U.S. Food and Drug Administration
Protecting and Promoting *Your* Health

Drug Safety Communications

FDA review finds no significant increase in risk of serious asthma outcomes with long-acting beta agonists (LABAs) used in combination with inhaled corticosteroids (ICS)

This is an update to the FDA Drug Safety Communication: FDA requires post-market safety trials for Long-Acting Beta-Agonists (LABAs) issued on April 15, 2011.

Safety Announcement

[12-20-2017] A U.S. Food and Drug Administration (FDA) review of four large clinical safety trials shows that treating asthma with long-acting beta agonists (LABAs) in combination with inhaled corticosteroids (ICS) does not result in significantly more serious asthma-related side effects than treatment with ICS alone. In 2011, we required the drug companies that market LABAs to conduct these trials to evaluate the safety of LABAs when used in combination with ICS, and we reviewed the results of these recently completed trials.

Based on our review, the *Boxed Warning*, our most prominent warning, about asthma-related death has been removed from the drug labels of medicines that contain both an ICS and LABA. A description of the four trials is now also included in the *Warnings and Precautions* section of the drug labels. These trials showed that LABAs, when used with ICS, did not significantly increase the risk of asthma-related hospitalizations, the need to insert a breathing tube known as intubation, or asthma-related deaths, compared to ICS alone.

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, chronic obstructive pulmonary disease (COPD), and wheezing caused by exercise. The labels of medicines that contain both an ICS and LABA 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.

Medicines that contain both an ICS and LABA are FDA-approved to treat both asthma and COPD. ICS medicines help decrease inflammation in the lungs. This inflammation can lead to breathing problems. LABAs help the muscles around the airways in the lungs stay relaxed to prevent symptoms such as wheezing, coughing, chest tightness, and shortness of breath. ICS/LABA medicines are marketed under several brand names, including Advair, Airduo, Breo, Dulera, and Symbicort (see Table 1).

Health care professionals should refer to the most recently approved drug labels for recommendations on using ICS/LABA medicines (see links in Table 1). **Patients and parents/caregivers** should talk to your health care professional if you have any questions or concerns. Do not stop taking your asthma medicines without first talking to your health care professional. Also read the patient information leaflet that comes with every prescription.

We evaluated four recently completed clinical trials involving 41,297 patients, three conducted in patients 12 years and older, and one in children 4 to 11 years. Patients in all the trials were treated for 6 months to evaluate serious asthma outcomes including asthma-related death, intubation, or hospitalization. The results of all trials showed that the use of LABA with ICS does not significantly increase the risk of serious asthma outcomes compared to ICS alone. The trials also showed that ICS/LABA combination medicines were more effective in decreasing asthma attacks (e.g., the need to use oral corticosteroids) compared to ICS alone. This additional information has been added to the ICS/LABA labels.

To assure the ongoing evaluation of the safety of all medicines, including LABAs and ICS, we urge patients and health care professionals to report side effects involving LABAs, ICS, or other medicines to the FDA MedWatch program, using the information in the "Contact FDA" box at the bottom of the page.

Table 1. List of Approved ICS/LABA Combination Medicines

Brand Name	Generic Names
Advair Diskus	fluticasone (ICS), salmeterol (LABA)
Advair HFA	fluticasone (ICS), salmeterol (LABA)
Airduo Respiclick	fluticasone (ICS), salmeterol (LABA)
Breo Ellipta	fluticasone (ICS), vilanterol (LABA)
Dulera	mometasone (ICS), formoterol (LABA)
Symbicort	budesonide (ICS), formoterol (LABA)

Data Summary

In 2011, FDA required the drug companies manufacturing fixed-dose combination drugs containing an ICS and LABA (GlaxoSmithKline, Merck, Astra Zeneca) to conduct several large, 26-week, randomized, double-blind, active-controlled clinical safety trials to evaluate the risk of serious asthma-related events when long-acting beta agonists (LABAs) were used in fixed-dose combination with an inhaled corticosteroid (ICS) compared to ICS alone in patients with asthma. We reviewed the results of four trials involving 41,297 patients. A fifth trial was originally required, however it was terminated early when Novartis withdrew Foradil (formoterol) from the U.S. market.

