Therapeutic Class Overview
Inhaled Beta-Agonist Combination Agents

INTRODUCTION

- Inhaled beta$_2$-agonist combination agents include a beta$_2$-agonist combined with an inhaled corticosteroid (ICS), inhaled anticholinergic, or both. Beta$_2$-agonists can be short-acting beta$_2$-agonists (SABA) or long-acting beta$_2$-agonists (LABA); most combinations contain a LABA. Similarly, inhaled anticholinergics, also known as muscarinic antagonists, can be short-acting muscarinic antagonists (SAMA) or long-acting muscarinic antagonists (LAMA); most combinations contain a LAMA.
- Individual beta$_2$-agonist combinations are Food and Drug Administration (FDA) approved for the treatment of asthma, chronic obstructive pulmonary disease (COPD), or both.
  - All combinations of a beta$_2$-agonist and an ICS are indicated for the treatment of asthma, and some are additionally indicated for the treatment of COPD.
  - Combinations of a beta$_2$-agonist and an anticholinergic medication are indicated for COPD, as is the one available LAMA/LABA/ICS triple combination.
  - Refer to Tables 2A, 2B, and 2C for specific indications for each product.
- Asthma is a chronic lung disease that inflames and narrows the airways. 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 (U.S.), more than 25 million people are known to have asthma, including about 7 million children (National Heart, Lung, and Blood Institute [NHLBI], 2017).
- 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, and cigarette smoking is a key risk factor. Airflow limitation is caused by a combination of small airway disease (eg, obstructive bronchiolitis) and parenchymal destruction (emphysema). 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 U.S. population and is a major contributor to mortality from chronic lower respiratory diseases, the third leading cause of death in the U.S. (Centers for Disease Control and Prevention, 2017).
- Medispan class/subclass: Sympathomimetics/Adrenergic Combinations

Table 1. Medications Included Within Class Review

Drug	Generic Availability
Beta$_2$-agonist & corticosteroid combinations	
ADVAIR DISKUS & ADVAIR HFA (fluticasone propionate/salmeterol)	-
AIRDUO RESPICLICK (fluticasone propionate/salmeterol)	✔ *
BREO ELLIPTA (fluticasone furoate/vilanterol)	-
DULERA (mometasone furoate/formoterol fumarate dihydrate)	-
SYMBICORT (budesonide/formoterol fumarate dihydrate)	-
Beta$_2$-agonist & anticholinergic combinations	
ANORO ELLIPTA (umeclidinium/vilanterol)	-
BEVESPI AEROSPHERE (glycopyrrolate/formoterol fumarate)	-
COMBIVENT RESPIMAT (ipratropium/albuterol)	-
DUONEB (ipratropium/albuterol)	✔
STIOLTO RESPIMAT (tiotropium/olodaterol)	-
UTIBRON NEOHALER (glycopyrrolate/indacaterol)	-
Triple combination	
TRELEGY ELLIPTA (fluticasone furoate/umeclidinium/vilanterol)	-

*Authorized generic

(Drugs@FDA 2017; Orange Book: Approved Drug Products with Therapeutic Equivalence Evaluations, 2017)

INDICATIONS

Table 2A. FDA-Approved Indications for Beta$_2$-agonist/Corticosteroid Combination Agents

Indication	ADVAIR DISKUS	ADVAIR HFA	AIRDUO RESPICLICK	BREO ELLIPTA	DULERA	SYMBICORT
Treatment of asthma	✔ (age ≥4 years)	✔ (age ≥12 years)	✔ (age ≥12 years)	✔ (age ≥18 years)	✔ (age ≥12 years)	✔ (age ≥6 years)
Maintenance treatment of airflow obstruction in patients with COPD, including chronic bronchitis and/or emphysema	✔ (250/50 strength only)			✔ (100/25 strength only)		✔ (160/4.5 strength only)
To reduce exacerbations of COPD in patients with a history of exacerbations	✔ (250/50 strength only)			✔ (100/25 strength only)		✔ (160/4.5 strength only)

(Prescribing information: ADVAIR HFA, 2017; ADVAIR DISKUS, 2017; AIRDUO RESPICLICK, 2017; BREO ELLIPTA, 2017; DULERA, 2017; SYMBICORT, 2017)

Table 2B. FDA-Approved Indications for Beta$_2$-agonist/Anticholinergic Combination Agents

Indication	ANORO ELLIPTA	BEVESPI AEROSPHERE	COMBIVENT RESPIMAT	DUONEB	STIOLTO RESPIMAT	UTIBRON NEOHALER
Long-term, once-daily, maintenance treatment of airflow obstruction in patients with COPD, including chronic bronchitis and/or emphysema	✔				✔	
Long-term, twice-daily, maintenance treatment of airflow obstruction in patients with COPD		✔				✔
For use in patients with COPD on a regular aerosol bronchodilator who continue to have evidence of bronchospasm and who require a second bronchodilator			✔			
For the treatment of bronchospasm associated with COPD in patients requiring more than one bronchodilator				✔		

(Prescribing information: ANORO ELLIPTA, 2017; BEVESPI AEROSPHERE, 2016; COMBIVENT RESPIMAT, 2016; DUONEB, 2012; STIOLTO RESPIMAT, 2016; UTIBRON NEOHALER, 2017)

Table 2C. FDA-Approved Indication for Triple Combination Agent

Indication	TRELEGY ELLIPTA
Long-term, once-daily, maintenance treatment of airflow obstruction in patients with COPD, including chronic bronchitis and/or emphysema, who are on a fixed-dose combination of fluticasone furoate and vilanterol for airflow obstruction and reducing exacerbations in whom additional treatment of airflow obstruction is desired or for patients who are already receiving umeclidinium and a fixed-dose combination of fluticasone furoate and vilanterol.	✔

(TRELEGY ELLIPTA prescribing information, 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

Beta$_2$-agonist/corticosteroid combinations for asthma and COPD

Comparisons to placebo, monotherapy, combined use of individual components, varied treatments, or usual care:

- Numerous trials have compared the combination ICS/LABA products to their respective individual components as monotherapy, and in general, results have demonstrated that administration of the combination product is more effective than monotherapy for improving lung function and/or achieving control of symptoms in asthma and COPD (Bateman et al, 2001; Bateman et al, 2004; Bateman et al, 2006; Bateman et al, 2014; Berger et al, 2010; Bernstein et al, 2015; Bleecker et al, 2014; Calverley et al, 2003; Corren et al, 2007; Eid et al, 2010; FDA AirDuo RespiClick Medical Review, 2017; Gappa et al, 2009; Hanania et al, 2003; Jenkins et al, 2006; Kerwin et al, 2009; Kerwin et al, 2013; Kuna et al, 2006; Lalloo et al, 2003; Lundback et al, 2006; Martinez et al, 2013; Meltzer et al, 2012; Morice et al, 2007; Murphy et al, 2008; Nelson et al, 2003a; Nathan et al, 2006; Noonan et al, 2006; O'Byrne et al, 2014; Pearlman et al, 2004; Pearlman et al, 2017; Pohl et al, 2006; Raphael et al, 2016; Raphael et al, 2017; Rennard et al, 2009; Rodrigo et al, 2016; Rodrigo et al, 2017; Sharafkaneh et al, 2012; Sher et al, 2016; Sher et al, 2017; Tal et al, 2002; Tashkin et al, 2008; Vaessen-Verberne et al, 2010; Vestbo et al, 2005; Weinstein et al, 2010). Results for reducing COPD exacerbations have been inconsistent (Dransfield et al, 2013; Ohar et al, 2014).
- Although a synergistic effect of combination inhalers has been suggested by some data, overall there is similar efficacy between the administration of the combination ICS/LABA products and their individual components used in combination (Chapman et al, 1999; Jenkins et al, 2006; Marceau et al, 2006; Noonan et al, 2006; Nelson et al, 2003b; Perrin et al, 2010; Rosenhall et al, 2002). Improved adherence with combination inhalers has also been suggested but not shown conclusively (Marceau et al, 2006; Perrin et al, 2010).
- A large, double-blind, randomized trial (N=6,112) compared fluticasone propionate/salmeterol 500/50 mcg twice daily to its individual components and to placebo over a three-year period in patients with COPD (Calverley et al, 2007). The primary endpoint, time to death from any cause, for the combination vs placebo failed to reach statistical significance (12.6% vs 15.2%; P=0.052). However, the difference in mortality between the combination therapy and fluticasone monotherapy did reach statistical significance (12.6% vs 16%; P=0.007). Treatment with the combination regimen resulted in significantly fewer exacerbations, improved health status, and improved lung function compared with placebo.
- A large, double-blind, randomized trial (SUMMIT; N=16,590) evaluated the use of fluticasone furoate/vilanterol vs fluticasone furoate alone, vilanterol alone, or placebo in a population of patients with moderate COPD and heightened cardiovascular risk (age ≥60 years and receiving medication for >2 of the following: hypercholesterolemia, hypertension, diabetes mellitus, or peripheral arterial disease) (Vestbo et al, 2016a). Compared with placebo, there was no significant benefit or worsening in all-cause mortality with combination therapy (hazard ratio [HR], 0.88 [95% confidence interval (CI), 0.74 to 1.04; P=0.137]) or with the components (fluticasone furoate HR, 0.91 [95% CI, 0.77 to 1.08; P=0.284]; vilanterol HR, 0.96 [95% CI, 0.81 to 1.14; P=0.655]). Composite cardiovascular events were also similar in the four groups (3.9% to 4.4%). All treatments reduced the risk of moderate to severe COPD exacerbations compared to placebo, with percent reductions of 29% (95% CI, 22 to 35), 12% (95% CI, 4 to 19), and 10% (95% CI, 2 to 18) in the fluticasone furoate/vilanterol, fluticasone furoate, and vilanterol groups, respectively.

