Therapeutic Class Overview
Inhaled Anticholinergics

INTRODUCTION

- The inhaled anticholinergics class includes short- and long-acting agents. Short-acting agents include Atrovent HFA (ipratropium bromide) inhalation aerosol, and ipratropium bromide solution for nebulization (available generically). Long-acting agents, also called long-acting muscarinic antagonists (LAMAs), include Spiriva Handihaler (tiotropium bromide) inhalation powder, Spiriva Respimat (tiotropium bromide) inhalation spray, and Incruse Ellipta (umeclidinium) inhalation powder, which are all administered once daily; Lonhala Magnair (glycopyrrolate) solution for nebulization is administered twice daily. Other relatively long-acting agents are Tudorza Pressair (aclidinium bromide) inhalation powder and Seebri Neohaler (glycopyrrolate) inhalation powder, which are administered twice daily. The predominant use of inhaled anticholinergics is for the treatment of chronic obstructive pulmonary disease (COPD); Spiriva Respimat is also indicated for selected patients with asthma.
- COPD is characterized by persistent respiratory symptoms and airflow limitation due to airway and/or alveolar abnormalities. The abnormalities are usually caused by exposure to noxious particles or gases. Airflow limitation is caused by a combination of small airway disease (eg, obstructive bronchiolitis) and parenchymal destruction (emphysema); the relative contributions of each component vary between patients. The most common symptoms of COPD include dyspnea, cough, and sputum production (*Global Initiative for Chronic Obstructive Lung Disease [GOLD] 2018*).
- COPD affects 6.4% of the United States population and is the major contributor to mortality from chronic lower respiratory diseases, the third leading cause of death in the United States (Centers for Disease Control and Prevention 2017). Globally, COPD is the fourth leading cause of death and is expected to be the third leading cause of death by 2020; the burden of COPD continues to increase due to continued exposure to risk factors and aging of the population (*GOLD 2018*).
- Cigarette smoking is the main risk factor for COPD; other risk factors include biomass fuel exposure (such as from cooking and heating in poorly ventilated dwellings) and air pollution. Host factors such as genetic abnormalities, abnormal lung development, and accelerated aging can predispose individuals to COPD development (*GOLD 2018*).
- Patients with COPD may experience exacerbations, which are periods of acute worsening of respiratory symptoms (*GOLD 2018*).
- Pharmacologic therapy for COPD can reduce symptoms, reduce the risk and severity of exacerbations, and improve patients' health status and exercise tolerance. There is no conclusive evidence that COPD medications modify the long-term decline in lung function characteristic of COPD (*GOLD 2018*).
- Pharmacologic options for COPD treatment comprise several classes, including beta-agonists, anticholinergics, methylxanthines, various combination products (including bronchodilators with inhaled corticosteroids [ICSs]), and the phosphodiesterase (PDE)-4 inhibitor, roflumilast. Pharmacologic treatments should be individualized based on symptom severity, risk of exacerbations, side effects, comorbidities, drug availability, and cost, as well as the patient's response, preference, and ability to use various drug delivery devices (*GOLD 2018*).
- In 2015, tiotropium inhalation spray became the first LAMA to be Food and Drug Administration (FDA)-approved for the treatment of asthma (See Table 2). Asthma is a chronic lung disease that inflames and narrows the airways, making it difficult to breathe. Asthma causes recurring periods of wheezing, chest tightness, shortness of breath, and coughing. Asthma affects people of all ages, but most often starts during childhood. In the United States, more than 25 million people are known to have asthma, including about 7 million children (*National Heart, Lung, and Blood Institute [NHLBI] 2014*).
- The most effective, commonly recommended long-term control medications for the treatment of asthma are ICSs. Alternative long-term control monotherapy medications, such as leukotriene modifiers, mast-cell stabilizers, and methylxanthines, are considered less effective as monotherapy compared to ICSs. Long-acting beta$_2$-agonists (LABAs) should not be used as monotherapy for asthma due to increased risk for serious adverse events including death; however, they are considered the most effective adjunctive therapy in patients not adequately controlled with an ICS alone. Tiotropium is an option for add-on therapy in certain patients requiring an additional controller medication. An interleukin-5 (IL-5) antagonist or the immunoglobulin E (IgE) antagonist, omalizumab, may be added if patients require a higher level of care. Omalizumab is used in patients with moderate to severe allergic asthma while IL-5 antagonists are used for severe eosinophilic asthma. Short-acting beta$_2$-agonists (SABAs) are the medication of choice for the relief of

bronchospasm during acute asthma exacerbations (*Xolair prescribing information 2017, Global Initiative for Asthma [GINA] 2018, NHLBI, 2007*).

- This review includes single-agent LAMAs. While some inhaled anticholinergics are available in combination with other bronchodilators such as SABAs and LABAs, combination agents are not included within this review.
- Medispan class: Bronchodilators – Anticholinergics

Table 1. Medications Included Within Class Review

Drug	Generic Availability
Atrovent HFA (ipratropium bromide)	-
Incruse Ellipta (umeclidinium bromide)	-
ipratropium bromide solution	✔
Lonhala Magnair (glycopyrrolate)	-
Seebri Neohaler (glycopyrrolate)	-
Spiriva Handihaler (tiotropium bromide)	-
Spiriva Respimat (tiotropium bromide)	-
Tudorza Pressair (aclidinium bromide)	-

(*Drugs@FDA 2018, Orange Book: Approved Drug Products with Therapeutic Equivalence Evaluations 2018*)

INDICATIONS

Table 2. Food and Drug Administration Approved Indications

Indication	Atrovent HFA (ipratropium bromide)	Incruse Ellipta (umeclidinium)	ipratropium bromide solution	Lonhala Magnair (glycopyrrolate)	Seebri Neohaler (glycopyrrolate)	Spiriva Handihaler (tiotropium)	Spiriva Respimat (tiotropium)	Tudorza Pressair (aclidinium)
Maintenance treatment of bronchospasm associated with COPD, including chronic bronchitis and emphysema	✔		✔					
Long-term maintenance treatment of airflow obstruction/ bronchospasm in patients with COPD		✔ *		✔	✔	✔ *	✔ *	✔
Reducing COPD exacerbations						✔	✔	
Long-term, once-daily maintenance treatment of asthma in patients ≥ 6 years of age							✔	

*Once-daily maintenance treatment

(*Prescribing information: Atrovent HFA 2012, Incruse Ellipta 2017, ipratropium solution 2013, Lonhala Magnair 2018, Seebri Neohaler 2017, Spiriva Handihaler 2018, Spiriva Respimat 2017, Tudorza Pressair 2017*)

- Information on indications, mechanism of action, pharmacokinetics, dosing, and safety has been obtained from the prescribing information for the individual products, except where noted otherwise.

CLINICAL EFFICACY SUMMARY

COPD

- Efficacy of the LAMAs for the management of COPD is well established through placebo-controlled trials and a number of systematic reviews and meta-analyses. The primary endpoint in most trials has focused on lung function, including measures of the forced expiratory volume in 1 second (FEV_1). Several studies have also evaluated the impact of LAMAs on measures of quality of life and health status, and frequency of COPD exacerbations.
  - All of the LAMAs have demonstrated improved FEV_1 compared to placebo (*Karner et al 2014, Kerwin et al 2016, Kerwin et al 2017, LaForce et al 2016, Ni et al 2014, Ni et al 2017, Pleasants et al 2016*).

- All of the LAMAs have demonstrated improvement in health status and/or COPD symptoms (*Karner et al 2014, Kerwin et al 2016, Kerwin et al 2017, LaForce et al 2016, Ni et al 2014, Ni et al 2017, Pleasants et al 2016*).
- Tiotropium and umeclidinium have demonstrated a significant reduction in moderate COPD exacerbations (*Karner et al 2014, Ni et al 2017, Pleasants et al 2016*).

