Therapeutic Class Overview
Respiratory Corticosteroid/Long-Acting β-Agonists Combinations

Therapeutic Class Overview/Summary: The combination inhaled corticosteroid (ICS)/long-acting β2-agonist (LABA) products include Advair® (fluticasone propionate/salmeterol), Breo Ellipta® (fluticasone furoate/vilanterol), Dulera® (mometasone/formoterol) and Symbicort® (budesonide/formoterol), with fluticasone furoate/vilanterol being the most recent agent to be approved by the Food and Drug Administration (FDA). Fluticasone propionate/salmeterol, mometasone/formoterol, budesonide/formoterol and fluticasone furoate/vilanterol are approved for the treatment of asthma; however, only fluticasone propionate/salmeterol, fluticasone furoate/vilanterol and budesonide/formoterol have been approved for the treatment of chronic obstructive pulmonary disease (COPD). The ICSs exert their anti-inflammatory effect by binding to the glucocorticoid receptors with a subsequent activation of genes involved in anti-inflammatory processes, as well as via the inhibition of pro-inflammatory genes involved in the asthmatic response. The LABAs have selective action on β2 receptors which stimulate adenyl cyclase, thereby increasing intracellular cyclic adenosine monophosphate level, and subsequently relaxing bronchial smooth muscles. The LABA medications also inhibit the release of mediators that are involved in immediate hypersensitivity. All of the combination products are associated with similar adverse events, precautions and contraindications.\textsuperscript{1-5} Moreover, the labeling for all of the combination products has been revised to reflect the results of an analysis which reported an increased risk of asthma exacerbations and hospitalizations in pediatric and adult patients, as well as death in some patients treated with LABA-containing medications.\textsuperscript{6} The combination ICS/LABA products appear to be equally efficacious for their respective indications, with the products differing in available dosage forms, dosing frequency (one vs two inhalations twice daily), pharmacokinetic profiles and ages for their FDA-approved indications.\textsuperscript{1-5}

<table>
<thead>
<tr>
<th>Generic 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>Budesonide/formoterol (Symbicort® HFA)</td>
<td>Maintenance treatment of airflow obstruction in patients with chronic obstructive pulmonary disease including bronchitis and/or emphysema* and treatment of asthma in patients 12 years of age and older</td>
<td>Meter dose aerosol inhaler (HFA): 80/4.5 µg 160/4.5 µg</td>
<td>-</td>
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<tr>
<td>Fluticasone propionate/salmeterol (Advair Diskus®, Advair HFA\textsuperscript{®})</td>
<td>Maintenance treatment of airflow obstruction in patients with chronic obstructive pulmonary disease including bronchitis and/or emphysema (Advair Diskus\textsuperscript{®})\textsuperscript{†}, treatment of asthma in patients four years of age and older (Advair Diskus\textsuperscript{®}) and treatment of asthma in patients 12 years of age and older (Advair HFA\textsuperscript{®})</td>
<td>Dry powder inhaler: 100/50 µg 250/50 µg 500/50 µg Meter dose aerosol inhaler (HFA): 45/21 µg 115/21 µg 230/21 µg</td>
<td>-</td>
</tr>
<tr>
<td>Fluticasone furoate/vilanterol (Breo Ellipta\textsuperscript{®})</td>
<td>Maintenance treatment of airflow obstruction in patients with chronic obstructive pulmonary disease and treatment of asthma in patients 18 years of age and older</td>
<td>Dry Powder Inhaler: 100 µg/25 µg 200 µg/25 µg</td>
<td>-</td>
</tr>
<tr>
<td>Mometasone/formoterol (Dulera\textsuperscript{®})</td>
<td>Treatment of asthma in patients 12 years of age and older</td>
<td>Meter dose aerosol inhaler (HFA): 100/5 µg 200/5 µg</td>
<td>-</td>
</tr>
</tbody>
</table>

\textsuperscript{HFA=hydrofluoroalkane}  
\textsuperscript{* Symbicort\textsuperscript{®} 160/4.5 µg is the only strength Food and Drug Administration (FDA) approved for this indication.}  
\textsuperscript{† Advair Diskus\textsuperscript{®} 250/50 µg is the only strength FDA approved for this indication.}
Evidence-based Medicine

