

## Therapeutic Class Overview

### Respiratory Beta-Agonists

#### INTRODUCTION

- Respiratory beta<sub>2</sub>-agonists are primarily used to treat reversible airway disease. They are Food and Drug Administration (FDA)-approved for the treatment of asthma, chronic obstructive pulmonary disease (COPD), exercise-induced asthma/bronchospasm, and/or reversible bronchospasm.
- 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 2019, asthma affected an estimated 20 million adults and 5.1 million children in the United States (U.S.). 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 (*Centers for Disease Control and Prevention [CDC] 2021, National Heart, Lung, and Blood Institute [NHLBI] Web site*).
- Current pharmacologic options for asthma management are categorized as: (1) control medications to achieve and maintain control of persistent asthma or prevent exacerbations, and (2) quick-relief medications used to treat acute symptoms and exacerbations (*NHLBI 2007, Global Initiative for Asthma [GINA] 2021*).
  - Control medications include:
    - Corticosteroids (inhaled corticosteroids [ICSs], or oral corticosteroids for severe exacerbations)
    - Long-acting beta<sub>2</sub>-agonists (LABAs)
    - Leukotriene receptor antagonists (LTRAs) in select patients
    - Methylxanthines (ie, theophylline) in select patients
    - Add-on immunomodulators (ie, omalizumab, mepolizumab, reslizumab, benralizumab, dupilumab) in patients with severe asthma
    - Add-on tiotropium in patients whose asthma is not well-controlled with ICS/LABA
    - Add-on azithromycin in patients whose asthma is not well-controlled with high dose ICS/LABA
  - Quick-relief/reliever medications include:
    - Short-acting beta<sub>2</sub>-agonists (SABAs) for relief of acute symptoms and prevention of exercise-induced bronchospasm
    - ICS-formoterol for relief of acute symptoms and if needed before exercise
    - Anticholinergics (ie, ipratropium bromide) as an alternative bronchodilator for those not tolerating a SABA
    - Systemic corticosteroids, although not short-acting, are used for moderate and severe exacerbations as part of initial treatment.
  - In recent years, additional medications have been made available for select subsets of patients with asthma, including the interleukin-5 (IL-5) antagonists benralizumab, mepolizumab, and reslizumab, and the interleukin-4 (IL-4) antagonist dupilumab, for the management of severe asthma with an eosinophilic phenotype (*Prescribing information: Cinqair 2020, Dupixent 2021, Fasentra 2021, Nucala 2020*) or with oral corticosteroid dependent asthma (*Dupixent prescribing information 2021*). Additionally, tiotropium, long used for COPD, is FDA-approved for the maintenance treatment of asthma (*Spiriva Respimat prescribing information 2020*).
  - ICSs are the most effective and most commonly recommended long-term control medications used for the treatment of asthma. The updated 2021 GINA Report on Global Strategy for Asthma Management and Prevention recommends initial treatment based on a patient's presenting symptoms. The preferred track for Step 1 and Step 2 therapy in adults and adolescents is low dose combination ICS-formoterol as needed. (*GINA 2021*).
  - LABAs should not be used as monotherapy for the management of asthma due to an increased risk for serious adverse events, including death; however, they are part of combination ICS-formoterol therapy and can be used as adjunctive therapy in patients who are not adequately controlled with an ICS alone (*GINA 2021*).
  - The preferred reliever medication recommended by GINA is low dose ICS-formoterol. SABA-only treatment is not recommended for the treatment of asthma in adults or adolescents. Children can be managed with as needed SABA or ICS-formoterol. (*GINA 2021*).
  - 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 but

are not recommended. An additional controller option is LTRAs. Add-on options for severe asthma include tiotropium, low dose macrolides, and biologic agents for severe allergic or severe Type 2 asthma (GINA 2021).

