Therapeutic Class Overview
Long-Acting Inhaled β2-Agonists (Single Entity)

Therapeutic Class

- **Overview/Summary:** Respiratory β_2-agonists are primarily used to treat reversible airway disease. The long-acting β_2-agonists (LABAs) are all Food and Drug Administration (FDA)-approved for chronic obstructive pulmonary disease with some agents also being approved for asthma maintenance therapy and exercise-induced asthma/bronchospasm.[1-7] 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.[1-6] The respiratory β_2-agonists can be divided into two categories: short-acting and long-acting. Only the inhaled long-acting β_2-agonists will be covered in this review and they include: arformoterol, formoterol, indacaterol salmeterol, and the newest agent olodaterol. 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.[1-6] Guidelines do not recommend one long-acting agent over another.[8-11] In addition, head-to-head clinical trials have been inconclusive to determine "superiority" of any one agent .[12-60] There are currently no generic formulations for the LABAs.

Table 1. Current Medications Available in the Therapeutic Class[1-6]

Generic (Trade Name)	Food and Drug Administration Approved Indications	Dosage Form/Strength	Generic Availability
Arformoterol (Brovana®)	Bronchoconstriction in patients with chronic obstructive pulmonary disease, including chronic bronchitis and emphysema; maintenance treatment	Solution for nebulization: 15 µg (2 mL)	-
Formoterol (Foradil®, Perforomist®)	Asthma (including nocturnal asthma) and bronchospasm prevention as concomitant therapy with a long-term asthma control medication†; bronchoconstriction in patients with chronic obstructive pulmonary disease, including chronic bronchitis and emphysema; maintenance treatment‡ exercise-induced bronchospasm prophylaxis, acute†	Capsule for inhalation: 12 µg Solution for nebulization: 20 µg/2 mL	-
Indacaterol (Arcapta Neohaler®)	Bronchoconstriction in patients with chronic obstructive pulmonary disease, including chronic bronchitis and emphysema; maintenance treatment§	Capsule for inhalation: 75 µg	-
Olodaterol (Striverdi Respimat®)	Bronchoconstriction in patients with chronic obstructive pulmonary disease, including chronic bronchitis and emphysema; maintenance treatment§	Solution for inhalation (breath activated, metered-dose inhaler): 2.5 µg	-
Salmeterol (Serevent Diskus®)	Asthma (including nocturnal asthma) and bronchospasm prevention as concomitant therapy with a long-term asthma control medication; bronchoconstriction in patients with chronic obstructive pulmonary disease, including chronic bronchitis and emphysema; maintenance treatment‡;	Dry powder inhaler: 50 µg (28 or 60 inhalations)	-

Generic (Trade Name)	Food and Drug Administration Approved Indications	Dosage Form/Strength	Generic Availability
	bronchoconstriction in patients with chronic obstructive pulmonary disease, including chronic bronchitis and emphysema; maintenance treatment		

COPD=chronic obstructive pulmonary disease
*Generic available in at least one dosage form or strength.
†Dry powder inhaler only
‡Twice-daily
§Once-daily

