

Therapeutic Class Overview

Respiratory Beta-Agonist Combination Agents

INTRODUCTION

- Respiratory beta₂-agonist combination agents include a beta₂-agonist combined with an inhaled corticosteroid (ICS), inhaled anticholinergic, or both. Beta₂-agonists can be short-acting beta₂-agonists (SABA) or long-acting beta₂-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 beta₂-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 beta₂-agonist and an ICS are indicated for the treatment of asthma, and some are additionally indicated for the treatment of COPD.
 - Combinations of a beta₂-agonist and an anticholinergic medication are indicated for COPD, as is the one available triple combination agent (consists of LAMA/LABA/ICS).
 - 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 2018**, asthma affected an estimated 19.2 million adults and 5.5 million children in the United States (U.S.) (*Centers for Disease Control and Prevention [CDC] 2020, National Heart, Lung, and Blood Institute [NHLBI] 2020*).
- 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] 2020a*). COPD affects 6.4% of the U.S. population and is a major contributor to mortality from chronic lower respiratory diseases, the fourth leading cause of death in the U.S. (*CDC 2019*).
- Medispan class/subclass: Sympathomimetics/Adrenergic Combinations

Table 1. Medications Included Within Class Review*

Drug	Generic Availability
Beta₂-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)	✓ †
Wixela Inhub (fluticasone propionate/salmeterol)	✓ ‡
Beta₂-agonist & anticholinergic combinations	
Anoro Ellipta (umeclidinium/vilanterol)	-
Bevespi Aerosphere (glycopyrrolate/formoterol fumarate)	-
Combivent Respimat (ipratropium/albuterol)	-
Duaklir Pressair (aclidinium/formoterol fumarate)	-
ipratropium/albuterol solution	✓
Stiolto Respimat (tiotropium/olodaterol)	-
Utibron Neohaler (glycopyrrolate/indacaterol)§	-
Triple combination	
Trelegy Ellipta (fluticasone furoate/umeclidinium/vilanterol)	-

* Branded product DuoNeb is no longer marketed.

† Authorized generic

‡ Wixela Inhub is the generic of Advair Diskus

§ The inhaled LABA and anticholinergic combination, Utibron Neohaler (indacaterol/glycopyrrolate), was discontinued by the manufacturer effective April 1, 2020 for business reasons. (OINDP news 2020). At the time of this review, Arcapta Neohaler was active in Medispan.

(Drugs @FDA 2020, Orange Book: Approved Drug Products with Therapeutic Equivalence Evaluations 2020)

INDICATIONS

Table 2A. FDA-Approved Indications for Beta₂-agonist/Corticosteroid Combination Agents

Indication	Advair Diskus	Advair HFA	AirDuo RespiClick	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)

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

Table 2B. FDA-Approved Indications for Beta₂-agonist/Anticholinergic Combination Agents

Indication	Anoro Ellipta	Bevespi Aerosphere	Combivent Respimat	Duaklir Pressair	ipratropium/albuterol solution	Stiolto Respimat	Utibron Neohaler
Long-term, once-daily, maintenance treatment of patients with COPD	✓					✓	
Long-term, twice-daily, maintenance treatment of airflow obstruction in patients with COPD				✓			✓
Long-term, twice-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 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 2019, Bevespi Aerosphere 2019, Combivent Respimat 2016, Duaklir Pressair 2020, ipratropium/albuterol solution 2018, Stiolto Respimat 2019, Utibron Neohaler 2019)

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

Indication	Trelegy Ellipta
Maintenance treatment of patients with COPD	✓

(*Trelegy Ellipta prescribing information 2019*)

- 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

Beta₂-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 (FEV₁) area under the curve and 1.069 (90% CI, 0.938 to 1.220) for day 29 trough FEV₁ (*Ng et al 2019*).
- 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 mcg/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 FEV₁, was significantly improved with mometasone furoate/formoterol compared with mometasone furoate (5.21; 95% CI, 3.22 to 7.20) (*Dulera Prescribing Information 2019*).
- 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 had ≥ 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 had 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 ≥ 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 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 ≥ 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 ≥ 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 ≥ 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 ≥ 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 FEV₁ 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) FEV₁ (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 FEV₁ (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, FEV₁, 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 FEV₁ 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 FEV₁ 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 FEV₁ (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 ≥ 200 mL increase from baseline in FEV₁ at 12 hours and 24 hours, and change from baseline in trough FEV₁. Another trial comparing fluticasone furoate/vilanterol with fluticasone propionate/salmeterol demonstrated noninferiority of fluticasone furoate/vilanterol to fluticasone propionate/salmeterol in evening trough FEV₁ at week 24 (*Bernstein et al 2018*).

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 FEV₁. 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 2017a*). The primary endpoint, trough FEV₁, 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 2016*). There was no significant difference in the primary endpoint, the change from baseline in wm FEV₁ (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 FEV₁ 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, Mahler et al 2015, 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 acclidinium/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 FEV₁ 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 Cochrane review (N = 7 trials; 5921 participants) found an improvement in dyspnea, lung function, and number of responders with fixed-dose acclidinium/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 acclidinium/formoterol compared to acclidinium, formoterol, or placebo monotherapy (*Ni et al 2018*).
- A post hoc pooled analysis of 3 studies (N = 1747) showed improved trough FEV₁ 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*).
- In a meta-analysis of 6 randomized trials in patients with COPD, tiotropium/olodaterol resulted in similar changes in lung function and similar tolerability compared to tiotropium alone (*He and Lin 2020*).
- A systematic review of 23 studies of beta₂-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 beta₂-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 LABA/ICSs for maintenance treatment of COPD. At 12 and 24 weeks, LAMA, LAMA/LABAs, and LABA/ICSs led to a significantly greater improvement in trough FEV₁ compared with placebo and SAMA monotherapy. With the exception of acclidinium/formoterol, all other LAMA/LABA therapies were superior to LAMA monotherapy and LABA/ICS therapy in improving trough FEV₁. Furthermore, LAMA/LABA therapy had the highest probability of being the best treatment for in FEV₁ improvement; similar trends were observed for the transition dyspnea index 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: FEV₁ peak and trough, SGRQ responder rate, mean SGRQ score, and use of rescue medication. At 12 weeks, LABA/LAMA improved FEV₁ 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% (RR, 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 beta₂-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 FEV₁, 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.
 - Two 12-week, double-blind, crossover trials compared glycopyrrolate/indacaterol to umeclidinium/vilanterol in a total of 712 patients with COPD (*Kerwin et al 2017b*). The primary endpoint, FEV₁ AUC (0 to 24 hr), was similar between treatment arms in both studies, with differences for glycopyrrolate/indacaterol vs umeclidinium/vilanterol of -11.5 mL (95% CI, -26.9 to 3.8) and -18.2 mL (95% CI, -34.2 to -2.3) in Studies 1 and 2, respectively. Although the trials failed to demonstrate noninferiority of glycopyrrolate/indacaterol to umeclidinium/vilanterol due to the noninferiority margin used in the study methodology, the differences between treatments were not considered clinically meaningful.
 - 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 FEV₁ 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 FEV₁ 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 FEV₁ 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, 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 FEV₁, SGRQ scores, TDI focal scores, and need for rescue medication use (*Huisman et al 2015*).
- Three systematic reviews/meta-analyses compared various LAMA/LABA combinations (*Calzetta et al 2016*, *Schlueter et al 2016*, *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 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 and umeclidinium/vilanterol appeared to improve lung function to a greater extent than tiotropium/olodaterol at 12 weeks, with differences in trough FEV₁ of 52 mL (95% credible interval [CrI], 18 to 86) and 38 mL (95% CrI, 13 to 63), respectively.
 - The *Schlueter et al* meta-analysis included 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), and 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 FEV₁ (0 to 24 hr) and a difference of 90 mL (95% CI, 55 to 125) in trough FEV₁. 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 FEV₁ (0 to 24 hr) and trough FEV₁ 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 ≥ 1 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, FEV₁ 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 = 3362) compared indacaterol/glycopyrrolate 110/50 mcg daily to fluticasone propionate/salmeterol 500/50 mcg twice daily in patients with COPD and a history of ≥ 1 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 FEV₁ 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 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, FEV₁ 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). FEV₁ AUC (12 to 24 hr) and FEV₁ 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 versus ICS/LABA. The analysis showed that umeclidinium/vilanterol, glycopyrrolate/indacaterol, and glycopyrrolate/formoterol were the most effective in improving FEV₁. Glycopyrrolate/indacaterol significantly decreased the risk of exacerbations compared with fluticasone/salmeterol (*Calzetta et al 2019*).