- COPD is characterized by persistent respiratory symptoms and airflow limitation due to airway and/or alveolar abnormalities. The abnormalities are usually caused by exposure to noxious particles or gases. Airflow limitation is caused by a combination of small airway disease (eg, obstructive bronchiolitis) and parenchymal destruction (emphysema); the relative contributions of each component vary between patients. The most common symptoms of COPD include dyspnea, cough, and sputum production (*Global Initiative for Chronic Obstructive Lung Disease [GOLD] 2021*).
  - COPD affects 6.4% of the U.S. population and is a major contributor to mortality from chronic lower respiratory diseases, the third leading cause of death in the U.S. (*CDC 2019*). Globally, COPD is responsible for 3 million deaths annually and is expected to cause 5.4 million annual deaths by 2060; the burden of COPD continues to increase due to continued exposure to risk factors and aging of the population (*GOLD 2021*).
  - 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 2021*).
  - Patients with COPD may experience exacerbations, which are periods of acute worsening of respiratory symptoms (*GOLD 2021*).
  - Pharmacologic therapy for COPD can reduce symptoms, reduce the frequency and severity of exacerbations, and improve patients' health status and exercise tolerance. There is no conclusive clinical trial evidence that COPD medications modify the long-term decline in lung function characteristics of COPD (*GOLD 2021*).
  - Pharmacologic options for COPD treatment comprise several classes, including beta<sub>2</sub>-agonists, anticholinergics, methylxanthines, various combination products (including bronchodilators with ICSs), mucolytic agents, 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 2021*).
  - Inhaled bronchodilators are central to COPD symptom management and are usually administered on a regular basis to prevent or reduce symptoms. Several short-acting and long-acting inhaled bronchodilators are available. Long-acting muscarinic antagonists (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 (*GOLD 2021*).
  - Beta<sub>2</sub>-agonists differ in their dosing requirements, pharmacokinetic parameters, and potential adverse effects. Several of the SABAs are available generically in at least 1 strength or formulation; however, there are no generic formulations for the LABAs.
- This review includes the single-agent inhaled and oral beta<sub>2</sub>-agonists. Although several agents are also available in combination inhalers along with an ICS or an anticholinergic, the combination products are not included in this review. Arcapta Neohaler (indacaterol) was previously available but was discontinued in March 2020 (*FDA Drug Shortages 2020*).
  - Tables in this review are organized by whether the drug product is short- or long-acting. Note that extended-release albuterol is categorized as short-acting for the purposes of this review, along with the other albuterol products.
- Medispan class/subclass: Respiratory sympathomimetics/beta adrenergics

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

Drug	Generic Availability
<b>Short-acting beta<sub>2</sub>-agonists (SABAs) (oral and inhaled)</b>	
albuterol inhalation aerosols and powder (ProAir HFA, ProAir Digihaler dry powder inhaler, ProAir RespiClick dry powder inhaler, Proventil HFA, Ventolin HFA)	✓ *
albuterol solution for nebulization	✓
albuterol, oral tablets, extended-release tablets, and syrup	✓
levalbuterol inhalation aerosol (Xopenex HFA and generic)	-†
levalbuterol solution for nebulization (Xopenex and generics)	✓
metaproterenol syrup	✓
terbutaline, oral tablets and injection	✓
<b>Long-acting beta<sub>2</sub>-agonists (LABAs) (inhaled)</b>	
Brovana (arformoterol) solution for nebulization	✓

Drug	Generic Availability
Perforomist (formoterol) solution for nebulization <sup>‡</sup>	✓
Serevent Diskus (salmeterol) inhalation powder	-
Striverdi Respimat (olodaterol) inhalation spray	-

**Abbreviation:** HFA = hydrofluoroalkane

\* AB-rated generics have been approved by the FDA for Proventil HFA and ProAir HFA, but no A-rated generics are approved for Ventolin HFA.

Authorized generics are available for these products. No generics are available for ProAir Digihaler or ProAir RespiClick.

† No A-rated generics are approved by the FDA for Xopenex-HFA; however, a generic product is available for this product.

‡ Formoterol was previously available as a dry powder inhaler (Foradil Aerolizer); however, this formulation is no longer marketed.

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

## INDICATIONS

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

Generic Name	Treatment and/or prevention of bronchospasm in patients with asthma/reversible obstructive airway disease	Prevention of exercise-induced bronchospasm	Maintenance treatment of bronchoconstriction/airflow obstruction in patients with COPD	Treatment of reversible bronchospasm occurring in association with emphysema and bronchitis
<b>Short-acting beta<sub>2</sub>-agonists</b>				
albuterol	✓ *	✓ *†		
levalbuterol	✓ ‡			
metaproterenol	✓			✓
terbutaline	✓ §			✓ §
<b>Long-acting beta<sub>2</sub>-agonists</b>				
arformoterol			✓	
formoterol			✓	
olodaterol			✓ **	
salmeterol	✓    ¶	✓ ¶	✓	

**Abbreviations:** COPD = chronic obstructive pulmonary disease; HFA = hydrofluoroalkane

\*Age ≥ 4 years (HFA inhalation aerosols and dry powder inhaler); age ≥ 2 (solution for nebulization); age ≥ 2 years (syrup); age ≥ 6 years (tablets and extended-release tablets)

†Inhalation aerosols and dry powder inhalers only

‡Age ≥ 4 years (Xopenex HFA); age ≥ 6 years (Xopenex inhalation solution)

§Age ≥ 12 years

||Only as a concomitant therapy with a long-term asthma control medication, such as an ICS

