PharmaNote®
Vol. 31, Issue 6 March 2016 Established 1985

Umeclidinium (Incruse Ellipta®): A Long-Acting Muscarinic Antagonist for the Treatment of COPD

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Chronic obstructive pulmonary disease (COPD) is the fourth leading cause of death in the world.[1] In the United States, the annual death rate from COPD is over 100,000 and approximately 33% of patients with COPD will require medical attention due to an exacerbation.[2] COPD is characterized by airflow limitation that is often caused by noxious particles or gas, such as cigarette smoke.[1] The disease is not reversible, but progression can be delayed and symptoms can be controlled with proper treatment.[1]

Drug therapy for COPD aims to reduce symptoms such as dyspnea, improve exercise tolerance, reduce exacerbations and hospitalizations, and improve quality of life.[1] Long-acting muscarinic antagonists (LAMAs) and long-acting beta adrenergic agonists (LABAs) are recommended for patients who are not adequately controlled with a short-acting beta adrenergic agonist (SABA).[1,3] LAMAs and LABAs are the mainstay of therapy for most patients and several new drugs in these classes have recently been granted FDA-approved indications for the treatment of COPD.[4] The most recently approved LAMA, umeclidinium, received an FDA-approved indication on April 30, 2014, as a once-daily maintenance treatment of airflow obstruction in patients with COPD.[4] The purpose of this article is to review the pharmacologic profile, clinical trials, side effects, dosing, and cost associated with umeclidinium.

Pharmacology

Activation of the muscarinic receptors by acetylcholine results in smooth muscle contraction and mucus secretion in the lungs, leading to bronchoconstriction of the airways.[5] Long-acting muscarinic antagonists, such as umeclinidium, prevent the actions of acetylcholine by binding to the muscarinic receptors, thereby preventing bronchoconstriction.[6] Umeclinidium can bind to muscarinic receptors M_1 through M_5; however, it has a higher affinity for the M_3 receptors, which are expressed predominantly on the smooth muscles of the lung airways.[6] The pharmacokinetic properties of umeclidinium are outlined in Table 1.

Clinical Trials

Phase II Trials

Phase II clinical trials were performed to determine the safety and efficacy of umeclidinium in both healthy individuals and those with COPD. The phase II trials evaluated multiple doses and dosing schedules for umeclidinium. The first trial, completed in March 2010, evaluated the safety and efficacy of umeclidinium administered once or twice daily compared to placebo in patients with COPD.[5] Included in this study were 176 patients aged 40 to 80 years, with a ≥10 pack-year history of smoking, and a diagnosis of COPD. Patients were randomly assigned in equal proportion to treatment with one of the following: umeclidinium 62.5 mcg, 125 mcg, 250 mcg, 500 mcg, or 1000 mcg, each administered once daily; umeclidinium 62.5 mcg, 125 mcg, or 250 mcg, each administered twice daily; placebo administered in the morning and the evening; or, tiotropium 18 mcg once daily. Patients completed three different treatment periods, lasting two weeks each, and were assigned a different treatment each time. After each two-week treatment regimen, forced expiratory volume in one second (FEV_1) was measured against baseline to assess any improvement. The primary outcome of this trial was the change in trough FEV_1 from baseline to day 15 of each treatment period. The results of this clinical trial showed that all once daily dosing regimens significantly improved pulmonary function compared to placebo. Improvements in trough FEV_1 ranged from 95 to 186 mL over placebo for the once daily umeclidinium doses and from 79 to 172 mL for the twice daily umeclidinium regimens. Additionally, once daily dosing was comparable to tiotropium in terms of FEV_1 improvement, which had a change in FEV_1 trough of 105 mL. The authors concluded that twice-daily dosing of umeclidinium provided no extra benefit compared to once-daily dosing of umeclidinium.[5]

Table 1 | Pharmacokinetics of umeclidinium. [7,8]

Absorption	
Cmax	5-15 minutes
Bioavailability	13% (inhaled); <1% (oral)
Distribution	
V_d	~86 L
Metabolism	CYP2D6 and substrate of P-gp transporters
Elimination	Oral: 92% in feces, < 1% in urine
Half-life	11 hours

Cmax = maximum concentration; **V_d =** volume of distribution.

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Table 2 | Study results from phase III trial for umeclidinium 62.5 mcg and 125 mcg once daily at day 85.[10]

Outcome	Umeclidinium 62.5 mcg	p-value	Umeclidinium 125 mcg	p-value
Trough FEV_1	127 mL (52 to 202 mL)	<0.001	152 mL (76 to 229 mL)	<0.001
Trough FVC	193 mL (74 to 313 mL)	0.002	236 mL (114 to 358 mL)	<0.001
0–6 h weighted mean FVC	243 mL (123 to 363 mL)	<0.001	318 mL (196 to 439 mL)	<0.001
TDI focal scores[a]	1.0 (0.0 to 2.0)	0.05	1.3 (0.3 to 2.3)	<0.05
Change in SGRQ total score[b]	-7.90 (-12.20 to -3.60)	<0.001	-10.87 (-15.25 to -6.49)	<0.001

Results are reported as the least square mean change from baseline compared to placebo (95% CI). Positive values indicate an increase in that variable; negative values indicate a decrease in that variable.
[a]Change in TDI focal score of ≥1 unit was considered a clinically meaningful improvement.
[b]SGRQ responders were defined as ≥4 unit reduction.
FEV_1 = forced expiratory volume in 1 second; **FVC =** forced vital capacity; **TDI =** transitional dyspnea score; **SGRQ =** St. George's respiratory questionnaire.

