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Dear Healthcare Professional:

Important new safety information

GlaxoSmithKline is writing to you, as a prescriber of Serevent® (salmeterol xinafoate), to communicate important safety information, and reinforce and reiterate advice on the appropriate prescribing of Serevent in patients with asthma.

Although the data are inconclusive, recent findings from an interim analysis of a large Serevent safety study have prompted further review of the potential association between Serevent and rare, but potentially serious, respiratory adverse events. The trial and the findings are described below.

SMART SAFETY STUDY

In July 1996, GSK initiated the Salmeterol Multi-center Asthma Research Trial (SMART), a 28-week safety study comparing Serevent and placebo in the treatment of asthma. The SMART study was designed, in agreement with the FDA, to assess the safety of Serevent following concerns regarding the safety of regular use of short-acting and long-acting β_2 -agonists in the management of asthma.

The primary endpoint of the SMART study was the combined number of respiratory-related deaths and respiratory-related life-threatening experiences (intubations and mechanical ventilation). Other endpoints included asthma-related events including deaths, and asthma-related deaths. In addition to their usual asthma therapy, patients in one arm of the study received 42 mcg of Serevent twice a day through an MDI, and patients in the other arm received placebo. All patients were treated according to the approved labeling for Serevent. The study protocol included a planned interim analysis once half of the patients were recruited.

INTERIM ANALYSIS OF THE SMART STUDY

Towards the end of 2002, an interim analysis of all available data on 25,858 patients was conducted. While this analysis showed no significant differences for the primary endpoint, a higher though not statistically significant number of asthma-related life-threatening experiences, including deaths, occurred in the patients treated with Serevent. Due to the low rate of primary events in the study, the findings of the planned interim analysis are not conclusive. Further analyses have been performed on certain sub-populations of patients.

Ethnic groups

In Caucasian patients (71% of the study population) there were no significant differences between treatment groups for primary events and asthma-related events.

In African Americans (17% of the study population) the study showed a statistically significant greater number of primary events and asthma-related events, including deaths, in patients taking salmeterol compared to those taking placebo. However, it is important to note that less than 1% of all African Americans enrolled in the study experienced such events during the 28-week trial.

The numbers of patients from other ethnic groups were too small to draw any conclusions in these populations.

In the SMART study, there were some differences between the African-American and Caucasian patients recruited into the study that may have contributed to the higher rate of asthma-related events among African Americans. African-American patients had more severe asthma at baseline than Caucasian patients, as indicated by frequency of symptoms, baseline PEF, and history of prior intubations, ER visits, and hospitalizations.

The SMART study was not designed to obtain robust results within or between sub-populations. Therefore, continuing the study would likely not answer the questions raised by the interim analysis. As a result, GSK has decided to discontinue the study, in agreement with the Data Safety Monitoring Board. The FDA is aware of this decision.

Inhaled corticosteroid use

In contrast to recommendations of current asthma management guidelines, there was a low level of inhaled corticosteroid use (47%) in the entire population in the SMART study. Only 50% of Caucasian patients were receiving treatment with an inhaled corticosteroid, and in African-American patients, only 38% were using inhaled corticosteroid therapy at baseline.

In the total population of patients receiving inhaled corticosteroids at baseline, no significant differences were seen for primary events and asthma-related events, including deaths.

However, in the total population of patients not receiving inhaled corticosteroids at baseline, there was a statistically significant greater number of asthma-related deaths in all patients taking salmeterol compared to those taking placebo.

Follow-Up Plans

Further review of the data from the SMART study interim analysis is ongoing and GSK is in discussions with the FDA regarding these findings. In addition, GSK is working with the FDA to review potential changes to the labeling for Serevent® (salmeterol xinafoate) that will reinforce guidance on appropriate and safe prescribing. GSK is also discussing with the FDA the design of other investigations to provide meaningful conclusions about the appropriate use of salmeterol in African Americans.

GSK RECOMMENDATIONS

National Asthma Education and Prevention Program (NAEPP) guidelines recommend patients requiring more than as-needed short-acting β_2 -agonists should be prescribed regular and adequate doses of an inhaled anti-inflammatory asthma medication, such as inhaled corticosteroids, for optimal benefit in the management of their asthma.¹

Consistent with these guidelines and reinforced by trends seen in the interim analysis of the SMART data, GSK recommends that patients receiving salmeterol for asthma should normally also be receiving regular and adequate doses of an effective asthma controller medication, such as inhaled corticosteroids.

IMPORTANT ADVICE FOR MANAGING YOUR PATIENTS

GSK and the FDA agree on the need to reiterate and reinforce advice for the management of patients, including African Americans, as established in the label for Serevent and national asthma management guidelines.

- Patients who are currently taking Serevent should not discontinue their treatment without first consulting a physician. Abruptly stopping medications may result in acutely deteriorating asthma control, which may be life-threatening.
- Salmeterol is not a replacement for inhaled corticosteroids, which should be continued at the same dose, and not stopped or reduced, when treatment with salmeterol is initiated.
- Salmeterol should not be initiated in patients with significantly worsening or acutely deteriorating asthma, which may be life-threatening.
- Salmeterol should not be used to treat acute symptoms.
- Patients on salmeterol must also have a short-acting bronchodilator (e.g., albuterol) for use as needed for acute symptoms.
- The increased need for using the short-acting bronchodilator is a sign of deteriorating asthma.
- Patients should be educated to recognize the signs of deteriorating asthma control and the need to seek medical attention promptly in such circumstances.

Given the similar basic mechanisms of action of all β_2 -agonists, it is possible that the findings seen in the SMART study may be consistent with a class effect.

If you have any questions regarding the use of salmeterol in patients with asthma, please contact our customer response center at 1-888-825-5249.

It is important that you forward any adverse event information associated with the use of Serevent® (salmeterol xinafoate) to GlaxoSmithKline at 1-888-825-5249. You can also report this information directly to the FDA via the MedWatch system at 1-800-FDA-1088, by fax at 1-800-FDA-0178, by mail (using a postage-paid form) to MedWatch, HF-2, FDA, 5600 Fishers Lane, Rockville, MD 20857, or by the Internet at www.FDA.gov/medwatch.

Enclosed, for your information, is a copy of the package insert for Serevent Inhalation Aerosol.

Yours sincerely,

A handwritten signature in cursive script that reads "Kathleen A. Rickard MD".

Kathleen A. Rickard
Vice President
Respiratory, Clinical Development & Medical Affairs

1. National Heart, Lung, and Blood Institute, National Institutes of Health. Expert Panel Report 2: Guidelines for the Diagnosis and Management of Asthma. April 1997. (NIH Publication No. 97 4051).