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 co-administration 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 FEV₁, 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 FEV₁ (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 FEV₁ (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.
- 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 FEV₁ 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).

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.
- The 2020 Global Initiative for Asthma (GINA) Global Strategy for Asthma Management and Prevention report also provides a stepwise approach to asthma management. It recommends as-needed low-dose ICS-formoterol as a preferred controller medication to prevent exacerbations and control symptoms in adult or adolescent patients with infrequent asthma symptoms (eg, $< \text{twice a month}$). If patients remain uncontrolled, an ICS or ICS/LABA is the next preferred controller options. The choice of a specific dose and combination depends on the age of the patient and step within the therapy. As-needed ICS-formoterol is also the preferred reliever medication for adults and adolescents, while as-needed SABAs are the only option for reliever medications in children; of note, a low dose ICS should be taken whenever a SABA is taken. At the highest step of therapy, the patient should be referred for add-on treatment (eg, tiotropium, azithromycin, omalizumab, mepolizumab, benralizumab, reslizumab, dupilumab) (GINA 2019, GINA 2020).
- The 2020 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 with or without LABA 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 (GINA 2020).

- 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 2020, NHLBI 2007*).
 - A meta-analysis of 16 randomized controlled trials evaluating the use of a LABA/ICS 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 (RR, 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 LABA/ICS, and in comparison with ICS controller therapy only.
- For a step-down process when asthma is well-controlled, GINA recommends reducing the ICS dose or switching to as-needed low dose ICS/formoterol (*GINA 2020*). *Chippis et al* propose using ICS/LABA combination with lower doses of ICS or switching from ICS to low-dose ICS/LABA combinations as patients move from higher to lower steps within asthma therapy (*Chippis et al 2019*).
- 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 2020 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. Of note, the 2020 GOLD guidelines no longer recognize the phrase "asthma-COPD overlap," instead, emphasize that asthma and COPD are unique disease states with some similar signs and symptoms. Key recommendations from the GOLD guidelines are as follows (*GOLD 2020a*):
 - 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.
 - Increases FEV₁ 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.
 - Triple inhaled therapy of LAMA/LABA/ICS improves lung function, symptoms, and health status and reduces exacerbations compared to ICS/LABA, LABA/LAMA, or LAMA monotherapy.
- 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 and/or findings suggestive of asthma or blood eosinophil count ≥ 300 cells/ μ 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 ≥ 300 cells/ μ 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 ≥ 100 cells/ μ L or addition of roflumilast or azithromycin if eosinophil count < 100 cells/ μ 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 (GOLD 2020b).

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

Abbreviations: CAT = COPD assessment test; mMRC = modified 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

Beta₂-agonist/corticosteroid combinations

- Beta₂-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 beta₂-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 (≥ 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.

Beta₂-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, Stiolto Respimat, and Utibron Neohaler are contraindicated without ICS in patients with asthma.
- Anoro Ellipta, Bevespi Aerosphere, Duaklir Pressair, Stiolto Respimat, and Utibron Neohaler 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), indacaterol (an active ingredient in Utibron Neohaler), 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, Stiolto 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: Beta₂-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 beta₂-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 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 (beta₂-agonist/anticholinergic/corticosteroid)

- Trelegy Ellipta is contraindicated in patients with severe hypersensitivity to milk proteins or any ingredients in the formulation.
- Similar to other combination agents for COPD (and/or asthma), Trelegy Ellipta has a number of additional warnings and precautions; these include:
 - 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 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	Route	Usual Recommended Frequency
Beta₂-agonist & corticosteroid combinations			
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
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
Beta₂-agonist & anticholinergic combinations			
Anoro Ellipta (umeclidinium/vilanterol)	Inhalation powder	Inhalation	Once daily

Data as of May 22, 2020 HJI-U/MG-U/ALS

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Drug	Available Formulations	Route	Usual Recommended Frequency
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
Stiolto RespiMat (tiotropium bromide/olodaterol)	Inhalation spray	Inhalation	Once daily
Utibron Neohaler (indacaterol/glycopyrrolate)	Inhalation powder	Inhalation	2 times daily
Triple combination			
Trelegy Ellipta (fluticasone furoate/ umeclidinium/vilanterol)	Inhalation powder	Inhalation	Once daily

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 beta₂-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 beta₂-agonists, ICS, or anticholinergics are also available. Beta₂-agonist combinations offer improved convenience over the use of multiple separate inhalers.
 - Trelegy Ellipta is the first fixed-dose combination inhaler combining a LAMA, a LABA, and an ICS, and provides an alternative to the use of multiple inhalers for patients with COPD in whom triple therapy is indicated.
- 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.
 - 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.
- 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 ≥ 300 cells/ μ 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 as-needed low-dose ICS/formoterol combination in lower steps of therapy.
 - Administration instructions and inhalation devices vary among products and should be considered in product selection.