A second phase II trial examined the efficacy of once daily versus twice daily dosing of umeclidinium compared to placebo.[9] The inclusion criteria and study design were similar to the aforementioned phase II trial, except for the use of different doses of umeclidinium. Patients (n=163) were randomly assigned to one of the following: umeclidinium 15.6 mcg, 31.25 mcg, 62.5 mcg, or 125 mcg, each administered once daily; umeclidinium 15.6 mcg or 31.25 mcg, each administered twice daily; placebo; or tiotropium as an active comparator arm.[9] Patients received three treatment regimens for one week each with a 10 to 14 day washout period between every treatment cycle. The primary outcome examined change in trough FEV_1 from baseline to day 8 of each treatment cycle. Both once- and twice-daily dosing of umeclidinium showed statistically significant change from baseline FEV_1 compared to placebo and had similar results to the tiotropium arm. The once-daily dosing regimens exhibited a range from 101 to 183 mL (all $p<0.001$ for the change from baseline) in trough FEV_1 and the twice-daily dosing ranged from 134 to 142 mL ($p<0.001$). The comparator arm of tiotropium once daily had a change in trough FEV_1 of 101 mL ($p<0.001$). Umeclidinium 62.5 mcg and umeclidinium 125 mcg once- daily dosing showed the greatest improvement in trough FEV_1 on day 8 of each treatment cycle and therefore were the two dosing regimens studied in phase III clinical trials.[9]

Phase III Trials

A phase III trial, completed in February 2012, evaluated the safety and efficacy of umeclidinium in patients with COPD.[10] In this study, 2016 patients were randomly assigned to receive umeclidinium 62.5 mcg or 125 mcg once daily, or matching placebo. Patients aged ≥40 years were included in the study if they had a 10 pack-year history of smoking and a diagnosis of COPD. The majority of enrolled subjects were men and the average age of the overall trial population was 63 years. All patients had an FEV_1 ≤79% and the majority of patients were GOLD stage II to III. The primary outcome was a change in FEV_1 from baseline to day 85 of the trial. The study also examined 0-6 hour weighted mean trough FVC, transitional dyspnea index (TDI), and health outcomes based on the St. George's Respiratory Questionnaire (SGRQ).

The study results showed a statistically significant improvement in FEV_1 from baseline to day 85 in both the umeclidinium 62.5 mcg and 125 mcg once daily treatment arms compared to placebo.[10] The least squares mean (LSM) change in placebo-adjusted FEV_1 after 85 days was 127 mL (95% CI, 52-202 mL) for the 62.5 mcg umeclidinium dose and 152 mL (95% CI, 76-229 mL) for the umeclidinium 125 mcg dose. Other end points are summarized in **Table 2**. Both doses were well tolerated over the 12 weeks of treatment with the adverse effects being similar among all 3 treatment arms (additional information on adverse effects are discussed below in the **Adverse Effects** section). Both umeclidinium doses were effective for treating COPD, with no greater efficacy observed in the group receiving umeclidinium 125 mcg. Thus, umeclidinium 62.5 mcg once daily received the FDA-approved indication for treatment in COPD.[4]

Another phase III trial was recently completed in June 2015 and evaluated umeclidinium 62.5 mcg once daily versus tiotropium 18 mcg once daily in patients with COPD.[11] The study included patients ≥40 years of age with ≥10 pack-year smoking history and a FEV_1/FVC <0.70. The results of the study have yet to be published.

Adverse Effects

The most commonly reported adverse events in the phase III trial were dry throat, dyspnea, cough and dysphonia.[10] **Table 3** summarizes adverse effects from phase III clinical trials for any adverse reaction with an incidence >2%. During the trial, seven patients total withdrew while on the umeclidinium 62.5 mcg dose and thirteen withdrew while taking umeclidinium 125 mcg daily. Of the seven patients that withdrew while on umeclidinium 62.5 mcg dose, five were from COPD exacerbations, one was from supraventricular tachycardia, and one withdrew consent. Three patients withdrew while on the umeclidinium 125 mcg dose from COPD exacerbations and two from adverse effects such as tachyarrhythmia and coronary artery stenosis. The remaining eight patients withdrew from lack of efficacy, ECG abnormalities, or being lost to follow-up.

Precautions & Drug Interactions

Precautions

Umeclidinium has an FDA-approved indication for maintenance treatment of COPD, and should not be used as a rescue inhaler for patients experiencing acute symptoms of shortness of breath due to a relatively slow onset of action.[7] Paradoxical bronchospasm can occur while taking this medication, which should prompt discontinuation of umeclidinium. Other precautions include hypersensitivity reactions in patients that have severe milk protein allergies, worsening of narrow-angle glaucoma, and worsening of urinary retention due to anticholinergic effects.

