event

In Studies 0126 and 0127, the combined incidences of all treatment-emergent adverse event (TEAE) were generally similar between the active treatment groups and placebo. The TEAE with the highest incidence (placebo vs revefenacin 88 mcg vs revefenacin 175 mcg) was worsening of COPD (11.5% vs 10.1% vs 10.6%), followed by cough (4.1% vs 4.1% vs 4.3%), dyspnoea (5.5% vs 3.1% vs 3.0%), and headache (2.6 % vs 5.0% vs 4.1%). The majority of TEAEs were of mild intensity. In Study 0128, a similar safety profile was observed and the frequency of TEAEs was generally comparable across revefenacin treatment groups and the active comparator, tiotropium.

In Studies 0126 and 0127, the incidence of serious AEs (SAE) was 5.0% in the placebo group, 5.0% in the revefenacin 88 mcg group and 3.8% in the revefenacin 175 mcg group. For all treatment groups, the most commonly reported SAE was worsening of COPD, with 1.9% in the revefenacin 88 mcg arm, 1.3% in the revefenacin 175 mcg arm, and 1.4% in the placebo arm. In Study 0128, worsening of COPD was also the most frequently reported SAE, occurring in slightly more patients in the revefenacin 88 mcg (3.6%) and tiotropium (3.7%) groups than in the revefenacin 175 mcg (2.4%) group. There were no deaths that were considered to be related to the study drugs.

The main AE of interest with long-acting muscarinic antagonist is the incidence of systemic anticholinergic side effects. In the pooled data for Studies 0126, 0127 and 0128, the overall incidence rate for any anticholinergic TEAE was 2.2% in the revefenacin 88 mcg group, 1.6% in the revefenacin 175 mcg group, 4.2% in the tiotropium group and 0.2% in the placebo group. Constipation and dry mouth were the most commonly reported AEs.

Overall, the safety profile of revefenacin was consistent with other long-acting muscarinic antagonist used for the treatment of COPD. There appears to be no increase in safety risk with the 175 mcg dose as compared with the 88 mcg dose. Appropriate warnings and precautions have been included in the package insert to address the identified safety risks.

E ASSESSMENT OF BENEFIT-RISK PROFILE

COPD is a common and progressive disease that is characterised by persistent respiratory symptoms and airflow limitation that is not fully reversible and is associated with high morbidity and mortality. Pharmacologic treatment of COPD with bronchodilators is central to the management of both the symptoms and the long-term risks of COPD.

The clinical benefit of revefenacin in the treatment of COPD was demonstrated based on statistically significant improvements from baseline versus placebo in the trough FEV_1 in two 12-week pivotal studies (LS mean difference of 79.2 mL and 160.5 mL for revefenacin 88 mcg; 146.3 mL and 147.0 mL for revefenacin 175 mcg in Study 0126 and 0127, respectively). While both revefenacin doses provided significant improvements over placebo in lung function in the overall population, the 175 mcg dose appeared to have a more consistent and greater effect than the 88 mcg dose. In a 52-week study, consistently greater improvements were also noted in patients treated with the revefenacin 175 mcg dose for trough FEV_1 compared to baseline.

Overall, the safety profile of revefenacin was consistent with that of other inhaled anticholinergic agents for COPD and no new safety signals were observed. The 175 mcg dose was well tolerated compared to the 88 mcg dose and the safety profile was generally similar between the two doses. While worsening COPD was the most commonly reported AE in the studies, the incidences in the revefenacin groups were generally comparable to placebo. Other common AEs were cough, headache, and dyspnoea and these events were mostly mild to moderate, and are expected AEs of long-acting muscarinic antagonists.

Overall, the clinical benefits have been demonstrated to outweigh the risks of revefenacin in the treatment of COPD and the efficacy and safety data supported the use of revefenacin 175 mcg once daily for the requested indication.

F CONCLUSION

Based on the review of quality, safety and efficacy data, the benefit-risk balance of revefenacin for the treatment of COPD was deemed favourable and approval of the product registration was granted on 28 September 2021.

APPROVED PACKAGE INSERT AT REGISTRATION

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HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use YUPELRI® (revefenacin) inhalation solution safely and effectively. See full prescribing information for YUPELRI (revefenacin) inhalation solution.

----------INDICATIONS AND USAGE----------

YUPELRI inhalation solution is an anticholinergic indicated for the maintenance treatment of patients with chronic obstructive pulmonary disease (COPD).

---------- DOSAGE AND ADMINISTRATION ----------

For oral inhalation use only. Do not swallow YUPELRI.

- One 175 mcg vial (3 mL) once daily. (2)
- For use with a standard jet nebulizer with a mouthpiece connected to an air compressor. (2)

---------- DOSAGE FORMS AND STRENGTHS ----------

Inhalation solution in a unit-dose vial for nebulization. Each vial contains 175 mcg/3 mL solution. (3)

---------- CONTRAINDICATIONS ----------

YUPELRI is contraindicated in patients with hypersensitivity to revefenacin or any component of this product. (4)

---------- WARNINGS AND PRECAUTIONS ----------

- Do not initiate YUPELRI in acutely deteriorating COPD or to treat acute symptoms. (5.1)
- If paradoxical bronchospasm occurs, discontinue YUPELRI and institute alternative therapy. (5.2)
- Worsening of narrow-angle glaucoma may occur. Use with caution in patients with narrow-angle glaucoma and instruct patients to contact a healthcare provider immediately if symptoms occur. (5.3)
- Worsening of urinary retention may occur. Use with caution in patients with prostatic hyperplasia or bladder-neck obstruction and instruct patients to contact a healthcare provider immediately if symptoms occur. (5.4)
- Immediate hypersensitivity reactions may occur. If such a reaction occurs, therapy with YUPELRI should be stopped at once and alternative treatments should be considered. (5.5)

---------- ADVERSE REACTIONS ----------

Most common adverse reactions (incidence greater than or equal to 2% and more common than placebo) include cough, nasopharyngitis, upper respiratory tract infection, headache, and back pain. (6.1)

