

FDA Talk Paper

T03-62
August 14, 2003

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FDA

Labeling Changes for Drug Products that Contain Salmeterol

The Food and Drug Administration is announcing the addition of new safety information and warnings to the labeling for drug products that contain salmeterol, a long-acting bronchodilator used to treat asthma and chronic obstructive pulmonary disease (COPD). The products affected by these changes are Serevent Inhalation Aerosol, Serevent Diskus, and Advair Diskus. The new labeling for these products will contain a boxed warning about a small, but significant, increased risk of life-threatening asthma episodes or asthma-related deaths observed in patients taking salmeterol in a recently completed large U.S. safety study.

On January 23, 2003, FDA released a talk paper announcing the preliminary results of an interim analysis of the Salmeterol Multi-center Asthma Research Trial (SMART), which compared the effects of salmeterol (Serevent Inhalation Aerosol, 42mcg twice-daily) to placebo in patients with asthma for a period of 28 weeks. Since that time, FDA has worked closely with GlaxoSmithKline, the sponsor of the study and the manufacturer of Serevent and Advair, to carefully review the study results and to develop appropriate labeling to reflect the new information provided by this study.

The primary endpoint for the SMART study was the occurrence of either respiratory-related death or a respiratory-related life-threatening experience (e.g., requirement for mechanical ventilation). Secondary endpoints included all-cause death, asthma-related death, and asthma-related death or life-threatening experience.

Although the study was intended to enroll 60,000 patients, the study was stopped by the sponsor after review of the results of a planned interim analysis, which was performed after approximately half of the intended number of patients was enrolled. The analysis includes 13,174 patients treated with Serevent, and 13,179 patients treated with placebo. The analysis showed no significant difference between treatment groups for the primary endpoint, however, a higher number of asthma-related deaths (13 vs. 4), and a higher number of asthma-related deaths or life-threatening experiences (36 vs. 23) were observed in the Serevent group compared to placebo. The SMART study was not prospectively designed to analyze differences in outcome based on demographic characteristics; however post-hoc subgroup analyses based on race and ethnicity were conducted. These analyses showed no increase in respiratory- or asthma-related events among Caucasian patients; however, among African-American patients there was a statistically significant increase in primary events (respiratory-related death of life-threatening experience) in the Serevent group (20 vs. 7). In addition, the occurrence of asthma-related death (8 vs. 1) and asthma-related death or life-threatening experience (19 vs. 4) was statistically significantly greater in African-American patients treated with Serevent compared to placebo.

FDA emphasizes that based on available data, the benefits of treatment with salmeterol in patients with asthma and COPD continue to outweigh the potential risks when used according to the instructions contained in the product labeling. FDA strongly advises patients that they should NOT stop taking products that contain salmeterol, or any other medication, for asthma or COPD without first talking to their physicians. Abruptly stopping drugs for the treatment of asthma and COPD can result in serious worsenings of these diseases that could be life-threatening. FDA further emphasizes that all asthma drugs, including salmeterol, should be prescribed as part of a

comprehensive plan that takes into account the patient's asthma severity and fully educates the patient in the disease and its proper treatment.

Serevent Inhalation Aerosol, Serevent Diskus, and Advair Diskus, which all contain salmeterol as an active ingredient, are manufactured by GlaxoSmithKline of Research Triangle Park, N.C.