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

Therapeutic Class
- **Overview/Summary:** Respiratory β₂-agonists are primarily used to treat reversible airway disease. The long-acting β₂-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 β₂-agonists act preferentially on the β₂-adrenergic receptors. Activation of these receptors on airway smooth muscle leads to the activation of adenyl 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 β₂-agonists can be divided into two categories: short-acting and long-acting. Only the inhaled long-acting β₂-agonists will be covered in this review and they include: arformoterol, formoterol, indacaterol salmeterol, and the newest agent olodaterol. Respiratory β₂-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>
<thead>
<tr>
<th>Generic (Trade Name)</th>
<th>Food and Drug Administration Approved Indications</th>
<th>Dosage Form/Strength</th>
<th>Generic Availability</th>
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</thead>
<tbody>
<tr>
<td>Arformoterol (Brovana®)</td>
<td>Bronchoconstriction in patients with chronic obstructive pulmonary disease, including chronic bronchitis and emphysema; maintenance treatment</td>
<td>Solution for nebulization: 15 µg (2 mL)</td>
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<tr>
<td>Formoterol (Foradil®, Perforomist®)</td>
<td>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 treatment⁵ exercise-induced bronchospasm prophylaxis, acute¹</td>
<td>Capsule for inhalation: 12 µg Solution for nebulization: 20 µg/2 mL</td>
<td>-</td>
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<tr>
<td>Indacaterol (Arcapta Neohaler®)</td>
<td>Bronchoconstriction in patients with chronic obstructive pulmonary disease, including chronic bronchitis and emphysema; maintenance treatment⁶</td>
<td>Capsule for inhalation: 75 µg</td>
<td>-</td>
</tr>
<tr>
<td>Olodaterol (Striverdi Respimat®)</td>
<td>Bronchoconstriction in patients with chronic obstructive pulmonary disease, including chronic bronchitis and emphysema; maintenance treatment⁶</td>
<td>Solution for inhalation (breath activated, metered-dose inhaler): 2.5 µg</td>
<td>-</td>
</tr>
<tr>
<td>Salmeterol (Serevent Diskus®)</td>
<td>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 treatment⁵</td>
<td>Dry powder inhaler: 50 µg (28 or 60 inhalations)</td>
<td>-</td>
</tr>
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Therapeutic Class Overview: long-acting inhaled β₂-agonists (single entity)

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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 β₂-agonists in providing relief from asthma, COPD exacerbations and exercise induced asthma.¹²⁻⁶¹
- Salmeterol and formoterol have been found to improve FEV₁ 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 FEV₁ 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 FEV₁ and FEV₁ AUC₀⁻³hr at weeks 12 and 24 when compared with placebo (no P value provided). In addition, four 6-week cross-over studies showed that FEV₁ AUC₀⁻¹₂hr and FEV₁ AUC₁₂⁻二十四hr 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 FEV₁ AUC₀⁻³ and trough FEV₁ 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 FEV₁ AUC₀⁻³ and trough FEV₁ responses without a significant increase in side effects when olodaterol was added to tiotropium. The mean difference in FEV₁ AUC₀⁻³ in ANHELTO 1 and 2 respectively were 0.117 L and 0.106 L (P<0.001 for both). Mean difference in FEV₁ 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:
  o Short-acting β₂-agonists are recommended for patients in all stages of asthma, for symptomatic relief of reversible airway disease and for exercise-induced bronchospasm.⁸,⁹
  o Short-acting β₂-agonists should be used on an as-needed or “rescue” basis.⁸,⁹
  o In the chronic management of asthma, the long-acting β₂-agonists should be used as add-on therapy in patients not adequately controlled on an inhaled corticosteroid.⁸,⁹
  o Long-acting β₂-agonists should not be used as monotherapy for the long-term control of asthma.⁸,⁹
  o Long-acting β₂-agonists can be used for exercise-induced bronchospasm and provide a longer period of coverage compared to short acting β₂-agonists.⁸,⁹
Long-acting β₂-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.

Long-acting β₂-agonists can be added to other COPD treatment regimens, including an anticholinergic agent, in efforts to decrease exacerbations.

Other Key Facts:
- The role of the short- and long-acting respiratory β₂-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 β₂-agonists are currently available generically.

References


