

## Therapeutic Class Overview

### Beta Agonist and Corticosteroid Combinations

#### INTRODUCTION

- Respiratory  $\beta_2$ -agonist/inhaled corticosteroid (ICS) combinations are used to treat asthma and/or chronic obstructive pulmonary disease (COPD). The specific indications vary based on the product and the strength. All  $\beta_2$ -agonist/ICS combinations are brand-name only at this time, with the exception of AIRDUO RESPICLICK (fluticasone propionate/salmeterol), for which an authorized generic is marketed.
- Asthma is a chronic lung disease that inflames and narrows the airways, making it difficult to breathe. Asthma causes recurring periods of wheezing, chest tightness, shortness of breath, and coughing. Asthma affects people of all ages, but most often starts during childhood. In the United States, more than 25 million people are known to have asthma, including about 7 million children (National Heart, Lung, and Blood Institute [NHLBI], 2014).
- The exact cause(s) of asthma are unknown. A combination of factors such as genetics, certain respiratory infections during childhood, and contact with airborne allergens can contribute to its development. Most patients with asthma have allergies (NHLBI, 2014).
- Current pharmacologic options for asthma management are categorized as: (1) long-term control medications to achieve and maintain control of persistent asthma, and (2) quick-relief medications used to treat acute symptoms and exacerbations (NHLBI, 2007).
- Long-term control medications for asthma include the following (NHLBI, 2007):
  - Corticosteroids (ICSs for long-term control, short courses of oral corticosteroids to gain prompt control of disease, long-term oral corticosteroids for severe persistent asthma)
  - Cromolyn sodium and nedocromil
  - Immunomodulators (ie, omalizumab)
  - Leukotriene modulators
  - Long-acting  $\beta$ -agonists (LABAs)
  - Methylxanthines (ie, theophylline)
- Quick-relief medications for asthma include the following (NHLBI, 2007):
  - Short-acting  $\beta$ -agonists (SABAs) (therapy of choice for relief of acute symptoms and prevention of exercise-induced bronchospasm)
  - Anticholinergics (ie, ipratropium bromide), as an alternative bronchodilator for those not tolerating a SABA
  - Systemic corticosteroids (not short-acting, but used for moderate and severe exacerbations) (NHLBI, 2007)
- In recent years, additional medications have been made available for select subsets of patients with asthma, including mepolizumab and reslizumab for the management of severe asthma with an eosinophilic phenotype (Prescribing information: CINQAIR, 2016; NUCALA, 2017). Additionally, tiotropium, long used for COPD, has been FDA approved for the treatment of asthma (SPIRIVA RESPIMAT prescribing information, 2017).
- ICSs are the most effective, most commonly recommended long-term control medications used for the treatment of asthma. Alternative long-term control medications include LABAs, leukotriene modifiers, mast-cell stabilizers, and methylxanthines (theophylline). The LABAs should not be used as monotherapy for the management of asthma; however, they are effective adjunctive therapy in patients who are not adequately controlled with an ICS alone. Theophylline and mast-cell stabilizers have weak to low efficacy in asthma. Theophylline has an unfavorable side-effect profile and may be life-threatening at high doses. Mast-cell stabilizers have a more favorable safety profile. Tiotropium is an option for add-on therapy in patients with a history of exacerbations. Omalizumab, mepolizumab, or reslizumab may be added if patients require a higher level of care. Omalizumab is used in patients with moderate to severe allergic asthma while mepolizumab or reslizumab are used for severe eosinophilic asthma. SABAs are the medication of choice for the relief of bronchospasm during acute exacerbations of asthma (NHLBI, 2007; Global Initiative for Asthma [GINA], 2017).
- COPD is characterized by persistent respiratory symptoms and airflow limitation due to airway and/or alveolar abnormalities. The abnormalities are usually caused by exposure to noxious particles or gases. Airflow limitation is caused by a combination of small airway disease (eg, obstructive bronchiolitis) and parenchymal destruction (emphysema); the relative contributions of each component vary between patients. The most common symptoms of

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COPD include dyspnea, cough, and sputum production (Global Initiative for Chronic Obstructive Lung Disease [GOLD], 2017).

- COPD affects 6.4% of the United States population and is the major contributor to mortality from chronic lower respiratory diseases, the third leading cause of death in the United States (Centers for Disease Control and Prevention, 2016). Globally, COPD is the fourth leading cause of death and is expected to be the third leading cause of death by 2020; the burden of COPD continues to increase due to continued exposure to risk factors and aging of the population (GOLD, 2017).
- Cigarette smoking is the main risk factor for COPD; other risk factors include biomass fuel exposure (such as from cooking and heating in poorly ventilated dwellings) and air pollution. Host factors such as genetic abnormalities, abnormal lung development, and accelerated aging can predispose individuals to COPD development (GOLD, 2017).
- Patients with COPD may experience exacerbations, which are periods of acute worsening of respiratory symptoms (GOLD, 2017).
- Pharmacologic therapy for COPD can reduce symptoms, reduce the risk and severity of exacerbations, and improve patients' health status and exercise tolerance. There is no conclusive evidence that COPD medications modify the long-term decline in lung function characteristic of COPD (GOLD, 2017).
- Pharmacologic options for COPD treatment comprise several classes, including  $\beta_2$ -agonists, anticholinergics, methylxanthines, various combination products (including bronchodilators with ICSs), and the phosphodiesterase (PDE)-4 inhibitor roflumilast. Pharmacologic treatments should be individualized based on symptom severity, risk of exacerbations, side effects, comorbidities, drug availability, and cost, as well as the patient's response, preference, and ability to use various drug delivery devices (GOLD, 2017).
- Inhaled bronchodilators are central to COPD symptom management, and are usually given on a regular basis to prevent or reduce symptoms. Several long-acting inhaled bronchodilators are available, and use of short-acting bronchodilators on a regular basis is not generally recommended (GOLD, 2017).
- An ICS combined with a LABA is more effective than the individual components in improving lung function and health status and reducing exacerbations in patients with exacerbations and moderate to very severe COPD. However, use of a long-acting muscarinic antagonist (LAMA)/LABA combination has been shown to decrease exacerbations more than an ICS/LABA combination, and regular treatment with an ICS increases the risk of pneumonia (GOLD, 2017).
- $\beta_2$ -agonists and ICSs can be administered separately or in combination products. Asthma patients with milder symptoms who do not require daily use of a LABA may benefit from separate administration of an ICS and use of a SABA for breakthrough symptoms. For patients requiring daily use of both an ICS and a LABA, combination products can provide a convenient option. In addition, it is important to note that for asthma treatment, a LABA should not be given without concomitant use of a long-term asthma control medication, such as an ICS. For patients with asthma who require the addition of a LABA to an ICS, a fixed-dose combination product can help ensure adherence with both drugs.
- This review includes the combination ICS/LABA combinations. The products in this category are shown in Table 1.
- Medispan class/subclass: Sympathomimetics/Adrenergic Combinations