Placebo-controlled trials

- Tiotropium administered via the Handihaler device has been compared to placebo in several randomized controlled trials.
  - A randomized double-blind trial (N = 623) demonstrated that tiotropium 18 mcg daily significantly improved trough forced expiratory volume in one second (FEV_1) over placebo. Improvements were also demonstrated in peak expiratory flow (PEF) rate, transitional dyspnea index (TDI) focal scores, and St. George's Respiratory Questionnaire (SGRQ) scores compared to placebo (*Donohue et al 2002*).
  - Another randomized double-blind trial (N = 1207) demonstrated that tiotropium 18 mcg daily compared to placebo led to a delayed time to first COPD exacerbation, fewer hospital admissions, fewer days in which patients could not perform their usual daily activities, improved TDI focal scores, and improved results on the SGRQ (*Brusasco et al 2003*).
  - A randomized double-blind trial (N = 457) in maintenance treatment-naïve patients with COPD GOLD stage II demonstrated that tiotropium 18 mcg daily compared to placebo significantly improved FEV_1 and physician's global assessments of overall health status (*Troosters et al 2014*).
  - In a small randomized double-blind trial (N = 105), patients receiving tiotropium 18 mcg daily showed a longer exercise endurance time compared to patients receiving placebo (*Casaburi et al 2005*).
  - A large, randomized, double-blind, four-year trial (N = 5993) (UPLIFT) demonstrated that tiotropium 18 mcg daily was associated with a significant delay in the time to first exacerbation and time to first hospitalization for an exacerbation. Although the improvement in FEV_1 with tiotropium was maintained throughout the trial, tiotropium did not lead to a significant difference in the rate of decline in FEV_1 over time. Improvements in SGRQ were demonstrated, but were less than what is generally accepted as clinically significant. Mortality was 14.9% in the tiotropium group and 16.5% in the placebo group (*Tashkin et al 2008*). A predefined subgroup analysis of UPLIFT demonstrated that for patients with moderate COPD (GOLD Stage II), the rate of decline for post-bronchodilator FEV_1 was lower in the tiotropium group compared to the placebo group. However, the rate of decline of pre-bronchodilator FEV_1 did not differ between groups (*Decramer et al 2009*).
  - A multicenter, randomized, double-blind trial in patients (N = 841) with mild or moderate COPD (ie, GOLD stage 1 or 2) demonstrated that tiotropium 18 mcg daily significantly improved change in FEV_1 before bronchodilator use from baseline to 24 months compared to placebo (between-group difference, 157 mL; 95% confidence interval [CI], 123 to 192; p<0.001) (*Zhou et al 2017*). Annual decline in FEV_1 after bronchodilator use was lower with tiotropium vs placebo (difference, 22 mL per year; 95% CI, 6 to 37; p = 0.006) but the annual decline in FEV_1 before bronchodilator use was not significantly different between groups.
- Tiotropium administered via the Respimat inhaler has also been compared to placebo in several randomized controlled trials.
  - Two one-year studies (total N = 1990) evaluated tiotropium 5 mcg or 10 mcg compared to placebo. Combined results for the 5 mcg dose demonstrated the following:
    - improved response on FEV_1 (difference, 127 mL; p < 0.0001)
    - improved response on SGRQ (difference, -3.5 units; p < 0.0001)
    - improved response on TDI focal score (difference, 1.05 units; p < 0.0001)
    - reduced exacerbations (odds ratio [OR], 0.75; p < 0.01) (*Bateman et al 2010a*)
  - A one-year study (N = 3991) compared tiotropium 5 mcg to placebo and demonstrated the following:
    - improved response on FEV_1 (difference, 102 mL; p < 0.0001)
    - a delayed time to first exacerbation (hazard ratio [HR], 0.69; p < 0.0001) (*Bateman et al 2010b*)
- A systematic review summarized the data on exacerbation risk reduction with tiotropium compared to placebo (as well as compared to other COPD maintenance treatments). A total of 29 articles were included, of which 20 compared tiotropium to placebo (16 with the Handihaler and 4 with the Respimat device). Although a formal meta-analysis was not conducted as part of this review, overall, the data demonstrated that tiotropium was associated with a longer time to first exacerbation and fewer exacerbations, including severe exacerbations, compared to placebo. Exacerbations were generally comparable with the Handihaler and Respimat formulations (*Halpin et al 2016*).

- A systematic review and meta-analysis of 22 trials and 23,309 participants evaluated the efficacy of tiotropium (delivered via the Respimat or Handihaler device) vs placebo. The analysis showed that tiotropium led to statistically and clinically significant improvements in quality of life vs placebo, as measured by SGRQ. Compared to placebo, tiotropium significantly reduced the number of exacerbations and led to fewer hospitalizations due to exacerbations, but no significant difference was found for all-cause hospitalization or mortality.Pooled analysis showed an improvement in trough FEV_1 with tiotropium vs placebo (mean difference, 119 mL; 95% CI, 113 to 125) (*Karner et al 2014*).
- Aclidinium has also been evaluated in a number of placebo-controlled trials.
  - In a large, randomized double-blind study (N = 828), patients were randomized to receive aclidinium 200 or 400 mcg twice daily or placebo over 24 weeks. The mean change from baseline in trough FEV_1, the primary endpoint, was significantly larger in patients treated with aclidinium 200 or 400 mcg compared to patients treated with placebo. In addition, a significantly higher proportion of patients treated with aclidinium 200 or 400 mcg experienced a clinically significant improvement in SGRQ score and TDI score when compared to patients treated with placebo (*Jones et al 2012*).
  - In the 12-week double-blind ACCORD COPD I study (N = 561), patients randomized to receive aclidinium 200 or 400 mcg twice daily experienced a statistically significant increase from baseline in trough FEV_1 compared to patients in the placebo group. Statistically significant improvements on SGRQ were demonstrated for both dose groups, but on average were less than those considered clinically meaningful. A higher proportion of patients receiving aclidinium achieved a clinically meaningful improvement in TDI scores compared to those in the placebo group (*Kerwin et al 2012*).
  - In the 12-week double-blind ACCORD COPD II study (N = 544), patients randomized to receive aclidinium 200 or 400 mcg twice daily experienced a statistically significant increase from baseline in trough FEV_1 compared to patients in the placebo group. SGRQ scores improved in all groups, but differences between aclidinium and placebo were not significant. A higher proportion of patients receiving aclidinium achieved a clinically meaningful improvement in TDI scores compared to those in the placebo group (*Rennard et al 2013*).
- A systematic review and meta-analysis of 12 multicenter randomized trials (total N = 9547) evaluated aclidinium vs placebo in patients with stable COPD. The analysis found that aclidinium resulted in a significant improvement in pre-dose FEV_1 compared to placebo (MD, 90 mL; 95% CI, 80 to 100 mL), a reduction in the number of patients with exacerbations requiring hospitalization (OR, 0.64; 95% CI, 0.46 to 0.88), and a reduced SGRQ score (MD, -2.34; 95% CI, -3.18 to -1.51]). However, no difference was demonstrated in all-cause mortality or in the number of patients with exacerbations requiring oral steroids and/or antibiotics (*Ni et al 2014*). A similar meta-analysis included seven trials (total N = 7001) evaluating aclidinium vs placebo for a duration of ≥ 12 weeks. This analysis found that compared to placebo, aclidinium did not significantly reduce the incidence of exacerbations (OR, 0.90; 95% CI, 0.75 to 1.07; P = 0.22) or all-cause mortality (OR, 0.92; 95% CI, 0.43 to 1.94; P = 0.82). However, a significant difference was demonstrated for the rate of hospitalization due to exacerbation (OR, 0.64; 95% CI, 0.47 to 0.89; P = 0.008) and improvement in SGRQ (MD, -2.34; 95% CI, -3.18 to
-1.51). Secondary endpoints, including FEV_1, forced vital capacity (FVC), and TDI, supported the efficacy of aclidinium on lung function and dyspnea symptoms (*Zou et al 2016*).
- Umeclidinium has been evaluated for the treatment of COPD in several Phase 3, multicenter, randomized, placebo-controlled trials.
  - One trial (N = 206) compared two doses of umeclidinium, 62.5 mcg and 125 mcg daily, to placebo over a period of 12 weeks. Patients receiving an ICS at baseline continued treatment at a stable dose. No other long-acting bronchodilators were permitted. Improvements in the primary endpoint, the least squares mean (LSM) change from baseline in FEV_1, were observed for umeclidinium 62.5 mcg daily vs placebo (127 mL; 95% CI, 52 to 202; $p < 0.001$) and for umeclidinium 125 mcg daily vs placebo (152 mL; 95% CI, 76 to 229; $p < 0.001$). Improvements were also noted for dyspnea, rescue medication use (62.5 mcg strength only), and SGRQ (*Trivedi et al 2014*).
  - A second trial (N = 1,536) compared umeclidinium 62.5 mcg daily, vilanterol 25 mcg daily, umeclidinium/vilanterol 62.5 mcg/25 mcg daily, and placebo over a period of 24 weeks. Concomitant use of ICSs at a stable dose was permitted. Improvements in the primary endpoint, the LSM change from baseline in FEV_1, were observed for all active treatments. For umeclidinium 62.5 mcg daily, the improvement vs placebo was 115 mL (95% CI, 76 to 155). Improvements were also noted for dyspnea and time to first COPD exacerbation (*Donohue et al 2013*).

- Two additional randomized, double-blind trials (published together, N = 862 and N = 872) evaluated the addition of umeclidinium to fluticasone propionate/salmeterol in patients with COPD. Patients received once-daily umeclidinium 62.5 mcg, umeclidinium 125 mcg, or placebo added to twice-daily fluticasone propionate/salmeterol 250/50 mcg for 12 weeks. In both studies, improvement in the primary endpoint, the trough FEV_1 on day 85, was significantly better in both umeclidinium groups vs placebo, with differences of 147 mL (95% CI, 107 to 187) and 127 mL (95% CI, 89 to 164) for the 62.5 mcg strength and 138 (95% CI, 97 to 178) and 148 (95% CI, 111 to 185) for the 125 mcg strength. Significant improvements were also demonstrated for the weighted mean FEV_1 over 0 to 6 hours post-dose and rescue albuterol use, while results on SGRQ and the COPD Assessment Test were mixed (*Siler et al 2016*).