Table 3 | Adverse effects with an incidence >2% observed in a phase III clinical trial of umeclidinium.[10]

Adverse Reaction	Umeclidinium 62.5 mcg (n=69)	Umeclidinium 125 mcg (n=69)	Placebo (n=68)
Headache	7%	14%	10%
Nasopharyngitis	12%	10%	10%
Cough	1%	7%	1%
Upper respiratory tract infections	3%	3%	0%

Drug Interactions

Umecidinium should be avoided in patients taking other anticholinergic medications as this combination may increase the risk of anticholinergic-related adverse effects such as dry mouth, constipation, and urinary retention.[7] Umeclidinium also should not be used with tiotropium or ipratropium as this combination will have additive anticholinergic effects. Umeclidinium should be used cautiously in patients taking oxymorphone due to increased risk of paralytic ileus and increased risk of respiratory and CNS depression.[12] One study showed that combining umeclidinium with verapamil, a P-gp inhibitor, led to an increase in AUC of umeclidinium; however, the clinical significance of this interaction is not known.[7] Umeclidinium given with CYP2D6 inhibitors, such as ritonavir, could result in increased umeclidinium plasma concentrations so close monitoring is advised when these agents are administered concurrently.[13,14]

Dosing and Administration

The recommended dose of umeclidinium is 62.5 mcg once daily.[7] Umeclidinium is dispensed as a dry powder inhaler that contains 30 doses per device. The device contains a dose counter and when opened, the powder is ready to be inhaled. Patients should be informed to only open the device when ready for use, as the dose will be lost if the inhaler is subsequently closed without being used. Proper inhaler technique is important for patients to receive the full benefit of the drug, thus patient counseling is necessary for all new prescriptions.

Umeclidinium was evaluated in both normal and poor CYP2D6 metabolizers.[7] No significant differences in drug exposure were seen between both groups of subjects, therefore no dosing adjustment is necessary based on CYP2D6 phenotype. Similarly, no dose adjustments are needed for patients with renal or hepatic impairment.

Cost

Umeclidinium is currently only available as brand name Incruse Ellipta®. A brief survey of local Gainesville retail pharmacies places the cash cost (i.e., without insurance or discounts) of this drug at ~$290 for a one month supply. However, coupons are available for patients without insurance that can reduce the cost to ~$240 per month supply; at the time of this writing, these coupons can be used indefinitely.[15] In comparison, Spiriva, another LAMA, has a cash cost of approximately $380 (~$330 with available coupons) per month.

Summary

Umeclidinium is a once-daily LAMA recently approved for the maintenance treatment of COPD.[4] This drug has shown similar efficacy and adverse effects as other LAMAs. Additional clinical trials have been completed to further elucidate the exact role in therapy for umeclidinium, particularly compared with tiotropium, however the results have yet to be published. Currently published clinical trials have shown that umeclidinium 62.5 mcg inhaled once daily is an effective therapy for the treatment of COPD as evidenced by significant improvement in FEV_1 after 12 weeks.[10] Based on pricing quoted in the Gainesville area, the cost of umeclidinium appears to be significantly less than its primary competitor, tiotropium; however, the publication of additional trial data comparing umeclidinium and tiotropium should help elucidate the place in therapy for these LAMAs for the treatment of COPD.[15]

References

1. Global Initiative for Chronic Obstructive Lung Disease. Global Strategy for the Diagnosis, Management, and Prevention of Chronic Obstructive Pulmonary Disease 2015. Available from: http:// www.goldcopd.org/. Accessed Septemeber 2015.
2. Pleasants, RA. Chronic Obstructive Pulmonary Disease. ACSAP Pulmonary and Preventive Care 2013;32-50.
3. Donohue JF, Kalberg C, Shah P, et al. Dose Response of Umeclidinium Administered Once or Twice Daily in Patients with COPD: A Pooled Analysis of Two Randomized, Double-Blind, Placebo-Controlled Studies. J Clin Pharmacol 2014:54(11):1214-20.
4. Food and Drug Administration. Incruse Ellipta® Label and Approval History. Center for Drug Evaluation and Research: Summary Review. Application number: 205382Orig1s000.
5. Donohue JF, Anzueto A, Brooks J, et al. A randomized, double-blind dose-ranging study of the novel LAMA GSK573719 in patients with COPD. Respir Med 2012;106 (7):970-9.
6. Cada DJ, Ingram K, Leonard, J, et al. Umeclidinium Bromide and Vilanterol Trifenatate Inhalation Powder. Hosp Pharm 2014;49(6):554–562.
7. Incruse Ellipta® [package insert]. Research Triangle Park, NC. GlaxoSmithKline Inc; 2014.
8. Incruse Ellipta® [product monograph]. Mississauga, Ontario. GlaxoSmithKline Inc; 2015.
9. Church A, Beerahee M, Brooks J, et al. Dose response of umeclidinium administered once or twice daily in patients with COPD: a randomised cross-over study. BMC Pulm Med 2014;14:2.
10. Trivedi R, Richard N, Mehta R, et al. Umeclidinum in patients with COPD: a randomised, placebo-controlled study. Eur Respir J 2014;43:72-81.
11. GlaxoSmithKline. A Randomized, Blinded, Double-dummy, Parallel-group Study to Evaluate the Efficacy and Safety of Umeclidinium (UMEC) 62.5 mcg Compared With Tiotropi-

um 18 mcg in Subjects With Chronic Obstructive Pulmonary Disease (COPD). Clinicaltrials.gov. ID: NCT02207829A.
12. Opano® ER[package insert]. Malvern, PA. Endo Pharmaceuticals Inc.: 2014.
13. Technivie® [package insert]. North Chicago, Il. AbbVie Inc.: 2014
14. Viekira Pak® [package insert]. North Chicago, Il. AbbVie Inc.: 2015.
15. GoodRxprices2015. Available from: http://www.goodrx.com/. Accessed September 2015.