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

Drug	Generic Availability
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)	-

\*Authorized generic

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

## INDICATIONS

**Table 2. Food and Drug Administration Approved Indications**

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

(Prescribing information: ADVAIR HFA, 2017; ADVAIR DISKUS, 2017; AIRDUO RESPICLICK, 2017; BREO ELLIPTA, 2017; DULERA, 2016; SYMBICORT, 2017)

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

## CLINICAL EFFICACY SUMMARY

### Comparisons to Placebo, Monotherapy, Combined use of Individual Components, Varied Treatments, or Usual Care:

- Numerous trials have compared the combination ICS/LABA products to their respective individual components as monotherapy, and in general, results have demonstrated that administration of the combination product is more effective than monotherapy for improving lung function and/or achieving control of symptoms in asthma and COPD (Bateman et al, 2001; Bateman et al, 2004; Bateman et al, 2006; Bateman et al, 2014; Berger et al, 2010; Bernstein et al, 2015; Bleecker et al, 2014; Calverley et al, 2003; Corren et al, 2007; Eid et al, 2010; 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; Nelson et al, 2003b; Nathan et al, 2006; Noonan et al, 2006; O'Byrne et al, 2014; Pearlman et al, 2004; Pohl et al, 2006; Rennard et al, 2009; Sharafkaneh et al, 2012; Tal et al, 2002; Tashkin et al, 2008; Vaessen-Verberne et al, 2010; Vestbo et al, 2005; Weinstein et al, 2010; Zangrilli et al, 2011). Results for reducing COPD exacerbations have been inconsistent. One head-to-head trial in patients with a recent exacerbation of COPD demonstrated no significant difference between fluticasone propionate/salmeterol 250/50 mcg twice daily and salmeterol 50 mcg twice daily in severe or moderate/severe COPD exacerbations (Ohar et al, 2014). Pooled results of two trials comparing varying doses of fluticasone furoate/vilanterol with vilanterol 25 mcg daily demonstrated a reduction in moderate/severe COPD exacerbations with fluticasone furoate/vilanterol compared to vilanterol alone (Dransfield et al, 2013).
- Additionally, there is similar efficacy between the administration of the combination ICS/LABA products and their individual components used in combination (Chapman et al, 1999; Jenkins et al, 2006; Marceau et al, 2006; Noonan et al, 2006; Nelson et al, 2003a; Perrin et al, 2010; Rosenhall et al, 2002; Zangrilli et al, 2011).
- AIRDUO RESPICLICK (fluticasone propionate/salmeterol) was approved by the FDA in April 2017 as a new combination delivered via the RespiClick device based on a clinical program consisting of three phase 2 placebo-controlled dose-ranging trials, two phase 3 efficacy trials, and a 26-week long-term safety trial in patients with persistent asthma (FDA medical review, 2017; Mansfield et al, 2016; Miller et al, 2016; Raphael et al, 2016; Raphael et al, 2017; Sher et al, 2016; Sher et al, 2017).
  - Two 12-week dose-ranging trials (total N=1,262) determined that fluticasone propionate 100 mcg delivered via the RespiClick resulted in a similar FEV<sub>1</sub> improvement compared with the marketed mid-dose fluticasone propionate (FLOVENT DISKUS) 100 mcg (295 mL vs. 234 mL, respectively); this supported the proposed fluticasone propionate low (50 mcg) and mid (100 mcg) doses delivered via the RespiClick (FDA medical review, 2017).
  - The FEV<sub>1</sub> change from baseline to week 12 for fluticasone propionate (FLOVENT DISKUS) 250 mcg was between the fluticasone propionate 100 mcg and 200 mcg RespiClick doses, which supported the proposed fluticasone propionate high (200 mcg) dose delivered via the RespiClick (FDA medical review, 2017).

