

## Therapeutic Class Overview

### Respiratory Beta-Agonist Combination Agents

#### INTRODUCTION

- Respiratory beta<sub>2</sub>-agonist combination agents include a beta<sub>2</sub>-agonist combined with an inhaled corticosteroid (ICS), inhaled anticholinergic, or both. Beta<sub>2</sub>-agonists can be short-acting beta<sub>2</sub>-agonists (SABA) or long-acting beta<sub>2</sub>-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<sub>2</sub>-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<sub>2</sub>-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<sub>2</sub>-agonist and an anticholinergic medication are indicated for COPD.
  - The 2 available triple combination agents (consisting of LAMA/LABA/ICS) are indicated for COPD and one is also indicated for asthma.
  - 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 in the lungs. 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 2019, asthma affected an estimated 20 million adults and 5.1 million children in the United States (U.S.) (*Centers for Disease Control and Prevention [CDC] 2021, National Heart, Lung, and Blood Institute [NHLBI] Web site*).
- 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] 2021*). 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. (*CDC 2019*).
- Utibron Neohaler (glycopyrrolate/indacaterol) was previously available but was discontinued in March 2020 (*FDA Drug Shortages 2020*).
- Medispan class/subclass: Sympathomimetics/Adrenergic Combinations

**Table 1. Medications Included Within Class Review\***

Drug	Generic Availability
<b>Beta<sub>2</sub>-agonist &amp; corticosteroid combinations</b>	
Advair Diskus & Advair HFA (fluticasone propionate/salmeterol)	✓ ‡
AirDuo RespiClick & AirDuo Digihaler (fluticasone propionate/salmeterol)	✓ †
Breo Ellipta (fluticasone furoate/vilanterol)	-
Dulera (mometasone furoate/formoterol fumarate dihydrate)	-
Symbicort (budesonide/formoterol fumarate dihydrate)	✓ †
Wixela Inhub (fluticasone propionate/salmeterol)	✓ ‡
<b>Beta<sub>2</sub>-agonist &amp; anticholinergic combinations</b>	
Anoro Ellipta (umeclidinium/vilanterol)	-
Bevespi Aerosphere (glycopyrrolate/formoterol fumarate)	-
Combivent Respimat (ipratropium/albuterol)	-
Duaklir Pressair (aclidinium/formoterol fumarate)	-

Drug	Generic Availability
ipratropium/albuterol solution	✓
Stiolto Respimat (tiotropium/olodaterol)	-
<b>Triple combination</b>	
Breztri Aerosphere (glycopyrrolate/formoterol/budesonide)	-
Trelegy Ellipta (fluticasone furoate/umeclidinium/vilanterol)	-

\* Branded product DuoNeb is no longer marketed.

† Authorized generic (for AirDuo RespiClick and Symbicort only)

‡ Wixela Inhub is the generic of Advair Diskus. No generic is available for Advair HFA.

(Drugs@FDA 2021, Orange Book: Approved Drug Products with Therapeutic Equivalence Evaluations 2021)

## INDICATIONS

**Table 2A. FDA-Approved Indications for Beta<sub>2</sub>-agonist/Corticosteroid Combination Agents**

Indication	Advair Diskus	Advair HFA	AirDuo RespiClick & Digihaler	Breo Ellipta	Dulera	Symbicort	Wixela Inhub
Treatment of asthma*	✓ (age ≥ 4 years)	✓ (age ≥ 12 years)	✓ (age ≥ 12 years)	✓ (age ≥ 18 years)	✓ (age ≥ 5 years)	✓ (age ≥ 6 years)	✓ (age ≥ 4 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)	✓ (250/50 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)	✓ (250/50 strength only)

\*Should only be used in patients not adequately controlled on an ICS or whose disease warrants initiation of both an ICS and a LABA.

(Prescribing information: Advair HFA 2021, Advair Diskus 2020, AirDuo Digihaler 2020, AirDuo RespiClick 2020, Breo Ellipta 2019, Dulera 2020, Symbicort 2019, Wixela Inhub 2021)

**Table 2B. FDA-Approved Indications for Beta<sub>2</sub>-agonist/Anticholinergic Combination Agents**

Indication	Anoro Ellipta	Bevespi Aerosphere	Combivent Respimat	Duaklir Pressair	ipratropium/albuterol solution	Stiolto Respimat
Long-term, once-daily, maintenance treatment of patients with COPD	✓					
Long-term, twice-daily, maintenance treatment of patients with COPD		✓		✓		
Long-term, once-daily, maintenance treatment of patients with COPD, including chronic bronchitis and/or emphysema						✓
For use in patients with COPD on a regular aerosol bronchodilator who continue to have evidence of bronchospasm			✓			

Indication	Anoro Ellipta	Bevespi Aerosphere	Combivent Respimat	Duaklir Pressair	ipratropium/albuterol solution	Stiolto Respimat
and who require a second bronchodilator						
For the treatment of bronchospasm associated with COPD in patients requiring more than 1 bronchodilator					✓	

(Prescribing information: Anoro Ellipta 2020, Bevespi Aerosphere 2020, Combivent Respimat 2020, Duaklir Pressair 2020, ipratropium/albuterol solution 2018, Stiolto Respimat 2020)

**Table 2C. FDA-Approved Indications for Triple Combination Agents**

Indication	Breztri Aerosphere	Trelegly Ellipta
Maintenance treatment of patients with COPD	✓	✓ (100/62.5/25 strength only)
Maintenance treatment of asthma		✓ (age ≥ 18 years)

(Prescribing information: Breztri Aerosphere 2020, Trelegly Ellipta 2020)