- A review and meta-analysis evaluated the use of umeclidinium compared to placebo (as well as compared to active controls). The meta-analysis included randomized trials with a duration of ≥ 12 weeks. A total of 10 trials were included. Key results from this meta-analysis were as follows (*Pleasants et al 2016*):
  - The weighted mean difference in FEV_1 change from baseline (primary endpoint) for umeclidinium 62.5 mcg vs placebo was 120 mL (95% CI, 100 to 130) (based on data from 7 studies).
  - The weighted mean difference in TDI change from baseline for umeclidinium 62.5 mcg vs placebo was 0.61 (95% CI, -0.17 to 1.39) (based on data from 2 studies).
  - The weighted mean difference in SGRQ change from baseline for umeclidinium 62.5 mcg vs placebo was -2.34 (95% CI, -4.59 to 0.08) (based on data from 5 studies).
  - Umeclidinium 62.5 mcg significantly improved the time to first COPD exacerbation, with an HR of 0.61 (95% CI, 0.41 to 0.90) (based on data from 1 study).
- A systematic review and meta-analysis of 4 randomized controlled trials with a duration ≥ 12 weeks evaluated umeclidinium compared to placebo in patients with moderate to severe COPD (n = 37,98). Key results from this meta-analysis were as follows (*Ni et al 2017*):
  - Odds of moderate exacerbations requiring steroids and/or antibiotics were reduced with umeclidinium vs placebo (OR, 0.61; 95% CI, 0.46 to 0.80), but there was no difference in odds of severe exacerbations requiring hospitalization between groups (based on data from 4 studies).
  - Umeclidinium reduced SGRQ total score compared to placebo (MD, -4.79 units; 95% CI, -8.84 to -0.75) and the odds of having an improvement ≥ 4 units in SGRQ total score was higher with umeclidinium vs placebo (OR, 1.45; 95% CI, 1.16 to 1.82) (based on data from 3 studies).
  - TDI focal score was improved with umeclidinium vs placebo (MD, 0.76 units; 95% CI, 0.43 to 1.09 units) (based on data from 3 studies).
  - Change from baseline in trough FEV_1 was higher with umeclidinium vs placebo (MD, 0.14 L; 95% CI, 0.12 to 0.17 L) (based on data from 4 studies).
- Glycopyrrolate has been evaluated for the treatment of COPD in Phase 3, randomized, multicenter, double-blind, placebo-controlled trials.
  - Two 12-week trials (N = 441 and 428) evaluated the efficacy of glycopyrrolate inhalation powder 15.6 mcg twice daily vs placebo. Both trials met their primary endpoint, demonstrating differences from placebo in the mean change from baseline in FEV_1 area under the curve (AUC) from 0 to 12 hours (FEV_1 AUC_{0-12}) of 139 mL (95% CI, 95 to 184; $p < 0.001$) and 123 mL (95% CI, 81 to 165; $p < 0.001$), respectively. Improvement in several secondary endpoints was also demonstrated, including trough FEV_1, and SGRQ score. The difference in the TDI score was significant in one of the two studies (*Clinicaltrials.gov 2015, Kerwin et al 2016, LaForce et al 2016*).
  - The efficacy of nebulized glycopyrrolate was evaluated in two replicate 12-week randomized controlled trials (GOLDEN 3 and 4; N = 653 and N = 641, respectively) in patients with moderate to very severe COPD. Compared with placebo, patients in the intention to treat analysis who were randomized to nebulized glycopyrrolate 25 mcg or 50 mcg twice daily experienced significant increases in the primary endpoint, FEV_1 from baseline (mean placebo-adjusted differences, 0.096 and 0.104, respectively, in GOLDEN 3; 0.081 and 0.074, respectively, in GOLDEN 4; all $p < 0.0001$). Improvements from baseline were also observed with both doses of nebulized glycopyrrolate vs placebo in FVC and SGRQ scores (*Kerwin et al 2017*).

Comparisons between different anticholinergics and formulations

- A small number of clinical trials have compared tiotropium to ipratropium.
  - A randomized, double-blind, double-dummy study (N = 288) compared tiotropium 18 mcg daily to ipratropium 40 mcg four times daily over 15 weeks. This study demonstrated that the FEV_1 response was significantly greater for tiotropium compared to ipratropium at all time points ($p < 0.05$). Differences in trough FEV_1 values were most

pronounced, whereas differences in peak FEV_1 did not reach statistical significance. Improvements were also greater for tiotropium for morning and evening PEF rate and use of rescue albuterol (*van Noord et al 2000*).
  - A second double-blind, double-dummy study (N = 535) also compared tiotropium 18 mcg daily to ipratropium 40 mcg four times daily. At the end of one year, trough FEV_1 was significantly better in the tiotropium group (difference, 150 mL; $p < 0.001$). FVC results paralleled those for FEV_1. Tiotropium also led to improved PEF rates and reduced use of rescue albuterol (*Vincken et al 2002*).
  - Two identical double-blind, double-dummy 12-week trials (total N = 719) compared tiotropium Respimat in both 5 mcg and 10 mcg daily doses to placebo and to ipratropium bromide. Results for the 5 mcg dose demonstrated that trough FEV_1 was improved significantly more with tiotropium vs placebo (difference, 118 mL; $p < 0.0001$) and compared to ipratropium (difference, 64 mL; $p < 0.01$) (*Voshaar et al 2008*).
- A meta-analysis demonstrated that compared to patients receiving ipratropium, patients receiving tiotropium were more likely to experience improvement in SGRQ scores and TDI scores. Patients receiving tiotropium also experienced a reduced rate of exacerbations compared to patients receiving ipratropium (*Yohannes et al 2011*).
- A systematic review and meta-analysis (N = 2 studies; 1073 patients) evaluated the safety and efficacy of tiotropium compared to ipratropium (*Cheyne et al 2015*). In one study, patients used tiotropium by Handihaler for 12 months, and in the other, patients used tiotropium by Respimat for 12 weeks. Primary endpoints included the trough FEV_1 at three months and serious adverse events.
  - Trough FEV_1 at three months was significantly increased with tiotropium compared to ipratropium (MD, 109 mL; 95% CI, 81 to 137; $I^2 = 62\%$).
  - Fewer patients experienced one or more non-fatal serious adverse events with tiotropium compared to ipratropium (OR, 0.5; 95% CI, 0.34 to 0.73). Patients taking tiotropium were also less likely to experience a COPD-related serious adverse event (OR, 0.59; 95% CI, 0.41 to 0.85).
  - Benefits were also demonstrated for tiotropium compared to ipratropium for secondary endpoints including exacerbations, hospital admissions, and quality of life. There was no significant difference in mortality between the two treatments.
- The large, randomized, double-blind TIOSPIR trial (N = 17,135) compared tiotropium Respimat at a dose of 2.5 mcg or 5 mcg daily to tiotropium Handihaler (18 mcg daily). During a mean follow-up of 2.3 years, tiotropium via Respimat and Handihaler were shown to have similar safety and efficacy profiles (*Wise et al 2013*).
  - Risk of death for tiotropium Respimat 5 mcg daily vs Handihaler: HR, 0.96; 95% CI, 0.84 to 1.09.
  - Risk of first exacerbation for tiotropium Respimat 5 mcg daily vs Handihaler: HR, 0.98; 95% CI, 0.93 to 1.03.
- A systematic review evaluated tiotropium Respimat 5 mcg daily vs tiotropium Handihaler 18 mcg daily on pharmacokinetic, efficacy, and safety data. Data were included from a total of 22 comparative studies (10 published studies, one submitted manuscript, and 11 Congress abstracts). Key results from this review were as follows (*Dahl et al 2016*):
  - Several clinical trials demonstrated similar pharmacokinetic profiles between the two formulations. Although it had previously been suggested that systemic exposure may be greater with tiotropium Respimat, a recent study showed that exposure may actually be slightly lower with the Respimat formulation.
  - Results of several randomized trials demonstrated that the efficacy and safety profiles are comparable between the two formulations, and results from post-hoc and pooled analyses provide further support for similarity on lung function, exacerbations, and safety outcomes in various patient subtypes.
  - Similar results for health-related quality of life were demonstrated with each formulation based on the SGRQ total score.
- A double-blind, double-dummy, randomized Phase 3b trial (N = 414) compared tiotropium 18 mcg daily to aclidinium 400 mcg twice daily. This trial demonstrated no significant differences between active treatments at week 6 in the change from baseline in FEV_1 AUC over 24 hours (AUC_{0-24}). FEV_1 AUC_{0-12} was numerically greater with tiotropium vs aclidinium, and AUC_{12-24} was numerically greater with aclidinium vs tiotropium; however, differences between active treatments were not statistically significant. The two groups also had comparable results for most COPD symptom measures (*Beier et al 2013*).
- A 48-week, open-label trial (GOLDEN 5; N = 1086) compared glycopyrrolate nebulizer solution 50 mcg twice daily to tiotropium 18 mcg daily in 1086 patients with moderate to very severe COPD. The trial demonstrated that the rates of treatment-emergent adverse events were generally similar between groups, while rates of respiratory events were somewhat higher with glycopyrrolate vs tiotropium (35.2% vs 28.8%, respectively); the authors attributed this in part to incorrect nebulizer technique early in treatment. There were no significant differences between groups in the change

from baseline in FEV_1 or SGRQ. There was a similar and numerically lower incidence of exacerbations with glycopyrrolate nebulizer solution vs tiotropium (18.5% and 22.5%, respectively) (*Ferguson et al 2017*).