---------- DRUG INTERACTIONS ----------

- Anticholinergics: May interact additively with concomitantly used anticholinergic medications. Avoid administration of YUPELRI with other anticholinergic-containing drugs. (7.1)
- Transporter-related drug interactions: Coadministration of YUPELRI with OATP1B1 and OATP1B3 inhibitors (e.g. rifampicin, cyclosporine, etc.) may lead to an increase in exposure of the active metabolite. Therefore, coadministration with YUPELRI is not recommended. (7.2, 12.3)

---------- USE IN SPECIFIC POPULATION ----------

Hepatic impairment: Avoid use of YUPELRI in patients with hepatic impairment. (8.6, 12.3)

See 17 for PATIENT COUNSELING INFORMATION

Revised: 5/2019

FULL PRESCRIBING INFORMATION: CONTENTS*

* Sections or subsections omitted from the full prescribing information are not listed.

FULL PRESCRIBING INFORMATION

1 INDICATIONS AND USAGE

YUPELRI inhalation solution is indicated for the maintenance treatment of patients with chronic obstructive pulmonary disease (COPD).

2 DOSAGE AND ADMINISTRATION

The recommended dose of YUPELRI inhalation solution is one 175 mcg unit-dose vial administered once daily by nebulizer using a mouthpiece.

YUPELRI should be administered by the orally inhaled route via a standard jet nebulizer connected to an air compressor (See Patient Information). The safety and efficacy of YUPELRI have been established in clinical trials when administered using the PARI LC® Sprint nebulizer with a mouthpiece and the PARI Trek® S compressor. The safety and efficacy of YUPELRI delivered from non-compressor based nebulizer systems have not been established.

The YUPELRI unit-dose vial should only be removed from the foil pouch and opened IMMEDIATELY BEFORE USE. The vial and any residual content should be discarded after use.

No dosage adjustment is required for geriatric patients, or patients with renal impairment *[see Clinical Pharmacology (8.5, 8.7, 12.3)]*.

The drug compatibility (physical and chemical), efficacy, and safety of YUPELRI when mixed with other drugs in a nebulizer have not been established.

3 DOSAGE FORMS AND STRENGTHS

YUPELRI inhalation solution is supplied as a sterile, clear, colorless, aqueous solution for nebulization in low-density polyethylene unit-dose vials. Each vial contains 175 mcg of revefenacin in 3 mL of aqueous solution.

4 CONTRAINDICATIONS

YUPELRI is contraindicated in patients with hypersensitivity to revefenacin or any component of this product.

5 WARNINGS AND PRECAUTIONS

5.1 Deterioration of Disease and Acute Episodes

YUPELRI should not be initiated in patients during acutely deteriorating or potentially life-threatening episodes of COPD. YUPELRI has not been studied in subjects with acutely deteriorating COPD. The initiation of YUPELRI in this setting is not appropriate.

YUPELRI is intended as a once-daily maintenance treatment for COPD and should not be used for relief of acute symptoms, i.e. as rescue therapy for the treatment of acute episodes of bronchospasm, and extra doses should not be used for that purpose. Acute symptoms should be treated with an inhaled, short-acting beta$_2$-agonist.

COPD may deteriorate acutely over a period of hours or chronically over several days or longer. If YUPELRI no longer controls symptoms of bronchoconstriction, the patient's inhaled, short-acting beta$_2$-agonist becomes less effective, or the patient needs more inhalations of a short-acting beta$_2$-agonist than usual, these may be markers of deterioration of disease. In this setting, a re-evaluation of the patient and the COPD treatment regimen should be undertaken at once. Increasing the daily dose of YUPELRI beyond the recommended dose is not appropriate in this situation.

5.2 Paradoxical Bronchospasm

As with other inhaled medicines, YUPELRI can produce paradoxical bronchospasm that may be life-threatening. If paradoxical bronchospasm occurs following dosing with YUPELRI, it should be treated immediately with an inhaled, short-acting bronchodilator; YUPELRI should be discontinued immediately and alternative therapy should be instituted.

5.3 Worsening of Narrow-Angle Glaucoma

YUPELRI should be used with caution in patients with narrow-angle glaucoma. Prescribers and patients should be alert for signs and symptoms of acute narrow-angle glaucoma (e.g. eye pain or discomfort, blurred vision, visual halos or colored images in association with red eyes from conjunctival congestion and corneal edema). Instruct patients to consult a physician immediately if any of these signs or symptoms develops.

5.4 Worsening of Urinary Retention

YUPELRI should be used with caution in patients with urinary retention. Prescribers and patients should be alert for signs and symptoms of urinary retention (e.g. difficulty passing urine, painful urination), especially in patients with prostatic hyperplasia or bladder-neck obstruction. Instruct patients to consult a healthcare provider immediately if any of these signs or symptoms develops.

5.5 Immediate Hypersensitivity Reactions

Immediate hypersensitivity reactions may occur after administration of YUPELRI. If such a reaction occurs, therapy with YUPELRI should be stopped at once and alternative treatments should be considered.

6 ADVERSE REACTIONS

The following potential adverse reactions are described in greater detail in other sections:

- Paradoxical bronchospasm *[see Warnings and Precautions (5.2)]*
- Worsening of narrow-angle glaucoma *[see Warnings and Precautions (5.3)]*
- Worsening of urinary retention *[see Warnings and Precautions (5.4)]*
- Immediate hypersensitivity reactions *[see Warnings and Precautions (5.5)]*

6.1 Clinical Trial Experience

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice.

The YUPELRI safety database included 2,285 subjects with COPD in two 12-week efficacy studies and one 52-week long-term safety study. A total of 730 subjects received treatment with YUPELRI 175 mcg once daily. The safety data described below are based on the two 12-week trials and the one 52-week trial.

12-Week Trials

YUPELRI was studied in two 12-week replicate placebo-controlled trials in patients with moderate to very severe COPD (Trials 1 and 2). In these trials, 395 patients were treated with YUPELRI at the recommended dose of 175 mcg once daily.