- 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<sub>2</sub>-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, Bateman et al 2018, 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, Laloo et al 2003, Lundback et al 2006, Martinez et al 2013, Meltzer et al 2012, Morice et al 2007, Murphy et al 2008, Nathan et al 2006, Nelson et al 2003a, Noonan et al 2006, O'Byrne et al 2014, Pearlman et al 2004, Pearlman et al 2017, Pohl et al 2006, Raphael et al 2018, Rennard et al 2009, Rodrigo et al 2016, Rodrigo et al 2017, Sharafkaneh et al 2012, Sher et al 2017, Tal et al 2002, Tang et al 2019, 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*).
- A randomized, double-blind, double-dummy trial showed therapeutic bioequivalence of Wixela Inhub (generic fluticasone/salmeterol) to Advair Diskus (brand fluticasone/salmeterol) in 1227 patients with asthma. The trial revealed least-squares mean (LSM) Wixela Inhub to Advair Diskus ratios of 1.120 (90% confidence interval [CI], 1.016 to 1.237) for day 1 forced expiratory volume in 1 second (FEV<sub>1</sub>) area under the curve and 1.069 (90% CI, 0.938 to 1.220) for day 29 trough FEV<sub>1</sub> (*Ng et al 2019*).
- The efficacy of the AirDuo Digihaler (fluticasone propionate/salmeterol) was based primarily on the dose-ranging trials and the confirmatory trials for the AirDuo RespiClick (fluticasone propionate/salmeterol). The AirDuo Digihaler contains a built-in electronic module which detects, records, and stores data on inhaler events, including peak inspiratory flow rate (L/minute), for transmission a mobile App. There is no evidence the use of the App leads to improved clinical outcomes, including safety and effectiveness (*AirDuo Prescribing information 2020*).
- Although a synergistic effect of combination inhalers has been suggested by some data, overall there are 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, Nelson et al 2003b, Noonan et al 2006, Perrin et al 2010,*

Rosenhall et al 2002). Improved adherence with combination inhalers has also been suggested but not been shown conclusively (Marceau et al 2006, Perrin et al 2010).

- A multicenter clinical trial (N = 181) compared mometasone furoate/formoterol 50/5 mcg to mometasone furoate 50 mcg in patients with asthma 5 to less than 12 years of age. The primary efficacy endpoint, defined as the change from baseline to week 12 in 60-minute morning post-dose % predicted FEV<sub>1</sub>, was significantly improved with mometasone furoate/formoterol compared with mometasone furoate (5.21; 95% CI, 3.22 to 7.20) (*Dulera Prescribing Information 2020*).
- A large, double-blind, randomized trial (N = 6112) compared fluticasone propionate/salmeterol 500/50 mcg twice daily to its individual components and to placebo over a 3-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% 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 4 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 = 2799) 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 experienced ≥ 1 exacerbations in the previous 3 years, and were taking regular maintenance inhaler therapy (≥ 1 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 experienced an exacerbation within 1 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 2 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 2013a*). For the number of patients who experienced ≥ 1 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 15 trials evaluated the use of ICS/LABA combinations compared to use of ICS monotherapy in patients with COPD (*Nannini et al 2013b*). This analysis demonstrated that exacerbation rates were significantly reduced with ICS/LABA combination therapy vs ICS monotherapy (rate ratio, 0.87; 95% CI, 0.80 to 0.94). Adverse events were similar between treatments; pneumonia rates as diagnosed by chest x-ray were lower than those reported in earlier trials.
- A meta-analysis of 14 trials (total N = 6641) 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  $\geq 12$  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  $\geq 3$  days or an asthma-related hospitalization or emergency department visit leading to the use of systemic glucocorticoids. At least 1 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 = 6208) 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  $\geq 3$  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  $\geq 12$  years of age (*Peters et al 2016*). Enrolled patients were receiving daily asthma medication and had experienced  $\geq 1$  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 (2 actuations of 80/4.5 mcg or 160/4.5 mcg) or budesonide alone (2 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  $\geq 3$  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).
- A trial of 4215 patients  $\geq 12$  years of age with mild asthma found that budesonide/formoterol as needed was noninferior to budesonide twice daily for the reduction of severe asthma exacerbation. The annualized rate of severe exacerbations was 0.11 (95% CI, 0.10 to 0.13) and 0.12 (95% CI, 0.10 to 0.14), respectively (rate ratio, 0.97; upper one-sided 95% confidence limit, 1.16) However, budesonide/formoterol was inferior to budesonide for symptom control as the change in ACQ-5 score showed a difference of 0.11 units (95% CI, 0.07 to 0.15) in favor of budesonide maintenance therapy (*Bateman et al 2018*).
- A 52-week randomized trial of adults with mild asthma (N = 675) revealed that budesonide/formoterol administered as needed was superior to albuterol as needed (relative rate, 0.49; 95% CI, 0.33 to 0.72;  $p < 0.001$ ) and similar to budesonide with albuterol as needed (relative rate, 1.12; 95% CI, 0.70 to 1.79;  $p = 0.65$ ) for prevention of asthma exacerbations. The rate of severe exacerbations was lower with budesonide/formoterol compared with albuterol as needed (relative risk, 0.40; 95% CI, 0.18 to 0.86) and budesonide with albuterol as needed (relative risk, 0.44; 95% CI, 0.20 to 0.96) (*Beasley et al 2019*).

#### Comparisons between different ICS/LABA combinations

- 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 5 minutes after the morning dose (*Partridge et al 2009*). However, the mean morning FEV<sub>1</sub> improved more with budesonide/formoterol at 5 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<sub>1</sub> (0 to 24 hr) (*Dransfield et al 2014*). However, 2 of these 3 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<sub>1</sub> (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 2 products (*Busse et al 2008*).
  - A meta-analysis of 5 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<sub>1</sub>, 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<sub>1</sub> 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<sub>1</sub> 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<sub>1</sub> (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  $\geq 12\%$  and  $\geq 200$  mL increase from baseline in FEV<sub>1</sub> at 12 hours and 24 hours, and change from baseline in trough FEV<sub>1</sub>. Another trial comparing fluticasone furoate/vilanterol with fluticasone propionate/salmeterol demonstrated noninferiority of fluticasone furoate/vilanterol to fluticasone propionate/salmeterol in evening trough FEV<sub>1</sub> at week 24 (*Bernstein et al 2018*).