REFERENCES

- Aalbers R, Backer V, Kava TT, et al. Adjustable maintenance dosing with budesonide/formoterol compared to fixed-dose salmeterol/fluticasone in moderate to severe asthma. *Curr Med Res Opin.* 2004;20(2):225-240.
- Aaron SD, Vandemheen KL, Fergusson D, et al. Tiotropium in combination with placebo, salmeterol, or fluticasone-salmeterol for treatment of chronic obstructive pulmonary disease: a randomized trial. *Ann Intern Med.* 2007;146(8):545-555.
- Advair Diskus [package insert], Research Triangle Park, NC: GlaxoSmithKline; January 2019.

- Advair HFA [package insert], Research Triangle Park, NC: GlaxoSmithKline; February 2019.
- Agusti A, de Teresa L, De Backer W, et al. A comparison of the efficacy and safety of once-daily fluticasone furoate/vilanterol with twice-daily fluticasone propionate/salmeterol in moderate to very severe COPD. *Eur Respir J*. 2014;43(3):763-772.
- AirDuo RespiClick [package insert], Parsippany, NJ: Teva Pharmaceuticals USA, Inc.; February 2020.
- Anoro Ellipta [package insert], Research Triangle Park, NC: GlaxoSmithKline; July 2019.
- Aziz MIA, Tan LE, Wu DB, et al. Comparative efficacy of inhaled medications (ICS/LABA, LAMA, LAMA/LABA and SAMA) for COPD: a systematic review and network meta-analysis. *Int J Chron Obstruct Pulmon Dis*. 2018;13:3203-3231. doi: 10.2147/COPD.S173472
- Bateman ED, Boushey HA, Bousquet J, et al. Can guideline-defined asthma control be achieved? The gaining optimal asthma control study. *Am J Respir Crit Care Med*. 2004;170(8):836-844.
- Bateman ED, Chapman KR, Singh D, et al. Acclidinium bromide and formoterol fumarate as a fixed-dose combination in COPD: pooled analysis of symptoms and exacerbations from two six-month, multicentre, randomised studies (ACLIFORM and AUGMENT). *Respir Res*. 2015;16:92. doi: 10.1186/s12931-015-0250-2.
- Bateman ED, Jacques L, Goldfrad C, et al. Asthma control can be maintained when fluticasone/salmeterol in a single inhaler is stepped down. *J Allergy Clin Immunol*. 2006;117(3):563-570.
- Bateman ED, O'Byrne PM, Busse WW, et al. Once-daily fluticasone furoate (FF)/vilanterol reduces risk of severe exacerbations in asthma versus FF alone. *Thorax*. 2014;69:312-319.
- Bateman ED, Reddel HK, O'Byrne PM, et al. As-needed budesonide-formoterol versus maintenance budesonide in mild asthma (SYGMA 2). *N Engl J Med*. 2018;378(20):1877-1887. doi: 10.1056/NEJMoa1715275.
- Bateman ED, Silins V, Bogolubov M. Clinical equivalence of salmeterol/fluticasone propionate in combination (50/100 microg twice daily) when administered via a chlorofluorocarbon-free metered dose inhaler or dry powder inhaler to patients with mild-to-moderate asthma. *Respir Med*. 2001;95:136-146.
- Beasley R, Holliday M, Reddel HK, et al. Controlled trial of budesonide-formoterol as needed for mild asthma. *N Engl J Med*. 2019;380(21):2020-2030. doi: 10.1056/NEJMoa1901963.
- Beeh KM, Derom E, Echave-Sustaeta J, et al. The lung function profile of once-daily tiotropium and olodaterol via Respimat is superior to that of twice-daily salmeterol and fluticasone propionate via Accuhaler (ENERGITO study). *Int J Chron Obstruct Pulmon Dis*. 2016;11:193-205.
- Beeh KM, Westerman J, Kirsten AM, et al. The 24-h lung-function profile of once-daily tiotropium and olodaterol fixed-dose combination in chronic obstructive pulmonary disease. *Pulm Pharmacol Ther*. 2015; 32:53-59.
- Berger WE, Bleecker ER, O'Dowd L, et al. Efficacy and safety of budesonide/formoterol pressurized metered-dose inhaler: randomized controlled trial comparing once- and twice-daily dosing in patients with asthma. *Allergy Asthma Proc*. 2010;31:49-59.
- Bernstein DI, Bateman ED, Woodcock A, et al. Fluticasone furoate (FF)/vilanterol (100/25 mcg or 200/25 mcg) or FF (100 mcg) in persistent asthma. *J Asthma*. 2015;52(10):1073-1083.
- Bernstein D, Andersen L, Forth R, Jacques L, Yates L. Once-daily fluticasone furoate/vilanterol versus twice-daily fluticasone propionate/salmeterol in patients with asthma well controlled on ICS/LABA. *J Asthma*. 2018;1-10. doi: 10.1080/02770903.2017.1386214.
- Bernstein DI, Hebert J, Cheema A, et al. Efficacy and onset of action of mometasone furoate/formoterol and fluticasone propionate/salmeterol combination treatment in subjects with persistent asthma. *Allergy Asthma Clin Immunol*. 2011;7(1):21.
- Bevespi Aerosphere [package insert], Wilmington, DE: AstraZeneca; May 2019.
- Bleecker ER, Lötvall J, O'Byrne PM, et al. Fluticasone furoate-vilanterol 100-25 mcg compared with fluticasone furoate 100 mcg in asthma: a randomized trial. *J Allergy Clin Immunol Pract*. 2014;2:553-561.
- Bone R, Boyars M, Braun S, et al. In chronic obstructive pulmonary disease, a combination of ipratropium and albuterol is more effective than either agent alone an 85-day multicenter trial. *Chest*. 1994;105:1411-1419.
- Breo Ellipta [package insert], Research Triangle Park, NC: GlaxoSmithKline; April 2019.
- Buhl R, Maltais F, Abrahams R, et al. Tiotropium and olodaterol fixed-dose combination versus mono-components in COPD (GOLD 2-4). *Eur Respir J*. 2015;45:869-871.
- Busse WW, Shah SR, Somerville L, et al. Comparison of adjustable- and fixed-dose budesonide/ formoterol pressurized metered-dose inhaler and fixed-dose fluticasone propionate/salmeterol dry powder inhaler in asthma patients. *J Allergy Clin Immunol*. 2008;121:1407-1414.
- Calverley PMA, Anderson JA, Celli B, et al. Salmeterol and fluticasone propionate and survival in chronic obstructive pulmonary disease. *N Engl J Med*. 2007;356(8):775-789.
- Calverley PMA, Anzueto AR, Carter K, et al. Tiotropium and olodaterol in the prevention of chronic obstructive pulmonary disease exacerbations (DYNAGITO): a double-blind, randomised, parallel-group, active-controlled trial. *Lancet Respir Med*. 2018;6(5):337-344. doi: 10.1016/S2213-2600(18)30102-4.
- Calverley P, Pauwels R, Vestbo J, et al. Combined salmeterol and fluticasone in the treatment of chronic obstructive pulmonary disease: a randomized controlled trial. *Lancet*. 2003;361:449-456.
- Calzetta L, Di Marco F, Blasi F, et al. Impact of ICS/LABA and LABA/LAMA FDCs on functional and clinical outcomes in COPD: a network meta-analysis. *Pulm Pharmacol Ther*. 2019;59:101855. doi: 10.1016/j.pupt.2019.101855.
- Calzetta L, Rogliani P, Matera MG, Cazzola M. A systematic review with meta-analysis of dual bronchodilation with LABA/LABA for the treatment of stable COPD. *Chest*. 2016;149:1181-1196.
- Celli B, Crater G, Kilbride S, et al. Once-daily umeclidinium/vilanterol 125/25 mcg in COPD: a randomized, controlled study. *Chest*. 2014;145(5):981-991. doi: 10.1378/chest.13-1579.
- Centers for Disease Control and Prevention (CDC). Basics about COPD. July 19, 2019. CDC Web site. https://www.cdc.gov/copd/basics-about.html#anchor_1510688194070. Accessed May 22, 2020.
- Centers for Disease Control and Prevention (CDC). Most recent national asthma data: national current asthma prevalence (2018). March 24, 2020. CDC Web site. https://www.cdc.gov/asthma/most_recent_national_asthma_data.htm. Accessed May 22, 2020.
- Chapman KR, Ringdal N, Backer V, et al. Salmeterol and fluticasone propionate (50/250 microg) administered via combination Diskus inhaler: as effective as when given via separate Diskus inhalers. *Can Respir J*. 1999;6:45-51.