Indacaterol/glycopyrrolate (Utibron TM Neohaler®): A New Maintenance Treatment for COPD

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Chronic obstructive pulmonary disease (COPD) is a respiratory condition marked by progressive and reversible airflow limitations.[1,2] The leading cause of COPD is exposure of lung tissue to irritants such as smoked tobacco products and other air pollutants.[3,4] More an 11 million people have been diagnosed with COPD, however an estimated 24 million may be living with the disease unaware.[5] COPD is the third leading cause of death in the United States, killing more than 120,000 Americans and 3 million people worldwide each year.[6-8] The U.S. Centers for Disease Control estimates that COPD results in $36 billion in annual financial costs in the United States, with a projected increase to an estimated $49 billion by 2020.[9]

Current treatment of COPD is aimed at prevention of the disease and guided by disease severity. Treatment options focus on controlling symptoms, decreasing the number of exacerbations, and improving patient quality of life.[10] Therapy should be guided based on the degree of airflow limitation as well as the severity of symptoms and the risk of exacerbations. For patients with more advanced disease, GOLD patient group B and C, addition of a second long-acting bronchodilator such as a long acting β agonist (LABA) in combination with a long acting muscarinic antagonist (LAMA) may provide a synergistic effect with potentially better results.[10,11]

Indacaterol/glycopyrrolate (Utibron Neohaler®) is a new LABA/LAMA combination product that recently received an FDA-approved indication for the long-term maintenance treatment of airflow obstruction in patients with chronic COPD. The purpose of this article is to review the pharmacology, clinical trials, dosing, adverse reactions, and cost associated with this new treatment option.

Pharmacology

Mechanism of Action

Indacaterol is a LABA, and when inhaled, acts locally to stimulate the β_2-adrenergic receptors in the lungs, causing relaxation of bronchial smooth muscle. Relaxation of smooth muscle produces bronchodilation and a resultant increase in bronchial airflow.[8] This process is believed to be mediated, in part by increased activity of adenyl cyclase, an intracellular enzyme responsible for the formation of cyclic-3',5' adenosine monophosphate (cAMP).[12] Increased cAMP levels cause relaxation of bronchial smooth muscle and inhibition of release of mediators of immediate hypersensitivity from cells, especially from mast cells.[8] Glycopyrrolate is a long-acting antagonist at muscarinic receptors and has similar affinity to each of the muscarinic receptor subtypes from M_1 to M_5.[13] In the lung airways, inhaled glycopyrrolate exhibits pharmacological effects through inhibition of M_3 receptor at the smooth muscle leading to bronchodilation.[8]

Pharmacokinetics

Following inhalation of indacaterol/glycopyrrolate, the median times to reach peak plasma concentrations of indacaterol and glycopyrrolate are approximately 15 minutes and 5 minutes, respectively.[8] Bioavailability of indacaterol after inhalation is approximately 43% to 45%. Systemic exposure occurs from a combination of pulmonary and intestinal absorption. Indacaterol steady-state is achieved within 12 to 15 days. Glycopyrrolate, following repeated once-daily inhalations, achieves steady-state within 1 week of initiating treatment. *In vitro* investigations indicate that UGT1A1 is the only UGT isoform that metabolizes indacaterol.[12] CYP3A4 is the main enzyme responsible for hydroxylation of indacaterol. *In vitro* studies show that indacaterol is a low affinity substrate for the efflux pump P-glycoprotein. Hydroxylation of glycopyrrolate results in a number of mono- and bis-hydroxylated metabolites. Hydrolysis results in the formation of a carboxylic acid derivative (M9).[13] Further *in vitro* studies have shown that multiple CYP enzymes contribute to the oxidative biotransformation of glycopyrrolate. Furthermore, the hydrolysis to M9 is likely catalyzed by cholinesterases from the swallowed dose fraction of orally inhaled glycopyrrolate.[13] The amount of indacaterol excreted unchanged via urine is generally lower than 2% of the dose.[12] Renal clearance of indacaterol is, on average, between 0.46 L/h and 1.20 L/h.[8] Following oral administration of indacaterol, the fecal route of excretion dominates the urinary route: indacaterol is excreted into human feces mainly as unchanged parent drug (54% of the dose).[8] Renal elimination of glycopyrrolate accounts for about 60% to 70% of total clearance of systemically available glycopyrrolate, whereas non-renal clearance processes account for about 30 to 40%.[13] Summary of pharmacokinetic properties for indacaterol and glycopyrrolate are located in **Table 1**.

Clinical Trials

Indacaterol/glycopyrrolate was evaluated in the phase III EXPEDITION trial program which consisted of two 12-week efficacy studies (FLIGHT 1 & 2) and one 52-week safety study (FLIGHT 3), which are summarized in **Table 2**.

Table 1 | Pharmacokinetic properties of indacaterol/glycopyrrolate.

Property	Indacaterol	Glycopyrrolate
t_{max}	15 minutes	5 minutes
$t_{1/2}$	40-56 hours	3 hours
Bioavailability	43-45%	40%
Protein binding	94-96%	38-41%
Elimination	Renal, 2-6%; Feces, 90%	Renal, 60-70%; Biliary, 30-40%
Metabolism	CYP3A4, CYP1A1, CYP2D6, UGT1A1	multiple CYP enzymes

t_{max} = time to maximum concentration; $t_{1/2}$ = half-life.