- o A Cochrane systematic review evaluated if there were differences in the risk for mortality or serious adverse events in patients with asthma receiving formoterol with an ICS compared to salmeterol with an ICS. A total of 12 studies (n = 11,572) in adults and adolescents and 2 studies (n = 723) children were included in the review. The risk for mortality was not assessed due to the low number of events. Evidence on all-cause non-fatal serious adverse events indicated that there is no difference between formoterol/budesonide and salmeterol/fluticasone inhalers (OR, 1.14; 95% CI, 0.82 to 1.59) (O'Shea et al 2021).

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

- A double-blind, double-dummy, 2-year trial (N = 1323) 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<sub>1</sub>. 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 = 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 2016). There was no significant difference in the primary endpoint, the change from baseline in w<sub>m</sub> FEV<sub>1</sub> (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 2 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.
- In a Cochrane review that included the Covelli et al 2016 trial and 1 additional 12 week trial comparing tiotropium to fluticasone furoate/vilanterol (N = 880 across both trials), there were no differences between treatments when considering the following outcomes: mortality, COPD exacerbation, pneumonia, St. George's respiratory questionnaire (SGRQ) score, hospital admissions, or use of rescue medication (Sliwka et al 2018).
- 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<sub>1</sub> and some other lung function, symptom score, and quality-of-life endpoints (Hanania et al 2012, Lee et al 2016, Rojas-Reyes 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, Rojas-Reyes et al 2016).

#### Beta2-agonist/anticholinergic combinations for COPD

##### Comparisons of combination beta2-agonist/anticholinergic products to bronchodilator monotherapy:

- Numerous trials have compared the combination beta2-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 (Bateman et al 2015, Beeh et al 2015, Bone et al 1994, Buhl et al 2015, Celli et al 2014, Decramer et al 2014, Donohue et al 2013, Dorinsky et al 1999, D'Urzo et al 2014, Friedman et al 1999, Hanania et al 2017, Maltais et al 2019a, Martinez et al 2017, Sethi et al 2019, Singh et al 2014).
- A randomized phase 3 study of patients with COPD (N = 1594) found that twice-daily aclidinium/formoterol improved lung function compared to once-daily tiotropium by week 24 (Sethi et al 2019).
- PINNACLE-4, a randomized phase 3 study of 1756 patients with moderate-to-severe COPD, showed that glycopyrrolate/formoterol significantly improved predose trough FEV<sub>1</sub> at week 24 compared with glycopyrrolate monotherapy, formoterol monotherapy, or placebo (all p < 0.0001). The combination therapy also improved other lung function endpoints compared with individual agents or placebo (Lipworth et al 2018).
- 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<sub>1</sub>, 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 Cochrane review (N = 7 trials; 5921 participants) found an improvement in dyspnea, lung function, and number of responders with fixed-dose aclidinium/formoterol compared to monotherapy with individual agents or placebo in patients

with stable COPD. However, no significant differences in exacerbations, hospital admissions, mortality, and adverse events were found with fixed-dose aclidinium/formoterol compared to aclidinium, formoterol, or placebo monotherapy (Ni *et al* 2018).

- A post hoc pooled analysis of 3 studies (N = 1747) showed improved trough FEV<sub>1</sub> with umeclidinium/vilanterol compared with tiotropium (p < 0.001) in patients with COPD (Maleki-Yazdi *et al* 2017).
- A large, randomized-controlled trial (N = 7880) of patients with COPD and a history of exacerbations did not find a difference in the rate of exacerbations between LAMA/LABA therapy with tiotropium/olodaterol vs LAMA therapy with tiotropium (relative risk [RR], 0.93; 99% CI, 0.85 to 1.02; p = 0.0498) (Calverley *et al* 2018).
- A systematic review of 23 studies of beta<sub>2</sub>-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<sub>2</sub>-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.
- A systematic review and network meta-analysis (N = 74 trials; 74,832 participants) evaluated the efficacy of SAMAs, LABAs, LAMA/LABAs and ICS/LABAs for maintenance treatment of COPD. At 12 and 24 weeks, LAMA, LAMA/LABA, and ICS/LABA led to a significantly greater improvement in trough FEV<sub>1</sub> compared with placebo and SAMA monotherapy. With the exception of aclidinium/formoterol, all other LAMA/LABA therapies were superior to LAMA monotherapy and ICS/LABA therapy in improving trough FEV<sub>1</sub>. Furthermore, LAMA/LABA therapy had the highest probability of being the best treatment for in FEV<sub>1</sub> improvement; similar trends were observed for the TDI and SGRQ scores. Authors concluded that there were no significant differences among the LAMAs and LAMA/LABAs within their respective classes (Aziz *et al* 2018).
- A systematic review and meta-analysis (N = 8 trials) compared tiotropium 5 or 18 mcg with LAMA/LABA therapy in patients with moderate-to-severe COPD; ICS therapy was also allowed and use ranged from 33.7% to 54.4% among included trials. Therapy with LABA/LAMA was superior to tiotropium monotherapy for all of the following outcomes at 12 and 24 weeks: FEV<sub>1</sub> peak and trough, SGRQ responder rate, mean SGRQ score, and use of rescue medication. At 12 weeks, LABA/LAMA improved FEV<sub>1</sub> trough by 63 mL compared to tiotropium alone (95% CI, 39.2 to 86.8; p < 0.01). During the same time period, LABA/LAMA improved mean SGRQ responder rate by 19% (rate ratio, 1.19; 95% CI, 1.09 to 1.28; p < 0.01) and reduced SGRQ total score by 1.87 points (95% CI, -2.72 to -1.02; p < 0.01) compared to tiotropium (Han *et al* 2018).