- Chipps BE, Bacharier LB, Murphy KR, et al. The asthma controller step-down Yardstick. *Ann Allergy Asthma Immunol.* 2019;122:241-262. doi: 10.1016/j.anai.2018.12.004.
- Combivent Respimat [package insert]. Ridgefield, CT: Boehringer Ingelheim; June 2016.
- Corren J, Korenblat PE, Miller CJ, et al. Twelve-week, randomized, placebo-controlled, multicenter study of the efficacy and tolerability of budesonide and formoterol in one metered-dose inhaler compared to budesonide alone and formoterol alone in adolescents and adults with asthma. *Clin Ther.* 2007;29(5):823-843.
- Covelli H, Pek B, Schenkenberger I, et al. Efficacy and safety of fluticasone furoate/vilanterol or tiotropium in subjects with COPD at cardiovascular risk. *Int J Chron Obstruct Pulmon Dis.* 2016;11:1-12.
- Criner GJ, Bourbeau J, Diekemper RL, et al. Prevention of acute exacerbations of COPD: American College of Chest Physicians and Canadian Thoracic Society Guideline. *Chest.* 2015;147(4):894-942.
- Dahl R, Chuchalin A, Gor D, et al. EXCEL: a randomized trial comparing salmeterol/fluticasone propionate and formoterol/budesonide combinations in adults with persistent asthma. *Resp Med.* 2006; 100:1152-62.
- Decramer M, Anzueto A, Kerwin E, et al. Efficacy and safety of umeclidinium plus vilanterol versus tiotropium, vilanterol, or umeclidinium monotherapies over 24 weeks in patients with chronic obstructive pulmonary disease: results from two multicentre, blinded, randomised controlled trials. *Lancet Respir Med.* 2014;2:472-486.
- Donohue JF, Maleki-Yazdi MR, Kilbride S, et al. Efficacy and safety of once-daily umeclidinium/vilanterol 62.5/25 mcg in COPD. *Respir Med.* 2013;107:1538-1546.
- Donohue JF, Worsley S, Zhu CQ, et al. Improvements in lung function with umeclidinium/vilanterol versus fluticasone propionate/salmeterol in patients with moderate-to-severe COPD and infrequent exacerbations. *Respir Med.* 2015;109:870-881.
- Dorinsky PM, Reisner C, Ferguson G, et al. The combination of ipratropium and albuterol optimizes pulmonary function reversibility testing in patients with COPD. *Chest.* 1999;115:966-971.
- Dransfield MT, Bourbeau J, Jones PW, et al. Once-daily inhaled fluticasone furoate and vilanterol versus vilanterol only for prevention of exacerbations of COPD: two replicate double-blind, parallel-group, randomised controlled trials. *Lancet Respir Med.* 2013;1:210-223.
- Dransfield MT, Feldman G, Korenblat P, et al. Efficacy and safety of once-daily fluticasone furoate/vilanterol (100/25 mcg) versus twice-daily fluticasone propionate/salmeterol (250/50 mcg) in COPD patients. *Respir Med.* 2014;108:1171-1179.
- Drugs@FDA: FDA approved drug products. Food and Drug Administration Web site. <https://www.accessdata.fda.gov/scripts/cder/daf/>. Accessed May 22, 2020.
- Duaklir Pressair [package insert]. Morrisville, NC: Circassia Pharmaceuticals Inc; February 2020.
- D'Urzo AD, Rennard SI, Kerwin EM, et al. Efficacy and safety of fixed-dose combinations of acclidinium bromide/formoterol fumarate: the 24-week, randomized, placebo-controlled AUGMENT COPD study. *Respir Res.* 2014;15:123. doi: 10.1186/s12931-014-0123-0.
- Dulera [package insert], Whitehouse Station, NJ: Merck Sharp & Dohme; August 2019.
- Dwan K, Milan SJ, Bax L, et al. Vilanterol and fluticasone furoate for asthma. *Cochrane Database Syst Rev.* 2016;9:CD010758. doi:10.1002/14651858.CD010758.pub2.
- Eid NS, Noonan MJ, Chipps B, et al. Once- vs twice-daily budesonide/formoterol in 6- to 15-year old patients with stable asthma. *Pediatrics.* 2010;126:e565-575.
- Feldman GJ, Sousa AR, Lipson DA, et al. Comparative efficacy of once-daily umeclidinium/vilanterol and tiotropium/olodaterol therapy in symptomatic chronic obstructive pulmonary disease: a randomized study. *Adv Ther.* 2017;34:2518-2533.
- FitzGerald MJ, Boulet LP, Follows RM. The CONCEPT trial: A 1-year, multicenter, randomized, double-blind, double-dummy comparison of a stable dosing regimen of salmeterol/fluticasone propionate with an adjustable maintenance dosing regimen of formoterol/budesonide in adults with persistent asthma. *Clin Ther.* 2005;27(4):393-406.
- Food and Drug Administration. AirDuo RespiClick Medical Review. FDA Web site. https://www.accessdata.fda.gov/drugsatfda_docs/nda/2017/208799Orig1s000TOC.cfm. April 14, 2017. Accessed May 22, 2020.
- Food and Drug Administration. FDA drug safety communication: FDA review finds no significant increase in risk of serious asthma outcomes with long-acting beta agonists (LABAs) used in combination with inhaled corticosteroids (ICS). FDA Web site. https://www.fda.gov/Drugs/DrugSafety/ucm589587.htm?utm_campaign=New%20FDA%20Drug%20Safety%20Communication%20update%20on%20ong-acting%20beta%20agonists%20%28LABAs%29&utm_medium=email&utm_source=Eloqua. Updated January 22, 2018. Accessed May 22, 2020.
- Friedman M, Serby CW, Menjoge SS, et al. Pharmacoeconomic evaluation of a combination of ipratropium plus albuterol compared with ipratropium alone and albuterol alone in COPD. *Chest.* 1999;115:635-641.
- Gappa M, Zachgo W, von Berg A, et al. Add-on salmeterol compared to double dose fluticasone in pediatric asthma: a double-blind, randomized trial (VIAPAD). *Pediatr Pulmonol.* 2009;44:1132-1142.
- Global Initiative for Asthma (GINA). Difficult-to-treat & severe asthma in adolescent and adult patients: diagnosis and management. 2019. <https://ginasthma.org/wp-content/uploads/2019/04/GINA-Severe-asthma-Pocket-Guide-v2.0-wms-1.pdf>. Accessed May 22, 2020.
- Global Initiative for Asthma (GINA). Global strategy for asthma management and prevention. April 3, 2020. www.ginasthma.org. Accessed May 22, 2020.
- Global Initiative for Chronic Obstructive Lung Disease (GOLD). Global strategy for the diagnosis, management, and prevention of chronic obstructive pulmonary disease. 2020a. <http://goldcopd.org/gold-reports/>. Accessed May 22, 2020.
- Global Initiative for Chronic Obstructive Lung Disease (GOLD). GOLD COVID-19 guidance. 2020b. <https://goldcopd.org/gold-covid-19-guidance/>. Accessed May 20, 2020.
- Han MK, Ray R, Foo J, Morel C, Hahn B. Systematic literature review and meta-analysis of US-approved LAMA/LABA therapies versus tiotropium in moderate-to-severe COPD. *NPJ Prim Care Respir Med.* 2018;28(1):32. doi: 10.1038/s41533-018-0099-1.
- Hanania NA, Crater GD, Morris AN, et al. Benefits of adding fluticasone propionate/salmeterol to tiotropium in moderate to severe COPD. *Respir Med.* 2012;106:91-101.
- Hanania NA, Darken P, Horstman D, et al. The efficacy and safety of fluticasone propionate (250 microg)/salmeterol (50 microg) combined in the discus inhaler for the treatment of COPD. *Chest.* 2003;124(3):834-843.