Table 2 | Summary of major clinical trials for indacaterol/glycopyrrolate

Study	FLIGHT 1[14]	FLIGHT 2[14]	FLIGHT 3[15]
Completed	02/2014	02/2014	06/2014
Sample size	1042	1001	614
NCT	01727141	01712516	01682863
Study Details	• Randomized • Double-blind • Parallel-group • Active control	• Randomized • Double blind • Parallel-group • Active control	• Randomized • Double-blind • Parallel assignment • Safety study
Inclusion Criteria	• Men or women ≥40 years • Stable COPD according to GOLD 2011 • FEV_1 of ≥30% and <80% predicted and FEV_1/FVC <0.70. • Current or ex-smoker (>10 pack year)	• Men or women ≥40 years • Stable COPD according to GOLD 2011 • FEV_1 of ≥30% and <80% predicted and FEV_1/FVC <0.70 • Current or ex-smoker (>10 pack year)	• Men or women with COPD according to GOLD 2011 • FEV_1 30% to 80% • Current or ex-smoker with ≥10 pack-year history
Exclusion criteria	• Type I or uncontrolled type II diabetes • Hx of QT syndrome or prolonged QTc • Clinically significant ECG abnormality • Hx of malignancy within last 5 years • Narrow-angle glaucoma • BPH or bladder-neck obstruction • Moderate-severe renal impairment • COPD exacerbation within 6 wks of screening • Long-term O_2 requirements >12 hrs/day • Asthma or onset of respiratory sx including COPD before age 40 • Eosinophil count >600 cells/mcl • Concomitant pulmonary disease • Alpha-1 antitrypsin deficiency. • Active pulmonary tuberculosis • In active pulmonary rehabilitation	• Type I or uncontrolled type II diabetes • Hx of QT syndrome or prolonged QTc • Clinically significant ECG abnormality • Hx of malignancy within last 5 years • Narrow-angle glaucoma • BPH or bladder-neck obstruction • Moderate-severe renal impairment • COPD exacerbation within 6 wks of screening • Long-term O_2 requirements >12 hrs/day • Asthma or onset of respiratory sx including COPD before age 40 • Eosinophil count >600 cells/mcl • Concomitant pulmonary disease • Alpha-1 antitrypsin deficiency • Active pulmonary tuberculosis • In active pulmonary rehabilitation	• Narrow angle glaucoma, BPH, or bladder-neck obstruction • COPD exacerbation within 6 wks prior to screening • Respiratory tract infection within 4 weeks prior to screening • Patients on long term O_2 for more than 12 hrs/day • Hx of asthma • Onset of respiratory sx including COPD diagnosis prior to age 40 • Eosinophil count >600 cells/mcl • Concomitant pulmonary disease • Hx cardiovascular co-morbid conditions • Hx of alpha-1 anti-trypsin deficiency • Active pulmonary tuberculosis • In active phase of pulmonary rehab program
Duration	12 weeks	12 weeks	52 weeks
Primary Outcome	Change in FEV_1 AUC_{0-12h}: 0.211 L for indacaterol/glycopyrrolate, 0.117 L for indacaterol, 0.112 L for glycopyrrolate, -0.021 L for placebo	Change in FEV_1 AUC_{0-12h}: 0.234 L for indacaterol/glycopyrrolate, 0.122 L for Indacaterol, 0.155 L for glycopyrrolate, -0.028 L for placebo	Data not available
Limitations	Short study period (12-week); did not measure lung volumes such as functional residual capacity and inspiratory capacity	Short study period (12-week); did not measure lung volumes such as functional residual capacity and inspiratory capacity	Short study period (52 week)

AUC = area under the curve; **BPH =** benign prostatic hyperplasia; **COPD =** chronic obstructive pulmonary disease; **ECG =** electrocardiogram; **FEV_1 =** forced expiratory volume in 1 second; **FVC =** forced vital capacity; **hrs =** hours; **Hx =** history; L= liter; **ms =** milliseconds; **Sx =** symptoms; **wks =** weeks.

The FLIGHT 1 and FLIGHT 2 studies were 12-week, multicenter, randomized, double-blind, parallel-group, placebo- and active-controlled studies.[14] Patients were randomly assigned in a 1:1:1:1 fashion to indacaterol/glycopyrrolate (27.5/15.6 mcg twice daily), indacaterol (27.5 mcg twice daily), glycopyrrolate (15.6 mcg twice daily), or placebo. The selection of the indacaterol/glycopyrrolate dose was based on the FDA-approved doses for once-daily indacaterol (75 mcg) and glycopyrrolate (15.6 mcg twice daily). To match the fine-particle doses of indacaterol in the combination with the monotherapy product, the dose of indacaterol in the combination of indacaterol/glycopyrrolate was adjusted from 75 mcg to 55 mcg, corresponding to a dose of 27.5 mcg twice daily.

The primary objective was to assess the indacaterol/glycopyrrolate combination compared to each individual component by comparing the standardized area under the curve from 0-12 hours for forced expiratory volume in 1 second (FEV_1) at 12 weeks. A secondary objective was to demonstrate the superiority of indacaterol/glycopyrrolate compared with placebo at week 12 in terms of the change in St. George's Respiratory Questionnaire (SGRQ) total score from baseline. Other secondary objectives were to demonstrate the superiority of indacaterol/glycopyrrolate compared with placebo in terms of FEV_1 AUC_{0-12h}, predose trough FEV_1, the transition dyspnea index (TDI) total score, daily rescue medication use, and daily symptoms as reported by patients in their e-diary at week 12.