¶Age ≥ 4 years

\*\*Indicated for long-term, once-daily maintenance treatment

(*Prescribing information: albuterol solution 2017, albuterol syrup 2020, albuterol tablets 2020, albuterol extended-release tablets 2015, Brovana 2019, metaproterenol syrup 2019, Perforomist 2019, ProAir HFA 2020, ProAir Digihaler 2020, ProAir RespiClick 2021, Proventil HFA 2018, Serevent Diskus 2020, Striverdi Respimat 2020, terbutaline injection 2011, terbutaline tablets 2018, Ventolin HFA 2021, Xopenex HFA 2017, Xopenex inhalation solution 2019*)

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

## CLINICAL EFFICACY SUMMARY

- Clinical trials have demonstrated the efficacy of SABAs and LABAs in providing relief from asthma exacerbations, COPD exacerbations and exercise-induced asthma (EIA).

### SABAs: Asthma and COPD

- In the clinical trials that evaluated SABAs for the treatment of mild asthma, all SABAs have been shown to be efficacious in improving forced expiratory volume in 1 second (FEV<sub>1</sub>). In the clinical trials that compared albuterol to levalbuterol,

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inconsistent results were found (*Carl et al 2003, Gawchik et al 1999, Milgrom et al 2001, Nelson et al 1998, Nowak et al 2004, Nowak et al 2006, Qureshi et al 2005, Schreck et al 2005, Sepracor Trial 1, Sepracor Trial 2, Skoner et al 2001*).

- In 2 studies (1 retrospective, 1 prospective), levalbuterol resulted in a significantly lower hospitalization rate compared to albuterol (*Carl et al 2003, Schreck et al 2005*).
- In another trial, when the 2 agents were given in the emergency department, there was no significant difference in the time to discharge (*Skoner et al 2001*).
- *Nowak et al* also reported that there was no difference in the time to discharge from the emergency room with albuterol compared to levalbuterol (76 and 78.5 minutes;  $p = 0.74$ ) (*Nowak et al 2006*).
- Overall, studies have shown no significant differences between the 2 agents in the peak change in FEV<sub>1</sub> and the number and incidence of adverse events experienced (*Carl et al 2003, Gawchik et al 1999, Milgrom et al 2001, Nelson et al 1998, Nowak et al 2004, Nowak et al 2006, Qureshi et al 2005, Schreck et al 2005, Sepracor Trial 1, Sepracor Trial 2, Skoner et al 2001*).
  - In an unpublished study, the difference in peak FEV<sub>1</sub> was statistically significant for albuterol hydrofluoroalkanes (HFA) compared to levalbuterol HFA ( $p = 0.018$ ) (*Sepracor Trial 2*).
- Albuterol dry powder inhaler (ProAir RespiClick) was compared to placebo dry powder inhaler in patients with asthma maintained on ICS treatment (*Raphael et al 2014*). Patients treated with albuterol dry powder inhaler had significantly improved FEV<sub>1</sub> area under the curve compared to placebo. In patients with exercise-induced bronchoconstriction undergoing treadmill exercise challenge, placebo-treated patients had a greater decrease in FEV<sub>1</sub> compared with albuterol dry powder inhaler-treated patients (*Ostrom et al 2014*). In a cumulative-dose, crossover study, albuterol dry powder inhaler (ProAir RespiClick) was compared with albuterol HFA with similar between-group improvements in FEV<sub>1</sub> at 30 minutes (*Miller et al 2014*). Additionally, albuterol dry powder inhaler (ProAir RespiClick) demonstrated favorable FEV<sub>1</sub> improvement in EIA compared to placebo in a crossover study (*Ostrom et al 2015*). Approval of ProAir Digihaler was based on efficacy data from studies with ProAir RespiClick (*ProAir Digihaler prescribing information 2020*).

#### **LABAs: Asthma**

- The LABAs, salmeterol and formoterol, have been found to improve FEV<sub>1</sub> in patients with mild to moderate asthma who require persistent use of SABAs. However, the SMART trial found that salmeterol had significant occurrences of combined respiratory-related deaths or respiratory-related life-threatening experiences compared to placebo ( $p < 0.05$ ) (*Nelson et al 2006*). In a meta-analysis, salmeterol and formoterol both demonstrated an increase in severe exacerbations that required hospitalization, life-threatening exacerbations, and asthma-related deaths in adults and children alike when compared to placebo (*Salpeter et al 2006*). Due to the results of these studies, all LABAs have a boxed warning stating that these agents may increase the risk of asthma-related death.