Evidence-based Medicine

- Clinical trials have demonstrated the efficacy long-acting β_2-agonists in providing relief from asthma, COPD exacerbations and exercise induced asthma .[12-61]
- Salmeterol and formoterol have been found to improve FEV_1 in patients with mild to moderate asthma who require persistent use of SABAs. 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.[13]
- A systematic review concluded that in patients with COPD, there was no difference in rate of mild exacerbation 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 (relative risk, 0.96; 95% CI, 0.89 to 1.02).[42]
- 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.[42-52]
- The safety and efficacy of olodaterol were evaluated in eight unpublished placebo- and/or active-controlled confirmatory clinical trials in patients with COPD. Results from four 48-week studies showed 5 µg olodaterol provided significant improvements in FEV_1 and FEV_1 $AUC_{0\text{-}3hr}$ at weeks 12 and 24 when compared with placebo (no P value provided). In addition, four 6-week cross-over studies showed that FEV_1 $AUC_{0\text{-}12hr}$ and FEV_1 $AUC_{12\text{-}24hr}$ was significantly improved with olodaterol when compared with placebo at the conclusion of the studies (no P value provided). No data was provided showing the results of the active comparators (formoterol and/or tiotropium) or whether the results were significantly different than olodaterol or not.[4]
- Two replicate, double-blind, placebo-controlled, multicenter, randomized studies evaluated FEV_1 $AUC_{0\text{-}3}$ and trough FEV_1 after 12 weeks of therapy after adding olodaterol (via Respimat® inhaler) to COPD patients being treated with tiotropium 18 µg via HandiHaler®. There was a significant improvement in both FEV_1 $AUC_{0\text{–}3}$ and trough FEV_1 responses without a significant increase in side effects when olodaterol was added to tiotropium. The mean difference in FEV_1 $AUC_{0\text{–}3}$ in ANHELTO 1 and 2 respectively were 0.117 L and 0.106 L ($P<0.001$ for both). Mean difference in FEV_1 responses were 0.062 L and 0.040 L ($P<0.001$ and $P=0.0029$).[57]

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.[8,9]
  - Short-acting β_2-agonists should be used on an as-needed or "rescue" basis. [8,9]
  - In the chronic management of asthma, the long-acting β_2-agonists should be used as add-on therapy in patients not adequately controlled on an inhaled corticosteroid. [8,9]
  - Long-acting β_2-agonists should not be used as monotherapy for the long-term control of asthma. [8,9]
  - Long-acting β_2-agonists can be used for exercise-induced bronchospasm and provide a longer period of coverage compared to short acting β_2-agonists. [8,9]

  - Long-acting β_2-agonists have a role in the treatment of chronic obstructive pulmonary disease (COPD), for patients who remain symptomatic even with current treatment with short-acting bronchodilators. [8,9]
  - Long-acting β_2-agonists can be added to other COPD treatment regimens, including an anticholinergic agent, in efforts to decrease exacerbations.[10,11]
- Other Key Facts:
  - The role of the short- and long-acting respiratory β_2-agonists in the treatment of asthma and COPD has been well established.
  - Studies have failed to consistently demonstrate significant differences between products.
  - None of the long-acting respiratory β_2-agonists are currently available generically.