- Hanania NA, Tashkin DP, Kerwin EM, et al. Long-term safety and efficacy of glycopyrrolate/formoterol metered dose inhaler using novel co-suspension delivery technology in patients with chronic obstructive pulmonary disease. *Respir Med.* 2017;126:1050115.
- He J, Lin JT. A comparison of tiotropium/olodaterol vs tiotropium alone in terms of treatment effect for chronic obstructive pulmonary disease: A meta-analysis. *Medicine (Baltimore).* 2020;99(16):e19789. doi:10.1097/MD.00000000000019789
- Holguin F, Cardet JC, Chung KF, et al. Management of severe asthma: a European Respiratory Society/American Thoracic Society guideline. *Eur Respir J.* 2020;55(1). pii: 1900588. doi: 10.1183/13993003.00588-2019.
- Huisman EL, Cockle SM, Ismaila AS, et al. Comparative efficacy of combination bronchodilator therapies in COPD: a network meta-analysis. *Int J Chron Obstruct Pulm Dis.* 2015;10:1863-1881.
- Ipratropium bromide and albuterol sulfate solution [package insert]. Columbus, OH: American Health Packaging; September 2018.
- Jenkins C, Kolarikova R, Kuna P, et al. Efficacy and safety of high-dose budesonide/formoterol (Symbicort) compared to budesonide administered either concomitantly with formoterol or alone in patients with persistent symptomatic asthma. *Respirology.* 2006;11:276-286.
- Kalberg C, O'Dell D, Galkin D, et al. Dual bronchodilator therapy with umeclidinium/vilanterol versus tiotropium plus indacaterol in chronic obstructive pulmonary disease: a randomized controlled trial. *Drugs R D.* 2016;16:217-227.
- Karner C, Cates CJ. Combination inhaled steroid and long-acting beta₂-agonist in addition to tiotropium versus tiotropium or combination alone for chronic obstructive pulmonary disease. *Cochrane Database Syst Rev.* 2011;(3):CD008532. doi: 10.1002/14651858.CD008532.pub2.
- Kerwin E, Ferguson GT, Sanjar S, et al. Dual bronchodilation with indacaterol maleate/glycopyrronium bromide compared with umeclidinium bromide/vilanterol in patients with moderate-to-severe COPD: results from two randomized, controlled, cross-over studies. *Lung.* 2017b;195:739-747.
- Kerwin EM, Kalberg CJ, Galkin DV, et al. Umeclidinium/vilanterol as step-up therapy from tiotropium in patients with moderate COPD: a randomized, parallel-group, 12-week study. *Int J Chron Obstruct Pulm Dis.* 2017a;12:745-755.
- Kerwin EM, Oppenheimer JJ, LaForce C, et al. Efficacy and tolerability of once-daily budesonide/formoterol pressurized metered-dose inhaler in adults and adolescents with asthma previously stable with twice-daily budesonide/formoterol dosing. *Ann Allergy Asthma Immunol.* 2009;103:62-72.
- Kerwin EM, Scott-Wilson C, Sanford L, et al. A randomized trial of fluticasone furoate/vilanterol (50/25 µg; 100/25 µg) on lung function in COPD. *Respir Med.* 2013;107:560-569.
- Kuna P, Creemers JPHM, Vondra V, et al. Once-daily dosing with budesonide/formoterol compared to twice-daily budesonide/formoterol and once-daily budesonide in adults with mild to moderate asthma. *Respir Med.* 2006;100(12):2151-2159.
- Laloo U, Malolepszy J, Kozma D, et al. Budesonide and formoterol in a single inhaler improves asthma control compared to increasing the dose of corticosteroid in adults with mild-to-moderate asthma. *Chest.* 2003;123:1480-1487.
- Lasserson TJ, Ferrara G, Casali L. Combination fluticasone and salmeterol versus fixed dose combination budesonide and formoterol for chronic asthma in adults and children. *Cochrane Database Syst Rev.* 2011;(12):CD004106. doi:10.1002/14651858.CD004106.pub4.
- Lee SD, Xie CM, Yunus F, et al. Efficacy and tolerability of budesonide/formoterol added to tiotropium compared with tiotropium alone in patients with severe or very severe COPD: a randomized, multicentre study in East Asia. *Respirology.* 2016; 21(1):119-127.