- A 12-month, randomized, open-label trial (Salford Lung Study; N=2,799) compared the use of fluticasone furoate/vilanterol 100/25 mcg daily to continuation of usual care in a real-world patient population in the United Kingdom (Vestbo et al, 2016b). Enrolled patients had COPD, had had one or more exacerbations in the previous three years, and were taking regular maintenance inhaler therapy (one or more long-acting bronchodilators; ICS alone or in combination with a long-acting bronchodilator; or a combination of ICS, LABA, and LAMA). The primary endpoint, the rate of moderate or severe exacerbations among patients who had had an exacerbation within one year before the trial, was 1.74 per year in the fluticasone furoate/vilanterol group and 1.90 per year in the usual-care group, for a difference of 8.4% (95% CI, 1.1 to 15.2; P=0.02). Serious adverse events, including pneumonia, were similar between the two groups.
- A meta-analysis of 19 trials evaluated the use of ICS/LABA combinations compared to placebo in patients with COPD, and demonstrated a significant reduction in exacerbation rate between fluticasone propionate/salmeterol and placebo and between budesonide/formoterol and placebo (Nannini et al, 2013). For the number of patients who experienced one or more exacerbations, the differences between fluticasone propionate/salmeterol vs placebo and mometasone furoate/formoterol 200/10 mcg strength vs placebo were not statistically significant; however, the mometasone furoate/formoterol 400/10 mcg strength was associated with a lower proportion of patients experiencing ≥1 exacerbation. This meta-analysis also demonstrated that when results for all combined inhalers vs placebo were pooled, there was an overall reduction in mortality (odds ratio [OR], 0.82; 95% CI, 0.68 to 0.99).
- A meta-analysis of 14 trials evaluated the use of ICS/LABA combinations compared to use of the same LABA as monotherapy in patients with COPD (Nannini et al, 2012). This analysis demonstrated that exacerbation rates were reduced with ICS/LABA combination therapy compared to LABA monotherapy (rate ratio, 0.76; 95% CI, 0.68 to 0.84). However, there was a significant increase in the incidence of pneumonia with combination therapy compared to LABA monotherapy (OR, 1.55; 95% CI, 1.2 to 2.01).
- A meta-analysis of 14 trials (total N=6,641) compared fluticasone furoate/vilanterol to placebo, fluticasone furoate monotherapy, fluticasone propionate monotherapy, vilanterol monotherapy, or fluticasone propionate/salmeterol in patients with asthma (Dwan et al, 2016). Primary endpoints included health-related quality of life (HRQoL) and severe asthma exacerbations (defined by hospital admission or treatment with oral corticosteroids). Fewer than half of the studies reported on these primary endpoints, and there were few opportunities to combine results from the included studies. One of the 14 studies evaluated HRQoL (as measured by the Asthma Quality of Life Questionnaire [AQLQ]) for fluticasone furoate/vilanterol 100/25 mcg vs placebo; it identified a significant advantage of fluticasone furoate/vilanterol (mean difference, 0.30; 95% CI, 0.14 to 0.46). Two studies compared fluticasone furoate/vilanterol 100/25 mcg vs placebo with respect to exacerbations; both studies reported no exacerbations in either treatment arm. No comparisons relevant to the primary outcomes were found for fluticasone furoate/vilanterol at a higher dose (200/25 mcg) vs placebo. There was insufficient evidence to assess whether once-daily fluticasone furoate/vilanterol had better or worse safety or efficacy compared to twice-daily fluticasone propionate/salmeterol. The authors stated that firm conclusions could not be drawn due to the limited number of studies, variety of endpoints, and short duration of most trials.
- Several large studies focused primarily on safety endpoints, with efficacy endpoints as secondary (Peters et al, 2016; Stempel et al, 2016a; Stempel et al, 2016b). The studies compared the use of ICS/LABA combinations to ICS monotherapy in patients with asthma. These studies each demonstrated non-inferiority of the ICS/LABA combination to ICS monotherapy for the risk of serious asthma-related events, offering reassurance for the safety of these agents.
  - A randomized, double-blind study (AUSTRI; N=11,679) enrolled adults and adolescents (age ≥12 years) with persistent asthma and a history of exacerbation within the previous year (Stempel et al, 2016a). Patients were randomized to receive fluticasone propionate/salmeterol or fluticasone propionate monotherapy for 26 weeks. Patients were stratified by their baseline asthma control questionnaire (ACQ)-6 score and current asthma medication to determine the fluticasone propionate dose (100, 250, or 500 mcg twice daily) and were randomized to receive this dose with or without concomitant salmeterol.
    - The primary safety endpoint was the first serious asthma-related event, a composite endpoint that included death, endotracheal intubation, and hospitalization. There were 36 events in 34 patients in the fluticasone propionate/salmeterol group and 38 events in 33 patients in the fluticasone propionate group (HR, 1.03; 95% CI, 0.64 to 1.66). Fluticasone propionate/salmeterol was shown to be non-inferior to fluticasone propionate for this endpoint. There were no asthma-related deaths.
    - The main efficacy endpoint was the first severe asthma exacerbation, defined as asthma deterioration leading to the use of systemic glucocorticoids for ≥3 days or an asthma-related hospitalization or emergency department visit leading to the use of systemic glucocorticoids. At least one severe asthma exacerbation was reported in 480

patients (8%) in the fluticasone propionate/salmeterol group and in 597 patients (10%) in the fluticasone propionate group (HR, 0.79; 95% CI, 0.70 to 0.89; P<0.001).
  - A similarly designed trial (VESTRI; N=6,208) enrolled pediatric patients 4 to 11 years of age (Stempel et al, 2016b). Enrolled patients had a history of exacerbation within the previous year and consistent use of asthma medication during the 4 weeks before enrollment. Patients were randomized, on the basis of pretrial medication, Childhood Asthma Control Test (C-ACT) score, and exacerbation history, to receive fluticasone propionate/salmeterol 100/50 mcg or 250/50 mcg or fluticasone propionate alone 100 mcg or 250 mcg twice daily for 26 weeks.
    - The primary safety endpoint, the first serious asthma-related event (death, intubation, or hospitalization), occurred in 27 patients in the fluticasone propionate/salmeterol group and 21 patients in the fluticasone propionate group (HR, 1.28; 95% CI, 0.73 to 2.27); this demonstrated non-inferiority for fluticasone propionate/salmeterol compared to fluticasone propionate (P=0.006). All of the events were asthma-related hospitalizations; there were no deaths or asthma-related intubations in either group.
    - The primary efficacy endpoint was the first severe asthma exacerbation, defined as asthma deterioration leading to the use of systemic glucocorticoids for ≥3 days or a depot injection of glucocorticoids. One or more severe asthma exacerbations occurred in 8.5% of patients in the fluticasone propionate/salmeterol group and 10.0% of patients in the fluticasone propionate group (HR, 0.86; 95% CI, 0.73 to 1.01).
  - An additional randomized, double-blind trial (N=11,693) compared the safety of formoterol/budesonide to budesonide alone in patients ≥12 years of age (Peters et al, 2016). Enrolled patients were receiving daily asthma medication and had had at least one exacerbation in the previous year. Patients were stratified to a dose level of budesonide on the basis of asthma control and prior treatment. Patients were then randomized to receive budesonide/formoterol (two actuations of 80/4.5 mcg or 160/4.5 mcg) or budesonide alone (two actuations of 80 mcg or 160 mcg) twice daily for 26 weeks.
    - The primary safety endpoint, the first serious adverse event (death, intubation, or hospitalization), occurred in 43 of 5,846 patients receiving budesonide/formoterol and 40 of 5,847 patients receiving formoterol alone (HR, 1.07; 95% CI, 0.70 to 1.65); this demonstrated non-inferiority for budesonide/formoterol vs budesonide alone. Two of the events (both in the budesonide/formoterol group) were asthma-related deaths; the remaining events were asthma-related hospitalizations.
    - The primary efficacy endpoint, the first asthma exacerbation (defined as a deterioration of asthma requiring systemic glucocorticoids for ≥3 days, inpatient hospitalization for asthma, or an emergency department visit for asthma that resulted in receipt of systemic glucocorticoids) occurred in 9.2% of patients in the budesonide/formoterol group and 10.8% of patients in the budesonide group (HR, 0.84; 95% CI, 0.74 to 0.94).

