Therapeutic Class Overview
Beta Agonists

INTRODUCTION

- Respiratory beta$_2$-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 the United States, more than 25 million people are known to have asthma, including about 7 million children. 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 (National Heart, Lung, and Blood Institute [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.
- Long-term control medications for asthma include (NHLBI, 2007):
    - Corticosteroids (inhaled 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 (NHLBI, 2007):
    - Anticholinergics (ie, ipratropium bromide), as an alternative bronchodilator for those not tolerating a short-acting beta-agonist (SABA)
    - SABAs (therapy of choice for relief of acute symptoms and prevention of exercise-induced bronchospasm)
    - Systemic corticosteroids (not short-acting, but used for moderate and severe exacerbations)
- 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, 2015). Additionally, tiotropium, long used for COPD, has been FDA approved for the treatment of asthma (SPIRIVA RESPIMAT prescribing information, 2016).
- ICSs are the most effective, most commonly recommended long-term control medications used for the treatment of asthma. Alternative long-term control medications include leukotriene modifiers, mast-cell stabilizers, and methylxanthines; however, these agents are considered less effective as monotherapy compared to ICSs. The LABAs should not be used as monotherapy for the management of asthma; however, they are considered the most effective adjunctive therapy in patients who are not adequately controlled with an ICS alone. Tiotropium is an option for add-on therapy in certain patients requiring an additional controller medication. SABAs are the medication of choice for the relief of bronchospasm during acute exacerbations of asthma (NHLBI, 2007; GINA, 2016).
- 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], 2017).

- COPD affects more than 5% of the adult 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, 2012). 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 frequency 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, ICSs, various combination products, 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).
- Beta$_2$-agonists differ in their dosing requirements, pharmacokinetic parameters, and potential adverse effects. Several of the SABAs are available generically in at least one strength or formulation; however, there are no generic formulations for the LABAs.
- This review includes the single-agent inhaled and oral beta$_2$-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.
- The 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: Sympathomimetics/Beta Adrenergics

Table 1. Medications Included Within Class Review

Drug	Manufacturer	FDA Approval Date	Generic Availability
Short-Acting beta$_2$-agonists (Oral and Inhaled)			
Albuterol inhalation aerosols and powder (PROAIR® HFA, PROAIR® RESPICLICK dry powder inhaler, PROVENTIL® HFA, VENTOLIN® HFA)	Various	08/15/1996*	-
Albuterol solution for nebulization	Various	02/21/1992	✔
Albuterol, oral tablets, extended-release tablets, and syrup (VOSPIRE® ER and generics)	Various	varied	✔
Levalbuterol inhalation aerosol (XOPENEX® HFA and generic)	Various	03/11/2005	-†
Levalbuterol solution for nebulization (XOPENEX® and generics)	Various	03/25/1999	✔
Metaproterenol, oral tablets and syrup	Various	05/13/1974	✔
Terbutaline, oral tablet and injection	Various	04/22/1975	✔
Long-Acting beta$_2$-agonists (Inhaled)			
Arformoterol solution for nebulization (BROVANA®)	Sunovion	10/06/2006	-
Formoterol solution for nebulization (PERFOROMIST®)‡	Mylan	05/11/2007	-

Drug	Manufacturer	FDA Approval Date	Generic Availability
Indacaterol (ARCAPTA® NEOHALER)	Novartis	07/01/2011	-
Olodaterol (STRIVERDI® RESPIMAT®)	Boehringer Ingelheim	07/31/2014	-
Salmeterol (SEREVENT® DISKUS)	GlaxoSmithKline	09/19/1997	-

*PROVENTIL HFA

†No A-rated generics have been approved by the FDA; however, an authorized generic is available.