The population had a mean age of 64 years (range from 41 to 88 years), with 50% males, 90% Caucasian, and had COPD with a mean post-bronchodilator forced expiratory volume in one second (FEV_1) percent predicted of 55%. Of subjects enrolled in the two 12-week trials, 37% were taking concurrent LABA or ICS/LABA therapy. Patients with unstable cardiac disease, narrow-angle glaucoma, or symptomatic prostatic hypertrophy or bladder outlet obstruction were excluded from these trials.

Table 1 shows the most common adverse reactions that occurred with a frequency of greater than or equal to 2% in the YUPELRI group and higher than placebo in the two 12-week placebo-controlled trials.

The proportion of subjects who discontinued treatment due to adverse reactions was 13% for the YUPELRI-treated subjects and 19% for placebo-treated subjects.

Table 1: Adverse Events with YUPELRI ≥2% Incidence and Higher than Placebo

	Placebo (N = 418)	YUPELRI 175 mcg (N = 395)
Respiratory, Thoracic and Mediastinal Disorders		
Cough	17 (4%)	17 (4%)
Infections and Infestations		
Nasopharyngitis	9 (2%)	15 (4%)
Upper respiratory tract infection	9 (2%)	11 (3%)
Nervous System Disorders		
Headache	11 (3%)	16 (4%)
Musculoskeletal and Connective Tissue Disorders		
Back pain	3 (1%)	9 (2%)

Other adverse reactions defined as events with an incidence of ≥1.0%, less than 2.0%, and more common than with placebo included the following: hypertension, dizziness, oropharyngeal pain, and bronchitis.

52-Week Trial

YUPELRI was studied in one 52-week, open-label, active-control (tiotropium 18 mcg once daily) trial in 1,055 patients with COPD. In this trial, 335 patients were treated with YUPELRI 175 mcg once daily and 356 patients with tiotropium. The demographic and baseline characteristics of the long-term safety trial were similar to those of the placebo-controlled 12-week studies described, with the exception that concurrent LABA or LABA/ICS therapy was used in 50% of patients. The adverse reactions reported in the long-term safety trial for YUPELRI were consistent with those observed in the placebo-controlled studies of 12-weeks.

7 DRUG INTERACTIONS

7.1 Anticholinergics

There is potential for an additive interaction with concomitantly used anticholinergic medicines. Therefore, avoid coadministration of YUPELRI with other anticholinergic-containing drugs as this may lead to an increase in anticholinergic adverse effects [*see Warnings and Precautions (5.3, 5.4)]*.

7.2 Transporter-Related Drug Interactions

OATP1B1 and OATP1B3 inhibitors (e.g. rifampicin, cyclosporine, etc.) could lead to an increase in systemic exposure of the active metabolite. Therefore, coadministration with YUPELRI is not recommended *[see Clinical Pharmacology (12.3)]*.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Risk Summary

There are no adequate and well-controlled studies with YUPELRI in pregnant women. Women should be advised to contact their physician if they become pregnant while taking YUPELRI. In animal reproduction studies, subcutaneous administration of revefenacin to pregnant rats and rabbits during the period of organogenesis produced no evidence of fetal harm at respective exposures approximately 209 times the exposure at the maximum recommended human dose (MRHD) (on an area under the curve [AUC] basis) *(see Data)*.

The estimated background risk of major birth defects and miscarriage for the indicated population is unknown. In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2-4% and 15-20%, respectively.

Data

Animal Data

In an embryo-fetal development study in pregnant rats dosed during the period of organogenesis from gestation days 6 to 17, revefenacin was not teratogenic and did not affect fetal survival at exposures up to 209 times the MRHD (based upon summed AUCs for revefenacin and its active metabolite at maternal subcutaneous doses up to 500 mcg/kg/day).

In an embryo-fetal development study in pregnant rabbits dosed during the period of organogenesis from gestation days 7 to 19, revefenacin was not teratogenic and did not affect fetal survival at exposures up to 694 times the MRHD (based upon summed AUCs for revefenacin and its active metabolite at maternal subcutaneous doses up to 500 mcg/kg/day).

Placental transfer of revefenacin and its active metabolite was observed in pregnant rabbits.

In a pre- and postnatal development (PPND) study in pregnant rats dosed during the periods of organogenesis and lactation from gestation day 6 to lactation day 20, revefenacin had no adverse developmental effects on pups at exposures up to 196 times the MRHD (based upon summed AUCs for revefenacin and its active metabolite at maternal subcutaneous doses up to 500 mcg/kg/day).

8.2 Lactation

Risk Summary

There is no information regarding the presence of revefenacin in human milk, the effects on the breastfed infant, or the effects on milk production. However, revefenacin was present in the milk of lactating rats following dosing during pregnancy and lactation *(see Data)*.

The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for YUPELRI and any potential adverse effects on the breastfed infant from YUPELRI or from the underlying maternal condition.

Data

Animal Data

In a PPND study *[see Pregnancy (8.1)]*, revefenacin and its active metabolite were present in milk of lactating rats on lactation day 22. Milk-to-plasma concentration ratios were up to 10 for revefenacin and its active metabolite.

8.4 Pediatric Use

YUPELRI is not indicated for use in children. The safety and efficacy in pediatric patients have not been established.

8.5 Geriatric Use

Based on available data, no adjustment of the dosage of YUPELRI in geriatric patients is necessary.

Clinical trials of YUPELRI included 441 subjects aged 65 years and older, and of those, 101 subjects were aged 75 years and older. No overall differences in safety or effectiveness were observed between these subjects and younger subjects, and other reported clinical experience has not identified differences in responses between the elderly and younger patients, but greater sensitivity of some older individuals cannot be ruled out.

8.6 Hepatic Impairment

The systemic exposure of revefenacin is unchanged while that of its active metabolite is increased in subjects with moderate hepatic impairment. The safety of YUPELRI has not been evaluated in COPD patients with mild-to-severe hepatic impairment. YUPELRI is not recommended in patients with any degree of hepatic impairment. *[see Clinical Pharmacology (12.3)]*.