#### **LABAs: COPD**

- A systematic review concluded that in patients with COPD, there was no difference in the rate of mild exacerbations between patients treated with an ICS or LABA (odds ratio, 1.63; 95% confidence interval [CI], 0.49 to 5.39) or in the rate of moderate or severe COPD exacerbations (rate ratio, 0.96; 95% CI, 0.89 to 1.02) (*Spencer et al 2011*).
- In 2 studies, patients diagnosed with COPD were treated with arformoterol, salmeterol, or placebo. These studies found that both arformoterol and salmeterol significantly improved morning trough FEV<sub>1</sub> throughout the 12 weeks of daily treatment compared to placebo ( $p < 0.001$  in both trials) (*Baumgartner et al 2007, Sepracor, 2005*). In a head-to-head study against salmeterol, formoterol was associated with a greater change from baseline in FEV<sub>1</sub> at 5 minutes post-dose on day 28 ( $p = 0.022$ ) (*Cote et al 2009*). Currently, there is a lack of head-to-head randomized, double-blind clinical trials to determine a preferential status of one agent over another for the treatment of COPD.
- Two replicate, multicenter, randomized, double-blind, placebo-controlled, parallel-group, Phase 3 studies investigated the long-term efficacy and safety of once-daily olodaterol via Respimat soft-mist inhaler **versus** placebo and formoterol over 48 weeks in patients with moderate to very severe COPD receiving usual-care background therapy. Patients were randomized to receive once-daily olodaterol 5 or 10 mcg, twice-daily formoterol 12 mcg, or placebo. Co-primary endpoints were FEV<sub>1</sub> area under the curve from 0 to 3 hours (AUC<sub>0-3</sub>), trough FEV<sub>1</sub>, and Mahler transition dyspnea index (TDI) total score after 24 weeks. Overall, in Study 1222.13 (N = 904) and Study 1222.14 (N = 934), patients who received treatment with olodaterol had significantly improved FEV<sub>1</sub> AUC<sub>0-3</sub> vs placebo in both studies ( $p < 0.0001$  for all comparisons) and trough FEV<sub>1</sub> **versus** placebo ( $p < 0.01$ ). Formoterol also showed statistically significant differences in both Study 1222.13 ( $p < 0.01$ ) and Study 1222.14 ( $p < 0.05$ ) (*Koch et al 2014*).

- Two replicate, randomized, double-blind, placebo-controlled, parallel-group, Phase 3 trials investigated the long-term safety and efficacy of olodaterol in patients with moderate to very severe COPD receiving usual-care background therapy. Patients received olodaterol 5 mcg or 10 mcg or placebo once daily for 48 weeks. Co-primary endpoints were FEV<sub>1</sub> AUC<sub>0-3</sub> (change from baseline) and trough FEV<sub>1</sub> at 12 weeks. Overall, Study 1222.11 (N = 624) and Study 1222.12 (N = 642) showed that olodaterol 5 mcg and 10 mcg significantly improved the FEV<sub>1</sub> AUC<sub>0-3</sub> response (p < 0.0001) and trough FEV<sub>1</sub> (Study 1222.11, p < 0.0001; Study 1222.12, p < 0.05, post hoc) at week 12. The incidence of adverse events was comparable with that of placebo (*Ferguson et al 2014*).
- Two replicate, multicenter, randomized, double-blind, double-dummy, placebo-controlled, 4-way cross-over group, Phase 3 studies investigated the long-term efficacy and safety of once-daily olodaterol via Respimat soft-mist inhaler vs placebo and formoterol over 6 weeks in patients with moderate to very severe COPD receiving usual-care background therapy. Patients were randomized to receive once-daily olodaterol 5 or 10 mcg, twice-daily formoterol 12 mcg, or placebo. Co-primary endpoints were FEV<sub>1</sub> area under the curve from 0 to 12 hours (AUC<sub>0-12</sub>) and FEV<sub>1</sub> area under the curve from 12 to 24 hours (AUC<sub>12-24</sub>) after 6 weeks. Overall, in Study 1222.24 (N = 99) and Study 1222.25 (N = 100), patients who received treatment with both doses of olodaterol and formoterol had significantly improved FEV<sub>1</sub> profiles (co-primary endpoints of FEV<sub>1</sub> AUC<sub>0-12</sub> and FEV<sub>1</sub> AUC<sub>12-24</sub> and the key secondary endpoint [FEV<sub>1</sub> AUC<sub>0-24</sub>]) **versus** placebo in both studies (for all comparisons p < 0.0001). No statistically significant differences were reported between the 3 active comparators (*Feldman et al 2014*).
- A meta-analysis that compared LABAs (salmeterol, formoterol, and indacaterol [no longer available]) to tiotropium demonstrated that tiotropium was more effective than LABAs as a group in preventing COPD exacerbations and disease-related hospitalizations. However, overall hospitalization rates, mortality, symptom improvement, and changes in lung function were similar among groups (*Chong et al 2012*). Another meta-analysis compared the use of LABAs plus tiotropium to the use of either LABAs alone or tiotropium alone. The analysis demonstrated that there was a significant improvement in FEV<sub>1</sub> with combination therapy compared to tiotropium alone. There was also a small mean improvement in health-related quality of life for patients receiving a LABA plus tiotropium compared to tiotropium alone, but the clinical significance of this small difference is unclear. Hospital admissions and mortality were not significantly different between groups. Data comparing LABA plus tiotropium to LABA alone were somewhat limited but demonstrated a significant improvement in health-related quality of life, FEV<sub>1</sub> and exacerbations (*Farne et al 2015*).