- Lipson DA, Barnacle H, Birk R, et al. FULFIL trial: once-daily triple therapy for patients with chronic obstructive pulmonary disease. *Am J Respir Crit Care Med.* 2017;196(4):438-446.
- Lipson DA, Barnhart F, Brealey N, et al; IMPACT Investigators. Single-inhaler triple versus dual therapy in patients with COPD. *N Engl J Med.* 2018;378(18):1671-1680. doi: 10.1056/NEJMoa1713901.
- Lipworth BJ1, Collier DJ2, Gon Y, et al. Improved lung function and patient-reported outcomes with co-suspension delivery technology glycopyrrolate/formoterol fumarate metered dose inhaler in COPD: a randomized phase III study conducted in Asia, Europe, and the USA. *Int J Chron Obstruct Pulm Dis.* 2018;13:2969-2984. doi: 10.2147/COPD.S171835.
- Lundback B, Ronmark B, Lindberg A, et al. Control of mild to moderate asthma over 1-year with the combination of salmeterol and fluticasone propionate. *Respir Med.* 2006;100:2-10.
- Mahler DA, Kerwin E, Ayers T, et al. FLIGHT1 and FLIGHT2: Efficacy and safety of QVA149 (indacaterol/glycopyrrolate) versus its monocomponents and placebo in patients with chronic obstructive pulmonary disease. *Am J Respir Crit Care Med.* 2015;192(9):1068-1079.
- Maleki-Yazdi MR, Singh D, Anzueto A, Tombs L, Fahy WA, Naya I. Assessing short-term deterioration in maintenance-naïve patients with COPD receiving umeclidinium/vilanterol and tiotropium: a pooled analysis of three randomized trials. *Adv Ther.* 2017;33(12):2188-2199. Epub 2016 Oct 28.
- Maltais F, Bjermer L, Kerwin EM, et al. Efficacy of umeclidinium/vilanterol versus umeclidinium and salmeterol monotherapies in symptomatic patients with COPD not receiving inhaled corticosteroids: the EMAX randomised trial. *Respir Res.* 2019a;20(1):238. doi: 10.1186/s12931-019-1193-9.
- Maltais F, Ferguson GT, Feldman GJ, et al. A randomized, double-blind, double-dummy study of glycopyrrolate/formoterol fumarate metered dose inhaler relative to umeclidinium/vilanterol dry powder inhaler in COPD. *Adv Ther.* 2019b;36(9):2434-2449. doi: 10.1007/s12325-019-01015-3.
- Marceau C, Lemiere C, Berbiche D, et al. Persistence, adherence, and effectiveness of combination therapy among adult patients with asthma. *J Allergy Clin Immunol.* 2006;118:574-581.
- Martinez FJ, Boscia J, Feldman G, et al. Fluticasone furoate/vilanterol (100/25; 200/25 µg) improves lung function in COPD: a randomized trial. *Respir Med.* 2013;107:550-559.
- Martinez FJ, Rabe KF, Ferguson GR, et al. Efficacy and safety of glycopyrrolate/formoterol MDI formulated using co-suspension delivery technology in patients with COPD. *Chest.* 2017;151(2):340-357.
- Matera MG, Rogliani P, Calzetta L, et al. Safety considerations with dual bronchodilator therapy in COPD: an update. *Drug Saf.* 2016;39(6):501-508.
- Meltzer EO, Kuna P, Nolte H, et al; P04073 Study Investigators. Mometasone furoate/formoterol reduces asthma deteriorations and improves lung function. *Eur Respir J.* 2012;39:279-289.
- Morice AH, Peterson S, Beckman O, Osmanliev D. Therapeutic comparison of a new budesonide/formoterol pMDI with budesonide pMDI and budesonide/formoterol DPI in asthma. *Int J Clin Pract.* 2007;61(11):1874-1883.
- Murphy K, Nelson H, Parasuraman B, et al. The effect of budesonide and formoterol in one pressurized metered-dose inhaler on patient-reported outcomes in adults with mild-to-moderate persistent asthma. *Curr Med Res Opin.* 2008;24(3):879-894.
- Nannini LJ, Lasserson TJ, Poole P. Combined corticosteroid and long-acting beta(2)-agonist in one inhaler versus long-acting beta(2)-agonists for chronic obstructive pulmonary disease. *Cochrane Database Syst Rev.* 2012;(9):CD006829. doi: 10.1002/14651858.CD006829.pub2.
- Nannini LJ, Poole P, Milan SJ, Holmes R, Normansell R. Combined corticosteroid and long-acting beta(2)-agonist in one inhaler versus placebo for chronic obstructive pulmonary disease. *Cochrane Database Syst Rev.* 2013a;(11):CD003794. doi: 10.1002/14651858.CD003794.pub4.