8.7 Renal Impairment

No dosage adjustment is required in patients with renal impairment. Monitor for systemic antimuscarinic side effects in COPD patients with severe renal impairment. *[see Clinical Pharmacology (12.3)]*.

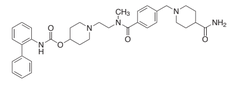
10 OVERDOSAGE

An overdose of YUPELRI may lead to anticholinergic signs and symptoms such as nausea, vomiting, dizziness, lightheadedness, blurred vision, increased intraocular pressure (causing pain, vision disturbances, or reddening of the eye), obstipation or difficulties in voiding. In COPD patients, orally inhaled administration of YUPELRI at a once-daily dose of up to 700 mcg (4 times the maximum recommended daily dose) for 7 days was well tolerated.

Treatment of overdosage consists of discontinuation of YUPELRI along with institution of appropriate symptomatic and/or supportive therapy.

11 DESCRIPTION

YUPELRI is a sterile, clear, colorless, aqueous solution of revefenacin. Revefenacin, the active component of YUPELRI, is an anticholinergic. The chemical name for revefenacin is 1-(2-{4-[(4-carbamoylpiperidin-1-yl)methyl]-*N*-methylbenzamido}ethyl)piperidin-4-yl *N*-([1,1'-biphenyl]-2-yl)carbamate; its structural formula is:



Revefenacin has a molecular weight of 597.76 and its empirical formula is $C_{35}H_{43}N_5O_4$. Revefenacin is a white to off-white crystalline powder and is slightly soluble in water.

YUPELRI is supplied as 3 mL of revefenacin solution packaged in a unit-dose low-density polyethylene vial overwrapped in a foil pouch. Each vial contains 175 mcg of revefenacin in 3 mL of an isotonic, sterile aqueous solution containing sodium chloride, citric acid, sodium citrate, and water for injection at pH 5.0.

YUPELRI does not require dilution prior to administration by nebulization. Like all other nebulized treatments, the amount delivered to the lungs will depend on patient factors, the nebulization system used, and compressor performance.

Using the PARI LC® Sprint nebulizer connected to a PARI Trek® S compressor under *in vitro* conditions, the mean delivered dose from the mouthpiece was approximately 62 mcg (35% of label claim), at a mean flow rate of 4 LPM. The mean nebulization time was 8 minutes. YUPELRI should only be administered via a standard jet nebulizer connected to an air compressor with an adequate airflow, and equipped with a mouthpiece.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

Revefenacin is a long-acting muscarinic antagonist, which is often referred to as an anticholinergic. It has similar affinity to the subtypes of muscarinic receptors M1 to M5. In the airways, it exhibits pharmacological effects through inhibition of M3 receptor at the smooth muscle leading to bronchodilation. The competitive and reversible nature of antagonism was shown with human and animal origin receptors and isolated organ preparations. In preclinical *in vitro* as well as *in vivo* models, prevention of methacholine- and acetylcholine-induced bronchoconstrictive effects was dose-dependent and lasted longer than 24 hours. The clinical relevance of these findings is unknown. The bronchodilation following inhalation of revefenacin is predominantly a site-specific effect.

12.2 Pharmacodynamics

Cardiac Electrophysiology

QTc interval prolongation was studied in a randomized, double-blind, placebo- and positive-controlled, single dose, crossover trial in 48 healthy subjects. Following a single dose of revefenacin 700 mcg (4 times the recommended dosage), no effects on prolongation of QTc interval were observed.

12.3 Pharmacokinetics

Revefenacin pharmacokinetic parameters are presented as the mean [standard deviation (SD)] unless otherwise specified. Following repeat dosing of inhaled YUPELRI, steady-state was achieved within 7 days with <1.6-fold accumulation. Revefenacin exposure (C_{max} and AUC) in COPD patients is approximately 60% lower as compared to healthy subjects. Exposure (C_{max} and AUC) of the active metabolite in COPD patients is approximately 2-fold higher as compared to healthy subjects. Revefenacin C_{max} was 0.16 ng/mL (0.11) and AUC was 0.22 ng·hr/mL (0.20) at steady-state after inhaled YUPELRI 175 mcg dose in COPD patients. C_{max} of the active metabolite was 0.20 ng/mL (0.13) and AUC was 0.69 ng·hr/mL (0.53) at steady-state after inhaled YUPELRI 175 mcg dose in COPD patients.

Revefenacin and its active metabolite exposure increased in a slightly greater than dose proportional manner with increasing revefenacin dose. After single or multiple once-daily dosing of YUPELRI, both AUC and C_{max} of revefenacin and its active metabolite increased by approximately 11-fold over the 88 to 700 mcg (8-fold) dose range.

Absorption

Following inhaled administration of YUPELRI in healthy subjects or COPD patients, C_{max} of revefenacin and its active metabolite occurred at the first postdose sampling time which ranged from 14 to 41 minutes after start of nebulization. The absolute bioavailability following an oral dose of revefenacin is low (<3%).

Distribution

Following intravenous administration to healthy subjects, the mean steady-state volume of distribution of revefenacin was 218 L suggesting extensive distribution to tissues. *In vitro* protein binding of revefenacin and its active metabolite in human plasma was on average 71% and 42%, respectively.

Elimination

The terminal half-life of revefenacin and its active metabolite after once-daily dosing of YUPELRI in COPD patients is 22 to 70 hours.

Metabolism

In vitro and *in vivo* data showed that revefenacin is primarily metabolized via hydrolysis of the primary amide to a carboxylic acid forming its major active metabolite. Following inhaled administration of YUPELRI in COPD patients, conversion to its active metabolite occurred rapidly, and plasma exposures of the active metabolite exceeded those of revefenacin by approximately 4- to 6-fold (based on AUC). The active metabolite is formed by hepatic metabolism and possesses activity at target muscarinic receptors that is lower (approximately one-third to one-tenth) than that of revefenacin. It could potentially contribute to systemic antimuscarinic effects at therapeutic doses.