References

1. Brovana® [Package insert]. Marlborough (MA): Sunovion Pharmaceuticals, Inc.; 2014 Feb.
2. Foradil® [Package insert]. Whitehouse Station (NJ): Merck Sharp & Dohme Corp.; 2012 Nov.
3. Perforomist® [Package insert]. Morgantown (WV): Mylan Specialty L.P.; 2013 Mar.
4. Arcapta NeoHaler® [Package insert]. East Hanover (NJ): Novartis Pharmaceutical Corp.; 2012 Sep.
5. Striverdi Respimat® [Package insert]. Boehringer Ingelheim Pharmaceuticals, Inc.; 2016 Jun.
6. Serevent Diskus® [Package insert]. Research Triangle Park (NC): GlaxoSmithKline LLC; 2015 Feb.
7. Micromedex® Healthcare Series [database on the Internet]. Greenwood Village (CO): Thomson Micromedex; 2014 [cited 2015 Jan 05]. Available from: http://www.thomsonhc.com.
8. 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 2015 Jan 05]. Available from: http://www.nhlbi.nih.gov/guidelines/asthma/asthgdln.htm.
9. Fitzgerald M, Bateman ED, Bousquet J, Cruz A, Haahtela T, O'Byrne P, et al. Global Initiative for Asthma. Global strategy for asthma management and prevention 2015 [guideline on the internet]. 2015. [cited 2015 Aug 21]. Available from: http://www.ginasthma.com.
10. Global Initiative for Chronic Lung Disease (GOLD). Global strategy for the diagnosis, management, and prevention of chronic obstructive pulmonary disease [guideline on the internet]. Global Initiative for Chronic Lung Disease World Health Organization; 2015 [cited 2015 Sep 8]. Available from: http://www.goldcopd.org/.
11. 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 2015 Jan 05]. Available from: www.nice.org.uk/guidance/CG101.
12. Kemp J, Armstrong L, Wan Y, Alagappan VK, Ohlssen D, Pascoe S. Safety of formoterol in adults and children with asthma: a meta-analysis. Ann Allergy Asthma Immunol. 2011 Jul;107(1):71-8.
13. Salpeter SR, et al. Meta-analysis: effect of long-acting B-agonists on severe asthma exacerbations and asthma-related deaths. Annals of Internal Medicine. 2006;144:904-13.
14. Boonsawat W, Charoenratanakul S, Pothirat C, et al. Formoterol (OXIS) turbuhaler as a rescue therapy compared to salbutamol pMDI plus spacer in patients with acute severe asthma. Respir Med. 2003;97:1067-74.
15. Pauwels RA, Sears MR, Cambell M, et al. Formoterol as relief medication in asthma: a worldwide safety and effectiveness trial. Eur Respir J. 2003;22:787-94.
16. Molimard M, Bourcereau J, Le Gros V, et al. Comparison between formoterol 12 µg bid. and on-demand salbutamol in moderate persistent asthma. Respir Med. 2001;94:64-70.
17. Pleskow W, LaForce CF, Yegen U, et al. Formoterol delivered via the dry powder aerolizer inhaler vs albuterol MDI and placebo in mild-to-moderate asthma: a randomized, double-blind, double-dummy trial. Journal of Asthma. 2003;40(5):505-14.
18. Bouros D, Bachlitzanakis N, Kottakis J, et al. Formoterol and beclomethasone vs higher dose beclomethasone as maintenance therapy in adult asthma. Eur Respir J. 1999;14:627-32.
19. Von Berg A, De Blic J, La Rosa M, et al. A comparison of regular salmeterol vs as required salbutamol therapy in asthmatic children. Respir Med. 1998;92:292-9.
20. Nelson HS, Weiss ST, Bleeker ER, et al. The salmeterol multicenter asthma research trial: a comparison of usual pharmacotherapy for asthma or usual pharmacotherapy plus salmeterol. Chest. 2006;129:15-26.
21. Boulet LP, Laviolette M, Boucher S, et al. A twelve-week comparison of salmeterol and salbutamol in the treatment of mild-to-moderate asthma: a Canadian Multicenter study. J Allergy Clin Immunol. 1997;99(1):13-21.
22. Faurschou P, Steffensen I, Jacques L. Effect of addition of inhaled salmeterol to the treatment of moderate-to-severe asthmatics uncontrolled on high-dose inhaled steroids. Eur Respir J. 1996;9:1885-90.
23. Vervloet D, Ekstrom T, Pela R, et al. A 6-month comparison between formoterol and salmeterol in patients with reversible obstructive airway disease. Respir Med. 1998;92:836-42.
24. Condemi JJ. Comparison of the efficacy of formoterol and salmeterol in patients with reversible obstructive airway disease: a multicenter, randomized, open-label trial. Clin Ther. 2001;23:1529-41.
25. Brambilla C, Le Gros V, Bourdeix I. Formoterol 12 µg bid administered via single-dose dry powder inhaler in adults with asthma suboptimally controlled with salmeterol or on demand salbutamol: a multicenter, randomized, open label, parallel-group study. Clin Ther. 2003;25(7);2022-36.
26. 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.
27. Brambilla C, Chastang C, Georges D, et al. Salmeterol compared to slow release terbutaline in nocturnal asthma. Allergy. 1994;49:421-6.