- A crossover study (N=72) determined the FEV<sub>1</sub> area under the curve 12 hours post-dose (FEV<sub>1</sub> AUC<sub>0-12</sub>) of the fluticasone propionate/salmeterol (ADVAIR DISKUS) 100/50 mcg dose was most comparable to that of the fluticasone propionate/salmeterol (AIRDUO RESPICLICK) 100/12.5 mcg dose (245 vs. 249 mL, respectively; P=0.8503), which supported the proposed fixed 12.5 mcg dose of salmeterol delivered via the RespiClick (Miller et al, 2016).
- Two 12-week studies (N=1,445) evaluated the efficacy of fluticasone propionate/salmeterol (AIRDUO RESPICLICK) 50/12.5 mcg, 100/12.5 mcg, and 200/12.5 mcg vs. the corresponding fluticasone propionate monotherapy doses delivered via the RespiClick device and placebo (FDA medical review, 2017; Raphael et al, 2016; Raphael et al, 2017; Sher et al, 2016; Sher et al, 2017).
  - In all studies, treatment with fluticasone propionate/salmeterol (AIRDUO RESPICLICK) significantly increased pulmonary function vs. placebo, and was significantly superior in improving FEV<sub>1</sub> vs. fluticasone propionate monotherapy delivered via the RespiClick, with a similar safety profile.
- Results from the long-term safety trial (N=674) demonstrated asthma exacerbation as the most frequently reported serious adverse event (4% overall), while treatment-related adverse events occurred more frequently with the high-dose fluticasone propionate/salmeterol (ADVAIR DISKUS) 500/50 mcg and fluticasone propionate (FLOVENT HFA) 220 mcg doses vs. fluticasone propionate/salmeterol (AIRDUO RESPICLICK) 100/12.5 mcg and 200/12.5 mcg doses and fluticasone propionate 100 mcg and 200 mcg delivered via the RespiClick due to a higher incidence of oral candidiasis (11 and 12%, respectively, vs. 0 to 5%) (FDA medical review, 2017; Mansfield et al, 2016).
- A large, double-blind, randomized trial (N=6,112) compared fluticasone propionate/salmeterol 500/50 mcg twice daily to its individual components and to placebo over a three-year period in patients with COPD. 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 (Calverley et al, 2007).
- A large, double-blind, randomized trial (SUMMIT; N=16,590) evaluated the use of fluticasone furoate/vilanterol vs fluticasone furoate alone, vilanterol alone, or placebo in a population of patients with moderate COPD and heightened cardiovascular risk (age ≥60 years and receiving medication for >2 of the following: hypercholesterolemia, hypertension, diabetes mellitus, or peripheral arterial disease) (Vestbo et al, 2016a). Compared with placebo, there was no significant benefit or worsening in all-cause mortality with combination therapy (hazard ratio [HR], 0.88 [95% confidence interval (CI), 0.74 to 1.04; P=0.137]) or with the components (fluticasone furoate HR, 0.91 [95% CI, 0.77 to 1.08; P=0.284]; vilanterol HR, 0.96 [95% CI, 0.81 to 1.14; P=0.655]). Composite cardiovascular events were also similar in the four groups (3.9% to 4.4%). All treatments reduced the risk of moderate to severe COPD exacerbations compared to placebo, with percent reductions of 29% (95% CI, 22 to 35), 12% (95% CI, 4 to 19), and 10% (95% CI, 2 to 18) in the fluticasone furoate/vilanterol, fluticasone furoate, and vilanterol groups, respectively.
- A 12-month, randomized, open-label trial (Salford Lung Study; N=2,799) compared the use of fluticasone furoate/vilanterol 100/25 mcg daily to continuation of usual care in a real-world patient population in the United Kingdom (Vestbo et al, 2016b). Enrolled patients had COPD, had had one or more exacerbations in the previous three years, and were taking regular maintenance inhaler therapy (one or more long-acting bronchodilators; ICS alone or in combination with a long-acting bronchodilator; or a combination of ICS, LABA, and LAMA). The primary endpoint, the rate of moderate or severe exacerbations among patients who had had an exacerbation within one year before the trial, was 1.74 per year in the fluticasone furoate/vilanterol group and 1.90 per year in the usual-care group, for a difference of 8.4% (95% CI, 1.1 to 15.2; P=0.02). Serious adverse events, including pneumonia, were similar between the two groups.
- A meta-analysis of 19 trials evaluated the use of ICS/LABA combinations compared to placebo in patients with COPD. This analysis demonstrated a significant reduction in exacerbation rate between fluticasone propionate/salmeterol and placebo and between budesonide/formoterol and placebo. Looking at the number of patients who experienced one or more exacerbations, the differences between fluticasone propionate/salmeterol vs placebo and mometasone furoate/formoterol (200/10 mcg strength) vs placebo were not statistically significant; however, the mometasone furoate/formoterol 400/10 mcg strength was associated with a lower proportion of patients experiencing ≥1 exacerbation. This meta-analysis also demonstrated that when results for all combined inhalers vs placebo were pooled, there was an overall reduction in mortality (odds ratio [OR], 0.82; 95% CI, 0.68 to 0.99) (Nannini et al, 2013).