## EIA

- For the treatment of EIA, albuterol, metaproterenol, and formoterol have demonstrated an improvement in FEV<sub>1</sub> compared to placebo (*Berkowitz et al 1986, Bonini et al 2013, Edelman et al 2000, Richter et al 2002, Shapiro et al 2002, Storms et al 2004*).
  - In 1 study, albuterol- and metaproterenol-treated patients had a lower incidence of exercise-induced bronchospasm compared to placebo (*Cote et al 2009*).
  - In another study comparing albuterol, formoterol, and placebo for EIA, both active treatment groups provided a statistically significant decrease in mean maximum percent of FEV<sub>1</sub> compared to placebo (p < 0.01) (*Shapiro et al 2002*).

## 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 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.

- A 2020 focused update of the 2007 NAEPP guideline provided updated recommendations on the use of intermittent ICSs and the use of LAMAs as add-on therapy (*Cloutier et al 2020*). The update did not address use of ICS-formoterol as an option for intermittent asthma. For mild, persistent asthma, the use of as needed concomitant ICS and SABA was added as an alternative to daily low-dose ICS with as needed SABA for management of mild, persistent asthma. Additionally, ICS-formoterol in a single inhaler used as both a daily controller and reliever therapy in moderate to severe persistent asthma was recommended over the use of a higher-dose ICS-LABA therapy with a SABA as needed. Finally, the addition of a LAMA can be considered for patients who have uncontrolled, persistent asthma despite ICS-LABA therapy.
- The 2021 GINA report also provides a stepwise approach to asthma management. Treatment recommendations are based on 2 tracks stratified by the choice of reliever. Track 1 includes ICS-formoterol as the reliever, and it is the preferred approach for most patients because it reduces the risk of severe exacerbations. Track 2 uses a SABA as the reliever. Treatment in adults and adolescents with a SABA only is not recommended. For Step 1 and 2 therapy, the preferred (track 1) approach is low dose ICS-formoterol as needed for symptom relief or if needed for exercise for patients with mild asthma. For Step 3, the preferred treatment is low dose ICS-formoterol as both maintenance and reliever therapy. Preferred therapy for Step 4 is a medium dose ICS-formoterol with as needed low dose ICS-formoterol as the reliever therapy. For patients with persistent symptoms or exacerbations despite Step 4 therapy, referral to a specialist with expertise in severe asthma management is recommended. Treatment options may include any of the following options: high dose ICS-LABA therapy, add-on LAMA (tiotropium or triple combination [ICS/LABA/LAMA] inhaler), azithromycin, low-dose oral corticosteroids, and biologic agents for severe allergic or severe Type 2 asthma (*GINA 2021*).
  - The 2021 GINA report provides interim guidance on the management of asthma in the context of the coronavirus disease 2019 (COVID-19) pandemic. Patients with asthma should continue their prescribed asthma medications, including ICS and add-on therapies, during the pandemic. Use of nebulizers should be avoided when possible to prevent transmission of the virus to other patients or healthcare workers. Vaccination for COVID-19 is recommended for people with asthma (*GINA 2021*).
- Recommendations have also been made for stepping down therapy among patients with asthma that has been well-controlled for an extended period of time. Reasons for stepping down therapy include reducing excess drug exposure (and potential adverse effects), improving adherence by simplifying a treatment regimen, and reducing cost (*Chippes et al 2019, GINA 2021*). Prior to stepping down therapy, patients need to be assessed for risk of asthma exacerbation, lung function, symptom control, and adherence to current therapy. Recommendations for step-to-step reductions include decreasing dose or frequency of ICS with concurrent use of LABA, switching to an oral agent (ie, an LTRA such as montelukast), or use of ICS-formoterol as needed, depending on the current step of therapy. During step-down therapy, patients need to be evaluated for asthma symptoms, use of rescue medications, and lung function.
- A European Respiratory Society/American Thoracic Society guideline on the management of severe asthma recommends the addition of tiotropium for patients with uncontrolled asthma despite GINA step 4 or 5 or NAEPP step 5 therapy, and a trial of chronic macrolide therapy to reduce exacerbations in patients who require additional control despite GINA step 5 or NAEPP step 5 therapy (*Holguin et al 2020*).