<u>Comparisons between different ICS/LABA combinations</u>

- There are some data available comparing different combination ICS/LABA products for the treatment of COPD.
  - One crossover study comparing budesonide/formoterol to fluticasone propionate/salmeterol demonstrated no significant difference between products for the primary endpoint, the increase from baseline in peak expiratory flow five minutes after the morning dose (Partridge et al, 2009). However, the mean morning forced expiratory volume in one second (FEV_1) improved more with budesonide/formoterol at five minutes and 15 minutes post-dose compared to fluticasone propionate/salmeterol.
  - Several published trials compared fluticasone furoate/vilanterol to fluticasone propionate/salmeterol in patients with COPD. Three of the trials were published together; pooled results demonstrated a greater improvement with fluticasone furoate/vilanterol 100/25 mcg once daily compared to fluticasone propionate/salmeterol 250/50 mcg twice daily on the primary endpoint, the weighted mean (wm) FEV_1 (0 to 24 hr) (Dransfield et al, 2014). However, two of these three trials did not demonstrate a significant difference on this endpoint. An additional trial compared fluticasone furoate/vilanterol 100/25 mcg daily to fluticasone propionate/salmeterol 500/50 mcg twice daily, and found no significant difference between groups on the wm FEV_1 (0 to 24 hr) (Agusti et al, 2014).
- There have been several trials comparing combination ICS/LABA products to one another for the treatment of asthma.
  - Several head-to-head trials have compared budesonide/formoterol to fluticasone propionate/salmeterol. The trials varied in their design and the doses of medications. In general, these head-to-head trials have failed to demonstrate that one product is consistently superior to the other. Some trials showed benefits for fluticasone propionate/salmeterol on some endpoints (Dahl et al, 2006; Fitzgerald et al, 2005; Price et al, 2007); some showed benefits for budesonide/formoterol (Aalbers et al, 2004; Palmqvist et al, 2001), and another showed no significant differences between the two products (Busse et al, 2008).

- A meta-analysis of five trials comparing fluticasone propionate/salmeterol 250/50 mcg twice daily vs varied doses of budesonide/formoterol twice daily failed to demonstrate significant differences in exacerbations, asthma-related serious adverse events, FEV_1, rescue medication use, symptom scores, or peak expiratory flow (Lasserson et al, 2011).
- A head-to-head trial comparing mometasone/formoterol to fluticasone propionate/salmeterol demonstrated non-inferiority for mometasone/formoterol for the primary endpoint of FEV_1 area under the curve (AUC) (0 to 12 hr) (Bernstein et al, 2011). Treatment with mometasone/formoterol demonstrated a rapid onset of action, with significantly greater effects on FEV_1 at all time points up to 30 minutes post-dose compared to fluticasone propionate/salmeterol. Other secondary endpoints were not significantly different between groups.
- A head-to-head trial comparing fluticasone furoate/vilanterol 100/25 mcg daily to fluticasone propionate/salmeterol 250/50 mcg twice daily demonstrated no significant differences between treatments on the primary endpoint, the wm FEV_1 (0 to 24 hr) (Woodcock et al, 2013). There were also no significant differences in key secondary endpoints, including the time to onset of bronchodilator effect, percentage of patients obtaining ≥12% and ≥200 mL increase from baseline in FEV_1 at 12 hours and 24 hours, and change from baseline in trough FEV_1.

ICS/LABA compared to tiotropium or in combination with tiotropium for COPD

- A double-blind, double-dummy, two-year trial (N=1,323) compared the use of fluticasone propionate/salmeterol 250/50 mcg twice daily to tiotropium 18 mcg daily in patients with COPD (Wedzicha et al, 2008). This trial demonstrated no significant difference between groups in the rate of exacerbations or post-dose FEV_1. The study demonstrated higher mortality in the tiotropium group (6%) compared to the fluticasone propionate/salmeterol group (3%). This study was limited by the high number of withdrawals, which were unevenly distributed between the study arms.
- A double-blind, double-dummy, 12-week trial (N=494) compared the use of umeclidinium/vilanterol 62.5/25 mcg daily to tiotropium 18 mcg daily in patients with COPD who had been treated with tiotropium monotherapy at the time of enrollment (Kerwin et al, 2017). The primary endpoint, trough FEV_1, showed improved efficacy in the group that stepped up to combination therapy, with a between-group difference of 88 mL (95% CI, 45 to 131; P<0.001). Improvements with umeclidinium/vilanterol were also observed in some secondary endpoints, including the use of rescue medication use and transition dyspnea index (TDI) score.
- A double-blind, double-dummy, 12-week trial (N=623) evaluated the use of fluticasone furoate/vilanterol 100/25 mcg daily and tiotropium 18 mcg daily in patients with moderate-to-severe COPD and an increased cardiovascular risk (Covelli et al, 2015). There was no significant difference in the primary endpoint, the change from baseline in wm FEV_1 (0 to 24 hr). Minor differences were noted in some secondary efficacy endpoints and in the safety profiles. Pneumonia occurred more frequently in the fluticasone furoate/vilanterol group, and two patients in the tiotropium group died following cardiovascular events. The duration of this trial was not long enough to allow any firm conclusions about the relative efficacy and safety of fluticasone furoate/vilanterol vs tiotropium.
- Several trials have evaluated the potential benefits of adding a combination ICS/LABA to tiotropium vs the use of tiotropium alone in patients with COPD. These trials generally demonstrated an improvement in FEV_1 and some other lung function, symptom score, and quality-of-life endpoints (Hanania et al, 2012; Lee et al, 2016; Welte et al, 2009). Some trials (Lee et al, 2016; Welte et al, 2009) also demonstrated a reduction in the risk of COPD exacerbations or severe exacerbations; however, other trials and a meta-analysis have not confirmed a significant benefit for exacerbations (Aaron et al, 2007; Hanania et al, 2012; Karner et al, 2011).

Beta$_2$-agonist/anticholinergic combinations for COPD

Comparisons of combination beta$_2$-agonist/anticholinergic products to bronchodilator monotherapy:

- Numerous trials have compared the combination beta$_2$-agonist/anticholinergic products to their respective individual components as monotherapy, and in general, results have demonstrated that administration of the combination product is more effective than monotherapy for improving lung function and/or achieving control of symptoms in COPD (Beeh et al, 2015; Bone et al, 1994; Buhl et al, 2015; Decramer et al, 2014; Donohue et al, 2013; Dorinsky et al, 1999; Friedman et al, 1999; Hanania et al, 2017; Mahler et al, 2015; Martinez et al, 2017).
- A systematic review of 23 studies of beta$_2$-agonist/anticholinergic combinations compared to their monocomponents and to other single-agent treatments in patients with COPD was conducted (Price et al, 2016). The analysis demonstrated that beta$_2$-agonist/anticholinergic combinations significantly improved lung function compared to their individual components. These combinations generally improved other outcomes compared to monotherapies as well, including

symptoms and health status, but there were some discrepancies between lung function results and these patient-reported outcomes.