Patients were included in the FLIGHT 1 and FLIGHT 2 studies if they were aged 40 years or older, and had stable but symptomatic, moderate-to-severe COPD according to the GOLD 2011 criteria.[14] Of the combined 2043 subjects included in both trials, 63% were men and 91% were white with a mean age of 63 years and an average smoking history of 47 pack-years (52% identified as current smokers). At screening, the mean post-bronchodilator percent predicted FEV_1 was 55%, the mean post-bronchodilator FEV_1/forced vital capacity (FVC) ratio was 50%, and the mean percent reversibility was 23%.

The pooled analysis of FLIGHT 1 and FLIGHT 2 looked at treatment difference FEV_1 AUC_{0-12h} by the end of 12 weeks as the primary outcome (**Table 2**). Indacaterol/glycopyrrolate treatment versus the respective monocomponents (indacaterol alone and glycopyrrolate alone), had treatment differences of 103 mL and 88 mL, respectively ($p<0.001$), in favor of the combination product.[14] In the same analysis, indacaterol/glycopyrrolate, compared with placebo, resulted in a treatment difference of 246 mL ($p<0.001$), favoring indacaterol/glycopyrrolate. Furthermore, indacaterol alone and glycopyrrolate alone, had treatment differences of 143 mL and 158 mL, respectively ($p<0.001$), verses placebo, favoring the active drugs. This pooled analysis supports the use of combination indacaterol/glycopyrrolate over either monocomponent alone.

Similarly, the key secondary objective of superior improvement in SGRQ total score and in the number of patients with a clinically meaningful improvement (defined as a decrease of 4 U in SGRQ total score) was achieved. Improvement in other lung function variables and quality of life (QoL) measurements were also statistically significant for the indacaterol/glycopyrrolate group compared to the other treatment arms. Finally dyspnea, rescue medication use, and daily symptoms were significantly reduced in patients receiving indacaterol/glycopyrrolate treatment.[15]

The FLIGHT 3 study was a 52-week, multicenter, double blind study that randomly assigned patients (1:1:1) to indacaterol/glycopyrrolate 27.5/12.5 mcg twice daily, indacaterol/glycopyrrolate 27.5/25 mcg twice daily, and indacaterol 75 mcg once daily.[15] The primary objective was to evaluate the safety and tolerability of varying indacaterol/glycopyrrolate doses compared to indacaterol in terms of adverse event (AE) reporting rates over a 52 week treatment period. Other objectives included evaluation of safety and tolerability in terms of vital signs, ECG, and laboratory parameters as well as time to treatment discontinuation.

Overall, 615 patients were randomly assigned to treatment, of which 88.8% completed the study. The incidence of all AEs and serious AEs were similar across the treatments.[15] Discontinuation from study treatment due to AEs were lowest for indacaterol/glycopyrrolate 27.5/12.5 mcg twice daily (2.5%) followed by indacaterol/glycopyrrolate 27.5/25 mcg twice daily (3.9%) and indacaterol 75 mcg once daily (5.8%). COPD worsening (exacerbation) was the most commonly reported AE. In total, 9 deaths were reported during the study and were comparable between treatment groups. None of the deaths were suspected to be related to the study medication. Major adverse cardiovascular events and cardiovascular deaths were comparable across the treatment groups. The study reported no clinically meaningful differences in laboratory tests, ECG and vital signs. The overall safety and tolerability of indacaterol/glycopyrrolate 27.5/12.5 mcg twice daily in patients with moderate to severe COPD was similar to indacaterol.

Adverse Events

A summary of adverse events from the FLIGHT 1 and FLIGHT 2 studies can be found in **Table 3**. Adverse reactions were similar in the long-term safety trial as well as the 12-week placebo-controlled trials. Adverse reactions that occurred with a frequency greater than or equal to 2% in the group receiving indacaterol/glycopyrrolate 27.5 mcg/15.6 mcg twice-daily that exceeded the frequency of indacaterol 75 mcg once-daily in this trial were upper and lower respiratory tract infection, pneumonia, diarrhea, headache, gastroesophageal reflux disease, hyperglycemia, and rhinitis.

Other common adverse reactions were nasopharyngitis and hypertension. The proportion of patients who discontinued treatment due to adverse reactions was 2.95% for the indacaterol/glycopyrrolate-treated patients and 4.13% for placebo-treated patients. Subjects received 1 dose twice-daily of the following: indacaterol/glycopyrrolate 27.5 mcg/15.6 mcg, indacaterol 27.5 mcg, glycopyrrolate 15.6 mcg, or placebo. Other adverse reactions occurring more frequently with indacaterol/glycopyrrolate than with placebo, but with an incidence of less than 1%, include dyspepsia, gastroenteritis, chest pain, fatigue, peripheral edema, rash/pruritus, insomnia, dizziness, bladder obstruction/urinary retention, atrial fibrillation, palpitations, tachycardia.

Although indacaterol has a higher affinity for β_2 versus β_1 receptors, adverse cardiovascular effects, such as tachycardia, palpitations, and ischemia, may be observed. Other common adverse effects due to activation of beta-receptors include skeletal muscle tremors, and cramps, insomnia, decreases in serum potassium, and increases in blood glucose.[8] Additionally indacaterol/ glycopyrrolate may cause immediate hypersensitivity reactions, worsening of narrow-angle glaucoma, and worsening of urinary retention.