- 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. 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) (Nannini et al, 2012).
- A meta-analysis of 7 trials evaluated the use of once-daily fluticasone furoate/vilanterol for adolescents and adults with symptomatic asthma compared to ICS monotherapy or twice-daily ICS/LABA formulations. All were double-blind, randomized trials and the duration ranged from 12 to 78 weeks (median, 24 weeks). The following results relating to fluticasone furoate/vilanterol compared to ICS monotherapy were demonstrated (Rodrigo et al, 2016):
  - Three trials in 3,667 patients comparing fluticasone furoate/vilanterol to fluticasone furoate 100 mcg demonstrated a significant increase in trough forced expiratory volume in one second (FEV<sub>1</sub>) (mean difference [MD], 90 mL; P<0.001) and in morning and evening peak expiratory flow (PEF) (MD, 20.1 L/min; P<0.001 and 18.9 L/min; P=0.003, respectively). There was also a significant improvement in the proportion of patients with ≥1 severe asthma exacerbation.
  - Three trials in 1,398 patients comparing fluticasone furoate/vilanterol to fluticasone propionate 500 mcg twice daily demonstrated a significant increase in weighted FEV<sub>1</sub> (MD, 140 mL; P=0.002) and in morning and evening PEF (MD, 32.6 L/min; P<0.001 and 25.7 L/min; P<0.001, respectively). There were also significant improvements in the proportion of patients with ≥1 severe asthma exacerbation.
- A meta-analysis of 14 trials (total N=6,641) compared fluticasone furoate/vilanterol to placebo, fluticasone furoate monotherapy, fluticasone propionate monotherapy, vilanterol monotherapy, or fluticasone propionate/salmeterol in patients with asthma (Dwan et al, 2016). Primary endpoints included health-related quality of life (HRQoL) and severe asthma exacerbations (defined by hospital admission or treatment with oral corticosteroids). Fewer than half of the studies reported on these primary endpoints, and there were few opportunities to combine results from the included studies. One of the 14 studies evaluated HRQoL (as measured by the Asthma Quality of Life Questionnaire [AQLQ]) for fluticasone furoate/vilanterol 100/25 mcg vs placebo; it identified a significant advantage of fluticasone furoate/vilanterol (MD, 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 cannot be drawn due to the limited number of studies, variety of endpoints, and short duration of most trials.
- Several recently published, large studies focused primarily on safety endpoints, with efficacy endpoints as secondary. 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 some reassurance for the safety of these agents (Peters et al, 2016; Stempel et al, 2016a; Stempel et al, 2016b).
  - A recent 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 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 group (HR, 1.03; 95% CI, 0.64 to 1.66). Fluticasone propionate/salmeterol was shown to be noninferior to fluticasone for this endpoint. There were no asthma-related deaths.
    - The main efficacy endpoint was the first severe asthma exacerbation, defined as asthma deterioration leading to the use of systemic glucocorticoids for ≥3 days or an asthma-related hospitalization or emergency department visit leading to the use of systemic glucocorticoids. At least one severe asthma exacerbation was reported in 480 patients (8%) in the fluticasone propionate/salmeterol group and in 597 patients (10%) in the fluticasone group (HR, 0.79; 95% CI, 0.70 to 0.89; P<0.001).

- A similarly designed trial (VESTRI; N=6,208) enrolled pediatric patients 4 to 11 years of age (Stempel et al, 2016b). Enrolled patients had a history of exacerbation within the previous year and consistent use of asthma medication during the 4 weeks before enrollment. Patients were randomized, on the basis of pretrial medication, Childhood Asthma Control Test (C-ACT) score, and exacerbation history, to receive fluticasone propionate/salmeterol 100/50 mcg or 250/50 mcg or fluticasone 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 group (HR, 1.28; 95% CI, 0.73 to 2.27); this demonstrated non-inferiority for fluticasone propionate/salmeterol compared to fluticasone (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 group (HR, 0.86; 95% CI, 0.73 to 1.01).
- An additional randomized, double-blind trial (N=11,693) compared the safety of formoterol/budesonide to budesonide alone in patients ≥12 years of age (Peters et al, 2016). Enrolled patients were receiving daily asthma medication and had had at least one exacerbation in the previous year. Patients were stratified to a dose level of budesonide on the basis of asthma control and prior treatment. Patients were then randomized to receive budesonide/formoterol (two actuations of 80/4.5 mcg or 160/4.5 mcg) or budesonide alone (two actuations of 80 mcg or 160 mcg) twice daily for 26 weeks.
  - The primary safety endpoint, the first serious adverse event (death, intubation, or hospitalization), occurred in 43 of 5,846 patients receiving budesonide/formoterol and 40 of 5,847 patients receiving formoterol alone (HR, 1.07; 95% CI, 0.70 to 1.65); this demonstrated noninferiority 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).

#### 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 PEF five minutes after the morning dose. However, the mean morning FEV<sub>1</sub> improved more with budesonide/formoterol at five minutes and 15 minutes post-dose compared to fluticasone propionate/salmeterol (Partridge et al, 2009).
  - Several published trials compared fluticasone furoate/vilanterol to fluticasone propionate/salmeterol in patients with COPD. Three of the trials were published together; pooled results demonstrated a greater improvement with fluticasone furoate/vilanterol 100/25 mcg once daily compared to fluticasone propionate/salmeterol 250/50 mcg twice daily on the primary endpoint, the weighted mean (wm) FEV<sub>1</sub> (0 to 24 hr). However, two of these three trials did not demonstrate a significant difference on this endpoint (Dransfield et al, 2014). An additional trial compared fluticasone furoate/vilanterol 100/25 mcg daily to fluticasone propionate/salmeterol 500/50 mcg twice daily, and found no significant difference between groups on the wm FEV<sub>1</sub> (0 to 24 hr) (Agusti et al, 2014).
- There have been several trials comparing combination ICS/LABA products to one another for the treatment of asthma:
  - Several head-to-head trials have compared budesonide/formoterol to fluticasone propionate/salmeterol. The trials varied in their design and the doses of medications. In general, these head-to-head trials have failed to demonstrate that one product is consistently superior to the other. Some trials showed benefits for fluticasone propionate/salmeterol on some endpoints (Dahl et al, 2006; Fitzgerald et al, 2005; Price et al, 2007); some

showed benefits for budesonide/formoterol (Aalbers et al, 2004; Kuna et al, 2007; Palmqvist et al, 2001), and another showed no significant differences between the two products (Busse et al, 2008).