Excretion

Following administration of a single intravenous dose of radiolabeled revefenacin to healthy male subjects, approximately 54% of total radioactivity was recovered in the feces and 27% was excreted in the urine. Approximately 19% of the administered radioactive dose was recovered in the feces as the active metabolite. Following administration of a single radiolabeled oral dose of revefenacin, 88% of total radioactivity was recovered in the feces and <5% was present in urine, suggesting low oral absorption. There was minimal renal excretion (<1%) of revefenacin and its active metabolite following inhaled administration of YUPELRI in COPD patients.

Specific Populations

Population pharmacokinetic analysis showed no evidence of a clinically significant effect of age (44 to 79 years), gender (59% male), smoking status (42% current smoker), or weight (46 to 155 kg) on systemic exposure of revefenacin and its active metabolite.

Patients with Hepatic Impairment: The pharmacokinetics of YUPELRI was evaluated in subjects with moderate hepatic impairment (Child-Pugh score of 7-9). There was no increase in C_{max} of revefenacin and 1.5-fold increase in C_{max} of the active metabolite. There was 1.2-fold increase in AUC of revefenacin and up to 4.7-fold increase in AUC of the active metabolite. YUPELRI has not been evaluated in subjects with severe hepatic impairment.

Patients with Renal Impairment: The pharmacokinetics of YUPELRI was evaluated in subjects with severe renal impairment (CrCl <30 mL/min). There was 1.5-fold increase in C_{max} of revefenacin and up to 2-fold increase in C_{max} of the active metabolite. There was up to 2.3-fold increase in AUC_{inf} of revefenacin; the active metabolite exposure (AUC_{inf}) was increased by up to 2.5-fold. YUPELRI has not been evaluated in subjects with end-stage renal disease.

Drug Interactions

Revefenacin and Cytochrome P450: Neither revefenacin nor its active metabolite inhibits the following cytochrome P450 isoforms: CYP1A2, CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP2D6, and CYP3A4/5. Neither revefenacin nor its active metabolite induces CYP1A2, CYP2B6, and CYP3A4/5.

Revefenacin and Efflux Transporters: Revefenacin is a substrate of P-gp and BCRP. Neither revefenacin nor its active metabolite is an inhibitor of these efflux transporters.

Revefenacin and Uptake Transporters: The active metabolite of revefenacin is a substrate of OATP1B1 and OATP1B3. Neither revefenacin nor its active metabolite is an inhibitor of the uptake transporters OATP1B1, OATP1B3, OAT1, OAT3, or OCT2.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Two-year inhalation studies in Sprague-Dawley rats and CD1 mice were conducted to assess the carcinogenic potential of revefenacin. No evidence of tumorigenicity was observed in male and female rats at inhaled doses up to 338 mcg/kg/day (approximately 35 times the MRHD based upon summed AUCs for revefenacin and its active metabolite). No evidence of tumorigenicity was observed in male and female mice at inhaled doses up to 326 mcg/kg/day (approximately 40 times the MRHD based on summed AUCs for revefenacin and its active metabolite).

Revefenacin and its active metabolite were negative for mutagenicity in the Ames test for bacterial gene mutation. Revefenacin was negative for genotoxicity in the *in vitro* mouse lymphoma assay and *in vivo* rat bone marrow micronucleus assay.

There were no effects on male or female fertility and reproductive performance in rats at subcutaneous revefenacin doses up to 500 mcg/kg/day (approximately 30 times the MRHD on an mg/m^2 basis for revefenacin).

14 CLINICAL STUDIES

The safety and efficacy of YUPELRI 175 mcg once daily were evaluated in two dose-ranging trials, two replicate 12-week, Phase 3 confirmatory clinical trials, and a 52-week safety trial. The efficacy of YUPELRI is primarily based on the two replicate 12-week, Phase 3 placebo-controlled trials in 1,229 subjects with COPD.

14.1 Dose-Ranging Trials

Dose selection for YUPELRI was supported by a 28-day, randomized, double-blind, placebo-controlled, parallel-group trial of 355 subjects diagnosed with moderate to severe COPD, which was conducted to evaluate four doses of YUPELRI. YUPELRI 44, 88, 175, and 350 mcg, or matching placebo were taken once daily in the morning via a standard jet nebulizer (PARI LC® Sprint Reusable Nebulizer) and evaluated using the primary efficacy endpoint of change from baseline in trough (predose) FEV_1 measured on Day 29. The LS mean differences in change from baseline in trough FEV_1 compared to placebo for the 44 mcg, 88 mcg, 175 mcg, and 350 mcg once-daily doses were 52 mL [95% CI: -17.3, 121.0], 187 mL [95% CI: 118.8, 256.1], 167 mL [95% CI: 97.3, 236.0], and 171 mL [95% CI: 101.9, 239.3], respectively.

Evaluations of the dosing interval by comparing once- and twice-daily dosing of YUPELRI in a 7-day, randomized, double-blind, placebo-controlled, crossover trial in 64 patients supported selection of the once-daily dosing interval for further evaluation in the confirmatory COPD trials.

The dose-ranging results supported the evaluation of two doses of YUPELRI, 88 mcg and 175 mcg once daily, in the confirmatory COPD trials.