Comparisons of combination beta$_2$-agonist/anticholinergic products to each other or to other bronchodilator combinations

- A 12-week, non-inferiority, randomized, double-blind, triple-dummy, parallel group study (N=967) compared umeclidinium/vilanterol (62.5/25 mcg once daily) to tiotropium (18 mcg once daily) plus indacaterol (150 mcg once daily) (Kalberg et al, 2016). When comparing trough FEV_1 on day 85, umeclidinium/vilanterol demonstrated non-inferiority to combination treatment with tiotropium and indacaterol. Other measures, including rescue medication use, TDI focal scores, and St. George's Respiratory Questionnaire (SGRQ) scores, were also similar between both treatment groups on day 85 (P values not provided).
- A meta-analysis of 26 randomized controlled trials comparing the efficacy of umeclidinium/vilanterol, indacaterol/glycopyrrolate, formoterol plus tiotropium, salmeterol plus tiotropium, or indacaterol plus tiotropium to tiotropium alone found that umeclidinium/vilanterol was comparable to other LAMA/LABA fixed dose combination agents with respect to trough FEV_1, SGRQ scores, TDI focal scores, and need for rescue medication use (Huisman et al, 2015).
- A meta-analysis of 27 trials (N=30,361) including 4 LAMA/LABA fixed-dose combination agents (aclidinium/formoterol 400/12 mcg [not FDA approved for use in the U.S.], glycopyrrolate/indacaterol 110/50 mcg, tiotropium/olodaterol 5/5 mcg, and umeclidinium/vilanterol 62.5/25 mcg) showed non-significant differences in efficacy, exacerbations, and discontinuation rates (Schlueter et al, 2016). Safety profiles were also similar among the products.

ICS/LABA compared to LAMA/LABA combinations for COPD

- A randomized, double-blind, 12-week trial (N=717) compared umeclidinium/vilanterol 62.5/25 mcg once daily to fluticasone propionate/salmeterol 500/50 mcg twice daily in patients with moderate to severe COPD and no exacerbations in the previous year (Singh et al, 2015). It should be noted that the dose of fluticasone propionate was higher than what is recommended in the U.S. for treatment of COPD. Treatment with umeclidinium/vilanterol resulted in greater improvement in lung function than fluticasone propionate/salmeterol, with a difference of 80 mL (95% CI, 46 to 113) in the wm FEV_1 (0 to 24 hr) and a difference of 90 mL (95% CI, 55 to 125) in trough FEV_1. Effects on rescue bronchodilator use, mean TDI focal score, and SGRQ total scores, and the incidence of adverse events, were similar between groups.
- Two randomized, double-blind, 12-week trials (N=707 and N=700; reported together) compared umeclidinium/vilanterol 62.5/25 mcg daily to fluticasone propionate/salmeterol 250/50 mcg twice daily in patients with moderate to severe COPD without exacerbations in the previous year (Donohue et al, 2015). These trials also demonstrated a greater improvement in lung function endpoints for umeclidinium/vilanterol compared to fluticasone propionate/salmeterol, with differences in wm FEV_1 (0 to 24 hr) and trough FEV_1 ranging from 74 to 101 mL ($P<0.001$ for all comparisons). Adverse event rates and effects on TDI score and SGRQ were similar between groups.
- A randomized, double-blind, 26-week trial (ILLUMINATE; N=523) compared indacaterol/glycopyrrolate 110/50 mcg daily to fluticasone propionate/salmeterol 500/50 mcg twice daily in patients with COPD and a history of at least one exacerbation during the previous year (Vogelmeier et al, 2013). The dosing regimens for indacaterol/glycopyrrolate and fluticasone propionate/salmeterol evaluated in this study are different from those available and/or recommended for COPD in the U.S. The primary endpoint, FEV_1 AUC (0 to 12 hr), was significantly higher with indacaterol/glycopyrrolate than fluticasone propionate/salmeterol, with a treatment difference of 138 mL (95% CI, 100 to 176; $P<0.0001$). Benefits were also seen for indacaterol/glycopyrrolate for some secondary endpoints, including additional lung function measures, change from baseline in rescue medication use, and TDI focal score; the difference in SGRQ was not statistically significant.
- A large, randomized, double-blind, 52-week trial (FLAME; N=3,362) compared indacaterol/glycopyrrolate 110/50 mcg daily to fluticasone propionate/salmeterol 500/50 mcg twice daily in patients with COPD and a history of at least one exacerbation during the previous year (Wedzicha et al, 2016). Again, these dosing regimens varied from U.S. recommendations. The primary endpoint, the annual rate of all COPD exacerbations, was 11% lower in the indacaterol/glycopyrrolate group than in the fluticasone propionate/salmeterol group (3.59 vs 4.03; rate ratio, 0.89; 95% CI, 0.83 to 0.96; P=0.003). Lung function was also improved to a greater extent with indacaterol/glycopyrrolate, with a difference in trough FEV_1 of 62 mL between groups ($P<0.001$).
- A randomized, double-blind, crossover trial (N=229) evaluated the use of tiotropium/olodaterol 2.5/5 mcg and 5/5 mcg once daily and fluticasone propionate/salmeterol 250/50 mcg and 500/50 mcg twice daily in patients with moderate to severe COPD; each patient received each of the four treatments for 6 weeks separated by 3-week washout periods

(Beeh et al, 2016). The lower dose of each combination is the dose available/recommended for COPD in the U.S. The primary endpoint, FEV_1 AUC (0 to 12 hr), was greater for the tiotropium/olodaterol regimens (range, 295 to 317 mL) than for the fluticasone propionate/salmeterol regimens (range, 188 to 192 mL) (P<0.0001). FEV_1 AUC (12 to 24 hr) and FEV_1 AUC (0 to 24 hr) also favored tiotropium/olodaterol. Rates of adverse events were similar among the treatments.