- Fluticasone propionate/salmeterol, fluticasone furoate/vilanterol, mometasone/formoterol and budesonide/formoterol have been studied for the treatment of asthma and COPD.7-49
- The safety and efficacy of mometasone/formoterol were established in two randomized, double-blind, parallel-group, multicenter trials of 12 and 26 week duration (N=1,509).
  - After 26 weeks of treatment, mometasone/formoterol was more effective than monotherapy with the individual components in controlling asthma and reducing the risk of asthma deteriorations in patients with persistent asthma uncontrolled on medium-dose inhaled corticosteroids (ICSs).7
  - After 12 weeks of treatment, mometasone/formoterol was more effective than mometasone monotherapy in improving asthma control and reducing nocturnal awakenings.
    - Patients poorly controlled on high-dose ICSs experienced significant improvements in asthma control, lung function and symptoms when treated with mometasone/formoterol compared to mometasone monotherapy.8
  - A long term safety trial demonstrated that treatment with mometasone/formoterol for up to one year is well tolerated.9
- A single prospective head-to-head trial comparing mometasone/formoterol to fluticasone propionate/salmeterol demonstrated noninferiority of mometasone/formoterol in regard to the forced expiratory volume in 1 second (FEV1) area under the curve from 0 to 12 hours. Mometasone/formoterol treatment was also associated with a significantly quicker onset of action and increase in FEV1 five minutes post dose compared to fluticasone propionate/salmeterol.10
- Numerous trials have evaluated the combination ICS/LABA products to their respective individual components as monotherapy, and results have generally demonstrated that administration of the combination product is more effective than monotherapy for improving lung function and achieving control of asthma symptoms. Moreover, there is similar efficacy between the administration of the combination ICS/LABA products to their individual components used in combination.11-36
- Head-to-head trials comparing budesonide/formoterol and fluticasone propionate/salmeterol have been conducted but failed to consistently demonstrate “superiority” of one product over the other.37-46
- Two studies comparing fluticasone propionate/salmeterol and fluticasone furoate/vilanterol did not demonstrate significant differences in improvement of 0 to 24 hour FEV1.47,48
- A meta-analysis of 33 studies that compared fluticasone furoate/vilanterol to fluticasone propionate/salmeterol and budesonide/formoterol found that treatment with fluticasone furoate/vilanterol was noninferior to fluticasone propionate/salmeterol and budesonide/formoterol treatments.49

Key Points within the Medication Class

- According to Current Clinical Guidelines:50-53
  - ICSs and β2-agonists are well established treatment options in the management of both asthma and COPD.
  - The addition of a LABA is the preferred treatment option in asthma patients who fail to achieve adequate control with a low to medium dose ICS.
  - β2-agonists are among the principal bronchodilators used in the treatment of COPD, and LABAs are more effective and convenient than short-acting bronchodilators.
  - ICSs are recommended as adjunctive agents to long-acting bronchodilators to decrease exacerbation frequency in patients with an FEV1 ≤60% predicted and repeated exacerbations.
  - ICS/LABA products are more effective than either component alone in reducing exacerbations or improving lung function in COPD patients.
  - No one ICS/LABA product is preferred over another for the treatment of asthma or COPD.
- Other Key Facts:
  - All LABA-containing medications carry a Black Box Warning regarding an increased risk of asthma-related deaths associated with their use.
Budesonide/formoterol and fluticasone furoate/vilanterol have quicker onsets of action (15 and 16 minutes) compared to fluticasone propionate/salmeterol (30 to 60 minutes). The onset of action of mometasone/formoterol has not been reported.1-5

All ICS/LABA products are available for twice-daily dosing, except fluticasone furoate/vilanterol which is administered once daily.1-5

For the treatment of asthma, Advair® HFA (fluticasone propionate/salmeterol), Dulera® (mometasone/formoterol), Symbicort® (budesonide/formoterol) are approved for use in patients 12 years of age and older, whereas Advair Diskus® (fluticasone propionate/salmeterol) is approved for use in patients four years of age and older. Breo Ellipta® (fluticasone furoate/vilanterol) was recently approved for the treatment of asthma in patients 18 years of age and older.

No generic products are available in this therapeutic class.