14.2 Confirmatory Trials

The clinical development program for YUPELRI included two 12-week, randomized, double-blind, placebo-controlled, multiple-dose, parallel-group, confirmatory trials in subjects with moderate to very severe COPD designed to evaluate the efficacy of once-daily YUPELRI's effect on lung function (Trial 1: NCT02459080 and Trial 2: NCT02512510). To be enrolled, subjects needed to be 40 years of age or older, have a clinical diagnosis of COPD, a history of smoking greater than or equal to 10 pack-years, moderate to very severe COPD (post-ipratropium FEV_1 less than or equal to 80% of predicted normal values but at least 700 mL), and an FEV_1/FVC ratio of 0.7 or less. Trials 1 and 2 included 1,229 subjects of which 395 received the 175 mcg dose administered via a standard jet nebulizer (PARI LC® Sprint Reusable Nebulizer). The study population had a mean age of 64 years (range: 41 to 88) and mean smoking history of 53 pack-years, with 48% identified as current smokers. At screening, the mean post-bronchodilator percent predicted FEV_1 was 55% (range: 10% to 90%), and the post-bronchodilator FEV_1/FVC ratio was 0.54 (range: 0.3 to 0.7). In addition, of the subjects enrolled, 37% were taking LABA or ICS/LABA therapy at study entry and remained on this concomitant therapy throughout the study.

Trials 1 and 2 evaluated YUPELRI 175 mcg once daily and placebo once daily. The primary endpoint was change from baseline in

trough (predose) FEV_1 at Day 85. In both trials, YUPELRI 175 mcg demonstrated significant improvement in lung function (mean change from baseline in trough (predose) FEV_1) compared to placebo.

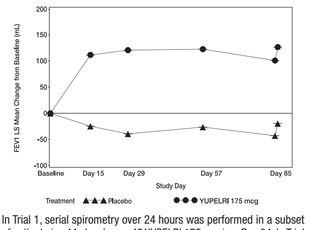
Table 2 presents the results from Trial 1 and Trial 2. The change from baseline in trough FEV_1 over time from Trial 1 is depicted in Figure 1.

Table 2: LS Mean Change from Baseline in Trough FEV_1 (mL) on Day 85 (ITT)

	Trial 1		Trial 2	
	Placebo (N = 209)	**YUPELRI 175 mcg QD (N = 198)**	**Placebo (N = 208)**	**YUPELRI 175 mcg QD (N = 197)**
n*	191	189	187	181
LS Mean (SE)	-19 (16.1)	127 (15.4)	-45 (18.8)	102 (18.5)
LS Mean Difference (SE) from Placebo	--	146 (21.6)	--	147 (25.5)
95% CI for LS Mean Difference from Placebo	--	(103.7, 188.8)	--	(97.0, 197.1)

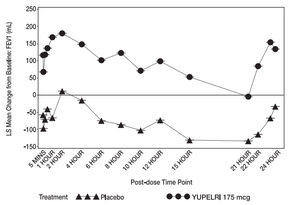
LS – Least Square, SE – Standard Error
*n=subjects in ITT population used in the statistical analyses.

Figure 1: LS Mean Change from Baseline in Trough FEV_1 (mL) over 12 Weeks (Trial 1)



In Trial 1, serial spirometry over 24 hours was performed in a subset of patients (n=44 placebo, n=45 YUPELRI 175 mcg) on Day 84. In Trial 2, similar testing was also performed (n=39 placebo, n=44 YUPELRI 175 mcg). That data for Trial 1 is shown in Figure 2.

Figure 2: LS Mean Change from Baseline in Trough FEV_1 (mL) over 24 Hours Day 84 (Trial 1 subset)



Peak FEV_1 was defined as the highest postdose FEV_1 within the first 2 hours after dosing on Day 1. The mean peak FEV_1 improvement on Day 1 relative to placebo was 133 mL and 129 mL in Trials 1 and 2, respectively.

The St. Georges Respiratory Questionnaire (SGRQ) was assessed in Trials 1 and 2. In Trial 1, the SGRQ responder rate (defined as an improvement in score of 4 or more as threshold) for the YUPELRI treatment arm on Day 85 was 49% compared to 34% for placebo [Odds Ratio: 2.11; 95% CI: 1.14, 3.92]. In Trial 2, the SGRQ responder rate for the YUPELRI treatment arm was 45% compared to 39% for placebo [Odds Ratio: 1.31; 95% CI: 0.72, 2.38].

16 HOW SUPPLIED/STORAGE AND HANDLING

YUPELRI inhalation solution is supplied as a 175 mcg/3 mL sterile, clear, colorless, aqueous solution in unit-dose low-density polyethylene vials. Each vial is overwrapped in a foil pouch and supplied in cartons containing either 30 individually pouched unit-dose vials (NDC 49502-806-93) or 7 individually pouched unit-dose vials (NDC 49502-806-77).

Storage and Handling

- Store YUPELRI in the protective foil pouch.
- Store at or below 30°C. Protect from direct sunlight and excessive heat.
- The YUPELRI solution unit-dose vial should only be removed from the foil pouch and opened IMMEDIATELY BEFORE USE. The vial and any residual content should be discarded after use.
- Discard any solution that is not clear and colorless.
- YUPELRI should only be administered via a standard jet nebulizer connected to an air compressor with an adequate airflow, and equipped with a mouthpiece.
- Do not swallow or inject YUPELRI.

17 PATIENT COUNSELING INFORMATION

Advise the patient to read the patient labeling (Patient Information and Instructions for Use) with each new prescription and refill.

Not for Acute Symptoms

Inform patients that YUPELRI is not meant to relieve acute symptoms of COPD and extra doses should not be used for that purpose. Advise patients to treat acute symptoms with an inhaled, short-acting $beta_2$-agonist such as albuterol. Provide patients with such medicine and instruct them in how it should be used.

Instruct patients to seek medical attention immediately if they experience any of the following:

- Decreasing effectiveness of inhaled, short-acting $beta_2$-agonists
- Need for more inhalations than usual of inhaled, short-acting $beta_2$-agonists
- Significant decrease in lung function as outlined by the physician

Tell patients they should not stop therapy with YUPELRI without healthcare provider guidance since symptoms may recur after discontinuation.

Paradoxical Bronchospasm

As with other inhaled medicines, YUPELRI can cause paradoxical bronchospasm. If paradoxical bronchospasm occurs, instruct patients to discontinue YUPELRI.

