

GlaxoSmithKline Briefing Document
For US Food and Drug Administration Advisory Committees Meeting Dec. 10-11
At-A-Glance

GlaxoSmithKline (GSK) has submitted to FDA three kinds of data spanning the past 20 years to evaluate the safety of long-acting beta-agonist (LABA) medicines in the treatment of asthma. These medicines include Serevent® (salmeterol), a LABA, and Advair® (fluticasone propionate and salmeterol), a combination product that includes a LABA plus an inhaled corticosteroid (ICS). The data submitted are:

- A GSK meta-analysis of more than 200 randomized controlled clinical studies in more than 100,000 patients. Outcomes of interest were all cause deaths, asthma-related deaths, asthma-related hospitalizations and asthma-related intubations. These outcomes were adjudicated from blinded case narratives by independent, external physicians.
- From the FDA's database of spontaneously reported serious adverse events.
- Observational studies of more than 120,000 adult and pediatric patients comparing *Advair* to an alternative controller therapy.

GSK conclusions include:

- For *Advair*, there was no evidence of increased risk for asthma-related death, asthma-related hospitalization, asthma-related intubation and all cause death compared to other treatments studied.
- The combination of salmeterol with an ICS (either as *Advair* or as *Serevent* plus an ICS) provides effective asthma control to patients by improving lung function, preventing daytime and nighttime symptoms and decreasing the use of rescue medications – all important measures of asthma control.
- The data showed no increased risk of serious asthma-related events when salmeterol is used appropriately with an ICS.
- There was an increased risk for serious asthma-related outcomes when salmeterol was used without an inhaled corticosteroid or when the use of inhaled corticosteroids could not be assured (e.g. not part of study treatment).

Some key findings behind these conclusions are:

Meta-analysis

- There were no asthma-related deaths in GSK clinical studies comparing *Advair* with ICS in more than 22,000 patients
- No increased risk of asthma-related hospitalizations in patients receiving *Advair* compared with ICS was observed.
- There were no asthma-related deaths in GSK clinical studies comparing *Advair* with ICS in more than 2,400 children.
- No increased risk of asthma-related hospitalizations in children receiving *Advair* compared with ICS was observed.
- In patients who received *Serevent* plus a separate ICS as part of study treatment, there was no increased risk of asthma-related deaths or hospitalizations than patients receiving an ICS alone.
- There were too few asthma-related deaths in children to conduct a meta-analysis. There was 1 asthma-related death in 37 clinical studies enrolling more than 7,400 children. That death occurred in a patient who was receiving albuterol four times daily. No deaths occurred in GSK clinical trials in children receiving salmeterol.
- Among patients who took *Serevent* without an ICS in GSK clinical trials, there were 8 asthma-related deaths among more than 9,000 patients taking *Serevent* compared to 0 deaths among almost 9,000 patients taking placebo.
- In a comparison of salmeterol versus non-LABA containing treatments, there were 28 asthma-related deaths in more than 57,000 patients in GSK clinical trials receiving salmeterol and 7 asthma-related deaths in more than 48,000 patients receiving a non-LABA. (30 of the 35 deaths occurred in 2 GSK studies, SMART and SNS, initiated in the early to mid 1990s, when ICS was not routinely prescribed with a LABA as it is today.)

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Observational Studies

- An analysis of nearly 80,000 adult patients in observational studies of *Advair* compared to ICS, found that those who received the drug had a 16% lower rate of emergency department visits and 15% lower rate of hospitalizations as compared to patients who received ICS alone.
- Similarly, observational studies of more than 40,000 children and adolescents, showed patients taking *Advair* experienced a 9% lower rate of emergency department visits and hospitalization than those receiving ICS alone.

Participants in the Dec. 10-11 meeting include the Pulmonary Allergy Drugs Advisory Committee, Drug Safety and Risk Management Advisory Committee and the Pediatric Advisory Committee.

In addition to GSK, other key companies and products involved are Astra Zeneca with Symbicort (ICS and LABA combination) and Novartis with Foradil (formoterol, LABA).

Asthma is a significant public health issue in this country. It affects over 22 million people, including more than 6 million children. Asthma-related deaths have been decreasing since the mid-1990s but asthma is still responsible for more than 3,563 deaths in the US each year (preliminary deaths for 2006).

Important Information about Advair Diskus

Advair Diskus is indicated for the maintenance treatment of asthma. *Advair Diskus* won't replace fast-acting inhalers for sudden symptoms and should not be taken more than twice a day. *Advair Diskus* contains salmeterol. In patients with asthma, medicines like salmeterol may increase the chance of asthma-related death. So *Advair Diskus* is not for people whose asthma is well controlled on another controller medicine. People should speak to their doctor about the risks and benefits of treating their asthma with *Advair Diskus*. People taking *Advair Diskus* should see their doctor if their asthma does not improve. People should tell their doctor if they have a heart condition or high blood pressure. Some people may experience increased blood pressure, heart rate, or changes in heart rhythm. *Advair Diskus* is for patients 4 years and older. For patients 4 to 11 years old, *Advair Diskus* 100/50 is for those who have asthma symptoms while on an inhaled corticosteroid.

Important information about Serevent Diskus

Serevent Diskus is indicated for the maintenance treatment of asthma in patients 4 years of age and older. *Serevent Diskus* does not replace fast-acting inhalers for sudden symptoms and should not be taken more than twice a day. In patients with asthma, medicines like *Serevent* may increase the chance of asthma-related death. People should talk to their doctor about this risk and the benefits of treating their asthma with *Serevent Diskus*. *Serevent Diskus* should not be the only controller medicine prescribed for a person's asthma and is not a substitute for anti-inflammatory medications (inhaled or oral corticosteroids). People should tell their doctor if they have a heart condition or high blood pressure. Some people may experience increased blood pressure, heart rate, or changes in heart rhythm. People should see their doctor if their asthma does not improve.

See full Prescribing Information and Medication Guide for *Advair* and *Serevent* at www.gsk.com.

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