- A meta-analysis of five trials comparing fluticasone propionate/salmeterol 250/50 mcg twice daily vs varied doses of budesonide/formoterol twice daily failed to demonstrate significant differences in exacerbations, asthma-related serious adverse events, FEV<sub>1</sub>, rescue medication use, symptom scores, or PEF (Lasserson et al, 2011).
- A head-to-head trial comparing mometasone/formoterol to fluticasone propionate/salmeterol demonstrated non-inferiority for mometasone/formoterol for the primary endpoint of FEV<sub>1</sub>AUC<sub>0-12</sub>. Treatment with mometasone/formoterol demonstrated a rapid onset of action, with significantly greater effects on FEV<sub>1</sub> at all time points up to 30 minutes post-dose compared to fluticasone propionate/salmeterol. Other secondary endpoints were not significantly different between groups (Bernstein et al, 2011).
- 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 w<sub>m</sub> FEV<sub>1</sub> (0 to 24 hr). There were also no significant differences in key secondary endpoints, including the time to onset of bronchodilator effect, percentage of patients obtaining ≥12% and ≥200 mL increase from baseline in FEV<sub>1</sub> at 12 hours and 24 hours, and change from baseline in trough FEV<sub>1</sub>(Woodcock et al, 2013).

#### ICS/LABA Compared to Leukotriene Modifiers and Leukotriene Modifier Combination Regimens for Asthma

- Several head-to-head trials have demonstrated the benefits of fluticasone propionate/salmeterol treatment compared to regimens containing leukotriene modifiers. In varied patient populations, fluticasone propionate/salmeterol was shown to be superior to montelukast and superior to a combination of fluticasone and montelukast for endpoints including PEF, FEV<sub>1</sub>, improvement in asthma symptoms, and reduction in exacerbations (Calhoun et al, 2001; Maspero et al, 2008; Ringdal et al, 2003).
- Results from a meta-analysis of studies comparing the leukotriene modifiers montelukast and zafirlukast to fluticasone propionate/salmeterol and other ICS/LABA combinations found that outcomes were consistent with those from head-to-head trials. Notably, the risk of having an exacerbation requiring systemic corticosteroids was modestly lower with the use of a LABA plus an ICS compared to a leukotriene modifier plus an ICS (risk ratio, 0.87; 95% CI, 0.76 to 0.99) (Chauhan et al, 2014).

#### ICS/LABA Compared to Tiotropium or in Combination with Tiotropium for COPD

- A double-blind, double-dummy, two-year trial (N=1,323) compared the use of fluticasone propionate/salmeterol 250/50 mcg twice daily to tiotropium 18 mcg daily in patients with COPD. This trial demonstrated no significant difference between groups in the rate of exacerbations or post-dose FEV<sub>1</sub>. The study demonstrated higher mortality in the tiotropium group (6%) compared to the fluticasone propionate/salmeterol group (3%). This study was limited by the high number of withdrawals, which were unevenly distributed between the study arms (Wedzicha et al, 2008).
- Several trials have evaluated the potential benefits of adding a combination ICS/LABA to tiotropium vs the use of tiotropium alone in patients with COPD. These trials generally demonstrated an improvement in FEV<sub>1</sub> and some other lung function, symptom score, and quality-of-life endpoints (Hanania et al, 2012; Welte et al, 2009). One double-blind trial (Welte et al, 2009) also demonstrated a reduction in the risk of severe COPD 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).

#### ICS/LABA Compared to LAMA/LABA Combinations

- Several LAMA/LABA combinations have recently been made available, and there are some data to support their benefits compared to ICS/LABA combinations in selected patients with COPD. One large, randomized, double-blind, 52-week trial (FLAME; N=3,362) compared indacaterol/glycopyrronium 110/50 mcg daily to fluticasone propionate/salmeterol 500/50 mcg twice daily in patients with COPD and a history of at least one exacerbation during the previous year (Wedzicha et al, 2016). (Indacaterol/glycopyrrolate has been FDA approved, but the dosing regimen in the U.S. product differs from that which was evaluated in this study.) The primary endpoint, the annual rate of all COPD exacerbations, was 11% lower in the indacaterol/glycopyrronium 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/glycopyrronium, with a difference in trough FEV<sub>1</sub> of 62 mL between

groups ( $P < 0.001$ ). A similar but smaller 26-week study (LANTERN;  $N = 744$ ) enrolling a predominantly Chinese population with not more than one exacerbation in the previous year demonstrated similar results (Zhong et al, 2015).

#### Off-label Use

- Some studies have evaluated ICS/LABA combinations for off-label uses. For example, the combination mometasone furoate/formoterol fumarate dihydrate (DULERA) is FDA-approved for the treatment of asthma, but has also been evaluated and demonstrated to be effective for the treatment of COPD (Doherty et al, 2012; Tashkin et al, 2012).
- Several clinical trials have evaluated SYMBICORT Maintenance And Reliever Therapy (SMART) dosing, a simplified management approach for asthma in which budesonide/formoterol is given as a maintenance inhaler, and additional doses are used for relief of symptoms (Atienza et al, 2013; Bousquet et al, 2007; Kew et al, 2013; Kuna et al, 2007; Quirce et al, 2011; Rabe et al, 2006; Riemersma et al, 2012; Scicchitano et al, 2004; Soes-Petersen et al, 2011; Vogelmeier et al, 2012). However, this approach to dosing is not FDA approved for budesonide/formoterol, and the prescribing information warns against excessive use of more than two inhalations twice daily. Budesonide/formoterol has also shown some effectiveness as an on-demand (rather than maintenance) treatment in patients with mild asthma and exercise-induced bronchoconstriction; however, this use is also not FDA approved (Lazarinis et al, 2014).
- The focus of this review is limited to FDA-approved uses for the ICS/LABA inhalers.