- Results were reported in abstract form of an open-label randomized control trial comparing tiotropium 18 mcg daily with aclidinium 400 mcg twice daily in addition to background therapy in adults with moderate to severe COPD. After 8 weeks of treatment, the primary endpoint, FEV_1 AUC_{0-3} was not significantly different between groups. Secondary outcomes evaluating other measures of lung function were not significantly different; however, SGRQ and Modified Medical Research Council scores were significantly improved with aclidinium (*Nakamura et al 2017*).
- A network meta-analysis (N = 21 studies; 22,542 patients) demonstrated no significant differences between tiotropium 18 mcg daily and aclidinium 400 mcg twice daily in FEV_1, SGRQ, or TDI score (*Karabis et al 2013*).
- A 12-week, blinded, double-dummy, randomized trial (N = 1107) compared umeclidinium 62.5 mcg daily delivered via the Ellipta device and tiotropium 18 mcg daily delivered via the Handihaler device (*Feldman et al 2016*). The primary endpoint, LSM change from baseline in trough FEV_1 at day 85 in the per-protocol population (N = 976), was greater with umeclidinium vs tiotropium (difference, 59 mL; 95% CI, 29 to 88; $p < 0.001$). Similar results were seen in the intention-to-treat population (difference, 53 mL; 95% CI, 25 to 81; $p < 0.001$). Improvements in the weighted mean FEV_1 over 0 to 24 hours post-dose were similar between treatments, but greater with umeclidinium vs tiotropium over 12 to 24 hours post-dose (difference, 70 mL; 95% CI, 14 to 127; $p = 0.015$). No differences were observed between umeclidinium and tiotropium in patient-reported outcomes (TDI and SGRQ), and the safety profiles were similar with both treatments. More patients preferred the Ellipta device compared to the Handihaler, including an overall device preference and scores for ease of use.
  - There were several limitations to this trial, including a short duration and incomplete blinding (markings differed among active tiotropium capsules and placebo, and stickers were used to obscure inhaler markings).
- A network meta-analysis (N = 24 studies; 21,311 participants) compared tiotropium 18 mcg daily to aclidinium 400 mcg twice daily, glycopyrronium 50 mcg daily (not the FDA-approved dosing), and umeclidinium 62.5 mcg daily in patients with COPD. All active treatments demonstrated favorable outcomes vs placebo for 12-week trough FEV_1, 24-week trough FEV_1, 24-week SGRQ, 24-week TDI, and 24-week rescue inhaler use (*Ismaila et al 2015*).
  - Based on 17 studies (11,935 participants) for the primary endpoint, the mean change from baseline in trough FEV_1 vs placebo at 12 weeks ranged from 101.4 to 136.7 mL, and was greatest for umeclidinium, followed by glycopyrronium, tiotropium, and aclidinium. However, the 95% credible interval (CrI) crossed zero in all between-treatment comparisons, so superiority was not demonstrated for any single LAMA over another.
- A network meta-analysis (N = 27 studies; 48,140 participants) compared tiotropium, aclidinium, and glycopyrronium for preventing COPD exacerbations (*Oba et al 2015*). All of the studied LAMAs reduced moderate-to-severe exacerbations compared to placebo; however, there were no significant differences demonstrated among the active treatments.
  - The analysis also evaluated the rate of severe exacerbations. Tiotropium dry powder inhaler was the only LAMA demonstrated to reduce severe exacerbations vs placebo (HR, 0.73; 95% CI, 0.6 to 0.86). However, the 95% CrI crossed zero in all between-treatment comparisons. The authors concluded that there were no statistically significant differences among LABAs in preventing COPD exacerbations.

<u>Comparisons between anticholinergics and $beta_2$-agonists or ICS/LABA combinations</u>

- In a meta-analysis of 4 trials, there was no statistically significant difference in short-term FEV_1 changes (up to 90 minutes post dose) between individuals receiving ipratropium compared to a $beta_2$-adrenergic agonist (albuterol, metaproterenol, or fenoterol) (*McCrory et al 2002*).
- Tiotropium has been compared to the LABAs salmeterol and indacaterol in several large comparative trials.
  - Two placebo-controlled trials of tiotropium 18 mcg daily also included an active control arm in which patients received salmeterol 50 mcg twice daily. In the first trial (N = 623), the improvement in trough FEV_1 at 24 weeks was greater with tiotropium compared to salmeterol (difference, 52 mL; $p < 0.01$). Differences also favored tiotropium for FVC (difference, 112 mL; $p < 0.01$) and PEF rate (difference, 5.9 L/minute; $p < 0.01$). Tiotropium was also better than salmeterol in improving TDI focal score (difference, 0.78 units; $p < 0.05$). The difference between active treatments in SGRQ was not statistically significant (*Donohue et al 2002*). In the second trial (N = 1207), improvements in FEV_1, FEV_1 area under the curve over three hours (AUC_{0-3}), and FVC were greater for tiotropium vs salmeterol; however, there were no significant differences among active treatment groups for time to first COPD exacerbation, hospital admissions, or TDI focal scores (*Brusasco et al 2003*).
  - A large double-blind randomized trial (N = 7348) (POET-COPD) demonstrated that tiotropium 18 mcg daily increased the time to first COPD exacerbation, the risk of moderate exacerbations, and the risk of severe exacerbations

compared to treatment with salmeterol (*Vogelmeier et al 2011*). Prolongation of time to the first exacerbation was also demonstrated in prespecified subgroups of patients with GOLD stage II COPD and patients who were maintenance-therapy-naïve (*Vogelmeier et al 2013*).
  - A randomized trial (N = 1683) compared two doses of the once-daily LABA indacaterol (150 mcg and 300 mcg) to tiotropium 18 mcg daily and to placebo. In this trial, patients receiving placebo or indacaterol were blinded, but tiotropium was open-label because blinded tiotropium was not available. The primary endpoint, trough FEV_1 at 12 weeks, was greater for indacaterol (both doses) than for tiotropium (difference, 40 mL; $p \leq 0.01$). Greater improvements were also demonstrated for indacaterol vs tiotropium for the proportions of patients achieving a clinically important improvement in TDI total score ($p \leq 0.01$), use of rescue albuterol ($p \leq 0.001$), and change from baseline in morning and evening PEF ($p < 0.05$). Rates of exacerbations did not differ among active treatment groups (*Donohue et al 2010*).
  - A randomized, double-blind, double-dummy trial compared tiotropium 18 mcg daily to indacaterol 150 mcg daily. In this trial, trough FEV_1 with tiotropium was determined to be non-inferior to indacaterol, but not superior (treatment difference, 0 mL; 95% CI, -20 to 20). However, FEV_1 and FVC were demonstrated to be greater with indacaterol on day one when evaluated five minutes, 30 minutes, and one hour after dosing. More patients receiving indacaterol compared to those taking tiotropium experienced a clinically significant improvement in TDI scores (OR, 1.49; $p < 0.001$) and SGRQ scores (OR, 1.43; $p < 0.001$). In addition, use of rescue medication was lower in the indacaterol group (*Buhl et al 2011*).
- Tiotropium has also been compared to combination ICS/LABAs.
  - Tiotropium 18 mcg daily has been compared to fluticasone/salmeterol 250 mcg/50 mcg in a randomized, double-blind, double-dummy, two-year trial (N = 1323). The primary endpoint in this trial, the rate of exacerbations over two years, was comparable in the tiotropium (1.32/year) and fluticasone/salmeterol (1.28/year) groups ($p = 0.656$). Patients randomized to tiotropium were significantly more likely to withdraw from the study than those randomized to fluticasone/salmeterol (HR, 1.29; 95% CI, 1.08 to 1.54; $p = 0.005$). In addition, mortality was significantly lower in the fluticasone/salmeterol group (3%) than in the tiotropium group (6%) (HR, 0.48; 95% CI, 0.27 to 0.85; $p = 0.012$) (*Wedzicha et al 2008*).
  - Tiotropium 18 mcg daily has also been compared to fluticasone furoate/vilanterol 100/25 mcg daily in a randomized, double-blind, double-dummy, 12-week trial (N = 623) in patients with COPD and cardiovascular disease (CVD) or CVD risk (≥ 1 risk factor of hypertension, hypercholesterolemia, or treated diabetes). The primary endpoint, change from baseline in weighted mean FEV_1 over 24 hours at 12 weeks, was similar in the two treatment arms (LSM change, 95 mL and 117 mL in the tiotropium and fluticasone furoate/vilanterol groups, respectively, with a difference of 22 mL [95% CI, -12 to 55; $p = 0.201$]). Trough FEV_1 after 12 weeks was improved to a similar extent in both groups. Some secondary endpoints seemed to favor tiotropium (change from baseline in FVC and inspiratory capacity), while other endpoints seemed to favor fluticasone furoate/vilanterol (onset of bronchodilation, rescue medication use, dyspnea, SGRQ, and COPD Assessment Test scores). Safety was generally similar, although pneumonia was reported more frequently in the fluticasone furoate/vilanterol group. Cardiovascular monitoring did not demonstrate an increased cardiovascular risk. The cardiovascular safety profile was similar between groups; however, there were 2 deaths from cardiovascular events in the tiotropium group (both patients had hypertension and one smoked and had a family history of CVD). Fewer patients experienced a COPD exacerbation in the fluticasone furoate/vilanterol group (2%) than the tiotropium group (4%) (*Covelli et al 2015*).
- Meta-analyses comparing tiotropium to LABAs do not consistently demonstrate superiority on key endpoints for either treatment. One meta-analysis (N = 7 trials; 12,223 participants) demonstrated a reduction in the proportion of patients experiencing one or more exacerbations with tiotropium compared to a LABA; however, one trial contributed the most weight to this analysis (Chong et al 2012).
- A systematic review and network meta-analysis (N = 71 trials; 73,062 participants) evaluated the efficacy of various treatment options for patients with COPD that could not be controlled by short-acting therapies alone. This analysis ranked ICS/LABA combinations first for results on SGRQ and trough FEV_1. LAMAs and LABAs were ranked second and third for each measure, and these two categories of medications had similar effects overall (*Kew et al 2014*).
- A systematic review and network meta-analysis (N = 10 trials; 10,894 participants) compared the effects of LABA/tiotropium combination therapy vs either therapy alone (*Farne et al 2015*).
  - Compared to tiotropium alone, combination treatment resulted in a slightly larger improvement in SGRQ (MD, -1.34; 95% CI, -1.87 to -0.8; 6709 participants; 5 studies). There were no significant differences in hospital admissions (4 studies; 4,856 participants) or all-cause mortality (10 studies; 9633 participants). The improvement in pre-