- Nannini LJ, Poole P, Milan SJ, Kesterton A. Combined corticosteroid and long-acting beta(2)-agonist in one inhaler versus inhaled corticosteroids alone for chronic obstructive pulmonary disease. *Cochrane Database Syst Rev.* 2013b;(8):CD006826. doi: 10.1002/14651858.CD006826.pub2.
- Nathan RA, Rooklin A, Schoaf L, et al. Efficacy and tolerability of fluticasone/salmeterol administered twice daily via hydrofluoroalkane 134a metered-dose inhaler in adolescents and adult patients with persistent asthma: a randomized, double blind, placebo-controlled, 12-week study. *Clin Ther.* 2006;28:73-85.
- National Heart, Lung, and Blood Institute Web site. Expert Panel Report 3: Guidelines for the diagnosis and management of asthma. <http://www.nhlbi.nih.gov/health-pro/guidelines/current/asthma-guidelines>. Updated August 2007. Accessed **May 22, 2020**.
- National Heart, Lung, and Blood Institute Web site. Asthma. <http://www.nhlbi.nih.gov/health/health-topics/topics/asthma>. Accessed **May 22, 2020**.
- Nelson HS, Chapman KR, Pyke SD, et al. Enhanced synergy between fluticasone and salmeterol inhaled from a single inhaler vs separate inhalers. *J Allergy Clin Immunol.* 2003b;112:29-36.
- Nelson HS, Wolfe JD, Gross G, et al. Efficacy and safety of fluticasone propionate 44 microg/salmeterol 21 microg administered in a hydrofluoroalkane metered-dose inhaler as an initial asthma maintenance treatment. *Ann Allergy Asthma Immunol.* 2003a;91:263-269.
- Ng D, Kerwin EM, White MV, et al. Clinical bioequivalence of Wixela Inhub and Advair Diskus in adults with asthma. *J Aerosol Med Pulm Drug Deliv.* 2019. doi: 10.1089/jamp.2019.1547.
- Ni H, Moe S, Soe Z, Myint KT, Viswanathan KN. Combined acclidinium bromide and long-acting beta2-agonist for chronic obstructive pulmonary disease (COPD). *Cochrane Database Syst Rev.* 2018;12: CD011594. doi: 10.1002/14651858.CD011594.pub2.
- Noonan M, Rosenwasser LJ, Martin P, et al. Efficacy and safety of budesonide and formoterol in one pressurized metered-dose inhaler in adults and adolescents with moderate to severe asthma. *Drugs.* 2006;66(17):2235-2254.
- O'Byrne PM, Bleecker ER, Bateman ED, et al. Once-daily fluticasone furoate alone or combined with vilanterol in persistent asthma. *Eur Respir J.* 2014;43(3):773-782.
- Ohar JA, Crater GD, Emmett A, et al. Fluticasone propionate/salmeterol 250/50 µg versus salmeterol 50 µg after chronic obstructive pulmonary disease exacerbation. *Respir Res.* 2014;15:105. DOI:10.1186/s12931-014-0105-2.
- OINDP news. FDA lists Arcapta, Seebri, and Utibron Neohalers as discontinued (updated) [press release]. March 12, 2020. <https://www.oindpnews.com/2020/03/fda-lists-arcapta-seebri-and-utibron-neohalers-as-discontinued/>. Accessed **May 22, 2020**.
- Orange Book: Approved drug products with therapeutic equivalence evaluations. Food and Drug Administration Web site. <https://www.accessdata.fda.gov/scripts/cder/ob/default.cfm>. Accessed **May 22, 2020**.
- Palmqvist M, Arvidsson P, Beckman O, et al. Onset of bronchodilation with budesonide/formoterol and salmeterol/fluticasone in single inhalers. *Pulm Pharmacol Ther.* 2001;14(1):29-34.
- Partridge MR, Schuermann W, Beckman O, et al. Effect on lung function and morning activities of budesonide/formoterol vs salmeterol/fluticasone in patients with COPD. *Ther Adv Respir Dis.* 2009;3(4):147-157.
- Pearlman DS, Eckerwall G, McLaren J, et al. Efficacy and safety of budesonide/formoterol pMDI vs budesonide pMDI in asthmatic children (6-<12 years). *Ann Allergy Asthma Immunol.* 2017;118:489-499.
- Pearlman DS, Peden D, Condemni JJ, et al. Efficacy and safety of fluticasone/salmeterol HFA 134A MDI in patients with mild-moderate persistent asthma. *J Asthma.* 2004;41:797-806.
- Perrin K, Williams M, Wijesinghe M, et al. Randomized controlled trial of adherence with single or combination inhaled corticosteroid/long-acting β-agonist inhaler therapy in asthma. *J Allergy Clin Immunol.* 2010;126:505-510.
- Peters SP, Bleecker ER, Canonica GW, et al. Serious asthma events with budesonide plus formoterol vs. budesonide alone. *N Engl J Med.* 2016;375:850-860.
- Pohl WR, Vetter N, Zwick H, et al. Adjustable maintenance dosing with budesonide/formoterol or budesonide: double blind study. *Respir Med.* 2006;100(3):551-560.
- Price D, Østrem A, Thomas M, Welte T. Dual bronchodilation in COPD: lung function and patient-reported outcomes – a review. *Int J Chron Obstruct Pulmon Dis.* 2016;12:141-168.
- Price DB, Williams AE, Yoxall S. Salmeterol/fluticasone stable-dose treatment compared to formoterol-budesonide adjustable maintenance dosing: impact on health-related quality of life. *Respir Res.* 2007;8:46.
- Raphael G, Yiu G, Sakov A, et al. Randomized, double-blind trial evaluating the efficacy and safety of fluticasone propionate and fluticasone propionate/salmeterol delivered via multidose dry powder inhalers in patients with persistent asthma aged 12 years and older. *J Asthma.* 2018;55(6):640-650. doi: 10.1080/02770903.2017.1350971.
- Rennard SI, Tashkin DP, McElhattan J, et al. Efficacy and tolerability of budesonide/formoterol in one hydrofluoroalkane pressurized metered-dose inhaler in patients with chronic obstructive pulmonary disease: results from a 1-year randomized controlled clinical trial. *Drugs.* 2009;69(5):549-565.
- Rodrigo GJ, Neffen H. A systematic review with meta-analysis of fluticasone furoate/vilanterol combination for the treatment of stable COPD. *Pulm Pharmacol Ther.* 2017;42:1-6.
- Rodrigo GJ, Plaza V, et al. Once-daily fluticasone furoate and vilanterol for adolescents and adults with symptomatic asthma: a systematic review and meta-analysis. *Ann Allergy Asthma Immunol.* 2016;116:565-570.
- Rojas-Reyes MX, García Morales OM, Dennis RJ, Karner C. Combination inhaled steroid and long-acting beta₂-agonist in addition to tiotropium versus tiotropium or combination alone for chronic obstructive pulmonary disease. *Cochrane Database Syst Rev.* 2016;(6):CD008532. doi: 10.1002/14651858.CD008532.pub3.
- Rosenhall L, Heinig JH, Lindqvist A, et al. Budesonide/formoterol (Symbicort) is well tolerated and effective in patients with moderate persistent asthma. *Int J Clin Pract.* 2002;56(6):427-433.
- Schlueter M, Gonzalez-Rojas N, Baldwin M, et al. Comparative efficacy of fixed-dose combinations of long-acting muscarinic antagonists and long-acting β₂-agonists: a systematic review and network meta-analysis. *Ther Adv Respir Dis.* 2016;10(2):89-104.
- Sethi S, Kerwin E, Watz H, et al. AMPLIFY: a randomized, Phase III study evaluating the efficacy and safety of acclidinium/formoterol vs monocomponents and tiotropium in patients with moderate-to-very severe symptomatic COPD. *Int J Chron Obstruct Pulmon Dis.* 2019;14:667-682. doi: 10.2147/COPD.S189138.
- Sharafkhaneh A, Southard JG, Goldman M, Uryniak T, Ubaldo JM. Effect of budesonide/formoterol pMDI on COPD exacerbations: a double-blind, randomized study. *Respir Med.* 2012;106:257-68.