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

(Drugs@FDA, 2016; Orange Book: Approved Drug Products with Therapeutic Equivalence Evaluations, 2016)

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
Short-Acting beta$_2$-agonists				
Albuterol	✔ *	✔ *†		
Levalbuterol	✔ ‡			
Metaproterenol	✔			✔
Terbutaline	✔ §			✔
Long-Acting beta$_2$-agonists				
Arformoterol			✔	
Formoterol			✔	
Indacaterol			✔ ***	
Olodaterol			✔ ***	
Salmeterol	✔ ¶**	✔ **	✔	

*Age ≥4 years (HFA inhalation aerosols and dry power inhaler); age 2 to 12 years (solution for nebulization); age ≥2 years (syrup); age ≥6 years (tablets and extended-release tablets)

†Inhalation aerosols and powder 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, 2014; albuterol syrup, 2009; albuterol tablets, 2006; ARCAPTA NEOHALER, 2012; BROVANA, 2014; metaproterenol syrup, 2014; metaproterenol tablets, 2010; PERFOROMIST, 2013; PROAIR HFA, 2016; PROAIR RESPICLICK, 2016; PROVENTIL HFA, 2012; SEREVENT DISKUS, 2016; STRIVERDI RESPIMAT, 2016; terbutaline injection, 2011; terbutaline tablets, 2011; VENTOLIN HFA, 2014; VOSPIRE ER, 2012; XOPENEX HFA, 2015; XOPENEX inhalation solution, 2015)

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

- Clinical trials have demonstrated the efficacy of short-acting and long-acting beta$_2$-agonists in providing relief from asthma exacerbations, COPD exacerbations and exercise-induced asthma (EIA). In the clinical trials that evaluated these products for the treatment of mild asthma, all SABAs have been shown to be efficacious in improving forced expiratory volume in 1 second (FEV_1). In the clinical trials that compared albuterol to levalbuterol, inconsistent results were found (Carl et al, 2003; Schreck et al, 2005; Qureshi et al, 2005; Skoner et al, 2001; Nowak et al, 2006; Nelson et al, 1998; Gawchik et al, 1999; Milgrom et al, 2001; Sepracor Trial 1; Sepracor Trial 2; Nowak et al, 2004). In two studies (one retrospective, one 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 two 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). In an unpublished study, the difference in peak FEV_1 was statistically significant for albuterol hydrofluoroalkanes (HFA) compared to levalbuterol HFA (P=0.018) (Sepracor Trial 2). Additionally, studies have shown no significant differences between the two agents in the peak change in FEV_1 and the number and incidence of adverse events experienced (Carl et al, 2003; Schreck et al, 2005; Qureshi et al, 2005; Skoner et al, 2001; Nowak et al, 2006; Nelson et al, 1998; Gawchik et al, 1999; Milgrom et al, 2001; Sepracor Trial 1; Sepracor Trial 2; Nowak et al, 2004).
- Albuterol dry powder inhaler 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_1 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_1 compared with albuterol dry powder inhaler-treated patients (Ostrom et al, 2014). In a cumulative-dose, crossover study, albuterol dry powder inhaler was compared with albuterol HFA with similar between-group improvements in FEV_1 at 30 minutes (Miller et al, 2014). Additionally, albuterol dry power inhaler demonstrated favorable FEV_1 improvement in EIA compared to placebo in a crossover study (Ostrom et al, 2015).
- The LABAs salmeterol and formoterol have been found to improve FEV_1 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 by Salpeter et al, 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 are assigned a boxed warning stating that these agents may increase the risk of asthma-related death.
- 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 (odd 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).
- The safety and efficacy of indacaterol were evaluated in randomized controlled trials that compared it to placebo and other agents used in the management of COPD (Feldman et al, 2010; Kornmann et al, 2011; Dahl et al, 2010; Korn et al, 2011; Magnussen et al, 2010; Balint et al, 2010; Donohue et al, 2010; Vogelmeier et al, 2010; Buhl et al, 2011; Chapman et al, 2011). Notably, most of these trials evaluated indacaterol in doses of 150, 300 and 600 µg once daily, rather than the FDA-approved dosing of 75 µg once daily (Feldman et al, 2010; Kornmann et al, 2011; Dahl et al, 2010; Korn et al, 2011; Magnussen et al, 2010; Balint et al, 2010; Donohue et al, 2010; Vogelmeier et al, 2010; Buhl et al, 2011; Chapman et al, 2011). However, results from placebo-controlled trials of indacaterol 75 µg have also been published, lending support to the use of the 75 µg dose (Kerwin et al, 2011; Gotfried et al, 2012).
- Overall, data from published clinical trials demonstrate that treatment with indacaterol consistently results in significantly higher mean trough FEV_1 after 12 weeks of treatment compared to placebo, formoterol, salmeterol and tiotropium. Patients treated with indacaterol also achieved significant improvements in COPD symptoms, as well as health-related quality of life compared to those treated with placebo. Compared to placebo, indacaterol significantly reduces the use of rescue medications, increases the days of no rescue medication use, and improves diary card-derived symptom variables (eg, nights with no awakenings, days with no daytime symptoms, days able to perform usual activities). In general, treatment with indacaterol is favored over other long-acting bronchodilators for these