#### Comparisons of combination beta<sub>2</sub>-agonist/anticholinergic products to each other or to other bronchodilator combinations

- Several head-to-head trials between different LAMA/LABA combinations have been published.
  - An 8-week, open-label, crossover trial compared umeclidinium/vilanterol and tiotropium/olodaterol in 236 patients with COPD (Feldman *et al* 2017). The primary endpoint, change from baseline in trough FEV<sub>1</sub>, was shown to be greater for umeclidinium/vilanterol, with a difference of 52 mL (95% CI, 28 to 77; p < 0.001 for superiority in the intention-to-treat population). Effects on secondary endpoints were mixed, with umeclidinium/vilanterol demonstrating a small improvement in rescue medication use but no significant differences in COPD Assessment Test (CAT) scores (a health status questionnaire) or EXACT Respiratory Symptoms (E-RS) scores at most weekly assessments.
  - A 24-week, double-blind, double-dummy, randomized phase 3 trial compared glycopyrrolate/formoterol and umeclidinium/vilanterol in 1119 patients with moderate-to-very severe COPD (Maltais *et al* 2019b). One of the primary endpoints, peak change from baseline in FEV<sub>1</sub> within 2 hours post-dose over 24 weeks, was similar between glycopyrrolate/formoterol and umeclidinium/vilanterol (LSM difference, -3.4 mL; 97.5% CI, -32.8 to 25.9). Glycopyrrolate/formoterol showed improved outcomes for another primary endpoint, change from baseline in morning pre-dose trough FEV<sub>1</sub> over 24 weeks, compared with umeclidinium/vilanterol (LSM difference, -87.2 mL; 97.5% CI, -117.0 to -57.4). The trial did not reveal any clinically meaningful differences in symptoms between the 2 treatments.
- 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<sub>1</sub> 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 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 (no longer available), 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<sub>1</sub>, SGRQ scores, TDI focal scores, and need for rescue medication use (Huisman et al 2015).
- Several systematic reviews/meta-analyses compared various LAMA/LABA combinations (Calzetta et al 2016, Lee et al 2020, Schlueter et al 2016, Siddiqui et al 2019, Sion et al 2017). Limitations to these analyses included the fact that trials evaluated some formulations/dose regimens not available in the U.S. and did not include the more recently approved products in some cases. Additionally, comparisons between different combinations were based on indirect data.
  - Overall, these meta-analyses demonstrated that all LAMA/LABA combinations showed improved lung function vs monocomponents, with few differences among products across lung function and patient-reported endpoints.
  - The analysis by Sion et al noted that both glycopyrrolate/indacaterol (no longer available) and umeclidinium/vilanterol appeared to improve lung function to a greater extent than tiotropium/olodaterol at 12 weeks, with differences in trough FEV<sub>1</sub> of 52 mL (95% credible interval [CrI], 18 to 86) and 38 mL (95% CrI, 13 to 63), respectively (Sion et al 2017).
  - The Schlueter et al meta-analysis of 27 trials (N = 30,361) including 4 LAMA/LABA fixed-dose combination agents (aclidinium/formoterol 400/12 mcg, glycopyrrolate/indacaterol 110/50 mcg [no longer available], tiotropium/olodaterol 5/5 mcg, and umeclidinium/vilanterol 62.5/25 mcg), and showed non-significant differences in efficacy, exacerbations, and discontinuation rates (Schlueter et al 2016). Safety profiles were also similar among the products. The only statistically significant result indicated that umeclidinium/vilanterol appeared to improve lung function to a greater extent than aclidinium/formoterol at 24 to 26 weeks (difference of 61 mL; 95% CrI, 18 to 103; in favor of umeclidinium/vilanterol).
  - The network meta-analysis by Lee et al included 16 randomized controlled trials evaluating 6 LAMA/LABA fixed-dose combination agents (tiotropium/salmeterol [not FDA approved], glycopyrrolate/indacaterol [no longer available], umeclidinium/vilanterol, tiotropium/olodaterol, aclidinium/formoterol, and glycopyrrolate/formoterol). No significant differences were found between the LAMA/LABA combinations for moderate to severe exacerbations, all-cause mortality, or major adverse cardiovascular events (Lee et al 2020).

### **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<sub>1</sub> (0 to 24 hr) and a difference of 90 mL (95% CI, 55 to 125) in trough FEV<sub>1</sub>. 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<sub>1</sub> (0 to 24 hr) and trough FEV<sub>1</sub> 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, 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 4 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<sub>1</sub> 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<sub>1</sub> AUC (12 to 24 hr) and FEV<sub>1</sub> AUC (0 to 24 hr) also favored tiotropium/olodaterol. Rates of adverse events were similar among the treatments.
- A network meta-analysis of 16 randomized controlled trials (N = 17,734) compared fixed-dose combinations of LABA/LAMA vs ICS/LABA. The analysis showed that umeclidinium/vilanterol, glycopyrrolate/indacaterol (no longer

available), and glycopyrrolate/formoterol were the most effective in improving FEV<sub>1</sub>. Glycopyrrolate/indacaterol significantly decreased the risk of exacerbations compared with fluticasone/salmeterol (*Calzetta et al 2019*).