Precautions & Contraindications

All LABAs are contraindicated in patients with asthma without the use of a long-term asthma maintenance medication. In-

Table 3 | Pooled Safety data from FLIGHT 1 and FLIGHT 2 studies

Adverse Event	Indacaterol/ Glycopyrrolate (n=508)	Indacaterol (n=511)	Glycopyrrolate (n=513)	Placebo (n=508)
Patients with at least one AE, n (%) any group	221 (43.5)	195 (38.2)	214 (41.7)	219 (43.11)
COPD	77 (15.2)	79 (15.5)	89 (17.4)	102 (20.1)
Nasopharyngitis	21 (4.1)	13 (2.5)	12 (2.3)	9 (1.8)
Hypertension	10 (1.9)	5 (1.0)	5 (1.0)	7 (1.4)
Headache	7 (1.4)	10 (2.0)	9 (1.8)	10 (2.0)
upper respiratory tract infection bacterial	9 (1.8)	15 (2.9)	14 (2.7)	16 (3.2)
Back pain	9 (1.8)	7 (1.4)	2 (0.4)	3 (0.6)
Cough	8 (1.8)	7 (1.4)	6 (1.2)	13 (2.6)
Oropharyngeal pain	8 (1.8)	4 (0.8)	8 (1.6)	6 (1.2)
Viral upper respiratory tract infection	6 (1.2)	5 (1.0)	5 (1.0)	9 (1.8)
Bronchitis	4 (0.8)	6 (1.2)	6 (1.2)	8 (1.6)
Dyspnea	--	2 (0.4)	1 (0.2)	11 (2.2)
Death	--	3 (0.6)	3 (0.6)	1 (0.2)
SAE	16 (3.2)	18 (3.5)	20 (3.9)	21 (4.1)
Cardiac disorders	3 (0.6)	5 (1.0)	2 (0.4)	2 (0.4)
Respiratory and mediastinal disorders	3 (0.6)	7 (1.4)	9 (1.8)	12 (2.4)
Patients with ≥1 adjudicated serious CCV AE	5 (1.0)	3 (0.6)	2 (0.4)	2 (0.4)
MACE*	3 (0.59)	2 (0.39)	1 (0.19)	1 (0.20)
Non-MACE serious CCV AE*	2 (0.39)	1 (0.20)	1 (0.19)	1 (0.20)
Discontinuation of treatment because of AE	15 (3.0)	10 (2.0)	8 (1.6)	21 (4.1)
Discontinuation of treatment because of SAE	7 (1.4)	6 (1.2)	2 (0.4)	6 (1.2)
Discontinuation of treatment because of non-SAE	10 (2.0)	5 (1.0)	6 (1.2)	15 (3.0)
AE requiring dose interruption	5 (1.0)	3 (0.6)	7 (1.4)	2 (0.4)
AE requiring additional therapy	131 (25.8)	112 (23.9)	129 (25.1)	134 (26.4)

Data are presented as n (%). **AE =** adverse event; **COPD =** chronic obstructive pulmonary disease; **CCV =** cardiovascular or cerebrovascular; **MACE =** major adverse cardiovascular event; **SAE =** serious adverse event.
*Adjudicated events.

dacaterol/glycopyrrolate is not indicated for the treatment of asthma. Indacaterol/glycopyrrolate is also contraindicated in patients who have demonstrated a hypersensitivity to indacaterol, glycopyrrolate or to any of the ingredients.[8] The drug should not be initiated in patients with acutely deteriorating or potentially life -threatening episodes of COPD; since it has not been studied in patients with acutely deteriorating COPD. Indacaterol/ glycopyrrolate should not be used for the relief of acute symptoms. When initiating indacaterol/glycopyrrolate, patients who have taken oral or inhaled, short-acting β_2-agonist on a regular basis (e.g., 4 times a day) should be counseled to stop the regular use of these drugs and use them only for symptomatic relief of acute respiratory symptoms.

Indacaterol/glycopyrrolate should not be used more often than recommended, at higher doses than recommended, or in combination with other medications containing LABAs, as an overdose can occur. Similar to other inhaled medicines, indacaterol/glycopyrrolate can produce paradoxical bronchospasm that may be life threatening. If paradoxical bronchospasm occurs following dosing with indacaterol/glycopyrrolate, patients should be treated immediately with an inhaled, short-acting bronchodilator. Immediate hypersensitivity reactions have also been reported after administration of indacaterol or glycopyrrolate. If signs suggesting allergic reaction occur, specifically angioedema, urticaria, or skin rash, indacaterol/glycopyrrolate should be discontinued and use of an alternative therapy should be considered. Indacaterol/glycopyrrolate should be used with caution in patients with severe hypersensitivity to milk proteins.

Indacaterol/glycopyrrolate, like all drugs containing sympathomimetic amines, should be used cautiously in patients with convulsive disorders or thyrotoxicosis, and in patients who are unusually sensitive to sympathomimetic amines. The drug should be used with caution in patients with narrow-angle glaucoma. Because of the included anticholinergic agent, this drug should be used with caution in patients with urinary retention.

β_2-adrenergic agonists may produce significant hypokalemia in some patients, and possibly adverse cardiovascular effects. The decrease in serum potassium is usually transient, and does not require supplementation. Inhalation of high doses of β_2-adrenergic agonists may also increase plasma glucose.