outcomes, but significant superiority is not consistently achieved (Feldman et al, 2010; Kornmann et al, 2011; Dahl et al, 2010; Korn et al, 2011; Magnussen et al, 2010; Balint et al, 2010; Donohue et al, 2010; Vogelmeier et al, 2010; Buhl et al, 2011; Chapman et al, 2011; Kerwin et al, 2011; Gotfried et al, 2012). Recent meta-analyses comparing indacaterol to tiotropium and to twice-daily LABAs (salmeterol or formoterol) demonstrated that patients treated with indacaterol had higher trough FEV_1 and greater improvements in the use of rescue medications and achieving improvements in dyspnea and health status compared to the alternative treatments. However, the trials included in this meta-analysis used indacaterol doses higher than FDA-approved daily doses of 75 µg (Rodrigo et al, 2012; Cope et al, 2013).

- Placebo-controlled trials demonstrate that within five minutes after administration of indacaterol, significant improvements in bronchodilation are achieved (Magnussen et al, 2010; Balint et al, 2010; Donohue et al, 2010; Vogelmeier et al, 2010; Kerwin et al, 2011; Gotfried et al, 2012). These results have also been observed when comparing indacaterol to salmeterol, salmeterol/fluticasone, and tiotropium (Korn et al, 2011; Vogelmeier et al, 2010; Buhl et al, 2011).
- In two 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_1 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_1 at five 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_1 area under the curve from 0 to 3 hours (AUC_{0-3}), trough FEV_1, 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 significantly improved FEV_1 AUC_{0-3} versus placebo in both studies (P<0.0001 for all comparisons) and trough FEV_1 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_1 AUC_{0-3} (change from baseline) and trough FEV_1 at 12 weeks. Overall, Study 1222.11 (N=624) and Study 1222.12 (N=642) showed olodaterol 5 mcg and 10 mcg significantly improved the FEV_1 AUC_{0-3} response (P<0.0001) and trough FEV_1 (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, four-way cross-over 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 six 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_1 area under the curve from 0 to 12 hours (AUC_{0-12}) and FEV_1 area under the curve from 12 to 24 hours (AUC_{12-24}) after six 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_1 profiles (co-primary endpoints of FEV_1 AUC_{0-12} and FEV_1 AUC_{12-24} and the key secondary endpoint [FEV_1 AUC_{0-24}]) versus placebo in both studies (for all comparisons P<0.0001). No statistically significant differences were reported between the three active comparators (Feldman et al, 2014).
- A meta-analysis compared LABAs (salmeterol, formoterol, and indacaterol) to tiotropium and 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_1 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 was somewhat limited, but demonstrated a significant improvement in health-related quality of life, FEV_1 and exacerbations (Farne et al, 2015).

- For the treatment of EIA, albuterol, metaproterenol, and formoterol have demonstrated an improvement in FEV_1 compared to placebo (Berkowitz et al, 1986; Shapiro et al, 2002; Richter et al, 2002; Edelman et al, 2000; Storms et al, 2004, Bonini et al, 2013). In one 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_1 compared to placebo ($P<0.01$) (Shapiro et al, 2002).

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, 2016).
- The Institute for Clinical Systems Improvement (ICSI) guideline follows a similar stepwise approach for asthma management (Sveum et al, 2012).
- 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 guidelines state 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).
- 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 American College of Allergy, Asthma & Immunology state that beta-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

- Beta-agonists are generally contraindicated in patients with hypersensitivity to the drug or components of the formulation. SEREVENT 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

- All LABAs have a boxed warning describing the increased risk of asthma-related deaths. Because of this risk, use of LABAs for the treatment of asthma without a concomitant long-term asthma control medication, such as an ICS, is contraindicated. LABAs should be used only as additional therapy for patients with asthma who are currently taking but are inadequately controlled on a long-term asthma control medication, such as an ICS.
- Beta-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

- It is also important to note that 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 (≥5% for at least one 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.