### **Triple combinations for COPD and asthma**

- Trelegy Ellipta (fluticasone furoate/umeclidinium/vilanterol) inhalation powder was the first FDA-approved “closed triple” inhaler – an inhaler containing 3 active ingredients from 3 different therapeutic classes: an ICS, a LAMA, and a LABA.
  - 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 for the treatment of patients with COPD (*Siler et al 2015*). In both studies, the primary endpoint, trough FEV<sub>1</sub>, 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<sub>1</sub> (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 in patients with COPD (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<sub>1</sub> (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 for COPD with fluticasone furoate/umeclidinium/vilanterol.
  - Once-daily triple therapy with fluticasone furoate/umeclidinium/vilanterol was compared to fluticasone furoate/vilanterol and umeclidinium/vilanterol in a 52-week, double-blind, randomized trial among patients with COPD (IMPACT; *Lipson et al 2018*). The primary endpoint of moderate or severe exacerbations was significantly lower with triple therapy in comparison both with fluticasone furoate/vilanterol (rate ratio, 0.85; 95% CI, 0.80 to 0.90) and with umeclidinium/vilanterol (rate ratio, 0.75; 95% CI, 0.70 to 0.81). The annual rate of severe exacerbation resulting in hospitalization was also significantly lower with triple therapy vs umeclidinium/vilanterol (rate ratio, 0.66; 95% CI, 0.56 to 0.78), but not vs fluticasone furoate/vilanterol. The mean change from baseline in trough FEV<sub>1</sub> was significantly increased with triple therapy by 97 and 54 mL vs fluticasone furoate/vilanterol and umeclidinium/vilanterol, respectively. The risk of pneumonia was significantly higher with triple therapy vs umeclidinium/vilanterol (HR, 1.53; 95% CI, 1.22 to 1.92), but not vs fluticasone furoate/vilanterol. Significant improvements in SGRQ total scores also occurred with triple therapy vs fluticasone furoate/vilanterol (mean difference, -1.8; 95% CI, -2.4 to -1.1) and vs umeclidinium/vilanterol (mean difference, -1.8; 95% CI, -2.6 to -1.0).
    - An updated, post hoc mortality analysis of IMPACT was published after the collection of additional vital status data. With known vital status for 99.6% of the intention-to-treat population (n = 10,335), there were 98 deaths (2.36%) in patients on umeclidinium/vilanterol/fluticasone furoate, 109 (2.64%) on vilanterol/fluticasone furoate, and 66 (3.19%) on umeclidinium/vilanterol. For triple therapy, the HR for death was 0.72 (95% CI, 0.53 to 0.99;  $p = 0.042$ ) vs umeclidinium/vilanterol and 0.89 (95% CI, 0.67 to 1.16;  $p = 0.387$ ) vs vilanterol/fluticasone furoate (*Lipson et al 2020*). The FDA noted several statistical and clinical issues with respect to interpretation of the mortality data, and the FDA Pulmonary-Allergy Drugs Advisory Committee voted 14-1 against a proposed labeling claim that Trelegy Ellipta reduces all-cause mortality in patients with COPD (*FDA Trelegy Ellipta briefing document 2020, Healo 2020*).
  - The 24- to 52-week double-blind CAPTAIN trial evaluated the safety and efficacy of triple therapy with Trelegy Ellipta (umeclidinium/vilanterol/fluticasone furoate) for the treatment of asthma in adult patients. Umeclidinium/vilanterol/fluticasone furoate was compared to Breo Ellipta (vilanterol/fluticasone furoate). For the comparison of triple vs dual therapy using the lower strength (100 mcg) of fluticasone furoate, there was a significant improvement in the primary endpoint of change in trough FEV<sub>1</sub> at week 24, with a difference of 110 mL (95% CI, 66 to 153;  $p < 0.0001$ ). The corresponding improvement for the higher strength (200 mcg fluticasone furoate) was also significant at 92 mL (95% CI, 49 to 135) (*Lee LA et al 2021*).
    - A numerical improvement in the annualized rate of moderate/severe exacerbations was seen between triple and dual therapy with the lower strength, but the difference did not reach statistical significance (rate ratio, 0.78 [95% CI, 0.61 to 1.01];  $p = 0.060$ ). The exacerbation rate was comparable between triple and dual therapy for the higher strength comparison (rate ratio, 0.97; 95% CI, 0.73 to 1.28;  $p = 0.80$ ).

- An additional triple therapy product, Breztri Aerosphere (glycopyrrolate/formoterol/budesonide) inhalation aerosol, was FDA-approved in 2020. Safety and efficacy were demonstrated in 2 double-blind trials comparing triple therapy to dual therapy with glycopyrrolate/formoterol (Bevespi Aerosphere) or formoterol/budesonide in patients with COPD (*Ferguson et al 2018*, *Rabe et al 2020*).
  - In the 24-week KRONOS study (N = 1902), the FEV<sub>1</sub> AUC (0 to 4 hr) was significantly improved for triple therapy vs formoterol/budesonide, with a difference of 116 mL (95% CI, 80 to 152; p < 0.0001); the difference in change from baseline in pre-dose trough FEV<sub>1</sub> was nominally significant, with a difference of 74 mL (95% CI, 47 to 102; p < 0.0001). These lung function endpoints were not significantly improved for the triple therapy vs glycopyrrolate/formoterol; however, improvements were demonstrated in some secondary endpoints including SGRQ and the incidence of moderate or severe COPD exacerbations for this comparison (*Ferguson et al 2018*).
  - The 52-week ETHOS study (N = 8588) enrolled patients with a documented history of COPD exacerbation(s) in the preceding year. The primary endpoint of annualized rate of moderate or severe COPD exacerbations was significantly improved for triple therapy (with the marketed dose) compared to the corresponding doses of either dual therapy. For triple therapy vs glycopyrrolate/formoterol, the rate ratio was 0.76 (95% CI, 0.69 to 0.83; p < 0.001), and for triple therapy vs formoterol/budesonide, the rate ratio was 0.87 (95% CI, 0.79 to 0.96; p = 0.003) (*Rabe et al 2020*).
    - An updated analysis of ETHOS data evaluated the risk for all-cause mortality after the collection of additional vital status data. With known vital status for 99.6% of the intention-to-treat population, the risk of death was significantly lower with triple therapy compared to glycopyrrolate/formoterol (HR, 0.51; 95% CI, 0.33 to 0.80), but triple therapy did not significantly reduce the risk of death compared to formoterol/budesonide (HR, 0.72; 95% CI, 0.44 to 1.16) (*Martinez et al 2021*).
- A meta-analysis evaluated 20 randomized controlled trials (N = 11,894) that compared triple therapy (ICS/LABA/LAMA) vs dual therapy with an ICS plus LABA in children and adults with persistent uncontrolled asthma. Triple therapy was associated with significant reductions in severe exacerbation risk (risk ratio, 0.83; 95% CI, 0.77 to 0.90) and improvement in asthma control (ACQ or ACT scores: standardized mean difference, -0.06; 95% CI, -0.10 to -0.02), but no significant differences were found between triple versus dual therapy in mortality (risk ratio, 0.96; 95% CI, 0.33 to 2.75) (*Kim et al 2021*).
- A network meta-analysis evaluated if there were significant differences between different triple therapy combinations for the treatment of COPD. Nine different combinations of triple therapy were identified in 21 randomized controlled trials (N = 29,892). The analysis found no significant differences between different triple therapies in clinical outcomes, including acute exacerbation risk and all-cause mortality (*Lee HW et al 2021*). A limitation to this analysis was inclusion of trials that evaluated some formulations/dose regimens not available in the U.S.