bronchodilator FEV_1 at the end of the study showed a statistically significant increase in the combination group compared to the tiotropium group (MD, 60 mL; 95% CI, 50 to 70; 10 studies; 9573 participants). Results for exacerbations were not pooled due to clinical heterogeneity.
  - Compared to LABA alone, combination treatment resulted in a small but statistically significant improvement in SGRQ (MD, -1.25; 95% CI, -2.14 to -0.37; 3378 participants; 4 studies). There were no significant differences in all-cause hospitalizations, hospitalizations for exacerbations, or all-cause mortality (3 studies; 3514 participants for all endpoints). The improvement in pre-bronchodilator FEV_1 at the end of the study showed a statistically significant increase in the combination group compared to the LABA group (MD, 70 mL; 95% CI, 60 to 90; 4 studies; 3513 participants). There was a significantly lower risk of exacerbation with combination treatment vs LABA monotherapy (OR, 0.8; 95% CI, 0.69 to 0.93; 3 studies; 3514 participants).
- There is little data on the use of aclidinium compared to $beta_2$-agonists. A small study (N = 79) compared various doses of aclidinium to the LABA formoterol in a crossover study in which each treatment was given for seven days. The primary endpoint, difference in FEV_1 $AUC_{0\text{-}12}$ on day seven, was not significantly different in the aclidinium 400 mcg twice daily and formoterol 12 mcg twice daily groups (208 mL and 210 mL, respectively). There also was no difference between treatment with aclidinium 400 mcg and formoterol with regard to changes in FEV_1 $AUC_{0–24}$; however, patients treated with aclidinium 400 mcg experienced a statistically significant improvement in FEV_1 $AUC_{12–24}$ compared to treatment with formoterol (56 mL; $p < 0.01$) *(Singh et al 2012*).

ASTHMA
- Clinical trials have demonstrated efficacy with the tiotropium Respimat vs placebo in patients with asthma not well controlled on baseline therapy that included at least an ICS.
- Efficacy of tiotropium for the treatment of asthma has also been established through many systematic reviews and meta-analyses.
  - A series of systematic reviews and meta-analyses have reported the efficacy of tiotropium in the treatment of asthma (*Rodrigo et al 2015a, Rodrigo et al 2015, Rodrigo et al 2017*). These analyses demonstrated the ability of tiotropium to improve lung function endpoints, including FEV_1 and/or PEF, while the impact on overall asthma control, asthma-related quality of life, and asthma exacerbations were mixed.
  - Focused meta-analyses have also demonstrated the efficacy of tiotropium for the management of asthma when added to an ICS compared to use of the ICS alone (*Anderson et al 2015, Wang et al 2018*), and when added to an ICS/LABA compared to ICS/LABA alone (*Kew et al 2016*). Studies generally supported the efficacy of tiotropium based on lung function, with less evidence for an impact on exacerbations and asthma-related quality of life.
  - A meta-analysis compared the addition of a LAMA (tiotropium) to addition of a LABA (salmeterol) in patients not adequately controlled on an ICS (*Kew et al 2015*). No significant differences were demonstrated in the rate of exacerbations requiring oral corticosteroids.

Placebo-controlled and trials
- Clinical trials have compared tiotropium Respimat to placebo in patients with asthma not well controlled on baseline therapy that included at least an ICS.
- A 12-week, Phase 3, multicenter, randomized trial (N = 465) compared tiotropium Respimat 2.5 mcg daily, 5 mcg daily, and placebo in adults with asthma who were symptomatic despite treatment with a low- to medium-dose ICS (200 to 400 mcg budesonide or equivalent), which was continued during the trial. The primary endpoint, change from baseline in peak FEV_1 within 3 hours of dosing (FEV_1 [0 to 3 hr]), was greater for both tiotropium doses compared to placebo, with adjusted MDs of 159 mL and 128 mL for the 2.5 mcg and 5 mcg doses, respectively ($p < 0.001$ for both comparisons vs placebo). Both doses of tiotropium were also superior to placebo with regard to the secondary endpoints of adjusted mean trough FEV_1 and FEV_1 $AUC_{0\text{ to }3}$ responses, and the other endpoints of morning and evening PEF. Adverse events were comparable across the treatment groups (*Paggiaro et al 2016*).
- Two 24-week, Phase 3, multicenter, randomized trials (total N = 2103) compared tiotropium Respimat 2.5 mcg daily, 5 mcg daily, salmeterol 50 mcg twice daily, or placebo in adults with asthma who were symptomatic despite treatment with a medium-dose ICS (400 to 800 mcg budesonide or equivalent) alone or in combination with a $beta_2$-agonist. During the study, patients continued their ICS, but pre-study LABAs were discontinued. Co-primary endpoints were the peak FEV_1 (0 to 3 hr), trough FEV_1, and responder rate according to the seven-question Asthma Control Questionnaire (ACQ-7). Pooled data demonstrated the following (*Kerstjens et al 2015*):

- The differences vs placebo in peak FEV_1 were 223 mL (95% CI, 185 to 262) in the tiotropium 2.5 mcg group, 185 mL (95% CI, 146 to 223) in the tiotropium 5 mcg group, and 196 mL (95% CI, 158 to 234) in the salmeterol group (all $p < 0.0001$ vs placebo).
- The differences in trough FEV_1 were 180 mL (95% CI, 138 to 221) in the tiotropium 2.5 mcg group, 146 mL (95% CI, 105 to 188) in the tiotropium 5 mcg group, and 114 mL (95% CI, 73 to 155) in the salmeterol group (all $p < 0.0001$ vs placebo).
- There were more ACQ-7 responders (improvement of ≥ 0.5) in the tiotropium 2.5 mcg group (OR, 1.33; 95% CI, 1.03 to 1.72; p = 0.031), tiotropium 5 mcg group (OR, 1.32; 95% CI, 1.02 to 1.71; p = 0.035), and salmeterol group (OR, 1.46; 95% CI, 1.13 to 1.89; p = 0.0039), than in the placebo group.
- Severe asthma exacerbations were recorded in 4%, 6%, 6%, and 8% of patients in the tiotropium 2.5 mcg, 5 mcg, salmeterol, and placebo groups, respectively. At least one episode of asthma worsening was recorded in 22%, 28%, 25%, and 32% of patients, respectively. The investigators noted a statistically significant reduction in risk of first severe exacerbation with tiotropium 2.5 mcg (p = 0.0084) and of first asthma worsening with tiotropium 2.5 mcg and salmeterol (p = 0.0007 and 0.013, respectively) vs placebo.
- The numbers of adverse events and serious adverse events were comparable among groups.