Triple combination for COPD

- Fluticasone furoate/umeclidinium/vilanterol is the first FDA-approved "closed triple" inhaler – an inhaler containing 3 active ingredients: an ICS, a LAMA, and a LABA. FDA approval was based primarily on the coadministration of umeclidinium plus the fluticasone furoate/vilanterol combination.
- Two 12-week randomized studies (N=619 and N=620; published together) evaluated the efficacy and safety of double-blind treatment with umeclidinium 62.5 mcg, umeclidinium 125 mcg, or placebo when added to open-label fluticasone furoate/vilanterol 100/25 mcg (Siler et al, 2015). In both studies, the primary endpoint, trough FEV_1, was significantly improved with the addition of umeclidinium, with improvements ranging from 111 to 128 mL (P<0.001 for all comparisons vs placebo). Improvement was also demonstrated on the secondary endpoint of wm FEV_1 (0 to 6 hr), with improvements ranging from 125 to 153 mL (P<0.001 for all comparisons vs placebo). SGRQ results were inconsistent. No substantial benefit was observed with umeclidinium 125 mcg over 62.5 mcg, which is consistent with findings in the umeclidinium monotherapy studies.
- Once-daily triple therapy with fluticasone furoate/umeclidinium/vilanterol has also been compared to twice-daily budesonide/formoterol 400/12 mcg in a 24-week, double-blind, double-dummy randomized trial (FULFIL; N=1810) (Lipson et al, 2017). The formulation/dosing regimen of budesonide/formoterol in this trial is different from the formulation available in the U.S. The trial demonstrated improvements in the change from baseline in trough FEV_1 (difference, 171 mL; 95% CI, 148 to 194; P<0.001), SGRQ (difference, -2.2; 95% CI, -3.5 to -1.0; P<0.001), and the rate of moderate/severe exacerbations (rate ratio, 0.65; 95% CI, 0.49 to 0.86; P=0.002). Although the comparator regimen is not available in the U.S., this trial further supports the efficacy of triple inhaler therapy with fluticasone furoate/umeclidinium/vilanterol.
- Preliminary information from the IMPACT study (N=10,335) has been made available from the fluticasone furoate/umeclidinium/vilanterol manufacturer (GlaxoSmithKline, 2017). This study demonstrated a reduction in moderate/severe exacerbations with fluticasone furoate/umeclidinium/vilanterol 100/62.5/25 mcg (0.91 exacerbations per year) compared to each of two dual COPD therapies, fluticasone furoate/vilanterol 100/25 mcg (1.07 per year) and umeclidinium/vilanterol 62.5/25 mcg (1.21 per year); P<0.001 for comparisons of fluticasone furoate/umeclidinium/vilanterol to each dual therapy. Significant improvements were also seen in key secondary endpoints, including trough FEV_1 and SGRQ.

CLINICAL GUIDELINES

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 ICS, 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. ICS 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).
  - LABA are used in combination with ICS for long-term control and prevention of symptoms in moderate or severe persistent asthma.
  - Of the adjunctive treatments available, a LABA is the preferred option to combine with an ICS in patients 12 years of age and older. This combination is also an option in selected patients 5 to 12 years of age.
- The Global Initiative for Asthma (GINA) guideline also provides a stepwise approach to asthma management. It recommends an ICS as a preferred 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, omalizumab, mepolizumab) (GINA, 2017).

- The available asthma guidelines are generally similar; however, one difference among them is the recommendation of ICS/formoterol as both maintenance and rescue therapy by the GINA guidelines. The NHLBI do not recommend LABA medications for the management of acute asthma symptoms or exacerbations (GINA, 2017; NHLBI, 2007).

COPD

- The 2017 GOLD guidelines underwent a significant update from prior guideline versions, and the 2018 GOLD report is a minor revision of the 2017 GOLD Report. The guidelines state that the management strategy for stable COPD should be predominantly based on an assessment of the patient's symptoms and future risk of exacerbations. The risk of exacerbations is now based solely on the exacerbation history, whereas in previous versions of the guideline, risk assessment also included consideration of airflow limitation assessed by spirometry. Key recommendations from the GOLD guidelines are as follows (GOLD, 2018):
  - Inhaled bronchodilators are recommended over oral bronchodilators.
  - LAMA and LABA are preferred over short-acting agents except for patients with only occasional dyspnea.
  - 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.
  - Combination treatment with a LABA and LAMA reduces exacerbations compared to monotherapy or ICS/LABA.
  - LAMA have a greater effect on exacerbation reduction compared to LABA and decrease hospitalizations.
  - Combination treatment with a LABA and LAMA increases FEV_1 and reduces symptoms compared to monotherapy.
  - Combinations of LAMA and LABA in a single inhaler improve lung function compared to placebo; the improvement is greater than long-acting bronchodilator monotherapy, but less than fully additive of effects for the individual components. In studies where patient-reported outcomes are the primary endpoint or in pooled analyses, combination bronchodilators have a greater impact on these endpoints compared to monotherapies.
  - Long-term monotherapy with ICS is not recommended. Long-term treatment with ICS may be considered in association with LABA for patients with a history of exacerbations despite treatment with long-acting bronchodilators.
  - An ICS combined with a LABA is more effective than the individual components in improving lung function and health status and reducing exacerbations in patients with exacerbations and moderate to very severe COPD. However, regular treatment with ICS increases the risk of pneumonia, especially in those with severe disease.
  - Triple inhaled therapy of ICS/LAMA/LABA 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 two bronchodilators is recommended (LAMA + LABA). For patients with severe breathlessness, initial therapy with two 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

Moderate/Severe 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

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

- Guidelines from the American College of Chest Physicians and the Canadian Thoracic Society for prevention of acute exacerbations of COPD state that LAMA/LABA combinations are effective in reducing acute COPD exacerbations, but do not state that this combination is superior to LAMA monotherapy (Criner et al, 2015).