Dosing & Administration

The recommended dose of indacaterol/glycopyrrolate is the inhalation of the contents of one capsule (27.5 mcg/15.6 mcg) twice daily using the Neohaler device. Administration should be at

the same time of the day (1 capsule in the morning and 1 capsule in the evening). More frequent administration or a greater number of inhalations of indacaterol/glycopyrrolate is not recommended. The capsules should be stored in the blister packs, and should only be removed immediately before use. Patients should be instructed to use a new inhaler with each prescription. No dosage adjustment is required for geriatric patients, patients with mild and moderate hepatic impairment, or patients with mild-to-moderate renal impairment.

Cost Comparison

Cost data for indacaterol/glycopyrrolate (Utibron Neohaler®) and other maintenance COPD medications have been summarized in Table 4. The average price for indacaterol/glycopyrrolate is comparable to other medications currently on the market with similar indications.

Table 4 | Price comparison between Utibron Neohaler® and other COPD medications.

Drug	Price[a]
Utibron Neohaler® (indacaterol/glycopyrrolate)	$330.09 - $335.31
Spiriva® (tiotropium)	$330.35 - $332.77
Serevent® (salmeterol)	$337.40 - $339.87
Brovana® (arformoterol)	$763.34 - $783.45
Arcapta® (indacaterol)	$221.49 - $227.70
Tudorza® (aclidinium)	$308.90 - $317.18

[a]Average price for 30 day supply in Gainesville, FL.[16]

Conclusion

Indacaterol/glycopyrrolate (Utibron Neohaler®) is a new LABA/LAMA combination product that recently received an FDA-approved indication for the long-term maintenance treatment of airflow obstruction in patients with chronic COPD. This new therapeutic option may be best indicated for patients presenting in GOLD stage II to IV whose symptoms are not well-controlled with a single long-acting bronchodilator. Clinical trials have shown that the combination drug is superior in terms of FEV_1 $AUC_{0\text{-}12h}$ when compared with the respective individual components and placebo. The approved dose is one capsule (containing 27.5 mcg indacaterol and 15.6 mcg glycopyrrolate) inhaled twice daily at the same time each day.

References

1. Buist AS, McBurnie MA, Vollmer WM, et al. International variation in the prevalence of COPD (the BOLD Study): a population-based prevalence study. Lancet 2007;370:741-50.
2. Gershon AS, Warner L, Cascagnette P, et al. Lifetime risk of developing chronic obstructive pulmonary disease: a longitudinal population study. Lancet 2011;378:991-6.
3. Centers for Disease Control and Prevention (CDC). Chronic obstructive pulmonary disease among adults--United States, 2011. MMWR Morb Mortal Wkly Rep 2012;61:938.
4. Miniño AM, Murphy SL, et al. Deaths: final data for 2008. Natl Vital Stat Rep 2011;59:1.
5. American Lung Association. CPD Fact Sheet. Available from: http://www.lung.org/lung-health-and-diseases/lung-disease-lookup/copd/learn-about-copd/how-serious-is-copd.html. Accessed January 2016
6. Arcapta Neohaler (indacaterol inhalation powder) package insert. East Hanover, NJ: Novartis Pharmaceuticals Corporation; 2012 Sept.
7. World Health Organization COPD 2015. Available from: http://www.who.int/mediacentre/factsheets/fs315/en/, Accessed January 2016.
8. Utibron Neohaler (indacaterol; glycopyrrolate) package insert. East Hanover, NJ: Novartis Pharmaceuticals Corporation; 2016 Jan.
9. Ford ES, Murphy LB, Khavjou O, et al. Total and state-specific medical and absenteeism costs of COPD among adults aged ≥18 years in the United States for 2010 and projections through 2020. Chest 2015;147(1):31-45.
10. Global Initiative for Chronic Obstructive Lung Disease (GOLD): Global Strategy for the Diagnosis, Management, and Prevention of COPD 2016. www.goldcopd.org. Accessed January 2016.
11. Farne HA, Cates CJ. Long-acting beta2-agonist in addition to tiotropium versus either tiotropium or long-acting beta2-agonist alone for chronic obstructive pulmonary disease. Cochrane Database Syst Rev 2015;10:CD008989.
12. Arcapta Neohaler (indacaterol inhalation powder) package insert. East Hanover, NJ: Novartis Pharmaceuticals Corporation; 2012 Sep.
13. Seebri Neohaler (glycopyrrolate) inhalation powder, for oral inhalation use package insert. East Hanover, NJ: Novartis Pharmaceuticals Corporation; 2016 Jan.
14. Mahler DA, Kerwin E, Ayers T, et al. FLIGHT1 and FLIGHT2: Efficacy and Safety of QVA149 (Indacaterol/Glycopyrrolate) versus Its Monocomponents and Placebo in Patients with Chronic Obstructive Pulmonary Disease. Am J Respir Crit Care Med 2015:192 (9):1068-79.
15. Ferguson GT, Fowler Taylor A, Thach C, et al. QVA149 is safe and well tolerated in patients with moderate-to-severe COPD: FLIGHT3, a 52-week safety study. [ATS abstract 63609; Session D36] Available at: http://www.atsjournals.org/doi/pdf/10.1164/ajrccm-conference.2015.191.1_MeetingAbstracts.A5762
16. GoodRx prices 2016. Available from: http://www.goodrx.com/. Accessed February 2016.

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