- Additional support for the safety and efficacy of tiotropium for asthma treatment was provided by the results of two 48-week, Phase 3, multicenter, randomized trials (total N = 912) comparing tiotropium Respimat 5 mcg daily to placebo in adults with asthma not adequately controlled on an ICS (≥ 800 mcg budesonide or equivalent) and a LABA. Tiotropium was superior to placebo for endpoints including mean change in peak FEV_1, trough FEV_1, and the time to first severe exacerbation. Adverse events were similar in the two groups. However, it should be noted that this study only evaluated a dose that is higher than the FDA-approved dose for asthma (*Kerstjens et al 2012*).
- Two randomized Phase 3 trials evaluated the use of tiotropium Respimat in adolescents 12 to 17 years of age.
  - A 12-week trial (N = 392) compared tiotropium Respimat 2.5 mcg daily, 5 mcg daily, and placebo in patients with severe asthma who were on background treatment of an ICS plus one or more controller medications, such as a LABA. The difference vs placebo for the primary endpoint, peak FEV_1 (0 to 3 hr), was 111 mL (95% CI, 2 to 220) for the 2.5 mcg dose and 90 mL (95% CI, -19 to 198) for the 5 mcg dose (*Hamelmann et al 2017*).
  - A 48 week trial (N = 398) compared tiotropium Respimat 2.5 mcg daily, 5 mcg daily, and placebo in patients with moderate asthma who were on background treatment of at least an ICS. The difference vs placebo in the primary endpoint, peak FEV_1 (0 to 3 hr) was 134 mL (95% CI, 34 to 234) for the 2.5 mcg dose and 174 mL (95% CI, 76 to 272) for the 5 mcg dose (*Clinicaltrials.gov 2014, Spiriva Respimat prescribing information 2017*).
- According to the prescribing information, efficacy of tiotropium in pediatric patients 6 to 11 years of age was based on extrapolation of efficacy in adults, and on two randomized, double-blind, placebo-controlled trials of 12 and 48 weeks duration. A total of 801 patients aged 6 to 11 years were enrolled in the two trials (271 receiving tiotropium 2.5 mcg daily 265 receiving tiotropium 5 mcg daily, and 265 receiving placebo). The primary endpoint in both trials was the change from baseline in the peak FEV_1 (0 to 3 hr), with the evaluation defined at week 12 in the 12-week trial and at week 24 in the 48-week trial (*Spiriva Respimat prescribing information 2017*).
  - The 12-week trial enrolled patients with severe asthma who were on background treatment of ICS plus ≥ 1 controller medication (eg, LABA). The mean difference vs placebo in the primary endpoint was 40 mL (95% CI, -30 mL to 100 mL; not significant).
  - The 48-week trial enrolled patients with moderate asthma on background treatment of at least an ICS. The mean difference vs placebo in the primary endpoint was 170 mL (95% CI, 110 to 230).
- An additional trial in children aged 6 to 11 years with severe symptomatic asthma randomized patients to double-blind tiotropium 5 mcg, 2.5 mcg, or placebo administered via a Respimat device in addition to background therapy with medium-dose ICS. After 12 weeks, tiotropium 5 mcg, but not 2.5 mcg, improved the primary end point, peak FEV_1 within 3 hours after dosing compared with placebo (MD, 139 mL; 95% CI, 75 to 203 and 35 mL; 95% CI, -28 to 99 for 5 and 2.5 mcg doses, respectively). Results were similar for the key secondary endpoint, trough FEV_1 *(Szefler et al 2017*).

Systematic reviews and network meta-analyses

- A systematic review and meta-analysis (N = 13 studies; 4966 patients) evaluated the efficacy and safety of tiotropium in patients with asthma. Tiotropium was given via the Respimat device in most studies, and the duration of the included studies ranged from 4 to 52 weeks (*Rodrigo et al 2015a*).
  - In 10 studies evaluating the addition of tiotropium to an ICS vs ICS alone in patients with mild or moderate asthma, the analysis demonstrated significant improvements in morning and evening PEF (MD, 22 to 24 L/min; $p < 0.00001$)

and peak and trough FEV_1 (MD, 150 mL; 95% CI, 110 to 180 and 140 mL; 95% CI, 110 to 160, respectively) with the addition of tiotropium. Tiotropium also significantly improved ACQ-7 and Asthma Quality of Life Questionnaire (AQLQ) scores from baseline (MD, -0.14 units; 95% CI, -0.19 to -0.09 and 0.07 units; 95% CI, 0.01 to 0.13, respectively). Tiotropium was also associated with a decrease in the number of patients with ≥ 1 asthma exacerbation (10.5% vs 13.3%; relative risk [RR], 0.74; 95% CI, 0.57 to 0.95).
    - In four studies comparing the addition of either tiotropium or LABA to an ICS in patients with moderate asthma, tiotropium improved morning PEF more than LABA, but the magnitude of the difference was small (6.6 L/min). There were no significant differences in evening PEF or peak or trough FEV_1. The addition of tiotropium was inferior to the addition of LABA for AQLQ (MD, -0.12 units; 95% CI, -0.06 to -0.18). There were no significant differences in ACQ-7 total score or the number of patients with ≥ 1 exacerbation.
    - In three studies comparing triple therapy (tiotropium with ICS/LABA) vs LABA with a high-dose ICS in patients with severe asthma, the analysis demonstrated significant improvements with triple therapy in morning and evening PEF (MD, 16 L/min; $p < 0.0004$ and 20 L/min; $p < 0.00001$, respectively). Peak and trough FEV_1 was also significantly greater with triple therapy (MD, 120 mL; 95% CI, 90 to 160 and 80 mL; 95% CI, 40 to 110, respectively). Triple therapy was associated with significant improvements in ACQ-7 and AQLQ (MD, -0.2 units; 95% CI, -0.25 to -0.09 and 0.12 units; 95% CI, 0.05 to 0.18, respectively). Patients treated with triple therapy also had a lower likelihood of experiencing ≥ 1 exacerbation (18.2% vs 24%; RR, 0.7; 95% CI, 0.53 to 0.94).
- A systematic review and meta-analysis (N = 3 studies; 895 patients) evaluated the use of tiotropium Respimat in adolescents aged 12 to 18 years with moderate to severe asthma. Patients were also receiving an ICS or ICS/LABA and the duration of the studies ranged from 4 to 48 weeks. Primary outcomes were peak and trough FEV_1 (*Rodrigo et al 2015b*).
    - Tiotropium was associated with significant improvements in peak and trough FEV_1 with mean changes from baseline of 120 mL and 100 mL vs placebo, respectively ($p < 0.001$ for both comparisons).
    - Benefits were also shown with tiotropium for the secondary endpoint of exacerbation risk. There were no significant differences in the rate of ACQ-7 response, rescue medication use, withdrawals, adverse events, or serious adverse events.
- A systematic review and meta-analysis (N = 3 studies; approximately 900 patients) evaluated the use of tiotropium Respimat in children aged 6 to 11 years with moderate to severe symptomatic asthma. Patients were also receiving maintenance therapy with ICS or ICS plus ≥ 1 controller medication and the duration of the studies ranged from 4 to 48 weeks. Primary outcomes were peak and trough FEV_1 (*Rodrigo et al 2017*).
    - Tiotropium demonstrated significant improvements in peak FEV_1 of 102 mL and trough FEV_1 of 82 mL vs placebo ($p < 0.0001$ for both comparisons).
    - Tiotropium significantly increased the rate of ACQ-7 responders ($p = 0.04$) and decreased the number of patients ≥ 1 exacerbations ($p = 0.002$) vs placebo.
    - There were no significant differences in rescue medication use, study withdrawals, adverse events, or withdrawals due to adverse events.
- A systematic review and meta-analysis (N = 5 studies; 2563 patients) evaluated the safety and efficacy of an ICS plus LAMA vs ICS alone in patients with asthma. The LAMA used was tiotropium Respimat in all studies, and the duration of treatment ranged from 12 to 52 weeks. All studies used a double-blind, double-dummy design. The primary outcomes included exacerbations requiring oral corticosteroids, quality of life, and all-cause serious adverse events (*Anderson et al 2015*).
    - Based on 4 studies in 2277 patients, the rate of exacerbations requiring oral corticosteroids was lower in patients taking a LAMA add-on than in those receiving the same dose of ICS alone (OR, 0.65; 95% CI, 0.46 to 0.93; $I^2 = 0\%$).
    - Based on 3 studies in 1713 patients, scores on the AQLQ were slightly higher for those taking a LAMA add-on compared to ICS alone (MD, 0.05; 95% CI, -0.03 to 0.12; $I^2 = 0\%$), but the difference was not statistically significant and was less than the established minimal clinically important difference of 0.5.
    - Based on five studies in 2,562 participants, patients taking a LAMA reported fewer serious adverse events, but the effect was too inconsistent and imprecise to suggest a definite benefit over an ICS alone (OR, 0.6; 95% CI, 0.23 to 1.57; $I^2 = 59\%$).
    - Benefits were also demonstrated with add-on LAMA therapy compared to ICS alone for the secondary endpoints including FEV_1 and PEF. Differences were not statistically significant for ACQ results or the number of exacerbations requiring hospitalization.