DOSING AND ADMINISTRATION

Table 3. Dosing and Administration

Generic Name	Available Formulations	Usual Recommended Dose (Adults)	Usual Recommended Dose (Pediatric)
Albuterol	Metered dose aerosol inhaler (HFA): 120 µg albuterol sulfate* (60† or 200 inhalations) Metered dose dry powder inhaler: 117 µg albuterol sulfate*/actuation (200 actuations) Solution for nebulization: 0.63 mg/3 mL 1.25 mg/3 mL 2.5 mg/3 mL 2.5 mg/0.5 mL Sustained-release tablet: 4 mg 8 mg Syrup: 2 mg/5 mL Tablet: 2 mg 4 mg	Treatment or prevention of bronchospasm in patients with asthma: Metered dose aerosol inhaler (HFA): 1 to 2 inhalations every 4 to 6 hours; maximum, 12 inhalations/day Dry powder inhaler: 2 inhalations every 4 to 6 hours; 1 inhalation every 4 hours may be sufficient for some patients Solution for nebulization: 2.5 mg three to four times daily Sustained-release tablet: 4 to 8 mg twice daily; maximum, 32 mg/day Syrup, tablet: 2 to 4 mg three to four times daily; maximum, 8 mg four times daily Exercise-induced bronchospasm: Aerosol and powder inhaler (HFA and dry powder): 2 inhalations 15 to 30 minutes before exercise	Treatment or prevention of bronchospasm in patients with asthma: Metered dose aerosol inhaler (HFA): 4 years of age and older: 1 to 2 inhalations every four to six hours; maximum, 12 inhalations/day Dry powder inhaler: 4 years of age and older: 2 inhalations every 4 to 6 hours: 1 inhalation every 4 hours may be sufficient for some patients Solution for nebulization: 2 to 12 years of age: 0.63 to 1.25 mg three to four times daily; maximum, 2.5 mg three to four times daily Sustained-release tablet: 6 to 12 years of age: 4 mg twice daily; maximum, 24 mg/day Syrup: 2 to 5 years of age: 0.1 mg/kg of body weight three times daily; maximum, 4 mg three times daily; 6 to 14 years of age: 2 mg three to four times daily; maximum, 24 mg/day Tablet: 6 to 12 years of age: 2 mg three to four times daily; maximum 24 mg/day

Generic Name	Available Formulations	Usual Recommended Dose (Adults)	Usual Recommended Dose (Pediatric)
			Exercise-induced bronchospasm: Metered dose aerosol inhaler (HFA): 4 years of age and older: 2 inhalations 15 to 30 minutes before exercise Dry powder inhaler: 4 years of age and older: 2 inhalations 15 to 30 minutes before exercise
Levalbuterol	Metered dose aerosol inhaler (HFA): 59 µg‡ (80 or 200 inhalations) Solution for nebulization: 0.31 mg 0.63 mg 1.25 mg (0.5 and 3 mL vials)	Treatment or prevention of bronchospasm in patients with asthma: Metered dose aerosol inhaler (HFA): 1 to 2 inhalations every 4 to 6 hours Solution for nebulization: 0.63 mg three times daily every 6 to 8 hours; maximum, 1.25 mg three times daily	Treatment or prevention of bronchospasm in patients with asthma: Metered dose aerosol inhaler (HFA): 4 years of age and older: 1 to 2 inhalations every 4 to 6 hours Solution for nebulization: 6 to 11 years of age: 0.31 mg three times daily; maximum, 0.63 mg three times daily
Metaproterenol	Syrup: 10 mg/5 mL Tablet: 10 mg 20 mg	Treatment or prevention of bronchospasm in patients with asthma and treatment of reversible bronchospasm occurring in association with emphysema and bronchitis: Syrup, tablet: 20 mg three to four times daily	Treatment or prevention of bronchospasm in patients with asthma: Syrup, tablet: 6 to 9 years of age (or weight under 60 lb): 10 mg three to four times daily
Terbutaline	Injection: 1 mg/mL (2 mL vial) Tablet: 2.5 mg 5 mg	Treatment or prevention of bronchospasm in patients with asthma: Injection: 0.25 mg subcutaneously in the lateral deltoid area, may repeat in 15 to 30 minutes if improvement does not occur; maximum, 0.5 mg in 4 hours Tablet: 2.5 to 5 mg three times daily, 6 hours apart; maximum, 15 mg in 24 hours Treatment of reversible bronchospasm occurring in association with emphysema and bronchitis: Injection: 0.25 mg subcutaneously in the lateral deltoid area, may repeat in 15 to 30 minutes if improvement does not occur; maximum, 0.5 mg in 4 hours	Treatment or prevention of bronchospasm in patients with asthma: Injection: Safety and efficacy in children less than 12 years of age have not been established. Tablet: 12 to 15 years of age: 2.5 mg three times daily, 6 hours apart; maximum, 7.5 mg in 24 hours

