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IMPORTANT SAFETY INFORMATION REGARDING SEREVENT® (salmeterol xinafoate) in Asthma and cessation of the SMART (Salmeterol Multi-center Asthma Research Trial)

In the United States, **the Salmeterol Multi-Center Research Trial** (SMART) was prematurely **stopped** by GlaxoSmithKline due to a small but significant increase in asthma-related deaths in patients receiving SEREVENT® (salmeterol xinafoate) versus those on placebo. Subgroup analyses suggest the risk may be greater in African American patients compared to Caucasians.

SEREVENT® (salmeterol xinafoate) is **not approved as an asthma monotherapy** in Canada.

SEREVENT® (salmeterol xinafoate) is **not a substitute for inhaled or oral corticosteroids**.

Dear Health Care Professional,

This letter is being sent out following discussions with Health Canada regarding the use of SEREVENT® (salmeterol xinafoate) in asthma. "SEREVENT® (salmeterol xinafoate) is indicated in the maintenance treatment of asthma in patients 4 years of age and older with reversible obstructive airway disease, who are using optimal corticosteroid treatment and experiencing breakthrough symptoms requiring regular use of a short-acting bronchodilator"[1].

Background

In January, GSK in the US, 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 US Food and Drug Administration (FDA) and has subsequently updated the prescribing information for SEREVENT® and ADVAIR® (salmeterol xinafoate / fluticasone propionate); salmeterol being the active component of SEREVENT® and one of the active components of ADVAIR®. The Canadian product monograph will also be updated as a result of the findings from the SMART study.

SMART Safety Study

In July 1996, GSK initiated the SMART, a 28-week safety study comparing SEREVENT® and placebo in the treatment of asthma. The study was initiated following concerns about the safety of the regular use of short and long-acting beta $_2$-agonists in the management of asthma that arose as a result of post-marketing reports of several asthma deaths associated with the use of SEREVENT® inhalation aerosol received by the US FDA, as well as the results of the SEREVENT® nationwide surveillance study[2].

[1] SEREVENT® (salmeterol xinafoate) Official Canadian Product Monograph. GlaxoSmithKline Inc., 7333 Mississauga Road North, Mississauga, Ontario L5N 6L4. Date of Revision: November 21, 2001

[2] Castle W et. al., Serevent nationwide surveillance study: comparison of salmeterol with salbutamol in asthmatic patients who require regular bronchodilator treatment. BMJ 1993; 306:1034-7.

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 a metered-dose inhaler (MDI), and patients in the other arm received placebo (N=13,179). In contrast to the situation in Canada, in the United States, SEREVENT® is approved as an asthma monotherapy. Therefore, not all patients enrolled in the SEREVENT® treatment arm of the SMART were taking optimal doses of corticosteroids at study entry.

The primary endpoint of SMART was the combined number of respiratory related deaths or respiratory related life-threatening experiences (intubations and mechanical ventilation). Secondary endpoints analyzed specific subsets of the primary endpoint, the combined number of asthma-related events (asthma-related intubations and asthma-related deaths) as well as asthma-related deaths alone. A planned interim analysis was conducted when approximately half of the intended number of patients were enrolled. Although 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 the United States, the prescribing information has been updated to include a boxed warning. In addition, other sections of the US 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 chronic obstructive pulmonary disease 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 inhaled fluticasone propionate, a component of ADVAIR®, 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 established in the Canadian Asthma Consensus Guidelines[3] and 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.

[3] Canadian Asthma Consensus Report, 1999. CMAJ 1999; 161 (11 Suppl).

- 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., salbutamol) 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.

The information on the SMART study will be incorporated into the Canadian Product monograph.

The identification, characterization, and management of drug-related adverse events are dependent on the active participation of health care professionals in adverse drug reaction reporting programs. Health care professionals are asked to report any suspected adverse reactions in patients receiving SEREVENT® (salmeterol xinafoate) or ADVAIR® (salmeterol xinafoate / fluticasone propionate) directly to GlaxoSmithKline or to the Marketed Health Products Directorate:

GlaxoSmithKline Inc.
7333 Mississauga Road N
Mississauga, Ontario
L5N 6L4
Tel: 1-800-387-7374

Canadian Adverse Reaction Monitoring Program (CADRMP)
Marketed Health Products Directorate
HEALTH CANADA
Address Locator: 0201C2
Ottawa, Ontario K1A 1B9
Tel: (613) 957-0337 or Fax: (613) 957-0335
cadrmp@hc-sc.gc.ca

The ADR Reporting Form can be found in *The Canadian Compendium of Pharmaceutical and Specialties*, or on the TPD website, along with the ADR Guidelines at:

http://www.hc-sc.gc.ca/dhp-mps/alt_formats/hpfb-dgpsa/pdf/medeff/ar-ei_form-eng.pdf
http://www.hc-sc.gc.ca/dhp-mps/medeff/report-declaration/index-eng.php

Your professional commitment in this regard has an important role in protecting the well-being of your patients by contributing to early signal detection and informed drug use.

Any questions from health care professionals may be directed to our Medical Information department via GlaxoSmithKline Customer Service at 1-800-387-7374.

Sincerely,

Anne Phillips, M.D., FRCPC
Vice President, Research & Development and Chief Medical Officer
GlaxoSmithKline Inc.

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