GlaxoSmithKline
PO Box 13398
Five Moore Drive
Research Triangle Park
North Carolina 27709

Tel. 919 483 2100
www.gsk.com

IMPORTANT REVISIONS TO PRESCRIBING INFORMATION FOR SEREVENT® (salmeterol xinafoate) AND ADVAIR DISKUS® (fluticasone propionate and salmeterol inhalation powder)

Dear Health Care Professional:

GlaxoSmithKline is writing to you as a prescriber of SEREVENT and/or ADVAIR, to communicate important new revisions to the prescribing information for SEREVENT and ADVAIR, which includes the following boxed warning.

BOXED WARNING FOR SEREVENT AND ADVAIR

WARNING: Data from a large placebo-controlled US study that compared the safety of salmeterol (SEREVENT Inhalation Aerosol) or placebo added to usual asthma therapy showed a small but significant increase in asthma-related deaths in patients receiving salmeterol (13 deaths out of 13,174 patients treated for 28 weeks) versus those on placebo (4 out of 13,179). Subgroup analyses suggest the risk may be greater in African-American patients compared to Caucasians.

BACKGROUND

In January, GSK communicated findings from an interim analysis of a large study investigating the use of SEREVENT in patients with asthma. This analysis reported an association between SEREVENT and rare, but potentially serious, asthma-related events. Since that time, GlaxoSmithKline has been reviewing the data with the Food and Drug Administration (FDA) and has subsequently updated the prescribing information for SEREVENT and ADVAIR; salmeterol being the active component of SEREVENT and one of the active components of ADVAIR.

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. In addition to their prescribed asthma therapy, patients in one arm of the study received 42 mcg of SEREVENT (N=13,174) twice a day through an MDI, and patients in the other arm received placebo (N=13,179). The primary endpoint of SMART was the combined number of respiratory related deaths or respiratory related life-threatening experiences (intubations and mechanical ventilation). Other endpoints included asthma-related life-threatening experiences (including deaths) and asthma-related deaths alone. A planned interim analysis was conducted when approximately half of the intended number of patients were enrolled. Even though SMART did not reach predetermined stopping criteria, the study was stopped due to findings in African-American patients and difficulties with enrollment.

The analysis of SMART showed no significant difference for the primary endpoint for the total population. However, a higher number of asthma-related deaths or life-threatening experiences (36 vs. 23) and a higher number of asthma-related deaths (13 vs. 4) occurred in the patients treated with SEREVENT Inhalation Aerosol. No significant increase was observed in respiratory or asthma-related episodes, including deaths, in Caucasian patients. In African-Americans, the study showed a small, though statistically significantly greater number of primary events (20 vs. 7), asthma-related deaths or life-threatening experiences (19 vs. 4), and asthma-related deaths (8 vs. 1) in patients taking SEREVENT Inhalation Aerosol compared to those taking placebo. However, due to the low rate of primary events in the study, the findings of the planned interim analysis were not conclusive.

In addition to the boxed warning, other sections of the package insert for SEREVENT and ADVAIR (Clinical Trials, Warnings, and Information for Patients) have been updated to include the results from SMART and the following additional information:

- Patients should not stop SEREVENT or ADVAIR therapy for asthma or SEREVENT for COPD without physician/provider guidance since symptoms may recur after discontinuation.

- Given the similar basic mechanisms of action of $beta_2$-agonists, it is possible that the findings seen in SMART may be consistent with a class effect.

- Data from SMART are not adequate to determine whether concurrent use of inhaled corticosteroids such as fluticasone propionate, a component of ADVAIR DISKUS, provides protection from this risk. Therefore, it is not known whether the findings seen with SEREVENT would apply to ADVAIR.

Important Advice for Managing Your Patients

GSK believes it is important to reiterate and reinforce advice for the management of patients as established in the prescribing information for SEREVENT and ADVAIR.

- Patients who are currently taking SEREVENT or ADVAIR 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.
- SEREVENT 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.
- SEREVENT or ADVAIR should not be initiated in patients with significantly worsening or acutely deteriorating asthma, which may be life-threatening.
- SEREVENT or ADVAIR should not be used to treat acute symptoms.
- Patients on SEREVENT or ADVAIR 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.

If you have any questions regarding the use of SEREVENT or ADVAIR 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 or ADVAIR 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 inserts for SEREVENT DISKUS and ADVAIR DISKUS.

Yours sincerely,

Kathleen A. Rickard, M.D.
Vice President
Respiratory, Clinical Development and Medical Affairs

AD2243R0