## **COPD**

- The 2021 GOLD guidelines state that the management strategy for stable COPD should be predominantly based on an assessment of the patient's symptoms and future risk of exacerbations; the risk of exacerbations is based on a patient's exacerbation history. Historically, "asthma-COPD overlap" was addressed, but they are now recognized as separate unique disease states with some similar signs and symptoms. Key recommendations from the GOLD guidelines are as follows (*GOLD 2021*):
  - Inhaled bronchodilators are central to symptom management in COPD and commonly given on a regular basis to prevent or reduce symptoms. Inhaled bronchodilators are recommended over oral bronchodilators.
- LAMAs and LABAs significantly improve lung function, dyspnea, and health status, and reduce exacerbation rates.
  - LAMAs and LABAs are preferred over short-acting agents except for patients with only occasional dyspnea, and for immediate relief of symptoms in patients already receiving long-acting bronchodilators for maintenance therapy.
  - LAMAs have a greater effect on exacerbation reduction compared to LABAs and decrease hospitalizations.
- Patients may be started on single long-acting bronchodilator therapy or dual long-acting bronchodilator therapy. In patients with persistent dyspnea on 1 bronchodilator, treatment should be escalated to 2 bronchodilators.
  - Combination treatment with a LABA and LAMA:

- Reduces exacerbations compared to monotherapy or ICS/LABA.
- Increases FEV<sub>1</sub> and reduces symptoms compared to monotherapy.
- Long-term monotherapy with 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. Long-term treatment with ICS may cause pneumonia in patients with severe disease.
- Treatment recommendations are given for patients with COPD based on their GOLD patient group (see Table 3).
  - **Group A:** Patients should be offered bronchodilator treatment (short- or long-acting), based on its effect on breathlessness. This should be continued if symptomatic benefit is documented.
  - **Group B:** Initial therapy should consist of a long-acting bronchodilator (LAMA or LABA). For patients with persistent breathlessness on monotherapy, use of 2 bronchodilators is recommended (LAMA + LABA). For patients with severe breathlessness, initial therapy with 2 bronchodilators may be considered. If the addition of a second bronchodilator does not improve symptoms, it is suggested that treatment could be stepped down to a single bronchodilator; switching to another device or molecules can also be considered.
  - **Group C:** Initial therapy should be a LAMA.
  - **Group D:** In general, it is recommended to start therapy with a LAMA. For patients with more severe symptoms, especially dyspnea and/or exercise limitation, LAMA/LABA may be considered for initial treatment. In some patients, initial therapy with an ICS + LABA may be the first choice; these patients may have a history and/or findings suggestive of asthma-COPD overlap or blood eosinophil count  $\geq 300$  cells/ $\mu$ L.
  - Follow-up treatments: The follow-up treatments apply to any patients receiving maintenance treatment irrespective of the patient GOLD group.
    - For persistent dyspnea: The use of 2 bronchodilators is recommended in patients receiving 1 long-acting bronchodilator and experiencing persistent breathlessness or exercise limitation. Patients with persistent dyspnea symptoms on LABA + ICS may benefit from LAMA + LABA + ICS.
    - For exacerbations: Patients with persistent exacerbations on long-acting bronchodilator monotherapy may benefit from adding a second long-acting bronchodilator (LAMA + LABA, preferred) or using an ICS + LABA. For patients who have a history and/or findings suggestive of asthma or blood eosinophil count  $\geq 300$  cells/ $\mu$ L, ICS + LABA is preferred. In patients who develop further exacerbations on LAMA + LABA therapy, alternative pathways include escalation to a LAMA + LABA + ICS if eosinophil count  $\geq 100$  cells/ $\mu$ L or addition of roflumilast or azithromycin if eosinophil count  $< 100$  cells/ $\mu$ L. In patients with additional exacerbations on LABA + ICS, patients should try LAMA + LABA + ICS therapy. If patients treated with a LAMA + LABA + ICS still have exacerbations, options for selected patients may include addition of roflumilast, addition of a macrolide, or stopping the ICS.
  - Patients with COPD should continue their usual therapy, including inhaled or oral corticosteroids during the coronavirus disease 2019 (COVID-19) pandemic.

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

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

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

- American Thoracic Society clinical practice guidelines recommend the following pharmacologic treatment for patients with COPD (Strong to conditional Strength of Recommendation/moderate Level of Evidence) (*Nici et al 2020*):
  - Those who complain of dyspnea or exercise intolerance: LAMA/LABA combination therapy is recommended over LABA or LAMA monotherapy.
  - Those who complain of dyspnea or exercise intolerance despite dual therapy with LAMA/LABA: use of triple therapy with LAMA/LABA/ICS is recommended over dual therapy with LAMA/LABA in those patients with a history of  $\geq 1$  exacerbation(s) in the past year requiring antibiotics or oral steroids or hospitalization.
  - Those receiving triple therapy (LAMA/LABA/ICS): it is suggested that the ICS can be withdrawn if the patient has had no exacerbations in the past year.