Generic Name	Available Formulations	Usual Recommended Dose (Adults)	Usual Recommended Dose (Pediatric)
		Tablet: 2.5 to 5 mg three times daily, 6 hours apart; maximum, 15 mg in 24 hours	
Arformoterol	Solution for nebulization: 15 µg (2 mL)	Maintenance treatment of bronchoconstriction in COPD: Solution for nebulization: 15 µg twice daily	Safety and efficacy in children have not been established.
Formoterol	Solution for nebulization: 20 µg/2 mL	Maintenance treatment of bronchoconstriction in COPD: Solution for nebulization: 20 µg twice daily; maximum 40 µg/day	Safety and efficacy in children have not been established.
Indacaterol	Capsule for inhalation: 75 µg	Maintenance treatment of airway obstruction in COPD: Capsule for inhalation: 75 µg daily	Safety and efficacy in children have not been established.
Olodaterol	Inhalation spray: 2.5 µg per actuation	Long-term, maintenance treatment of airway obstruction in COPD: 5 µg (two inhalations) once daily at the same time of day	Safety and efficacy in children have not been established.
Salmeterol	Dry powder inhaler: 50 µg (28 or 60 inhalations)	Treatment or prevention of bronchospasm in patients with asthma: Dry powder inhaler: 1 inhalation twice daily Exercise-induced bronchospasm: Dry powder inhaler: 1 inhalation at least 30 minutes before exercise Maintenance treatment of bronchoconstriction in COPD: Dry powder inhaler: 1 inhalation twice daily	Treatment or prevention of bronchospasm in patients with asthma: Dry powder inhaler: 1 inhalation twice daily Exercise-induced bronchospasm: Dry powder inhaler: 1 inhalation at least 30 minutes before exercise

*Delivering 108 µg of albuterol (90 µg albuterol base).
†VENTOLIN HFA available as 60 and 200 inhalations; other albuterol inhalers available only as 200 inhalations.
‡Delivering 45 µg levalbuterol base.

SPECIAL POPULATIONS

Table 4. Special Populations

Generic Name	Population and Precaution				
	Elderly	Pediatrics	Renal Dysfunction	Hepatic Dysfunction	Pregnancy* and Nursing
Short Acting beta$_2$-agonists					
Albuterol	Limit initial dose to 2 mg three to four times daily in the elderly population (oral IR dosage forms) Not sufficiently studied in patients 65 years of age and older (inhalation dosage forms)	Approved for use in children 2 years of age and older (oral IR and solution for nebulization dosage forms) Approved for use in children 4 years of age and older (HFA inhaler and dry powder inhaler) Approved for use in children 6 years of age and older (oral ER tablet)	No dosage adjustment required	No dosage adjustment required	Pregnancy Category C† Unknown whether excreted in breast milk
Levalbuterol	Not sufficiently studied in patients 65 years of age and older	Approved for use in children 4 years of age and older (HFA inhaler) Approved for use in children 6 years of age and older (solution for nebulization)	Decrease in racemic albuterol clearance; use caution	Not studied	Pregnancy Category C Unknown whether excreted in breast milk
Metaproterenol	Not sufficiently studied in patients 65 years of age and older	Tablets not recommended for children under 6 years Syrup has been studied in a limited number of children under 6 years; daily doses of 1.3 to 2.6 mg/kg were well-tolerated	Not reported	Not reported	Pregnancy Category C Unknown whether excreted in breast milk
Terbutaline	Not sufficiently studied in patients 65 years of age and older	Approved in children 12 years of age and older	Not reported	Not reported	Pregnancy Category C Unknown whether excreted in