- A systematic review and meta-analysis compared the use of a LAMA vs a LABA when added to an ICS in patients with asthma. A total of seven trials were included in the narrative review, and four of these trials (N = 2049) were included in the meta-analysis. All of the studies included in the meta-analysis used tiotropium as the LAMA and salmeterol as the LABA, and the duration of the trials ranged from 14 to 24 weeks. The primary outcomes included exacerbations requiring oral corticosteroids, quality of life, and serious adverse events (*Kew et al 2015*).
  - Based on 3 studies in 1753 patients, there was no significant difference in the rate of exacerbations requiring oral corticosteroids between the LAMA and LABA groups (OR, 1.05; 95% CI, 0.50 to 2.18).
  - Based on 4 studies in 1,745 patients, those treated with a LAMA scored slightly worse than those treated with a LABA for quality of life measured on the AQLQ (MD, -0.12; 95% CI, -0.18 to -0.05). The difference was statistically significant, but both results fell below the established minimal clinically important difference of 0.5.
  - There was no difference detected in the rate of serious adverse events (OR, 0.84; 95% CI, 0.41 to 1.73); however, the rate of serious adverse events was too low for this result to be considered reliable.
  - Secondary endpoints showed little or no difference between the LAMA and LABA groups; these included FEV_1, PEF, FVC, exacerbations requiring hospitalization, and ACQ results.
- A systematic review and meta-analysis evaluated the addition of a LAMA to adults with asthma not well controlled by an ICS/LABA. Three double-blind trials (total N = 1197) comparing LAMA to placebo were included, and all trials evaluated tiotropium (mostly 5 mcg once daily via Respimat) (*Kew et al 2016*).
  - Based on two studies enrolling 907 patients, it was found that patients taking tiotropium plus an ICS/LABA had numerically fewer exacerbations requiring oral corticosteroids than those taking an ICS/LABA alone, but the confidence intervals did not rule out lack of a difference (OR, 0.75; 95% CI, 0.57 to 1.07). No benefit on quality of life was seen with the addition of tiotropium, based on results from the AQLQ (MD, 0.09; 95% CI, -0.03 to 0.20).
  - Secondary endpoints demonstrated a benefit on lung function, but no significant improvement in exacerbations requiring hospital admission or scores on asthma control measured by the ACQ.
- A meta-analysis of 4 randomized controlled trials evaluated tiotropium when added to low- to medium-dose ICS in adults with moderate uncontrolled asthma, and found significant improvement with tiotropium in FEV percent predicted (3.46%; 95% CI, 2.20 to 4.63), peak FEV_1 (146.85 mL; (114.89 to 178.82), trough FEV_1 (122.03 mL; 95% CI, 92.92 to 151.13). These results were consistent among subgroups treated with different doses of tiotropium (*Wang et al 2018*).

CLINICAL GUIDELINES

COPD

- The 2018 GOLD guidelines state that the management strategy for stable COPD should be predominantly based on an assessment of the patient's symptoms and risk of exacerbations; the risk of exacerbations is based on a patient's exacerbation history. Key recommendations from the GOLD guidelines are as follows (*GOLD 2018*):
  - Inhaled bronchodilators are central to symptom management in COPD and commonly given on a regular basis to prevent or reduce symptoms.
    - Inhaled bronchodilators are recommended over oral bronchodilators.
  - LAMAs and LABAs significantly improve lung function, dyspnea, and health status, and reduce exacerbation rates.
    - LAMAs and LABAs are preferred over short-acting agents except for patients with only occasional dyspnea.
    - LAMAs have a greater effect on exacerbation reduction compared to LABAs and decrease hospitalizations.
  - Patients may be started on single long-acting bronchodilator therapy or dual long-acting bronchodilator therapy. In patients with persistent dyspnea on one bronchodilator, treatment should be escalated to two bronchodilators.
  - Combination treatment with a LABA and LAMA:
    - Reduces exacerbations compared to monotherapy or ICS/LABA.
    - Increases FEV_1 and reduces symptoms compared to monotherapy.
  - Long-term monotherapy with ICSs is not recommended. Long-term treatment with ICSs may be considered in association with LABAs for patients with a history of exacerbations despite treatment with long-acting bronchodilators.
  - Triple inhaled therapy of LAMA/LABA/ICS improves lung function, symptoms, and health status and reduces exacerbations compared to ICS/LABA or LAMA monotherapy.
  - Treatment recommendations are given for patients with COPD based on their GOLD patient group (see Table 3 below).
    - Group A: Patients should be offered bronchodilator treatment (short- or long-acting). This should be continued if symptomatic benefit is documented.
    - Group B: Initial therapy should consist of a long-acting bronchodilator (LAMA or LABA). For patients with persistent breathlessness on monotherapy, use of 2 bronchodilators is recommended (LAMA + LABA). For patients with

severe breathlessness, initial therapy with 2 bronchodilators may be considered. If the addition of a second bronchodilator does not improve symptoms, it is suggested that treatment could be stepped down to a single bronchodilator.

- Group C: Initial therapy should be a LAMA. Patients with persistent exacerbations may benefit from adding a second long-acting bronchodilator (LAMA + LABA, preferred) or using an ICS + LABA.
- Group D: It is recommended to start therapy with a LAMA + LABA combination. In some patients, initial therapy with an ICS + LABA may be the first choice; these patients may have a history and/or findings suggestive of asthma-COPD overlap. In patients who develop further exacerbations on LAMA + LABA therapy, alternative pathways include escalation to a LAMA + LABA + ICS (preferred) or a switch to an ICS + LABA. If patients treated with a LAMA + LABA + ICS still have exacerbations, options for selected patients may include addition of roflumilast, addition of a macrolide, or stopping the ICS.

Table 3. Assessment of symptoms and risk of exacerbations to determine GOLD patient group

Exacerbation history	Symptoms	
	mMRC 0 to 1 CAT < 10	mMRC ≥ 2 CAT ≥ 10
≥ 2 (or ≥ 1 leading to hospital admission)	C	D
0 or 1 (not leading to hospital admission)	A	B

Abbreviations: CAT = COPD assessment test; mMRC = modified British Medical Research Council questionnaire

- Guidelines for the prevention of acute exacerbations of COPD from the American College of Chest Physicians and the Canadian Thoracic Society state that a LAMA is recommended over either a short-acting muscarinic antagonist or a LABA. The guidelines state that certain combination bronchodilators or bronchodilator/ICS combinations may reduce exacerbations, but does not state that any combination is superior to LAMA monotherapy in patients with stable COPD (*Criner et al 2015*).

Asthma

- The National Asthma Education and Prevention Program (NAEPP) guideline from the NHLBI states that the initial treatment of asthma should correspond to the appropriate asthma severity category, and it provides a stepwise approach to asthma management. Long-term control medications such as ICSs, long-acting bronchodilators, leukotriene modifiers, cromolyn, theophylline, and immunomodulators should be taken daily on a long-term basis to achieve and maintain control of persistent asthma. ICSs are the most potent and consistently effective long-term asthma control medication. Quick-relief medications such as SABAs and anticholinergics are used to provide prompt relief of bronchoconstriction and accompanying acute symptoms such as cough, chest tightness, and wheezing. Systemic corticosteroids are important in the treatment of moderate or severe exacerbations because these medications prevent progression of the exacerbation, speed recovery, and prevent relapses (*NHLBI 2007*).
  - Ipratropium provides additive benefit to a SABA in moderate-to-severe asthma exacerbations, and may be used as an alternative bronchodilator for patients who do not tolerate a SABA.
  - The guideline states that ipratropium and tiotropium have not demonstrated effectiveness in the long-term management of asthma; however, it should be noted that this guideline has not been updated since 2007.
- The GINA guideline also provides a stepwise approach to asthma management. It recommends an ICS as a preferred initial controller medication choice, with an increased ICS dose and/or addition of a LABA for increasing symptom severity (higher steps). At the highest step, it is recommended that the patient be referred for add-on treatment (eg, tiotropium, anti-IgE, or anti-IL5 agent) (*GINA 2018*).

- Tiotropium by mist inhaler is recommended as an add-on controller option in patients at higher steps (4 and 5). At step 4, it is recommended under “other controller options” (not preferred), and at step 5, it is recommended as one of several preferred add-on treatment options. In this setting, tiotropium is recommended as an add-on treatment for patients with a history of exacerbations; however, the guideline states that tiotropium is not for use in children less than 12 years of age.
- Add-on tiotropium by mist inhaler improves lung function and increases the time to severe exacerbation.