SAFETY SUMMARY

Beta$_2$-agonist/corticosteroid combinations

- Beta$_2$-agonist/ICS combinations are generally contraindicated for the primary treatment of status asthmaticus or other acute episodes of asthma/COPD where intensive measures are required.
- Beta$_2$-agonist/ICS combinations are generally contraindicated in patients with hypersensitivity to any ingredients in the formulation. ADVAIR DISKUS, AIRDUO RESPICLICK, and BREO ELLIPTA are specifically contraindicated in patients with a severe hypersensitivity to milk proteins.
- Previously, ICS/LABA combinations had a boxed warning about an increased risk of asthma-related death, which had been observed with the LABA salmeterol. However, the boxed warning was removed from the prescribing information for ICS/LABA combinations in December 2017 based on an FDA review of four large clinical safety trials, which demonstrated that these combinations do not result in a significantly increased risk of asthma-related death, hospitalizations, or the need for intubation compared to ICS alone. There is still a warning/precaution in the prescribing information of ICS/LABA combinations related to the increased risk of asthma-related death with LABA monotherapy. A description of the clinical safety trials with ICS/LABA combinations has been added to the prescribing information for these products (FDA, 2017).
- Other key warnings and precautions include:
  - Significant cardiovascular effects and fatalities with excessive use of beta$_2$-agonists
  - Cardiovascular and/or central nervous system effects from beta-adrenergic stimulation (seizures, angina, hypertension or hypotension, tachycardia, arrhythmias, nervousness, headache, tremor, palpitation, nausea, dizziness, fatigue, malaise, and insomnia)
  - Paradoxical bronchospasm
  - Hypercorticism and adrenal suppression due to systemic absorption of the corticosteroid
  - The need for caution when transferring patients from systemic corticosteroid therapy (deaths due to adrenal insufficiency have occurred)
  - Lower respiratory tract infections/pneumonia
  - Local infections of the mouth and pharynx with *candida albicans*
  - Reduced growth velocity in pediatric patients
  - The potential for drug interactions with strong cyp3a4 inhibitors; concomitant use is not recommended due to the potential for increased systemic effects
  - The potential for developing glaucoma, increased intraocular pressure, or cataracts
  - Immunosuppression
  - Hypersensitivity
  - Reduction in bone mineral density
- It is also important to note that ICS/LABA combinations should not be initiated in the setting of disease deterioration or potentially life-threatening episodes.
- Commonly reported adverse events (≥5% for at least one medication in the class) include oral candidiasis, hoarseness/dysphonia, nasopharyngitis/pharyngitis, pharyngolaryngeal/oropharyngeal pain, sinusitis, upper respiratory

tract infection, upper respiratory tract inflammation, bronchitis, cough, headache, gastrointestinal discomfort, and nausea/vomiting.

Beta$_2$-agonist/anticholinergic combinations

- Both albuterol/ipratropium combination products are contraindicated in patients with hypersensitivity to any component of the product, or hypersensitivity to atropine or its derivatives. ANORO ELLIPTA is contraindicated in patients with hypersensitivity to any component of the product, as well as in patients with severe hypersensitivity to milk proteins. BEVESPI AEROSPHERE and UTIBRON NEOHALER are contraindicated in patients with hypersensitivity to any component of the product. BEVESPI AEROSPHERE, STIOLTO RESPIMAT, and UTIBRON NEOHALER are all contraindicated in patients with asthma without use of a long-term asthma control medication (and are not indicated for the treatment of asthma).
- There are no boxed warnings for the albuterol/ipratropium combination products. ANORO ELLIPTA, BEVESPI AEROSPHERE, STIOLOTO RESPIMAT and UTIBRON NEOHALER have boxed warnings stating that LABA increase the risk of asthma-related death. Data from a large placebo-controlled U.S. trial that compared the safety of another LABA (salmeterol) with placebo added to usual asthma therapy showed an increase in asthma-related deaths in subjects receiving salmeterol. This finding with salmeterol is considered a class effect of all LABA, including formoterol, one of the active ingredients in BEVESPI AEROSPHERE, indacaterol, one of the active ingredients in UTIBRON NEOHALER, vilanterol, one of the active ingredients in ANORO ELLIPTA, and olodaterol, one of the active ingredients in STIOLOTO RESPIMAT. The safety and efficacy of ANORO ELLIPTA, BEVESPI AEROSPHERE, STIOLOTO RESPIMAT, and UTIBRON NEOHALER in patients with asthma have not been established, and these products are not indicated for the treatment of asthma.
- Warnings and precautions are very similar among products, and include the following:
  - Paradoxical bronchospasm: May produce paradoxical bronchospasm, which can be life-threatening. If it occurs, the product should be discontinued and alternative therapy instituted.
  - Cardiovascular effect: Beta$_2$-agonists can produce a significant cardiovascular effect in some patients, as measured by pulse rate, blood pressure, and/or symptoms. If these symptoms occur, the product may need to be discontinued. In addition, electrocardiogram (ECG) changes may occur. These products should be used with caution in patients with cardiovascular disorders, especially coronary insufficiency, cardiac arrhythmias, and hypertension.
  - Ocular effects: Ipratropium and other anticholinergic agents may increase intraocular pressure, which may precipitate or worsen narrow-angle glaucoma. They should be used with caution in patients with narrow-angle glaucoma. In addition, patients should avoid spraying product into eyes, as this can cause eye pain and visual symptoms.
  - Urinary retention: Ipratropium and other anticholinergic agents may cause urinary retention. Caution is advised when administering to patients with prostatic hyperplasia or bladder-neck obstruction.
  - The recommended dose should not be exceeded: Fatalities have been reported in association with excessive use of inhaled sympathomimetic drugs in patients with asthma.
  - Hypersensitivity reactions: Urticaria, angioedema, rash, pruritus, bronchospasm, laryngospasm, oropharyngeal edema, and anaphylaxis may occur. If such a reaction occurs, therapy should be discontinued and alternative treatment considered.
  - Coexisting conditions: Due to the beta$_2$-agonist component, caution is advised in patients with convulsive disorders, hyperthyroidism, or diabetes mellitus, and in patients who are unusually responsive to sympathomimetic amines.
  - Hypokalemia: β-agonists may produce significant hypokalemia in some patients, which has the potential to produce adverse cardiovascular effects. The decrease in serum potassium is usually transient, not requiring supplementation.
  - Drug interactions with strong cytochrome P4503A4 inhibitors; increased cardiovascular effects may occur (ANORO ELLIPTA only).
  - Reports of anaphylactic reactions in patients with severe milk protein allergy (ANORO ELLIPTA only).
  - Deterioration of disease and acute episodes; drug has not been studied in this setting and is not to relieve acute symptoms (ANORO ELLIPTA and STIOLTO RESPIMAT only).
- Adverse reactions are similar among products and include back pain, bronchitis, upper respiratory infection, lung disease, headache, dyspnea, nasopharyngitis/pharyngitis, and cough.
- In a 12-week trial comparing COMBIVENT RESPIMAT to COMBIVENT inhalation aerosol, rates of adverse reactions were very similar between groups. In a 48-week safety trial, most adverse reactions were similar in type and rate between treatment groups; however, cough occurred more frequently in patients enrolled in the COMBIVENT RESPIMAT group (7%) than the COMBIVENT inhalation aerosol group (2.6%).