28. Estelle F, Simmons R. A comparison of beclomethasone, salmeterol, and placebo in children with asthma. N Engl J Med. 1997;337:1659-65.
29. Lazarus SC, Boushey HA, Fahy JV, et al. Long-acting β_2-agonist monotherapy vs continued therapy with inhaled corticosteroids in patients with persistent asthma. JAMA. 2001;285:2583-93.
30. 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.
31. Hermansson BA, Jenkins RJ. A 4-week comparison of salmeterol and terbutaline in adult asthma. Allergy. 1995;50:551-8.
32. Spencer S, Evans DJ, Karner C, Cates CJ. Inhaled corticosteroids vs long-acting beta(2)-agonists for chronic obstructive pulmonary disease. Cochrane Database Syst Rev. 2011 Oct 5;(10):CD007033.
33. Hanania N, Donohue J, Nelson H, Sciarappa K, Goodwin E, Baumgartner R, et al. The safety and efficacy of arformoterol and formoterol in COPD (abstract). COPD. 2010;7(1):17-31.
34. Baumgartner RA, Hanania NA, Calhoun WJ, et al. Nebulized arformoterol in patients with COPD: a 12-week, multicenter, randomized, double-blind, double-dummy, placebo-and active-controlled trial. Clin Ther. 2007; 29:261-78.
35. Data on file, Sepracor Inc. A double-blind, double-dummy, randomized, placebo- and active-controlled, multicenter, parallel-group study of arformoterol in the treatment of subjects with chronic obstructive pulmonary disease. Protocol No: 091-051. Date of Final Report: 27 September 2005.
36. Benhamou D, Cuvelier A, Muir JF, et al. Rapid onset of bronchodilation in COPD: a placebo-controlled study comparing formoterol (Foradil Aerolizer) with salbutamol (Ventodisk). Respir Med. 2001;95:817-21.
37. Cote C, Pearle JL, Sharafkhaneh A, Spangenthal S. Faster onset of action of formoterol vs salmeterol in patients with chronic obstructive pulmonary disease: a multicenter, randomized study. Pulm Pharmacol Ther. 2009 Feb;22(1):44-9.
38. Gross NJ, Nelson HS, Lapidus RJ, et al. Efficacy and safety of formoterol fumarate delivered by nebulization to COPD patients. Resp Med. 2008;102:189-97.
39. Sutherland E, Brazinsky A, Feldman G, McGinty J, Tomlinson L, Denis-Mize K. Nebulized formoterol effect on bronchodilation and satisfaction in COPD patients compared to QID ipratropium/albuterol MDI. Current Medical Research & Opinion. 2009;25(3):653-61.
40. Hanania N, Darken P, Horstman D, et al. The efficacy and safety of fluticasone propionate (250 µg)/salmeterol (50 µg) combined in the discus inhaler for the treatment of COPD. Chest. 2003 Sep;124(3):834-43.
41. Vogelmeier C, Hederer B, Glaab T, Schmidt H, Rutten-van Mölken MP, Beeh KM et al. Tiotropium vs salmeterol for the prevention of exacerbations of COPD. N Engl J Med. 2011 Mar 24;364(12):1093-1103.
42. Feldman G, Siler T, Prasad N, Jack D, Piggott S, Owen R, et al. Efficacy and safety of indacaterol 150 µg once-daily in COPD: a double-blind, randomized, 12-week study. BMC Pulm Med. 2010;10:11.
43. To Y, Kinoshita M, Lee SH, Hang LW, Ichinose M, Fukuchi Y, et al. Assessing efficacy of indacaterol in moderate and severe COPD patients: a 12-week study in an Asian population. Respir Med. 2012 Dec;106(12):1715-21.
44. Kornmann O, Dahl R, Centanni S, Dogra A, Owen R, Lassen C, et al. Once-daily indacaterol vs twice-daily salmeterol for COPD: a placebo-controlled comparison. Eur Respir J. 2011;37:273-9.