- A guideline on the definition, evaluation, and treatment of severe asthma is available from the European Respiratory Society (ERS) and the American Thoracic Society (ATS) (*Chung et al 2014*).
  - The guideline notes that ipratropium is commonly used in severe asthma patients in an attempt to reduce the daily use of beta$_2$-agonists, as well as in the treatment of asthma exacerbations. Although considered to be less effective, ipratropium is well tolerated and may be used alternately with beta$_2$-agonists for as-needed use throughout the day.
  - Tiotropium has been shown to improve lung function and symptoms in moderate-to-severe asthma patients not controlled on a moderate- to high-dose ICS with or without a LABA. In patients taking high doses of an ICS and a LABA, the addition of tiotropium has provided improvements in FEV_1, reduced as-needed SABA use, and modestly reduced the risk of a severe exacerbation. However, there have been no studies of tiotropium in children with asthma.

SAFETY SUMMARY

- Ipratropium solution and Atrovent HFA are contraindicated in patients with hypersensitivity to ipratropium, atropine and its derivatives, or components of the product. Incruse Ellipta and Tudorza Pressair are contraindicated in patients with severe hypersensitivity to milk proteins or hypersensitivity to any ingredient. Seebri Neohaler is contraindicated in patients with known hypersensitivity to glycopyrrolate or any of the product ingredients. Spiriva Handihaler and Spiriva Respimat are contraindicated in patients with hypersensitivity to tiotropium, ipratropium, or components of the product.
- Key warnings and precautions are similar among the anticholinergics, and include hypersensitivity, paradoxical bronchospasm, urinary retention, and ocular effects/narrow-angle glaucoma. It should also be noted that anticholinergics are for maintenance treatment and are not for initial treatment of acute episodes of bronchospasm where rescue therapy is required.
- The most common adverse effects reported for each anticholinergic are as follows:
  - Atrovent HFA (> 5% incidence): bronchitis, COPD exacerbation, dyspnea, and headache
  - Ipratropium solution (> 5% incidence): bronchitis, upper respiratory tract infection, dyspnea, and headache
  - Incruse Ellipta (≥ 2% incidence): nasopharyngitis, upper respiratory tract infection, cough, arthralgia
  - Seebri Neohaler (≥ 2% incidence): upper respiratory tract infection and nasopharyngitis
  - Spiriva Handihaler (> 5% incidence): upper respiratory tract infection, dry mouth, sinusitis, pharyngitis, non-specific chest pain, urinary tract infection, dyspepsia, and rhinitis
  - Spiriva Respimat (> 3% incidence in COPD): pharyngitis, cough, dry mouth, and sinusitis;
    Spiriva Respimat (> 2% incidence in asthma, adults): pharyngitis, sinusitis, bronchitis, and headache
  - Tudorza Pressair (> 5% incidence): headache and nasopharyngitis
- Although earlier trials raised some concerns about increased mortality with tiotropium when administered by the Respimat inhaler, a large, randomized, double-blind trial revealed no increased mortality for patients treated with tiotropium Respimat compared to tiotropium Handihaler (*Wise et al 2013*).
- Spiriva Handihaler, Tudorza, Incruse, and Seebri are Pregnancy Category C, while Atrovent HFA and ipratropium solution are pregnancy category B; Spiriva Respimat and Lonhala Magnair are not currently assigned a Pregnancy Category.

DOSING AND ADMINISTRATION

- Administration devices vary among products, and ease of use may vary based on patients’ dexterity and coordination. Notably, Seebri Neohaler and Spiriva Handihaler require inserting individual capsules into the inhaler prior to each dose, and Spiriva Respimat requires coordination of inhalation with actuation of the device. The patient’s ability to use an inhalation device is an important consideration in product selection.

Table 4. Dosing and Administration

Drug	Available Formulations	Route	Usual Recommended Frequency	Comments
Atrovent HFA (ipratropium bromide)	Inhalation aerosol	Inhalation	Four times a day	• May use additional inhalations as required; maximum 12 inhalations per 24 hours • Canister-style inhaler; requires inserting the canister and priming before use • Hand/breath coordination is required
Incruse Ellipta (umeclidinium)	Inhalation powder	Inhalation	Once daily	• Disc-shaped inhaler with self-contained foil blister strips; opening the inhaler prepares a dose • Breath-activated; hand/breath coordination not required
ipratropium bromide solution	Inhalation solution	Inhalation (with nebulizer)	Three to 4 times per day	• May be mixed in nebulizer with albuterol or metaproterenol if used within 1 hour
Lonhala Magnair (glycopyrrolate)	Inhalation solution	Inhalation (with nebulizer)	Twice daily	• Lonhala should only be administered with the Magnair device. • Supplied in vials with complete Magnair nebulizer system (starter kit) or refill handset (refill kit) • 2 to 3 minutes to administer, plus cleaning/prep time
Seebri Neohaler (glycopyrrolate)	Inhalation powder	Inhalation	Twice daily	• Capsules should not be swallowed • Dry powder inhaler; requires insertion of a capsule into the inhaler and piercing before each dose • Breath-activated; hand/breath coordination not required
Spiriva Handihaler (tiotropium bromide)	Inhalation powder	Inhalation	Once daily	• Capsules should not be swallowed • Dry powder inhaler; requires insertion of a capsule into the inhaler and piercing before each dose • Breath-activated; hand/breath coordination not required
Spiriva Respimat (tiotropium bromide)	Inhalation spray	Inhalation	Once daily	• Inhaler should be primed before first use and if not used for > 3 days • Maximum benefits in asthma treatment may take up to 4 to 8 weeks • Canister-style inhaler; requires inserting the canister and priming before use • Twisting the canister prepares a dose for inhalation • Hand/breath coordination is required
Tudorza Pressair (aclidinium bromide)	Inhalation powder	Inhalation	Twice daily	• Dry powder inhaler; pressing a button prepares a dose • Breath-activated; hand/breath coordination not required

See the current prescribing information for full details

CONCLUSION

- The inhaled anticholinergics are used predominantly for the management of COPD, with an additional asthma indication specific to Spiriva Respimat (tiotropium).
  - Short-acting inhaled anticholinergics include Atrovent HFA (ipratropium bromide) inhalation aerosol and ipratropium bromide solution for nebulization.
  - The LAMAs include 4 molecular entities in 6 formulations: Incruse Ellipta (umeclidinium) inhalation powder, Lonhala Magnair (glycopyrrolate) inhalation solution and Seebri Neohaler (glycopyrrolate) inhalation powder, Spiriva

Handihaler (tiotropium) inhalation powder and Spiriva Respimat (tiotropium) inhalation spray, and Tudorza Pressair (aclidinium) inhalation powder.

- All LAMAs are indicated for the long-term maintenance treatment of airflow obstruction in patients with COPD, while Spiriva Handihaler and Respimat are also indicated to reduce COPD exacerbations. Spiriva Respimat is additionally indicated for the maintenance treatment of asthma.
  - Spiriva Handihaler (tiotropium bromide), Spiriva Respimat (tiotropium bromide), and Incruse Ellipta (umeclidinium) are all administered once daily, while the Seebri Neohaler and Tudorza Pressair are administered twice daily.
  - Lonhala Magnair is administered twice daily via the Magnair nebulizer. This product is appropriate for a small percentage of COPD patients who are unable to effectively use other inhalation devices.
  - Devices and administration methods vary among products, and some may be favored over others for patients with dexterity issues, suboptimal peak inspiratory flow rate, and/or difficulty with coordinating actuation of the device with inhalation.
- Current clinical evidence supports the efficacy of all products in this class for their FDA-approved indications, and efficacy is well established through placebo-controlled trials and systematic reviews and meta-analyses. Improvement in lung function, health status and/or respiratory symptoms vs placebo has been demonstrated for all products.
  - Limited comparisons among LAMAs have been conducted. Some have demonstrated differences, particularly for the lung function endpoints (ie, FEV_1), but no clear differences in symptoms or other patient-reported outcomes.
  - Tiotropium and umeclidinium have evidence supporting a reduction in COPD exacerbations; however, only tiotropium is indicated to reduce exacerbations per FDA-approved labeling.
- Safety is comparable among products. Key warnings/precautions include paradoxical bronchospasm, urinary retention, and ocular effects/narrow-angle glaucoma. Spiriva Handihaler, Tudorza, Incruse, and Seebri are pregnancy category C, while Atrovent HFA and ipratropium solution are pregnancy category B; Spiriva Respimat and Lonhala Magnair are not currently assigned a Pregnancy Category.
- GOLD guidelines recommend LAMAs for most patients with COPD, as they improve lung function, dyspnea, and health status, and reduce exacerbations.
  - There is no preference stated for one LAMA compared to another; however, the choice of agent should be based on an assessment of the patient's symptoms and risk of exacerbations.
  - LAMAs have a greater effect on exacerbation reduction compared to LABAs.
  - Guidelines emphasize that the use of long-acting bronchodilators is recommended over short-acting bronchodilators except for patients with only occasional dyspnea, and inhaled therapy is preferred.
- GINA guidelines recommend tiotropium Respimat be considered in patients aged ≥ 12 years whose asthma is not well controlled with an ICS/LABA combination; its FDA-approved indication extends its use to patients aged ≥ 6 years.

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