#### CLINICAL GUIDELINES

- The National Asthma Education and Prevention Program (NAEPP) guideline from the NHLBI states that the initial treatment of asthma should correspond to the appropriate asthma severity category, and it provides a stepwise approach to asthma management. Long-term control medications such as ICSs, long-acting bronchodilators, leukotriene modifiers, cromolyn, theophylline, and immunomodulators should be taken daily on a long-term basis to achieve and maintain control of persistent asthma. ICSs are the most potent and consistently effective long-term asthma control medication. Quick-relief medications such as SABAs and anticholinergics are used to provide prompt relief of bronchoconstriction and accompanying acute symptoms such as cough, chest tightness, and wheezing. Systemic corticosteroids are important in the treatment of moderate or severe exacerbations because these medications prevent progression of the exacerbation, speed recovery, and prevent relapses (NHLBI, 2007).
  - LABAs are used in combination with ICSs for long-term control and prevention of symptoms in moderate or severe persistent asthma.
  - Of the adjunctive treatments available, a LABA is the preferred option to combine with an ICS in patients 12 years of age and older. This combination is also an option in selected patients 5 to 12 years of age.
- The Global Initiative for Asthma (GINA) guideline also provides a stepwise approach to asthma management. It recommends an ICS as a preferred controller medication choice, with an increased ICS dose and/or addition of a LABA for increasing symptom severity (higher steps). At the highest step, it is recommended that the patient be referred for add-on treatment (eg, tiotropium, omalizumab, mepolizumab) (GINA, 2017). The Institute for Clinical Systems Improvement (ICSI) endorsed the updated GINA guideline (ICSI, 2016).
- The available asthma guidelines are generally similar; however, one difference among them is the recommendation of ICS/formoterol as both maintenance and rescue therapy by the GINA guidelines. The NHLBI do not recommend LABA medications for the management of acute asthma symptoms or exacerbations (GINA, 2017; NHLBI, 2007).
- The 2017 GOLD guidelines underwent a significant update from prior guideline versions. The guidelines state that the management strategy for stable COPD should be predominantly based on an assessment of the patient's symptoms and future risk of exacerbations. The risk of exacerbations is now based solely on the exacerbation history, whereas in previous versions of the guideline, risk assessment also included consideration of airflow limitation assessed by spirometry. Key recommendations from the GOLD guidelines are as follows (GOLD, 2017):
  - Inhaled bronchodilators are recommended over oral bronchodilators.
  - LAMAs and LABAs are preferred over short-acting agents except for patients with only occasional dyspnea.
  - Patients may be started on single long-acting bronchodilator therapy or dual long-acting bronchodilator therapy. In patients with persistent dyspnea on one bronchodilator, treatment should be escalated to two.
  - Long-term monotherapy with ICSs is not recommended. Long-term treatment with ICSs may be considered in association with LABAs for patients with a history of exacerbations despite treatment with long-acting bronchodilators.
  - Treatment recommendations are given for patients with COPD based on their GOLD patient group (see Table 3 below).



- **Group A:** Patients should be offered bronchodilator treatment (short- or long-acting). This should be continued if symptomatic benefit is documented.
- **Group B:** Initial therapy should consist of a long-acting bronchodilator (LAMA or LABA). For patients with persistent breathlessness on monotherapy, use of two bronchodilators is recommended (LAMA + LABA). For patients with severe breathlessness, initial therapy with two bronchodilators may be considered. If the addition of a second bronchodilator does not improve symptoms, it is suggested that treatment could be stepped down to a single bronchodilator.
- **Group C:** Initial therapy should be a LAMA. Patients with persistent exacerbations may benefit from adding a second long-acting bronchodilator (LAMA + LABA, preferred) or using an ICS + LABA.
- **Group D:** It is recommended to start therapy with a LAMA + LABA combination. In some patients, initial therapy with an ICS + LABA may be the first choice; these patients may have a history and/or findings suggestive of asthma-COPD overlap. In patients who develop further exacerbations on LAMA + LABA therapy, alternative pathways include escalation to a LAMA + LABA + ICS (preferred) or a switch to an ICS + LABA. If patients treated with a LAMA + LABA + ICS still have exacerbations, options for selected patients may include addition of roflumilast, addition of a macrolide, or stopping the ICS.

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

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

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

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

## SAFETY SUMMARY

### Contraindications:

- $\beta_2$ -agonist/ICS combinations are generally contraindicated for the primary treatment of status asthmaticus or other acute episodes of asthma/COPD where intensive measures are required.
- $\beta_2$ -agonist/ICS combinations are generally contraindicated in patients with hypersensitivity to any ingredients in the formulation. ADVAIR DISKUS, AIRDUO RESPICLICK, and BREO ELLIPTA are specifically contraindicated in patients with a severe hypersensitivity to milk proteins.

