

Long-acting beta agonists (LABAs) used in combination with inhaled corticosteroids (ICS) – Safety Update

- On December 20, 2017, the [FDA announced](#) that the *Boxed Warning* regarding asthma-related death has been removed from the [Advair Diskus[®] \(fluticasone/salmeterol\)](#), [Advair[®] HFA \(fluticasone/salmeterol\)](#), [Airduo[™] Respiclick[®] \(fluticasone/salmeterol\)](#), [Breo[®] Ellipta[®] \(fluticasone/vilanterol\)](#), [Dulera[®] \(mometasone/formoterol\)](#), and [Symbicort[®] \(budesonide/formoterol\)](#) drug labels.
 - Combination ICS/LABA products are FDA-approved to treat both asthma and chronic obstructive pulmonary disease (COPD).
- The FDA reviewed four large clinical safety trials which showed that treating asthma with LABAs in combination with ICS does not result in significantly more serious asthma-related side effects such as asthma-related hospitalizations, intubations, or asthma-related deaths than treatment with ICS alone.
 - A description of these safety trials is also included in the *Warnings and Precautions* section of the updated ICS/LABA combination product drug labels.
- Using LABAs alone to treat asthma without an ICS to treat lung inflammation is associated with an increased risk of asthma-related death. Therefore, the *Boxed Warning* stating this will remain in the labels of all single-ingredient LABA medicines, which are approved to treat asthma, COPD, and wheezing caused by exercise.
- The ICS/LABA combination product drug labels also retain a *Warning and Precaution* related to the increased risk of asthma-related death when LABAs are used without an ICS to treat asthma.
- Healthcare providers should refer to the most recently approved drug labels for recommendations on using ICS/LABA medicines.
- Patients should not stop taking their asthma medicines without first talking to their healthcare provider. Patients and parents/caregivers should talk to their healthcare provider if they have any questions or concerns regarding their medication and read the patient information leaflet that comes with every prescription.
- In 2011, the FDA required the manufacturers of ICS/LABA combination drugs (GlaxoSmithKline, Merck, AstraZeneca) to conduct several large, clinical safety trials to evaluate the risk of serious asthma-related events when LABAs were used in fixed-dose combination with an ICS vs. ICS alone in patients with asthma.
- Four studies involved a total of 41,297 patients. Three studies were conducted in patients ≥ 12 years of age and one was conducted in children 4 to 11 years of age. Patients in all trials were treated for 6 months to evaluate asthma-related death, intubation, or hospitalization.
 - A meta-analysis of the three adult/adolescent trials demonstrated that the use of ICS/LABA in fixed-dose combination did not result in a significant increase in the risk of serious asthma-related events vs. ICS alone (number of serious asthma-related events: 116 vs. 105, respectively; HR = 1.10, 95% CI: 0.85, 1.44).
 - There were a greater number of asthma related deaths with ICS/LABA vs. ICS alone (2 vs. 0, respectively).

- There were 115 asthma-related hospitalizations with ICS/LABA vs. ICS alone (115 vs. 105, respectively).
 - There was 1 asthma-related intubation with ICS/LABA vs. 2 with ICS alone.
- In the pediatric safety trial, 0.9% patients randomized to fluticasone/salmeterol and 0.7% patients randomized to fluticasone experienced a serious asthma-related event. There were no asthma-related deaths or intubations.
 - Fluticasone/salmeterol did not show a significantly increased risk of serious asthma-related events vs. fluticasone (HR = 1.29; 95% CI: 0.73, 2.27).
- The trials also showed that ICS/LABA combination medicines were more effective in decreasing asthma attacks (eg, the need to use oral corticosteroids) vs. ICS alone.



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