Therapeutic Class Overview
Short-acting β2-Agonists

Therapeutic Class

- **Overview/Summary:** Respiratory short acting β_2-agonists (SABAs) are Food and Drug Administration (FDA)-approved indications include asthma, chronic obstructive pulmonary disease, exercise-induced bronchospasm (EIB), and/or and reversible bronchospasm. Respiratory β_2-agonists act preferentially on the β_2-adrenergic receptors. Activation of these receptors on airway smooth muscle leads to the activation of adenylyl cyclase and an increase in intracellular cyclic-3',5'-adenosine monophosphate (cyclic AMP). The increase in cyclic AMP leads to activation of protein kinase A and the inhibition of myosin phosphorylation resulting in lower intracellular ionic calcium and smooth muscle relaxation. Increased cyclic AMP levels also inhibit the release of mediators from mast cells in the airways.[1-15] The β_2-agonists can be divided into two categories: short-acting and long-acting. The short-acting respiratory β_2-agonists consist of albuterol (ProAir HFA®, ProAir RespiClick®, Proventil HFA®, Proventil HFA®, Ventolin HFA®), levalbuterol (Xopenex®, Xopenex HFA®), metaproterenol and terbutaline. Respiratory β_2-agonists elicit a similar biologic response in patients suffering from reversible airway disease, but differ in their dosing requirements, pharmacokinetic parameters and potential adverse events.[1-15] As a result of the Clean Air Act and the Montreal Protocol on Substances that Deplete the Ozone Layer, the FDA made the decision to end production, marketing and sale of all albuterol metered dose inhalers (MDIs) containing chlorofluorocarbons (CFCs) as their propellant by December 31, 2008. These inhalers were replaced by MDIs which use hydrofluoroalkanes (HFAs). There is no difference in the safety or efficacy of the HFA inhalers compared to the CFC inhalers; however, there may small differences in taste and/or feel with the HFA inhalers. The deadline for removal of the pirbuterol (Maxair®) CFC inhaler is December 31, 2013.[16]

Table 1. Current Medications Available in the Therapeutic Class[1-15]

Generic (Trade Name)	Food and Drug Administration Approved Indications	Dosage Form/Strength	Generic Availability
Short-Acting β_2-agonists			
Albuterol (AccuNeb®*, ProAir HFA®, ProAir RespiClick®, Proventil HFA®, Ventolin HFA®, VoSpire ER®*)	Relief of bronchospasm in patients with asthma†,‖, treatment or prevention of bronchospasm in patients with reversible obstructive airway disease†‡§, prevention of exercise-induced bronchospasm†‡	Dry Powder Inhaler: 90 µg Meter dose aerosol inhaler (HFA): 120 µg albuterol sulfate# Solution for nebulization: 0.63 mg 1.25 mg 2.5 mg 0.5% concentrated solution (3 mL unit dose vials) Sustained-release tablet: 4 mg 8 mg Syrup:	✔

Generic (Trade Name)	Food and Drug Administration Approved Indications	Dosage Form/Strength	Generic Availability
		2 mg/5 mL Tablet: 2 mg 4 mg	
Levalbuterol (Xopenex®*, Xopenex HFA®)	Treatment or prevention of bronchospasm in patients with reversible obstructive airway disease†	Meter dose aerosol inhaler (HFA): 59 µg¶ Solution for nebulization: 0.31 mg 0.63 mg 1.25 mg (3 mL vials)	✔
Metaproterenol*	Prevention and treatment of asthma and reversible bronchospasm, which may occur in association with bronchitis and emphysema	Syrup: 10 mg/5 mL Tablet: 10 mg 20 mg	✔
Terbutaline*	Prevention and treatment of asthma and reversible bronchospasm, which may occur in association with bronchitis and emphysema	Injection: 1 mg/mL (2 mL vial) Tablet: 2.5 mg 5 mg	✔

*Generic available in at least one dosage form or strength.
†Inhalation solution.
‡Metered-dose inhaler.
§Dry powder inhaler.
‖Oral formulations.
¶Delivering 45 µg levalbuterol base.
#Delivering 108 µg of albuterol (90 µg albuterol base).