### Key Warnings and Precautions:

- All medications that include a LABA have a boxed warning about the increased risk of asthma-related death. The increased risk was observed in a trial using salmeterol, but is considered a class effect of LABAs. Currently available data are inadequate to determine whether concurrent use of ICSs or other long-term asthma control drugs mitigates the increased risk of asthma-related death from LABAs. When treating patients with asthma, a combination ICS/ $\beta_2$  agonist should only be used for patients not adequately controlled on a long-term asthma control medication, such as an ICS, or whose disease severity clearly warrants initiation of treatment with both an ICS and a LABA.
- Other key warnings and precautions include:
  - significant cardiovascular effects and fatalities with excessive use of  $\beta_2$ -agonists
  - cardiovascular and/or central nervous system effects from  $\beta$ -adrenergic stimulation (seizures, angina, hypertension or hypotension, tachycardia, arrhythmias, nervousness, headache, tremor, palpitation, nausea, dizziness, fatigue, malaise, and insomnia)
  - paradoxical bronchospasm

- hypercorticism and adrenal suppression due to systemic absorption of the corticosteroid
- the need for caution when transferring patients from systemic corticosteroid therapy (deaths due to adrenal insufficiency have occurred)
- lower respiratory tract infections/pneumonia
- local infections of the mouth and pharynx with *Candida albicans*
- reduced growth velocity in pediatric patients
- the potential for drug interactions with strong CYP3A4 inhibitors; concomitant use is not recommended due to the potential for increased systemic effects
- the potential for developing glaucoma, increased intraocular pressure, or cataracts
- It is also important to note that ICS/ $\beta_2$ -agonist combinations should not be initiated in the setting of disease deterioration or potentially life-threatening episodes.

**Adverse Events**

- Commonly reported adverse events ( $\geq 5\%$  for at least one medication in the class) include oral candidiasis, hoarseness/dysphonia, nasopharyngitis/pharyngitis, pharyngolaryngeal/oropharyngeal pain, sinusitis, upper respiratory tract infection, upper respiratory tract inflammation, bronchitis, cough, headache, gastrointestinal discomfort, and nausea/vomiting.

**DOSING AND ADMINISTRATION**

**Table 4. Dosing and Administration**

Drug	Dosage Form: Strength	Usual Recommended Dose	Comments
ADVAIR DISKUS (fluticasone propionate/salmeterol)	Inhalation powder: 100/50 mcg, 250/50 mcg, 500/50 mcg	<u>Asthma: adults and children <math>\geq 12</math> years of age:</u> Initial, one inhalation twice a day; maximum, 500/50 mcg twice a day  <u>Asthma: children 4 to 11 years of age:</u> One 100/50 mcg inhalation twice a day (for patients not controlled on an ICS)  <u>Maintenance treatment of airflow obstruction in patients with COPD*:</u> One 250/50 mcg inhalation twice a day	Patient should rinse mouth with water without swallowing after inhalation.  Starting dose should be based upon the patient's asthma severity.  Dose may be increased if patient does not adequately respond after 2 weeks of therapy.
ADVAIR HFA (fluticasone propionate/salmeterol)	Metered dose aerosol inhaler: 45/21 mcg, 115/21 mcg, 230/21 mcg	<u>Asthma: adults and children <math>\geq 12</math> years of age:</u> Initial, two inhalations twice a day; maximum, two 230/21 mcg inhalations twice a day	Patient should rinse mouth with water without swallowing after inhalation.  Starting dose should be based upon the patient's asthma severity.  Dose may be increased if patient does not adequately respond after 2 weeks of therapy.
AIRDUO RESPICLICK (fluticasone propionate/salmeterol)	Inhalation powder: 55/14 mcg, 113/14 mcg, 232/14 mcg	<u>Asthma: adults and children <math>\geq 12</math> years of age:</u> One 55/14 mcg, 113/14 mcg, or 232/14 mcg inhalation twice a day	Patient should rinse mouth with water without swallowing after inhalation.  Starting dose should be based upon prior asthma therapy and disease severity.  Dose may be increased if patient does not adequately respond after 2 weeks of therapy.

Drug	Dosage Form: Strength	Usual Recommended Dose	Comments
BREO ELLIPTA (fluticasone furoate/ vilanterol)	Inhalation powder: 100/25 mcg, 200/25 mcg	<u>COPD:</u> One 100/25 mcg inhalation daily  <u>Asthma: patients ≥ 18 years of age:</u> Initial, one 100/25 mcg or one 200/25 mcg inhalation daily; maximum, one 200/25 mcg inhalation once daily	Patient should rinse mouth with water without swallowing after inhalation.  Starting dose should be based upon the patient's asthma severity.  For patients who do not respond adequately to 100/25 mcg, increasing the dose to 200/25 mcg may provide additional improvement in asthma control.
DULERA (mometasone furoate/ formoterol fumarate dihydrate)	Metered dose aerosol inhaler: 100/5 mcg, 200/5 mcg	<u>Asthma: adults and children ≥12 years of age:</u> Initial, two 100/5 mcg inhalations twice a day if previous therapy with medium dose ICS, or two 200/5 mcg inhalations twice a day if previous therapy with high dose ICS; maintenance, two inhalations twice a day; maximum, two 200/5 mcg inhalations twice a day	Inhaler should be shaken well before each use.  Patient should rinse mouth with water without swallowing after inhalation.  Dose may be increased if patient does not adequately respond after 2 weeks of therapy.
SYMBICORT (budesonide/ formoterol fumarate dihydrate)	Metered dose aerosol inhaler: 80/4.5 mcg, 160/4.5 mcg	<u>Asthma: adults and children ≥12 years of age:</u> Initial, two inhalations twice a day; Maximum; two 160/4.5 mcg inhalations twice a day. Starting dose should be based upon the patient's asthma severity; Dose may be increased if patient does not adequately respond after one to 2 weeks of therapy.  <u>Asthma: children 6 to 11 years of age:</u> Two 80/4.5 mcg inhalations twice a day  <u>Maintenance treatment of airflow obstruction in patients with COPD<sup>†</sup>:</u> Two 160/4.5 mcg inhalations twice a day	Patient should rinse mouth with water without swallowing after inhalation.