Worsening of Narrow-Angle Glaucoma

Instruct patients to be alert for signs and symptoms of acute narrow-angle glaucoma (e.g. eye pain or discomfort, blurred vision, visual halos, or colored images in association with red eyes from conjunctival congestion and corneal edema). Instruct patients to consult a healthcare provider immediately if any of these signs or symptoms develops.

Worsening of Urinary Retention

Instruct patients to be alert for signs and symptoms of urinary retention (e.g. difficulty passing urine, painful urination). Instruct patients to consult a healthcare provider immediately if any of these signs or symptoms develops.

Instructions for Administering YUPELRI

It is important for patients to understand how to correctly administer YUPELRI using a standard jet nebulizer [see Instructions for Use]. Instruct patients that YUPELRI should only be administered via a standard jet nebulizer. Patients should be instructed not to inject or swallow the YUPELRI solution. Patients should be instructed not to mix other medications with YUPELRI.

Patients should not inhale more than one dose at any one time. The daily dosage of YUPELRI should not exceed one unit-dose vial. Inform patients to use the contents of one vial of YUPELRI orally inhaled daily at the same time every day. Patients should throw the plastic dispensing vials away immediately after use. Due to their small size, the vials pose a danger of choking to young children.

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Mylan®

Manufactured for:
Mylan Ireland Limited,
Newenham Court,
Northern Cross, Dublin 17, Ireland

Manufactured by: **The Ritedose Corporation**
1 Technology Circle, Columbia, SC 29203
USA

RPIN0114

PATIENT INFORMATION
YUPELRI® (you-PELL-ree)
(revefenacin)
inhalation solution, for oral inhalation

Important: For oral inhalation only. Do not swallow or inject YUPELRI.

What is YUPELRI?

- YUPELRI is a prescription medicine used to treat chronic obstructive pulmonary disease (COPD). COPD is a long-term (chronic) lung disease that includes chronic bronchitis, emphysema, or both.
- YUPELRI is an anticholinergic medicine. Anticholinergic medicines help the muscles around the airways in your lungs stay relaxed to prevent symptoms such as wheezing, cough, chest tightness, and shortness of breath.
- YUPELRI is used long-term as 1 vial of YUPELRI, 1 time each day inhaled through your nebulizer to improve symptoms of COPD for better breathing.
- **YUPELRI is not used to relieve sudden breathing problems and will not replace an inhaled rescue medicine.**
- YUPELRI should not be used in children. It is not known if YUPELRI is safe and effective in children.

Do not use YUPELRI if you have had an allergic reaction to revefenacin or any of the ingredients in YUPELRI. Ask your healthcare provider if you are not sure. See the end of this Patient Information leaflet for a complete list of ingredients in YUPELRI.

Before using YUPELRI, tell your healthcare provider about all your medical conditions, including if you:

- have eye problems such as glaucoma. YUPELRI may make your glaucoma worse.
- have prostate or bladder problems, or problems passing urine. YUPELRI may make these problems worse.
- have liver problems.
- are allergic to any of the ingredients in YUPELRI or any other medicines. See **"What are the ingredients in YUPELRI?"** below for a complete list of ingredients.
- are pregnant or plan to become pregnant. It is not known if YUPELRI may harm your unborn baby.
- are breastfeeding. It is not known if the medicine in YUPELRI passes into your breast milk and if it can harm your baby.

Tell your healthcare provider about all the medicines you take, including prescription and over-the-counter medicines, vitamins, and herbal supplements. YUPELRI and certain other medicines may interact with each other. This may cause serious side effects.

Especially tell your healthcare provider if you take:

- other anticholinergic medicines (including tiotropium, ipratropium, aclidinium, umeclidinium, glycopyrrolate)
- atropine

Know the medicines you take. Keep a list of them to show your healthcare provider and pharmacist each time you get a new medicine.

How should I use YUPELRI?

Read the step-by-step instructions for using YUPELRI at the end of this Patient Information leaflet.

- **YUPELRI is only for use with a nebulizer.**
- **Do not** use YUPELRI unless your healthcare provider has taught you how to use it with your nebulizer and you understand how to use it correctly.
- Use YUPELRI exactly as your healthcare provider tells you to use it. **Do not** use YUPELRI more often than prescribed.
- YUPELRI is taken as a breathing treatment (by oral inhalation) and should be used with a standard jet nebulizer with a mouthpiece connected to an air compressor.
- **Do not** mix YUPELRI with other medicines in your nebulizer.
- Use 1 vial of YUPELRI, 1 time each day. **Do not** use more than 1 vial of YUPELRI a day.
- Use YUPELRI at the same time each day.
- If you use too much YUPELRI, call your healthcare provider or go to the nearest hospital emergency room right away if you have any unusual symptoms, such as worsening shortness of breath, chest pain, or increased heart rate.
- **Do not use other medicines that contain an anticholinergic for any reason.** Ask your healthcare provider or pharmacist if any of your other medicines are anticholinergic medicines.
- **YUPELRI does not relieve sudden symptoms of COPD and you should not use extra doses of YUPELRI to relieve these sudden symptoms.** Always have an inhaled rescue medicine with you to treat sudden symptoms. If you do not have an inhaled rescue medicine, call your healthcare provider to have one prescribed for you.
- **Do not** stop using YUPELRI, even if you are feeling better, unless your healthcare provider tells you to because your symptoms might get worse.
- Call your healthcare provider or get emergency medical care right away if:
  - your breathing problems get worse.
  - you need to use your inhaled rescue medicine more often than usual.
  - your inhaled rescue medicine does not relieve your symptoms.

What are the possible side effects with YUPELRI?