- No recommendation is made for or against ICS as an additive therapy to long-acting bronchodilators in patients with COPD and blood eosinophilia, except for those patients with a history of  $\geq 1$  exacerbation(s) in the past year requiring antibiotics or oral steroids or hospitalization, for whom ICS as an additive therapy is suggested.
- Guidelines for the prevention of acute exacerbations of COPD from the American College of Chest Physicians and the Canadian Thoracic Society state that a LAMA is recommended over either a short-acting muscarinic antagonist or a LABA. The guidelines state that certain combination bronchodilators or bronchodilator/ICS combinations may reduce exacerbations but do not state that any combination is superior to LAMA monotherapy in patients with stable COPD (*Criner et al 2015*).

### **Exercise-induced bronchoconstriction**

- For exercise-induced bronchoconstriction, guidelines from the American Thoracic Society recommend administration of an inhaled SABA 15 minutes prior to exercise. The guidelines also recommend a controller agent added whenever SABA therapy is used at least once daily. Additional guidelines are set forth for patients with symptoms despite using an inhaled SABA before exercise (*Parsons et al 2013*). Joint guidelines from the American Academy of Allergy, Asthma & Immunology, the American College of Allergy, Asthma & Immunology, and the Joint Council of Allergy, Asthma & Immunology state that beta<sub>2</sub>-agonists (SABAs or LABAs) are most effective at short-term protection against exercise-induced bronchoconstriction and for accelerating recovery from exercise-induced bronchoconstriction. However, daily use of a SABA or LABA will lead to tolerance. Additional or adjunctive options include daily use of leukotriene inhibitors or ICSs, cromolyn sodium before exercise, or ipratropium for patients who have not responded to other agents (*Weiler et al 2016*).

### **SAFETY SUMMARY**

- Contraindications:
  - Serevent Diskus, ProAir Digihaler, and ProAir RespiClick are contraindicated in patients with a severe hypersensitivity to milk proteins.
  - LABAs should generally not be used as a primary treatment of status asthmaticus or other acute episodes of asthma or COPD that require intensive measures; this is listed as a contraindication for Serevent Diskus.
  - All LABAs are contraindicated for use in patients with asthma without concomitant use of a long-term asthma control medication.
- Key warnings and precautions:
  - Salmeterol has a boxed warning for asthma-related deaths and should be prescribed only as an additional therapy to ICS.
  - All LABAs have a warning describing the increased risk of asthma-related deaths and asthma-related hospitalizations (mainly in pediatric and adolescent patients) when used as monotherapy. The fixed-dose combinations of LABA and ICS do not increase serious asthma-related events compared with ICS alone. The use of a LABA without an ICS is contraindicated in patients with asthma. Patients with COPD do not experience increased mortality with the use of LABAs.
  - Beta<sub>2</sub>-agonists may also lead to:
    - paradoxical bronchospasm
    - fatalities with excessive use
    - cardiovascular effects such as increased heart rate, blood pressure, and/or electrocardiogram changes
    - central nervous system effects and/or seizures
  - LABAs should not be used to treat acute symptoms or initiated in the setting of acutely deteriorating asthma or COPD.
- Adverse events
  - Commonly-reported adverse events ( $\geq 5\%$  for at least 1 medication in the class) include chest pain, palpitations, tachycardia, dizziness, excitement, fatigue, headache, nervousness, shakiness, somnolence, tremor, rash, diarrhea, nausea, vomiting, pain, asthma exacerbation, bronchitis, cough, influenza, nasal congestion, nasopharyngitis/pharyngitis, respiratory disorder, rhinitis, throat irritation, upper respiratory tract infection, viral respiratory infection, accidental injury, fever, and viral infection.
- Albuterol solution, syrup, tablets, and extended-release tablets, metaproterenol, and terbutaline injection are Pregnancy Category C; arformoterol, levalbuterol, ProAir HFA, Proventil HFA, ProAir Digihaler, ProAir HFA, ProAir RespiClick, Ventolin HFA, formoterol, olodaterol, salmeterol, and terbutaline tablets are not assigned a Pregnancy Category.