## 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*).
  - LABAs 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.
  - A 2020 focused update of the 2007 NAEPP guideline provided updated recommendations on the use of intermittent ICSs and the use of LAMAs as add-on therapy (*Cloutier et al 2020*). The update did not address use of ICS-formoterol as an option for intermittent asthma. For mild, persistent asthma, the use of as needed concomitant ICS and SABA was added as an alternative to daily low-dose ICS with as needed SABA for management of mild, persistent asthma. Additionally, ICS-formoterol in a single inhaler used as both a daily controller and reliever therapy in moderate to severe persistent asthma was recommended over the use of a higher-dose ICS/LABA therapy with a SABA as

needed. Finally, the addition of a LAMA can be considered for patients who have uncontrolled, persistent asthma despite ICS/LABA therapy.

- The 2021 GINA report also provides a stepwise approach to asthma management. Treatment recommendations are based on 2 tracks stratified by the choice of reliever. Track 1 includes ICS-formoterol as the reliever, and it is the preferred approach for most patients because it reduces the risk of severe exacerbations. Track 2 uses a SABA as the reliever. Treatment in adults and adolescents with a SABA only is not recommended. For Step 1 and 2 therapy, the preferred (track 1) approach is low dose ICS-formoterol as needed for symptom relief or if needed for exercise for patients with mild asthma. For Step 3, the preferred treatment is low dose ICS-formoterol as both maintenance and reliever therapy. Preferred therapy for Step 4 is a medium dose ICS-formoterol with as needed low dose ICS-formoterol as the reliever therapy. For patients with persistent symptoms or exacerbations despite Step 4 therapy, referral to a specialist with expertise in severe asthma management is recommended. Treatment options may include any of the following options: high dose ICS-LABA therapy, add-on LAMA (tiotropium or triple combination [ICS/LABA/LAMA] inhaler), azithromycin, low-dose oral corticosteroids, and biologic agents for severe allergic or severe Type 2 asthma (GINA 2021).
  - Tiotropium by mist inhaler (age ≥ 6 years) may be considered as an add-on controller option in patients with persistently uncontrolled asthma despite use of a medium or high dose ICS/LABA; alternatively a triple combination ICS/LABA/LAMA inhaler can be used in patients ≥18 years of age. In step 4 therapy, it is recommended under track 2 (less preferred), and at step 5, it is recommended as one of several preferred add-on treatment options.
  - The 2021 GINA report provides interim guidance on the management of asthma in the context of the coronavirus disease 2019 (COVID-19) pandemic. Patients with asthma should continue their prescribed asthma medications, including ICS and add-on therapies, during the pandemic. Use of nebulizers should be avoided when possible to prevent transmission of the virus to other patients or healthcare workers. Vaccination for COVID-19 is recommended for people with asthma (GINA 2021).
- Recommendations have also been made for stepping down therapy among patients with asthma that has been well-controlled for an extended period of time. Reasons for stepping down therapy include reducing excess drug exposure (and potential adverse effects), improving adherence by simplifying a treatment regimen, and reducing cost (Chippis et al 2019, GINA 2021). Prior to stepping down therapy, patients need to be assessed for risk of asthma exacerbation, lung function, symptom control, and adherence to current therapy. Recommendations for step-to-step reductions include decreasing dose or frequency of ICS with concurrent use of LABA, switching to an oral agent (ie, an LTRA such as montelukast), or use of ICS-formoterol as needed, depending on the current step of therapy. During step-down therapy, patients need to be evaluated for asthma symptoms, use of rescue medications, and lung function.
- 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 does not recommend LABA medications for the management of acute asthma symptoms or exacerbations (GINA 2021, NHLBI 2007).
  - A meta-analysis of 16 randomized controlled trials evaluating the use of a ICS/LABA as single maintenance and reliever therapy found that it was associated with a significant reduction in the risk of asthma exacerbations compared with controller therapy with the same dose of ICS and LABA (rate ratio, 0.68; 95% CI, 0.58 to 0.80) (Sobieraj et al 2018). Of the 16 trials, 15 studied budesonide/formoterol in a dry powder inhaler. Results were similar in comparisons with doses of ICS and LABA controller therapy that were higher than the combined ICS/LABA and in comparison with ICS controller therapy only.
- A European Respiratory Society/American Thoracic Society guideline on the management of severe asthma recommends the addition of tiotropium for patients with uncontrolled asthma despite GINA step 4 or 5 or NAEPP step 5 therapy, and a trial of chronic macrolide therapy to reduce exacerbations in patients who require additional control despite GINA step 5 or NAEPP step 5 therapy (Holguin et al 2020).