- Sher LD, Yiu G, Sakov A, et al. Fluticasone propionate and fluticasone propionate/salmeterol multidose dry powder inhalers compared with placebo for persistent asthma. *Allergy Asthma Proc.* 2017;38(5):343-353. doi: 10.2500/aap.2017.38.4069.
- Siler TM, Kerwin E, Sousa AR, et al. Efficacy and safety of umeclidinium added to fluticasone furoate/vilanterol in chronic obstructive pulmonary disease: results of two randomized studies. *Respir Med.* 2015;109(9):1155-1163.
- Singh D, Jones PW, Bateman ED, et al. Efficacy and safety of aclidinium bromide/formoterol fumarate fixed-dose combinations compared with individual components and placebo in patients with COPD (ACLIFORM-COPD): a multicentre, randomised study. *BMC Pulm Med.* 2014;178. doi: 10.1186/1471-2466-14-178.
- Singh D, Worsley S, Zhu CQ, et al. Umeclidinium/vilanterol versus fluticasone propionate/salmeterol in COPD: a randomised trial. *BMC Pulm Med.* 2015;15:91.
- Sion KY, Huisman EL, Puneekar YS, et al. A network meta-analysis of long-acting muscarinic antagonist (LAMA) and long-acting β 2-agonist (LABA) combinations in COPD. *Pulm Ther.* 2017;3:297-316.
- Sliwka A, Jankowski M, Gross-Sondej I, et al. Once-daily long-acting beta(2)-agonists/inhaled corticosteroids combined inhalers versus inhaled long-acting muscarinic antagonists for people with chronic obstructive pulmonary disease. *Cochrane Database Syst Rev.* 2018;8:CD012355. doi: 10.1002/14651858.CD012355.pub2.
- Sobieraj DM, Weeda ER, Nguyen E, et al. Association of inhaled corticosteroids and long-acting beta-agonists as controller and quick relief therapy with exacerbations and symptom control in persistent asthma: a systematic review and meta-analysis. *JAMA.* 2018;319(14):1485-1496. doi: 10.1001/jama.2018.2769.
- Stempel DA, Raphiou IH, Kral KM, et al. Serious adverse events with fluticasone plus salmeterol versus fluticasone alone. *N Engl J Med.* 2016a;374:1822-1830.
- Stempel DA, Szeffler SJ, Pedersen S, et al. Safety of adding salmeterol to fluticasone propionate in children with asthma. *N Engl J Med.* 2016b;375:840-849.
- Stiolto Respimat [package insert], Ridgefield, CT: Boehringer Ingelheim Pharmaceuticals, Inc.; May 2019.
- Symbicort [package insert], Wilmington, DE: AstraZeneca; July 2019.
- Tal A, Simon G, Vermeulen JH, et al. Budesonide/formoterol in a single inhaler vs inhaled corticosteroids alone in the treatment of asthma. *Pediatr Pulmonol.* 2002;34:342-350.
- Tang B, Wang J, Luo LL, Li QG, Huang D. Comparative efficacy of budesonide/formoterol with budesonide, formoterol or placebo for stable chronic obstructive pulmonary disease: a meta-analysis. *Med Sci Monit.* 2019;25:1155-1163. doi: 10.12659/MSM.912033.
- Tashkin DP, Rennard SI, Martin P, et al. Efficacy and safety of budesonide and formoterol in one pressurized metered-dose inhaler in patients with moderate to very severe chronic obstructive pulmonary disease: results of a 6-month randomized clinical trial. *Drugs.* 2008;68(14):1975-2000.
- Trelegy Ellipta [package insert], Research Triangle Park, NC: GlaxoSmithKline; May 2019.
- Utibron Neohaler [package insert], Marlborough, MA: Sunovion; May 2019.
- Vaessen-Verberne AAPH, van den Berg NJ, van Nierop JC, et al. Combination therapy salmeterol/fluticasone vs doubling dose of fluticasone in children with asthma. *Am J Respir Crit Care Med.* 2010;182:1221-1227.
- Vestbo J, Anderson JA, Brook RD, et al. Fluticasone furoate and vilanterol and survival in chronic obstructive pulmonary disease with heightened cardiovascular risk (SUMMIT): a double-blind randomised controlled trial. *Lancet.* 2016a;387:1817-1826.
- Vestbo J, Leather D, Bakerly ND, et al. Effectiveness of fluticasone furoate-vilanterol for COPD in clinical practice. *N Engl J Med.* 2016b;375:1253-1260.
- Vestbo J, Pauwels R, Anderson J, et al. Early onset of effect of salmeterol and fluticasone propionate in chronic obstructive pulmonary disease. *Thorax.* 2005;60:301-304.
- Vogelmeier CF, Bateman ED, Pallante J, et al. Efficacy and safety of once-daily QVA149 compared with twice-daily salmeterol-fluticasone in patients with chronic obstructive pulmonary disease (ILLUMINATE): a randomised, double-blind, parallel group study. *Lancet Respir Med.* 2013;1:51-60.
- Wedzicha JA, Banerji D, Chapman KR, et al. Indacaterol-glycopyrronium versus salmeterol-fluticasone for COPD. *N Engl J Med.* 2016;374(23):2222-2234.
- Wedzicha JA, Calverley PMA, Seemungal TA, et al. The prevention of chronic obstructive pulmonary disease exacerbations by salmeterol/fluticasone propionate or tiotropium bromide. *Am J Respir Crit Care Med.* 2008;177:19-26.
- Weinstein SF, Corren J, Murphy K, et al. Twelve-week efficacy and safety study of mometasone furoate/formoterol 200/10 microg and 400/10 microg combination treatments in patients with persistent asthma previously receiving high-dose inhaled corticosteroids. *Allergy Asthma Proc.* 2010;31:280-289.
- Welte T, Miravittles M, Hernandez P, et al. Efficacy and tolerability of budesonide/formoterol added to tiotropium in patients with chronic obstructive pulmonary disease. *Am J Respir Crit Care Med.* 2009;180:741-750.
- Wixela Inhub [package insert]. Morgantown, WV: Mylan Pharmaceuticals Inc; December 2019.
- Woodcock A, Bleecker ER, Lötval J, et al. Efficacy and safety of fluticasone furoate/vilanterol compared with fluticasone propionate/salmeterol combination in adult and adolescent patients with persistent asthma: a randomized trial. *Chest.* 2013;144(4):1222-1229.

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