- The choice of a specific LAMA/LABA fixed dose combination product is not based on any difference in the safety profile (Matera et al, 2016).

Triple combination

- TRELEGY ELLIPTA is contraindicated in patients with severe hypersensitivity to milk proteins or any ingredients in the formulation.
- TRELEGY ELLIPTA has a boxed warning noting that LABA such as vilanterol increase the risk of asthma-related death. TRELEGY ELLIPTA is not indicated for the treatment of asthma.
- Similar to other combination agents for COPD (and/or asthma), TRELEGY ELLIPTA has a number of additional warnings and precautions; these include:
  - Not initiating in patients with rapidly deteriorating COPD
  - Avoiding excessing use
  - Local effects of ICS
  - Risk of pneumonia
  - Immunosuppression
  - Using caution when transferring patients from systemic corticosteroid therapy
  - Hypercorticism and adrenal suppression
  - Drug interactions with strong cytochrome P450 3A4 inhibitors
  - Paradoxical bronchospasm
  - Hypersensitivity reactions
  - Cardiovascular effects
  - Reduction in bone mineral density
  - Glaucoma and cataracts
  - Urinary retention
  - Using caution in patients with certain coexisting conditions such as convulsive disorders or thyrotoxicosis
  - Hypokalemia and hyperglycemia
- The most common adverse reactions with TRELEGY ELLIPTA include headache, back pain, dysgeusia, diarrhea, cough, oropharyngeal pain, and gastroenteritis.

DOSING AND ADMINISTRATION

Table 4. Dosing and Administration

Drug	Available Formulations	Components/ Dose Strengths	Route	Usual Recommended Frequency
Beta$_2$-agonist & corticosteroid combinations				
ADVAIR DISKUS	Inhalation powder	fluticasone propionate/salmeterol 100/50, 250/50 & 500 mcg	Inhalation	2 times daily
ADVAIR HFA	Aerosol inhaler	fluticasone propionate/salmeterol 45/21, 115/21 & 230/21 mcg	Inhalation	2 times daily
AIRDUO RESPICLICK	Inhalation powder	fluticasone propionate/salmeterol 55/14, 113/14 & 232/14 mcg	Inhalation	2 times daily
BREO ELLIPTA	Inhalation powder	fluticasone furoate/vilanterol 100/25 & 200/25 mcg	Inhalation	Once daily
DULERA	Aerosol inhaler	mometasone furoate/ formoterol fumarate dihydrate 100/5 & 200/5 mcg	Inhalation	2 times daily
SYMBICORT	Aerosol inhaler	budesonide/ formoterol fumarate dihydrate 80/4.5 & 160/4.5 mcg	Inhalation	2 times daily
Beta$_2$-agonist & anticholinergic combinations				
ANORO ELLIPTA	Inhalation powder	umeclidinium/vilanterol 62.5/25 mcg	Inhalation	Once daily

Drug	Available Formulations	Components/ Dose Strengths	Route	Usual Recommended Frequency
BEVESPI AEROSPHERE	Inhalation spray	glycopyrrolate/formoterol fumarate 9/4.8 mcg	Inhalation	2 times daily
COMBIVENT RESPIMAT	Inhalation spray	ipratropium bromide/albuterol 20/100 mcg	Inhalation	4 times daily
DUONEB	Nebulizer solution	ipratropium bromide/albuterol sulfate 0.5/3 mg	Inhalation (nebulizer)	4 times daily
STIOLTO RESPIMAT	Inhalation spray	tiotropium bromide/olodaterol 2.5/2.5 mcg	Inhalation	Once daily
UTIBRON NEOHALER	Inhalation powder	indacaterol/glycopyrrolate 27.5/15.6 mcg	Inhalation	2 times daily
Triple combination				
TRELEGY ELLIPTA	Inhalation powder	fluticasone furoate/ umeclidinium/vilanterol 100/62.5/25 mcg	Inhalation	Once daily

See the current prescribing information for full details.

CONCLUSION

- Inhaled medications are a mainstay of treatment for asthma and COPD, and a large amount of clinical evidence supports the safety and efficacy of beta$_2$-agonist combinations for these indications.
- Trials have demonstrated that the combination products have efficacy that is superior to the individual separate components given as monotherapy for the treatment of both asthma and COPD.
- For the treatment of asthma, current guidelines support the use of combination ICS/LABA products for long-term control and prevention of symptoms in patients who do not achieve sufficient symptom control with an ICS as monotherapy (GINA, 2017; NHLBI, 2007). Single-agent LABA therapy should not be used for asthma management due to the increased risk of asthma-related death, as well as asthma-related hospitalization in pediatric and adolescent patients. However, recent drug safety information from the FDA states that no significantly increased risk of serious asthma outcomes has been seen with the use of ICS/LABA combinations, and boxed warnings about this potential risk have been removed from the prescribing information for the ICS/LABA combinations (FDA, 2017).
  - A practical benefit of ICS/LABA combinations is that their use ensures that patients are not using a LABA without concomitant ICS.
- For the treatment of COPD, GOLD guidelines recommend the use of ICS/LABA products as an option for some patients at higher risk of exacerbations; however, the use of bronchodilator(s) without an ICS is recommended as first-line treatment for most COPD patients. The use of LAMA/LABA combination therapy as a first- or second-line treatment is recommended in most patients with COPD, with the exception of low-risk patients with milder symptoms (GOLD, 2018).
- None of the current asthma or COPD treatment guidelines recommend the use of one specific combination product over another (Criner et al, 2015; GINA, 2017; GOLD, 2018; NHLBI, 2007).
- Several single-ingredient inhalers containing beta$_2$-agonists, ICS, or anticholinergics are also available. Beta$_2$-agonist combinations offer improved convenience over the use of multiple separate inhalers.

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