## **COPD**

- The 2021 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. Historically, "asthma-COPD overlap" was addressed, but they are now recognized as separate unique disease states with some similar signs and symptoms. Key recommendations from the GOLD guidelines are as follows (GOLD 2021):
  - 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, and for immediate relief of symptoms in patients already receiving long-acting bronchodilators for maintenance therapy.
    - 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 1 bronchodilator, treatment should be escalated to 2 bronchodilators.
    - Combination treatment with a LABA and LAMA:
      - Reduces exacerbations compared to monotherapy or ICS/LABA.
      - Increases FEV<sub>1</sub> and reduces symptoms compared to monotherapy.
  - Long-term monotherapy with ICS is not recommended. Long-term treatment with ICS may be considered in association with LABAs for patients with a history of exacerbations despite treatment with long-acting bronchodilators. Long-term treatment with ICS may cause pneumonia in patients with severe disease.
  - Treatment recommendations are given for patients with COPD based on their GOLD patient group (see Table 3).
    - **Group A:** Patients should be offered bronchodilator treatment (short- or long-acting), based on its effect on breathlessness. 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; switching to another device or molecules can also be considered.
    - **Group C:** Initial therapy should be a LAMA.
    - **Group D:** In general, it is recommended to start therapy with a LAMA. For patients with more severe symptoms, especially dyspnea and/or exercise limitation, LAMA/LABA may be considered for initial treatment. In some patients, initial therapy with an ICS + LABA may be the first choice; these patients may have a history of asthma or blood eosinophil count  $\geq 300$  cells/ $\mu$ L.
    - Follow-up treatments: The follow-up treatments apply to any patients receiving maintenance treatment irrespective of the patient GOLD group.
      - For persistent dyspnea: The use of 2 bronchodilators is recommended in patients receiving 1 long-acting bronchodilator and experiencing persistent breathlessness or exercise limitation. Patients with persistent dyspnea symptoms on LABA + ICS may benefit from LAMA + LABA + ICS.
      - For exacerbations: Patients with persistent exacerbations on long-acting bronchodilator monotherapy may benefit from adding a second long-acting bronchodilator (LAMA + LABA, preferred) or using an ICS + LABA. For patients who have a history and/or findings suggestive of asthma or blood eosinophil count  $\geq 300$  cells/ $\mu$ L, ICS + LABA is preferred. In patients who develop further exacerbations on LAMA + LABA therapy, alternative pathways include escalation to a LAMA + LABA + ICS if eosinophil count  $\geq 100$  cells/ $\mu$ L or addition of roflumilast or azithromycin if eosinophil count  $< 100$  cells/ $\mu$ L. In patients with additional exacerbations on LABA + ICS, patients should try LAMA + LABA + ICS therapy. 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.
- Patients with COPD should continue their usual therapy, including inhaled or oral corticosteroids during the coronavirus disease 2019 (COVID-19) pandemic.

**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 $\geq 2$ CAT $\geq 10$
$\geq 2$ (or $\geq 1$ leading to hospital admission)	C	D
0 or 1 (not leading to hospital admission)	A	B

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

- American Thoracic Society clinical practice guidelines recommend the following pharmacologic treatment for patients with COPD (Strong to conditional Strength of Recommendation/moderate Level of Evidence) (*Nici et al 2020*)

- Those who complain of dyspnea or exercise intolerance: LAMA/LABA combination therapy is recommended over LABA or LAMA monotherapy.
- Those who complain of dyspnea or exercise intolerance despite dual therapy with LAMA/LABA: use of triple therapy with LAMA/LABA/ICS is recommended over dual therapy with LAMA/LABA in those patients with a history of  $\geq 1$  exacerbation(s) in the past year requiring antibiotics or oral steroids or hospitalization.
- Those receiving triple therapy (LAMA/LABA/ICS): it is suggested that the ICS can be withdrawn if the patient has had no exacerbations in the past year.
- No recommendation is made for or against ICS as an additive therapy to long-acting bronchodilators in patients with COPD and blood eosinophilia, except for those patients with a history of  $\geq 1$  exacerbation(s) in the past year requiring antibiotics or oral steroids or hospitalization, for whom ICS as an additive therapy is suggested.
- 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<sub>2</sub>-agonist/corticosteroid combinations**

- Beta<sub>2</sub>-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.
- Advair Diskus, AirDuo RespiClick, Breo Ellipta, and Wixela Inhub are 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 4 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<sub>2</sub>-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, blurred vision, central serous chorioretinopathy, 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 ( $\geq 5\%$  for at least 1 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<sub>2</sub>-agonist/anticholinergic combinations**

- Both albuterol/ipratropium combination products are contraindicated in patients with hypersensitivity to atropine or its derivatives. Anoro Ellipta and Duaklir Pressair are contraindicated in patients with hypersensitivity to any component of the product, as well as in patients with severe hypersensitivity to milk proteins. Anoro Ellipta, Bevespi Aerosphere, Duaklir Pressair, and Stiolto Respimat are contraindicated without ICS in patients with asthma.
- Anoro Ellipta, Bevespi Aerosphere, Duaklir Pressair, and Stiolto Respimat have a warning stating that LABAs 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 (an active ingredient in Bevespi Aerosphere and Duaklir Pressair), vilanterol (an active ingredient in Anoro Ellipta), and olodaterol (an active ingredient in Stiolto Respimat). The safety and efficacy of Anoro Ellipta, Bevespi Aerosphere, Duaklir Pressair, and Stiolto Respimat 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<sub>2</sub>-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<sub>2</sub>-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 CYP3A4 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, Duaklir Pressair, and Stiolto Respimat only).
- Adverse events 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 events were very similar between groups. In a 48-week safety trial, most adverse events 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 (beta<sub>2</sub>-agonist/anticholinergic/corticosteroid [LAMA/LABA/ICS])**

- Contraindications with Trelegy Ellipta include:
  - Severe hypersensitivity to milk proteins or any ingredients in the formulation.
  - Primary treatment of status asthmaticus or acute episodes of COPD or asthma requiring intensive measures

- Similar to other combination agents for COPD (and/or asthma), Trelegy Ellipta and Breztri Aerosphere have a number of additional warnings and precautions including:
  - Increased risk of asthma-related death
  - Not indicated for treatment of asthma
  - Not initiating in patients with rapidly deteriorating COPD
  - Avoiding excess 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 (CYP) 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 events with Trelegy Ellipta include:
  - COPD (incidence  $\geq 1\%$ ): upper respiratory tract infection, pneumonia, bronchitis, oral candidiasis, headache, back pain, arthralgia, influenza, sinusitis, pharyngitis, rhinitis, dysgeusia, constipation, urinary tract infection, diarrhea, gastroenteritis, oropharyngeal pain, cough, and dysphonia.
  - Asthma (incidence  $\geq 2\%$ ): pharyngitis/nasopharyngitis, upper respiratory tract infection/viral upper respiratory tract infection, bronchitis, respiratory tract infection/viral respiratory tract infection, sinusitis/acute sinusitis, urinary tract infection, rhinitis, influenza, headache, and back pain.
- The most common adverse events (incidence  $\geq 2\%$ ) with Breztri Aerosphere include upper respiratory tract infection, pneumonia, back pain, oral candidiasis, influenza, muscle spasm, urinary tract infection, cough, sinusitis, and diarrhea.