YUPELRI can cause serious side effects, including:

- **Sudden breathing problems immediately after inhaling your medicine.** If you have sudden breathing problems immediately after inhaling your medicine, stop using YUPELRI and call your healthcare provider right away.
- **New or worsened eye problems including acute narrow-angle glaucoma.** Acute narrow-angle glaucoma can cause permanent loss of vision if not treated. Symptoms of acute narrow-angle glaucoma may include:
  - red eyes
  - blurred vision
  - seeing halos or bright colors around lights
  - eye pain or discomfort
  - nausea or vomiting

  If you have any of these symptoms, call your healthcare provider right away before using another dose of YUPELRI.
- **Urinary retention.** People who use YUPELRI may develop new or worse urinary retention. Symptoms of urinary retention may include:
  - difficulty urinating
  - urinating frequently
  - urination in a weak stream or drips
  - painful urination

  If you have any of these symptoms, call your healthcare provider right away before using another dose of YUPELRI.
- **Serious allergic reactions.** See **"Do not use YUPELRI if you** have had an allergic reaction to revefenacin or any of the ingredients in YUPELRI."

  Call your healthcare provider or get emergency medical care if you get any of the following symptoms of a serious allergic reaction:
  - rash
  - hives
  - severe itching
  - swelling of your face, mouth, and tongue
  - difficulty breathing or swallowing
- **Common side effects of YUPELRI include:**
  - cough
  - runny nose
  - upper respiratory tract infection
  - headache
  - back pain

These are not all the possible side effects of YUPELRI.

Call your doctor for medical advice about side effects.

How should I store YUPELRI?

- Store YUPELRI at or below 30°C.
- Store YUPELRI in the unopened protective foil pouch and **only open the foil pouch right before you are ready to use YUPELRI.**
- Keep YUPELRI away from light and heat.
- **Throw away the vial of YUPELRI and any leftover medicine after use.**
- **Throw away the vial of YUPELRI if the solution is not clear and colorless.**
- Do not use YUPELRI after the expiration date provided on the foil pouch and vial.
- **Keep YUPELRI and all medicines out of the reach of children.**

General Information about the safe and effective use of YUPELRI.

Medicines are sometimes prescribed for purposes other than those listed in a Patient Information leaflet. Do not use YUPELRI for a condition for which it was not prescribed. Do not give YUPELRI to other people, even if they have the same symptoms that you have. It may harm them.

You can ask your healthcare provider or pharmacist for information about YUPELRI that is written for health professionals.

What are the ingredients in YUPELRI?

Active ingredient: revefenacin

Inactive ingredients: sodium chloride, citric acid, sodium citrate, and water for injection

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Theravance Biopharma Ireland Limited

Mylan®

Manufactured for:
Mylan Ireland Limited,
Newenham Court,
Northern Cross, Dublin 17, Ireland

Made in USA

For more information about YUPELRI, go to www.YUPELRI.com

This leaflet was last revised in May.2019

INSTRUCTIONS FOR USE
YUPELRI® (you-PELL-ree)
(revefenacin)
inhalation solution, for oral inhalation

YUPELRI is used only in a standard jet nebulizer machine with a mouthpiece connected to an air compressor. Make sure you know how to use your nebulizer machine before you use it to breathe in YUPELRI or other medicines.

Important Information:

- **Do not** mix YUPELRI with other medicines in your nebulizer.
- YUPELRI comes in a vial that is sealed in a foil pouch. **Do not** open the sealed pouch until you are ready to use a dose of YUPELRI.
- **Use your YUPELRI right away after opening.**

Using YUPELRI:

Read the following Steps before using YUPELRI. If you have any questions, ask your healthcare provider or pharmacist.

Step 1. Open Pouch: Open the foil pouch by tearing along the seam of the pouch. Remove the vial of YUPELRI from the foil pouch (Figure 1).

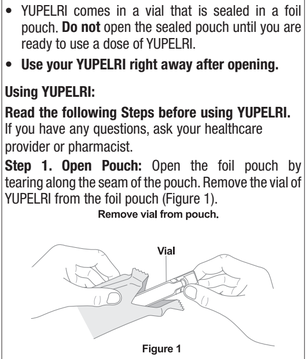

Figure 1

Open Vial: Carefully twist open the top of the vial and use it right away (Figure 2).

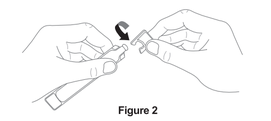

Figure 2

Step 2. Add Medicine: Squeeze all of the medicine from the vial into the nebulizer cup (reservoir) (Figure 3).

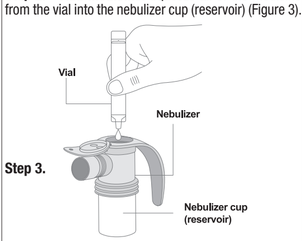

Figure 3

Step 4. Attach Mouthpiece: Connect the mouthpiece to the nebulizer cup (reservoir) with the expiratory valve facing up (Figure 4).

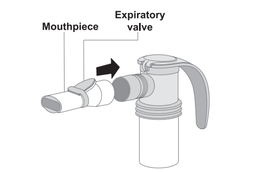

Figure 4

Step 5. Connect the Nebulizer to the Compressor: Firmly insert one end of the tubing to the compressor. Insert the other end of the tubing to the bottom of the nebulizer cup (reservoir) (Figure 5).

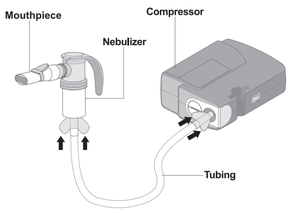

Figure 5

Step 6. Prepare for Treatment: Sit in a comfortable, upright position. Place the mouthpiece in your mouth and close your lips around the mouthpiece.

Step 7. Begin Treatment: Turn **on** the compressor to begin your treatment (Figure 6).

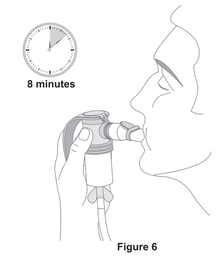

Figure 6

Step 8. Breathe in Medicine: Breathe as calmly, deeply, and evenly as possible until no more mist is seen in the nebulizer reservoir. Your treatment will take about 8 minutes. When you do not see any mist in the nebulizer, your treatment is finished. Turn the compressor **off**.

Step 9. Clean Nebulizer: Clean and store your nebulizer. See the manufacturer's instructions that come with your nebulizer for how to clean and store your nebulizer.

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