\*ADVAIR 250/50 mcg is the only strength FDA-approved for this indication.

†SYMBICORT 160/4.5 mcg is the only strength FDA-approved for this indication.

## CONCLUSION

- The combination ICS/LABA products are all FDA-approved for the treatment of asthma, and some are also indicated for the treatment of COPD. In some cases, the specific indications vary by the strength of the inhaler. FDA approval also varies by age for the treatment of children with asthma; ADVAIR DISKUS is the only ICS/LABA product approved for treating asthma in children aged 4 to 11 years, while SYMBICORT is approved for treating asthma in children aged 6 to 11 years.
- The combination ICS/LABA products are not available generically, with the exception of the AIRDUO RESPICLICK authorized generic. The individual components of the inhalers are also not available generically.
- Trials have demonstrated that the combination products are superior to the individual separate components given as monotherapy for the treatment of both asthma and COPD. Data from comparative trials do not consistently demonstrate superiority for any one combination ICS/LABA over another.

- For the treatment of asthma, current guidelines support the use of combination ICS/LABA products for long-term control and prevention of symptoms in patients who do not achieve sufficient symptom control with an ICS as monotherapy (GINA, 2017; ICSI, 2016; NHLBI, 2007).
- For the treatment of COPD, guidelines from the Global Initiative for Chronic Obstructive Lung Disease recommend the use of ICS/LABA products as an option for some patients at higher risk of exacerbations; however, bronchodilators (one or two, depending on symptom severity) *without* an ICS are recommended as first-line treatments for all COPD patients (GOLD, 2017).
- None of the current asthma or COPD treatment guidelines recommend the use of one combination ICS/LABA product over another (Criner et al, 2015; GINA, 2017; GOLD, 2017; NHLBI, 2007).
- A practical benefit of combination ICS/LABAs is that their use ensures that patients are not using a LABA without concomitant ICS. This is particularly important for patients with asthma, because LABAs increase the risk of asthma-related death and should only be used to treat asthma in patients also taking a long-term asthma controller, such as an ICS. Combination products also provide added patient convenience. However, a disadvantage to combination therapy is that doses of the ICS cannot be titrated as easily as when the ICS is administered separately.

**Table 6. Advantages and Disadvantages of Combination ICS/LABAs**

Drug	Advantages	Disadvantages
ADVAIR DISKUS and ADVAIR HFA (fluticasone propionate and salmeterol)	<ul style="list-style-type: none"> <li>• Available as an inhalation powder (ADVAIR DISKUS) in three strengths and as an inhalation aerosol (ADVAIR HFA) in three strengths</li> <li>• FDA-approved to treat asthma (all formulations/strengths) and COPD (ADVAIR DISKUS 250/50 mcg)</li> <li>• Indicated for maintenance treatment of airflow obstruction and for reducing COPD exacerbations (ADVAIR DISKUS 250/50 mcg)</li> <li>• ADVAIR DISKUS is FDA-approved to treat asthma in children aged 4 years and older</li> <li>• Established therapy (initial FDA approval in 2000)</li> </ul>	<ul style="list-style-type: none"> <li>• Administered twice daily</li> <li>• ADVAIR HFA is FDA-approved to treat asthma in patients aged ≥12 years; not in young children</li> </ul>
AIRDUO RESPICLICK (fluticasone propionate and salmeterol)	<ul style="list-style-type: none"> <li>• Available as an inhalation powder in three strengths</li> <li>• FDA-approved to treat asthma (all formulations/strengths)</li> <li>• May subject patients to lower fluticasone propionate exposure which may reduce oral candidiasis risk, and lower salmeterol exposure vs. ADVAIR DISKUS and ADVAIR HFA</li> </ul>	<ul style="list-style-type: none"> <li>• Administered twice daily</li> <li>• Not FDA-approved for treatment of COPD</li> <li>• Approved to treat asthma in patients aged ≥12 years; not in young children</li> </ul>
BREO ELLIPTA (fluticasone furoate and vilanterol)	<ul style="list-style-type: none"> <li>• Administered once daily</li> <li>• Indicated for maintenance treatment of airflow obstruction and for reducing COPD exacerbations (BREO ELLIPTA 100/25); also indicated to treat asthma (both strengths, adults only)</li> </ul>	<ul style="list-style-type: none"> <li>• Approved to treat asthma in patients aged ≥18 years; not in children</li> </ul>
DULERA (mometasone furoate and formoterol fumarate dihydrate)	<ul style="list-style-type: none"> <li>• Available in two strengths</li> </ul>	<ul style="list-style-type: none"> <li>• Administered twice daily</li> <li>• Not FDA-approved for treatment of COPD</li> <li>• Approved to treat asthma in patients aged ≥12 years</li> </ul>
SYMBICORT (budesonide and formoterol fumarate dihydrate)	<ul style="list-style-type: none"> <li>• Available in two strengths</li> <li>• FDA-approved to treat asthma (both strengths) and COPD (SYMBICORT 160/4.5)</li> <li>• FDA-approved to treat asthma in children aged 6 years and older</li> </ul>	<ul style="list-style-type: none"> <li>• Administered twice daily</li> <li>• Approved to treat asthma in patients aged ≥12 years</li> <li>• Not FDA-approved to reduce COPD exacerbations, only for maintenance treatment of airflow obstruction</li> </ul>

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