Evidence-based Medicine

- Clinical trials have demonstrated the efficacy SABAs in providing relief from reversible bronchospasms and EIA.[21-41]
- Safety and efficacy of albuterol dry powder inhaler (ProAir Respiclick®) was evaluated in two 12-week randomized, double-blind, placebo-controlled studies. Forced expiratory volume in one second (FEV_1) was significantly improved with albuterol dry powder inhaler compared with placebo (no P value reported).[7]
- In clinical trials that comparing albuterol to levalbuterol, inconsistent results have been reported and have not consistently demonstrated improved outcomes with levalbuterol compared to albuterol. Moreover, studies have shown no significant differences between the two agents in the peak change in FEV_1 or the number and incidence of adverse events.[21-31]

Key Points within the Medication Class

- According to Current Clinical Guidelines:
  - Short-acting β_2-agonists are recommended for patients in all stages of asthma, for symptomatic relief of reversible airway disease and for exercise-induced bronchospasm.[17-20]
  - Short-acting β_2-agonists should be used on an as-needed or "rescue" basis. [17-20]

  - Anticholinergics may also be used for the treatment of acute exacerbations but are considered less effective than SABAs.[17-20]
  - The addition of a systemic corticosteroid may be required if patients do not respond immediately to treatment with a SABA or if the exacerbation is severe.[17-20]
  - The use of LABAs to treat acute symptoms or exacerbations of asthma is not recommended.[17]
- Other Key Facts:
  - Studies have failed to consistently demonstrate significant differences between products.
  - Albuterol oral solution, oral tablets, and solution for nebulization, levalbuterol solution for nebulization, metaproterenol oral solution and oral tablets, and terbutaline oral tablets and solution for injection are available generically.
  - There are currently branded albuterol hydrofluoroalkanes (HFA) inhalers and one dry-powder inhaler; however, no generic equivalents are available.

References

1. Albuterol tablet [package insert]. Morgantown (WV): Mylan Pharmaceuticals Inc.; 2006 Mar.
2. VoSpire ER® [package insert]. East Hanover (NJ): DAVA Pharmaceuticals, Inc.; 2012 Jul.
3. Albuterol sulfate syrup [package insert]. North Wales (PA): Teva Pharmaceuticals USA, Inc; 2015 Sep.
4. ProAir HFA® [package insert]. Horsham (PA): Teva Specialty Pharmaceuticals LLC.; 2012 May.
5. Ventolin HFA® [package insert]. Research Triangle Park (NC): GlaxoSmithKline. 2014 Dec.
6. Proventil HFA® [package insert]. Kenilworth (NJ): Schering Corporation; 2013 Sep.
7. ProAir Respiclick® [package insert]. Horsham (PA): TEVA Respiratory, LLC; 2016 Apr.
8. Xopenex HFA® [package insert]. Marlborough (MA): Sunovion Pharmaceuticals Inc.; 2015 Mar.
9. Xopenex® [package insert]. Marlborough (MA): Sunovion Pharmaceuticals Inc.; 2015 Feb.
10. Xopenex concentrate® [package insert]. Marlborough (MA): Sunovion Pharmaceuticals Inc.; 2014 Aug.
11. Metaproterenol syrup [package insert]. Spring Valley (NY): Silarx Pharmaceuticals Inc.; 2001 Jan.
12. Metaproterenol tablets [package insert]. Spring Valley (NY): Par Pharmaceutical Companies Inc.; 2010 Jul.
13. Terbutaline tablets [package insert]. Hayward (CA): Impax Laboratories, Inc.; 2001 Apr.
14. Terbutaline injection [package insert]. Bedford (OH): Bedford Laboratories; 2004 Mar.
15. Micromedex® Healthcare Series [database on the Internet]. Greenwood Village (CO): Thomson Micromedex; 2014 [cited 2014 Jan 25]. Available from: http://www.thomsonhc.com.
16. Asthma and COPD inhalers that contain ozone-depleting CFCs to be phased out; alternative treatments available [press release on the Internet]. Rockville, MD: Food and Drug Administration: 2010 Apr 13 [cited 2014 Jan 25]. Available from: http://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm208302.htm.
17. National Heart, Lung, and Blood Institute and National Asthma Education and Prevention Program. Expert panel report 3: guidelines for the diagnosis and management of asthma full report 2007. [guideline on the internet]. 2007. [cited 2014 Jan 25]. Available from: http://www.nhlbi.nih.gov/guidelines/asthma/asthgdln.htm.
18. Global Initiative for Asthma. Global strategy for asthma management and prevention 2014 [guideline on the internet]. 2015. [cited 2015 July 9]. Available from: http://www.ginasthma.org.
19. From the Global Strategy for the Diagnosis, Management and Prevention of COPD, Global Initiative for Chronic Obstructive Lung Disease (GOLD) 2015. Available from: http://www.goldcopd.org/.
20. National Institute for Health and Clinical Excellence. Management of chronic obstructive pulmonary disease in adults in primary and secondary care (partial update). [guideline on the internet]. 2010 [cited 2014 Jan 25]. Available from: www.nice.org.uk/guidance/CG101.
21. Carl JC, Myers TR, Kirchner HL, et al. Comparison of racemic albuterol and levalbuterol for the treatment of acute asthma. J Pediatr. 2003;143:731-6.
22. Schreck DM, Babin S. Comparison of racemic albuterol and levalbuterol in the treatment of acute asthma in the ED. Am J Emerg Med. 2005;23:842-7.
23. Qureshi F, Zaritsky A, Welch C, et al. Clinical efficacy of racemic albuterol vs levalbuterol for the treatment of acute pediatric asthma. Ann Emerg Med. 2005;46:29-36.
24. Skoner DP, Greos LS, Roach JM, et al, for the levalbuterol Pediatric Study Group. Evaluation and safety and efficacy of levalbuterol in 2-5 year old patients with asthma. Pediatric Pul. 2001;40:477-86
25. Nowak R, Emerman C, Hanrahan, et al. A comparison of levalbuterol with racemic albuterol in the treatment of acute severe asthma exacerbations in adults. Am J Emerg Med. 2006;24:259-67.
26. Nelson HS, Bensch G, Pleskow WW, et al. Improved bronchodilation with levalbuterol compared to racemic albuterol in patients with asthma. J Allergy Clin Immunol. 1998;102(6):943-52.
27. Gawchik SM, Saccar CL, Noonan M, et al. The safety and efficacy of nebulized levalbuterol compared to racemic albuterol and placebo in the treatment of asthma in pediatric patients. J Allergy Clin Immunol. 1999;103:615-21.
28. Milgrom H, Skoner DP, Bensch G, et al. Low-dose levalbuterol in children with asthma: safety and efficacy in comparison with placebo and racemic albuterol. J Allergy Clin Immunol. 2001;108:938-45.
29. Data on file, Sepracor, Marlborough, MA. Adult registration trial 1:051-353.
30. Data on file, Sepracor, Marlborough, MA. Adult registration trial 2:051-355.
31. Nowak RM, Emerman CL, Schaefer K et al. Levalbuterol compared to racemic albuterol in the treatment of acute asthma: results of a pilot study. Am J Emerg Med. 2004;22:29-36.