45. Dahl R, Chung KF, Buhl R, Magnussen H, Nonikov V, Jack D, et al. Efficacy of a new once-daily long-acting inhaled β_2-agonist indacaterol vs twice-daily formoterol in COPD. Thorax. 2010;65:473-9.
46. Korn S, Kerwin E, Atis S, Amos C, Owen R, Lassen C, et al. Indacaterol once-daily provides superior efficacy to salmeterol twice-daily in COPD: a 12 week study. Respir Med. 2011;105:719-26.
47. Magnussen H, Verkindre C, Jack D, Jadayel D, Henley M, Woessner R, et al. Indacaterol once-daily is equally effective dosed in the evening or morning in COPD. Respir Med. 2010;104:1869-76.
48. Balint B, Watz H, Amos C, Owen R, Higgins M, Kramer B, et al. Onset of action of indacaterol in patients with COPD: comparison with salbutamol and salmeterol-fluticasone. Int J Chron Obstruct Pulmon Dis. 2010 Sep 7;5:311-8.
49. Donohue JF, Fogarty C, Lotvall J, Mahler DA, Worth H, Yorgancioglu A, et al. Once-daily bronchodilators for chronic obstructive pulmonary disease: indacaterol vs tiotropium. Am J Respir Crit Care Med. 2010;182:155-62.
50. Vogelmeier C, Ramos-Barbon D, Jack D, Piggott S, Owen R, Higgins M, et al. Indacaterol provides 24-hour bronchodilation in COPD: a placebo-controlled blinded comparison with tiotropium. Respir Res. 2010 Oct 5;11:135.
51. Buhl R, Dunn LJ, Disdier C, Lassen C, Amos C, Henley M, et al. Blinded 12-week comparison of once-daily indacaterol and tiotropium in COPD. Eur Respir J. 2011 Oct;38(4):797-803.
52. Chapman KR, Rennard SI, Dogra A, Owen R, Lassen C, Kramer B, et al. Long-term safety and efficacy of indacaterol, a long-acting β_2-agonist, in subjects with COPD: a randomized, placebo-controlled study. Chest. 2011 Jul;140(1):68-75.
53. Han J, Dai L, Zhong N. Indacaterol on dyspnea in chronic obstructive pulmonary disease: a systematic review and meta-analysis of randomized placebo-controlled trials. BMC Pulm Med. 2013 Apr 25;13:26.
54. Wang J, Nie B, Xiong W, Xu Y. Effect of long-acting beta-agonists on the frequency of COPD exacerbations: a meta-analysis. J Clin Pharm Ther. 2012 Apr;37(2):204-11.
55. Rodrigo GJ, Neffen H. Comparison of indacaterol with tiotropium or twice-daily long-acting β -agonists for stable COPD: a systematic review. Chest. 2012 Nov;142(5):1104-10.
56. Lee TA, Pickard AS, Au DH, et al. Risk for death associated with medications for recently diagnosed chronic obstructive pulmonary disease. Ann Intern Med. 2008;149:380-90.
57. ZuWallack R, Allen L, Hernandez G, Ting N, Abrahams R. Efficacy and safety of combining olodaterol Respimat(®) and tiotropium HandiHaler(®) in patients with COPD: results of two randomized, double-blind, active-controlled studies. Int J Chron Obstruct Pulmon Dis. 2014 Oct 14;9:1133-44. doi: 10.2147/COPD.S72482. eCollection 2014.
58. 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.
59. 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.
60. Edelman JM, Turpin JA, Brodsky EA, et al. Oral montelukast compared to inhaled salmeterol to prevent exercise induced bronchoconstriction a randomized, double blind trial. Ann Intern Med. 2000;132:97-104.

61. Storms W, Czerwinski P, Ghana AF, et al. A Comparison of the effects of oral montelukast and inhaled salmeterol on response to rescue bronchodilation after challenge. Respir Med. 2004;98:1051-62.