Three of the four trials included adults and adolescents 12 years and older. One of the trials compared fluticasone/salmeterol (Advair Diskus) to fluticasone, one compared mometasone/formoterol (Dulera) to mometasone, and one compared

budesonide/formoterol (Symbicort) to budesonide. The fourth trial included pediatric patients 4-11 years and compared fluticasone/salmeterol to fluticasone. The primary safety endpoint for all four trials was serious asthma-related events (hospitalizations, intubations, and deaths). All hospitalizations, intubations, and deaths were adjudicated to determine relatedness to asthma. The three adult/adolescent trials were designed to rule out a risk margin of 2.0, and the pediatric trial was designed to rule out a risk margin of 2.7. Each individual trial met this objective. Although each individual trial met this objective, the trials were not designed to show that there is no increase in risk with ICS/LABA compared to ICS. Data from the three trials conducted in adults and adolescents were combined in a meta-analysis to provide greater precision of the risk of serious asthma-related events with ICS/LABA products. The results demonstrate that the use of ICS/LABA in fixed-dose combination does not result in a significant increase in the risk of serious asthma-related events compared to ICS alone, with 95% confidence limits ranging from 0.85 to 1.44 (See Table 2 below). The results of subgroup analyses for gender, adolescents 12-18 years, and African Americans are consistent with the primary endpoint results.

Table 2. Meta-analysis of Serious Asthma-Related Events in Patients with Asthma 12 Years and Older[*]

	ICS/LABA (N=17,537)[†]	**ICS (N=17,552)[†]**	**ICS/LABA vs. ICS Hazard Ratio (95% CI)[‡]**
Serious asthma-related events[§]	116	105	1.10 (0.85, 1.44)
Asthma-related deaths	2	0	
Asthma-related intubations	1	2	
Asthma-related hospitalizations	115	105	

[*] Randomized patients who took at least one dose of study medication.

[†]Patients could have more than one event. Planned treatment used for analysis.

[‡]Estimated using a Cox proportional hazards model for time to first event with baseline hazards stratified by each of the three trials.

[§]Events that occurred within 6 months after the first use of study drug or 7 days after the last date of study drug treatment, whichever date was later. A single, blinded, independent adjudication committee determined whether events were asthma-related.

The pediatric safety trial included 6,208 patients 4-11 years who received fluticasone/salmeterol or fluticasone. In this trial, 27/3,107 (0.9%) patients randomized to fluticasone/salmeterol and 21/3,101 (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 compared to fluticasone based on the pre-specified risk margin (2.7), with an estimated hazard ratio of time to first event of 1.29 (95% confidence interval: 0.73, 2.27).

The four trials also assessed efficacy of the ICS/LABA products. The primary efficacy endpoint was asthma exacerbation, defined as a deterioration of asthma requiring the use

of systemic corticosteroids for at least 3 days, or an in-patient hospitalization or emergency department visit due to asthma that required systemic corticosteroids. The results showed that the ICS/LABA combination reduced asthma exacerbations compared to ICS alone (see Table 3 below), noting that the majority of these exacerbations were those that required at least 3 days of systemic corticosteroids. This efficacy information has been added to the *Clinical Studies* section of the ICS/LABA drug labels.

Table 3. Efficacy Results

	Advair (Adult/Adolescent)		Advair (Pediatrics)		Symbicort (Adult/Adolescent)		Dulera (Adult/Adolescent)	
	Advair N=5,834	fluticasone N=5,845	Advair N=3,107	fluticasone N=3,101	Symbicort N=5,846	budesonide N=5,847	Dulera N=5,868	mometasone N=5,861
Patients with exacerbations, n (%)	480 (8)	597 (10)	265 (9)	309 (10)	539 (9.2)	633 (10.8)	708 (12.1)	779 (13.3)
Hazard Ratio (95% CI)	0.79 (0.70, 0.89)		0.86 (0.73, 1.01)		0.84 (0.75, 0.94)		0.89 (0.80, 0.98)	

Related Information

Long-Acting Beta Agonist (LABA) Information

Drugs@FDA: FDA Approved Drug Products
Access drug labels by searching the drug name

The FDA's Drug Review Process: Ensuring Drugs Are Safe and Effective

Think It Through: Managing the Benefits and Risks of Medicines