32. Jat KR, Khairwa A. Levalbuterol vs albuterol for acute asthma: a systematic review and meta-analysis. Pulm Pharmacol Ther. 2013 Apr;26(2):239-48.
33. Wolfe JD, Shapiro GG, Ratner PH. Comparison of albuterol and metaproterenol syrup in the treatment of childhood asthma. Pediatrics.1991;88(2):312-9.
34. Martin JM, Kraft M, Beaucher WN, et al. Comparative study of extended release albuterol sulfate and long-acting inhaled salmeterol xinafoate in the treatment of nocturnal asthma. Ann Allergy Asthma Immunol. 1999;83:121-6.
35. Brambilla C, Chastang C, Georges D, et al. Salmeterol compared to slow release terbutaline in nocturnal asthma. Allergy. 1994;49:421-6.
36. Tattersfield AE, Lofdahl CG, Postma DS, et al. Comparison of formoterol and terbutaline for as needed treatment of asthma: a randomized trial. Lancet. 2001;357:257-61.
37. Hermansson BA, Jenkins RJ. A 4-week comparison of salmeterol and terbutaline in adult asthma. Allergy. 1995;50:551-8.
38. Hancox RJ, Cowan JO, Flannery EM, et al. Randomized trial of an inhaled β2 agonist, inhaled corticosteroid and their combination in the treatment of asthma. Thorax. 1999;54:482-7.
39. Berkowitz R, Schwartz E, Bukstein D, et al. Albuterol protects against exercise-induced asthma longer than metaproterenol sulfate. Pediatrics. 1986;77(2):173-8.
40. Shapiro GS, Yegen U, Xiang J, et al. A randomized, double-blind, single-dose, crossover clinical trial of the onset and duration of protection from exercise-induced bronchospasm by formoterol and albuterol. Clin Ther. 2002;24(12):2077-87.
41. Richter K, Janicki S, Jorres RA, et al. Acute protection against exercise-induced bronchoconstriction by formoterol, salmeterol and terbutaline. Eur Respir J. 2002;19:865-71.