CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: 20-692 S001/002

PHARMACOLOGY REVIEW(S)

DIVISION OF PULMONARY DRUG PRODUCTS
REVIEW AND EVALUATION OF PHARMACOLOGY AND TOXICOLOGY
Amendment to Label Review

NDA 20-692/S002

Reviewer: Lawrence F. Sancilio, Ph.D.

Date of Submission: 9/24/97

Date Completed: 9/24/98

Sponsor: Glaxo Inc.
5 Moore Drive
Research Triangle Park, NC 27709

Drug Name: Salmeterol xinafoate (Serevent Diskus Inhaler)

Chemical Name: 4-Hydroxy-α^1-[[[6-(4-phenylbutoxy)hexyl) amino]-methyl]-1,3-benzenedimethanol, 1-hydroxy-2-naphthalenecarboxylate

Class: B_2 Adrenoceptor Agonist

Indication: Treatment of exercise-induced bronchospasm in patients >4 years old.

Formulation: Salmeterol xinafoate powder with lactose. Each blister strip contains 50 mcg of salmeterol base as the xinafoate salt in 12.5 mg of lactose. The actual amount of salmeterol delivered was 47 mcg.

Route of administration: Inhalation.

Maximum Daily Inhalation Dose: The maximum daily dose of the salmeterol xinafoate was 94 mcg of salmeterol base to adults and children ≥ 4 years old.

This amendment was made since the daily dose was actually 94 mcg instead of the [redacted] mcg reported in the 9/24/98-label review. This was primarily due to the manner the dose was described in the submitted label; it was interpreted to be 50 mcg of the salmeterol salt and not 50 mcg of the salmeterol base.

The changes made in the 9/24/98 review are in **bold** and the deletions are ~~strikeout.~~

Carcinogenesis, Mutagenesis, Impairment of Fertility: In an 18-month carcinogenicity study in CD-mice, salmeterol at oral doses of 1.4 mg/kg and above (approximately 20 times the maximum recommended daily inhalation dose in adults and children based on comparison of the area-under-the plasma concentration versus time curves [AUCs]) caused a dose-related increase in the incidence of smooth muscle hyperplasia, cystic glandular hyperplasia and leiomyomas of the uterus and cysts in the ovaries. The incidence of leiomyosarcomas was not statistically significant. No tumors were seen at 0.2 mg/kg approximately 3 times the maximum recommended daily inhalation doses in adults and children based on comparison of the AUCs).

In a 24-month oral and inhalation carcinogenicity study in Sprague-Dawley rats, salmeterol caused a dose related increase in the incidence of mesovarian leiomyomas and ovarian cysts at doses of 0.68 mg/kg and above (approximately **60** times the maximum recommended daily inhalation dose in adults and approximately **30** times the maximum recommended daily inhalation dose in children on a mg/m^2 basis). No tumors were seen at 0.21 mg/kg (approximately **20** times the maximum recommended daily inhalation dose in adults and approximately **9** times the maximum recommended daily inhalation dose in children on a mg/m^2 basis). These findings in rodents are similar to those reported previously for other beta-adrenergic agonist drugs. The relevance to these findings to human use is unknown.

Salmeterol produced no detectable or reproducible increases in microbial and mammalian gene mutation in vitro. No clastogenic activity occurred in vitro in human lymphocytes or in vivo in a rat micronucleus test.

No effects on fertility were identified in male and female rats treated with salmeterol at oral doses up to 2 mg/kg (approximately **170** times the maximum recommended daily inhalation dose in adults on a mg/m^2 basis).

Pregnancy: Teratogenic Effects: Category C: No teratogenic effects occurred in the rat at oral doses up to 2 mg/kg (approximately **170** times to the maximum recommended daily inhalation dose in adults on a mg/m^2 basis). In Dutch rabbits administered oral doses of 1 mg/kg and above (approximately 50 times the maximum recommended daily inhalation dose in adults based on comparison of the AUCs), salmeterol exhibited fetal toxic effects characteristically resulting from beta-adrenoceptor stimulation. These included precocious eyelid openings, cleft palate, sternebral fusion, limb and paw flexures and delayed ossification of the frontal cranial bones. No significant effects occurred at an oral dose of 0.6 mg/kg (approximately 20 times the maximum recommended daily inhalation dose in adults based on comparison of the AUCs).

New Zealand white rabbits were less sensitive since only delayed ossification of the frontal bones was seen at an oral dose of 10 mg/kg (approximately **1700** times the maximum recommended daily inhalation dose in adults on a mg/m^2 basis). Extensive use of other beta-agonists has provided no evidence that these class effects in animals are relevant to their use in humans. There are no adequate and well-controlled studies with

SEREVENT DISKUS in pregnant women. SEREVENT DISKUS should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Nursing Mothers: Plasma levels of salmeterol after inhaled therapeutic doses are very low. In rats, salmeterol xinafoate is excreted in the milk. However, since there is no experience with the use of SEREVENT by nursing mothers, a decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother. Caution should be exercised when salmeterol xinafoate is administered to a nursing woman.

Overdosage: No deaths were seen in rats at an inhalation dose of 2.9 mg/kg (approximately 250 times the maximum recommended daily inhalation dose in adults and approximately **120** times the maximum recommended daily inhalation dose in children on a mg/m^2 basis) and in dogs at an inhalation dose of 0.7 mg/kg (approximately **200** times the maximum recommended daily inhalation dose in adults and approximately **95** times the maximum recommended daily inhalation dose in children on a mg/m^2 basis). By the oral route, no deaths occurred in mice at 150 mg/kg (approximately **6,500** times the maximum recommended daily inhalation dose in adults and approximately **3,100** times the maximum recommended daily inhalation dose in children on a mg/m^2 basis) and in rats at 1000 mg/kg (approximately **86,000** times the maximum recommended daily inhalation dose in adults **and** approximately **41,000** times the maximum recommended daily inhalation dose in children on a mg/m^2 basis).

APPEARS THIS WAY
ON ORIGINAL

/S/ 9/24/98
Lawrence F. Sancilio, Ph.D.
Pharmacologist/Toxicologist

/S/ Sept. 24, 1998

cc: NDA 20-692
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Approved by J. Sun

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