Generic Name	Population and Precaution				
	Elderly	Pediatrics	Renal Dysfunction	Hepatic Dysfunction	Pregnancy* and Nursing
					breast milk
Long Acting beta$_2$-agonists					
Arformoterol	Dosage adjustment not required in the elderly population	Safety and efficacy in children not established	No dosage adjustment required	Use with caution	Pregnancy Category C Unknown whether excreted in breast milk
Formoterol	Dosage adjustment not required in the elderly population	Safety and efficacy in children not established	Not studied	Not studied	Pregnancy Category C Unknown whether excreted in breast milk
Indacaterol	No evidence of overall differences in safety or efficacy observed between elderly and younger adult patients	Safety and efficacy in children not established	Not studied	No dosage adjustment required for mild or moderate impairment; not studied in severe impairment	Pregnancy Category C Unknown whether excreted in breast milk
Olodaterol	Dosage adjustment not required in the elderly population	Safety and efficacy have not been established	No dosage adjustments required in patients with severe renal impairment	No dosage adjustment required for mild or moderate impairment; not studied in severe impairment	Pregnancy Category C Probable that STRIVERDI RESPIMAT is excreted in breast milk; use with caution
Salmeterol	Dosage adjustment not required in the elderly population	Approved in children 4 years of age and older	Not studied	Not studied; however, since drug is cleared through hepatic metabolism, impairment may lead to accumulation. Monitor closely	Pregnancy Category C Unknown whether excreted in breast milk

ER=extended-release, IR=immediate-release

*Pregnancy Category C = Risk cannot be ruled out. Animal reproduction studies have shown an adverse effect on the fetus and there are no adequate and well-controlled studies in humans, but potential benefits may warrant use of the drug in pregnant women despite potential risks.

†Although most albuterol products are in Pregnancy Category C, the FDA's Pregnancy and Lactation Labeling Rule (PLLR) directs that pregnancy categories be replaced with a risk summary, clinical considerations, and other data. Labeling changes will be phased in gradually; currently, PROAIR RESPICLICK is not assigned a pregnancy category. Please see prescribing information for additional details.

CONCLUSION

- The single-entity respiratory beta$_2$-agonists are FDA-approved for the treatment of asthma, COPD, reversible airway obstruction and/or exercise-induced bronchospasm. The agents in this class are classified as short-acting or long-acting beta$_2$-agonists based on their onset and duration of action. These agents are available in a variety of dosage forms, including solution for nebulization, aerosol inhaler, dry powder inhaler, oral solution, tablet, and solution for injection. The SABAs are generally dosed multiple times per day for the treatment or prevention of symptoms. When used for maintenance treatment of COPD, the LABAs are typically administered twice daily, with the exception of indacaterol and olodaterol, which are administered once daily.
- The National Heart, Lung, and Blood Institute/National Asthma Education and Prevention Program guidelines, as well as other national and international guidelines, recommend the use of SABAs for patients in all stages of asthma, for symptomatic relief of reversible airway disease and for exercise-induced bronchospasm. These medications should generally be used on an as-needed or "rescue" basis. Guidelines recommend that in the chronic management of asthma, LABAs should be used as add-on therapy in patients not adequately controlled on an ICS as an alternative to maximizing the dose of the ICS. LABAs can also be used for exercise-induced bronchospasm and provide a longer period of coverage (typically 12 hours or more) compared to the SABAs; however, daily use of a β_2-agonist can lead to tolerance, and daily use of LABA monotherapy is not recommended (NHLBI, 2007; GINA, 2016; Sveum et al, 2012; Parsons et al, 2013; Weiler et al, 2016).
- The 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. Depending on the COPD patient subtype, initial COPD management may include use of a β_2-agonist and/or an anticholinergic agent (GOLD, 2017).
- Overall, SABAs have demonstrated similar efficacy and safety. Similarly, guidelines do not recommend one LABA over another, and head-to-head clinical trials have been inconclusive to determine superiority of any one agent. All LABAs have a boxed warning stating that these agents may increase the risk of asthma-related death. It is important to note that 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 if patients are not adequately controlled on the ICS alone.

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