**DOSING AND ADMINISTRATION**
**Table 4. Dosing and Administration**

Generic Name	Available Formulations	Route	Usual Recommended Frequency	Comments
<b>Short-acting beta<sub>2</sub>-agonists</b>				
albuterol	Inhalation: metered dose aerosol inhaler (HFA), metered dose dry powder inhaler, solution for nebulization  Oral: extended-release tablets, syrup, tablets	Inhalation, oral	<u>Treatment or prevention of bronchospasm in patients with asthma:</u> <ul style="list-style-type: none"> <li>• Aerosol/dry powder inhaler: 1 to 2 inhalations every 4 to 6 hours</li> <li>• Solution for nebulization: 3 to 4 times daily</li> <li>• Extended-release tablets: twice daily</li> <li>• Syrup, tablets: 3 to 4 times daily</li> </ul> <u>Exercise-induced bronchospasm:</u> <ul style="list-style-type: none"> <li>• Aerosol/dry powder inhaler: 2 inhalations 15 to 30 minutes before exercise</li> </ul>	The ProAir Digihaler inhalation device is a digital dry powder inhaler with built-in sensors to detect when it is used and to measure inspiratory flow. It is designed to be used with a companion mobile app.
levalbuterol	Metered dose aerosol inhaler (HFA), solution for nebulization	Inhalation	<u>Treatment or prevention of bronchospasm in patients with asthma:</u> <ul style="list-style-type: none"> <li>• Aerosol inhaler: 1 to 2 inhalations every 4 to 6 hours</li> <li>• Solution for nebulization: 3 times daily</li> </ul>	
metaproterenol	Syrup	Oral	3 to 4 times daily	
terbutaline	Injection, tablets	Subcutaneous injection, oral	<ul style="list-style-type: none"> <li>• Injection: 1 subcutaneous injection, may repeat in 15 to 30 minutes if improvement does not occur; maximum, 0.5 mg in 4 hours</li> <li>• Tablets: 3 times daily, 6 hours apart</li> </ul>	Injection: Safety and efficacy in children < 12 years of age have not been established.
<b>Long-acting beta<sub>2</sub>-agonists</b>				
arformoterol	Solution for nebulization	Inhalation	Twice daily	Safety and efficacy in children have not been established.
formoterol	Solution for nebulization	Inhalation	Twice daily	Safety and efficacy in children have not been established.
olodaterol	Inhalation spray	Inhalation	Once daily	Safety and efficacy in children have not been established.
salmeterol	Dry powder inhaler	Inhalation	<u>Treatment or prevention of bronchospasm in patients with asthma/maintenance treatment of bronchoconstriction in COPD</u> 1 inhalation twice daily	

Generic Name	Available Formulations	Route	Usual Recommended Frequency	Comments
			<u>Exercise-induced bronchospasm:</u> 1 inhalation at least 30 minutes before exercise; at least 12 hours should elapse between doses	

**Abbreviations:** COPD = chronic obstructive pulmonary disease; HFA = hydrofluoroalkane

See the current prescribing information for full details.

## CONCLUSION

- Single-entity respiratory beta<sub>2</sub>-agonist agents are FDA-approved for the treatment of asthma, COPD, reversible airway obstruction and/or exercise-induced bronchospasm.
  - Beta<sub>2</sub>-agonists are classified as short- or long-acting based on their onset and duration of action, and are available in various dosage forms, including solution for nebulization, aerosol inhaler, dry powder inhaler, oral solution, immediate- and extended-release tablets, and solution for injection.
  - SABAs are generally dosed multiple times per day for the treatment or prevention of symptoms.
  - LABAs are typically administered twice daily for COPD, with the exception of olodaterol, which **is** administered once daily.
- Overall, SABAs have demonstrated similar efficacy and safety. Similarly, for LABAs, head-to-head clinical trials have not determined the superiority of any one agent.
- All LABAs (salmeterol also has a boxed warning) have a warning describing the increased risk of asthma-related deaths and asthma-related hospitalizations (mainly in pediatric and adolescent patients) when used as monotherapy.
  - In the treatment of asthma, LABAs should not be used as monotherapy, but rather added on to another long-acting controller medication such as an ICS.
- According to GINA and NHLBI guidelines, as-needed SABAs may provide symptomatic relief in patients with asthma, including children, adolescents, and adults. The GINA guideline advises against the use of SABAs without ICS; a low dose ICS should be taken whenever a SABA is taken. 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 as-needed basis), ICS, or ICS/LABA depending on the age of a patient and severity of symptoms. **Use of maintenance and as-needed combination ICS-formoterol is the preferred treatment approach for adults and adolescents.**
- GOLD guidelines state that inhaled bronchodilators are a key component of COPD treatment, and long-acting agents are generally preferred over short-acting agents for maintenance therapy. For most patients with COPD, LAMAs are recommended as they have a greater effect on exacerbation reduction compared to LABAs.
- The majority of the current asthma or COPD treatment guidelines do not recommend the use of one specific inhaled beta<sub>2</sub>-agonist product over another, except for the GINA guideline which lists low-dose ICS-formoterol as the preferred controller and reliever medication in adults and adolescents.
  - Administration instructions and inhalation devices vary among products and should be considered in product selection.

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