## DOSING AND ADMINISTRATION

**Table 4. Dosing and Administration**

Drug	Available Formulations	Route	Usual Recommended Frequency
<b>Beta<sub>2</sub>-agonist &amp; corticosteroid combinations</b>			
Advair Diskus (fluticasone propionate/salmeterol)	Inhalation powder	Inhalation	2 times daily
Advair HFA (fluticasone propionate/salmeterol)	Aerosol inhaler	Inhalation	2 times daily
AirDuo RespiClick (fluticasone propionate/salmeterol)	Inhalation powder	Inhalation	2 times daily
AirDuo Digihaler (fluticasone propionate/salmeterol)*	Inhalation powder	Inhalation	2 times daily
Breo Ellipta (fluticasone furoate/vilanterol)	Inhalation powder	Inhalation	Once daily
Dulera (mometasone furoate/formoterol fumarate dihydrate)	Aerosol inhaler	Inhalation	2 times daily
Symbicort (budesonide/formoterol fumarate dihydrate)	Aerosol inhaler	Inhalation	2 times daily
Wixela Inhub (fluticasone propionate/salmeterol)	Inhalation powder	Inhalation	2 times daily
<b>Beta<sub>2</sub>-agonist &amp; anticholinergic combinations</b>			
Anoro Ellipta (umeclidinium/vilanterol)	Inhalation powder	Inhalation	Once daily
Bevespi Aerosphere (glycopyrrolate/formoterol fumarate)	Inhalation spray	Inhalation	2 times daily
Combivent Respimat (ipratropium bromide/albuterol)	Inhalation spray	Inhalation	4 times daily
Duaklir Pressair (aclidinium/formoterol fumarate)	Inhalation powder	Inhalation	2 times daily
ipratropium bromide/albuterol	Nebulizer solution	Inhalation (nebulizer)	4 times daily



Drug	Available Formulations	Route	Usual Recommended Frequency
Stiolto Respimat (tiotropium bromide/olodaterol)	Inhalation spray	Inhalation	Once daily
<b>Triple combination</b>			
Trelegly Ellipta (fluticasone furoate/umeclidinium/vilanterol)	Inhalation powder	Inhalation	Once daily
Breztri Aerosphere (glycopyrrolate/formoterol/budesonide)	Inhalation spray	Inhalation	2 times daily

\*The AirDuo Digihaler contains a built-in electronic module which detects, records, and stores data on inhaler events, including peak inspiratory flow rate (L/minute), for transmission to mobile App. Use of the App is not required for administration of medication to the patient.

See the current prescribing information for full details.

## CONCLUSION

- Respiratory medications, including bronchodilators and corticosteroids, are a mainstay of treatment for asthma and COPD, and a large amount of clinical evidence supports the safety and efficacy of combination beta<sub>2</sub>-agonist agents for these indications.
  - Clinical trials have demonstrated that the combination products have superior efficacy compared with the individual separate components when given as monotherapy for the treatment of both asthma and COPD. The combination products are generally well tolerated.
- Several single-ingredient inhalers containing beta<sub>2</sub>-agonists, ICS, or anticholinergics are also available. Beta<sub>2</sub>-agonist combinations offer improved convenience over the use of multiple separate inhalers.
  - Trelegly Ellipta and Breztri Aerosphere are fixed-dose “triple therapy” combination inhalers combining a LAMA, a LABA, and an ICS. Both agents provide an alternative to the use of multiple inhalers for patients with COPD in whom triple therapy is indicated; Trelegly Ellipta is also an option for adult patients with asthma who require triple therapy.
- The GINA guideline supports the use of combination ICS/LABA products for long-term control and prevention of symptoms and exacerbations in patients with asthma. **Triple combination inhalers are a treatment option for patients with persistent symptoms or exacerbations despite Step 4 therapy.**
  - 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.
  - An advantage of the ICS/LABA combination products is that their use ensures that patients are not using a LABA without a concomitant ICS.
  - In adults and adolescents, low dose ICS-formoterol is the preferred reliever medication. For chronic management of asthma, the preferred controller options consist of ICS-formoterol (on an as-needed basis), ICS, or ICS/LABA depending on the age of a patient and severity of symptoms. **Use of daily and as-needed combination ICS-formoterol is the preferred treatment approach for adults and adolescents.**
- The 2020 focused update of the NAEPP guideline recommends the use of ICS-formoterol in a single inhaler used as both a daily controller and reliever therapy in moderate to severe persistent asthma.
- GOLD guidelines recommend the use of combination ICS/LABA products as an option for some patients at higher risk of exacerbations, a history and/or findings suggestive of asthma, or blood eosinophil count  $\geq 300$  cells/ $\mu$ L; however, the use of 1 or more bronchodilator without an ICS is recommended as first-line treatment for most COPD patients.
  - A LAMA is recommended as first-line treatment in most patients with COPD, with the exception of low-risk patients with milder symptoms, or patients with more severe symptoms.
- The current asthma and COPD treatment guidelines do not recommend the use of one specific combination product over another. The GINA guideline discusses the use of budesonide/formoterol as the preferred **maintenance and as-needed ICS/formoterol combination for asthma treatment.**
  - Administration instructions and inhalation devices vary among products and should be considered in product selection.

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