CLINICAL REVIEW

Application Type	NDA
Submission Number	20-236, S035
Submission Code	SE8
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Reviewer Name	Sally Seymour, M.D.
Review Completion Date	May 30, 2006
Established Name	Salmeterol Xinafoate
(Proposed) Trade Name	Serevent Inhalation Aerosol
Therapeutic Class	Long acting $beta_2$-adrenergic agonist
Applicant	GlaxoSmithKline
Priority Designation	S
Formulation	Inhalation Aerosol
Dosing Regimen	None proposed
Indication	Asthma, reactive airways disease
Intended Population	Children 6 months to < 4 years

1 EXECUTIVE SUMMARY

1.1 Recommendation on Regulatory Action

In this efficacy supplement for salmeterol xinafoate inhalation aerosol, the Applicant submitted a complete response to Amended Written Request (WR) #5 issued by the Agency on November 18, 2004. The Applicant conducted four clinical studies in children < 4 years of age using valved holding chambers. The Applicant did not request an indication for salmeterol xinafoate inhalation aerosol in children < 4 years of age. However, the Applicant submitted revised labeling, which describes the safety results from the pediatric clinical studies.

In order to interpret the safety and efficacy data from the clinical studies, it is important to understand how the delivery of salmeterol xinafoate inhalation aerosol is affected by the use of a valved holding chamber. The Applicant provided some in vitro data; however, the data is not adequate to characterize the use of salmeterol xinafoate inhalation aerosol with valved holding chambers in children < 4 years of age. It is unclear whether the children in the studies received study medication, which limits interpretation of the results of the clinical studies.

To determine whether the clinical data can provide evidence that the children in the studies received study medication, the efficacy and pharmacokinetic data are important. In terms of efficacy, the clinical studies failed to demonstrate the efficacy of salmeterol over placebo. In fact, the efficacy data did not even show a trend towards efficacy in the salmeterol groups and the secondary endpoints did not support the efficacy of salmeterol. In addition, pharmacokinetic data were not obtained in any of the clinical studies.

Based upon the inadequate in vitro characterization, interpretation of the clinical studies is limited. In addition, the lack of evidence of efficacy with salmeterol and lack of PK data cannot assure drug delivery. Therefore, the proposed labeling with description of the study results is not acceptable. Thus, the recommended regulatory action for this efficacy supplement is approvable.

The Applicant will need to provide adequate in vitro characterization data for salmeterol xinafoate inhalation aerosol with valved holding chambers in order to consider labeling regarding the use of salmeterol xinafoate inhalation aerosol with a valved holding chamber.

1.2 Recommendation on Postmarketing Actions

There are no recommendations for postmarketing actions.

1.2.1 Risk Management Activity

There are no postmarketing risk management activities recommended.

1.2.2 Required Phase 4 Commitments

There are no recommendations for required phase 4 commitments.

1.2.3 Other Phase 4 Requests

There are no recommendations for additional phase 4 requests.

1.3 Summary of Clinical Findings

Before addressing the results of the clinical studies, it is important to note that the inadequate in vitro characterization of salmeterol xinafoate inhalation aerosol with valved holding chambers limits interpretation of the safety and efficacy data from the clinical studies. That being said, the safety and efficacy data from the clinical studies were reviewed in detail and are discussed in this review. However, no conclusions can be drawn regarding the safety and efficacy of salmeterol xinafoate with valved holding chambers in children < 4 years of age.

In this efficacy supplement, the Applicant submitted data from four clinical studies with salmeterol xinafoate inhalation aerosol with valved holding chambers in children < 4 years of age. The efficacy data do not establish the superiority of salmeterol xinafoate inhalation aerosol over placebo in children ≤ 4 years of age. In general, the safety data shows that adverse events (AEs) were more common in children 6 to 23 months of age than in children 24 months to < 4 years of age. Many of the AEs reported were consistent with AEs reported in clinical studies with salmeterol inhalation aerosol in adults and adolescents > 12 years of age. In general, there were no clinically significant differences between treatment groups in terms of vital signs, ECGs, and laboratories.

1.3.1 Brief Overview of Clinical Program

The clinical program included four clinical studies in children < 4 years of age: two dose ranging studies and two 4-week safety and efficacy studies. Each of the studies is briefly described below.

- **Study SMS20010** was a randomized, double-blind, double-dummy, placebo-controlled, two-period, crossover, study of 3 doses of salmeterol xinafoate inhalation aerosol and placebo administered via a holding chamber with facemask in 21 children with asthma aged 24 to 47 months.
- **Study SMS20011** was a randomized, double-blind, double-dummy, placebo-controlled, two-period, crossover, study of 3 doses of salmeterol xinafoate inhalation aerosol and placebo administered via a holding chamber with facemask in 21 children with asthma aged 6 to 23 months.
- **Study SMS30076** was a 4-week, randomized, double-blind, double-dummy, placebo-controlled, parallel group safety and efficacy clinical study of salmeterol xinafoate inhalation aerosol and placebo administered via a holding chamber with facemask in 338 children with asthma aged 24 to 47 months.

- **Study SMS30077** was a 4-week, randomized, double-blind, double-dummy, placebo-controlled, parallel group safety and efficacy clinical study of salmeterol xinafoate inhalation aerosol and placebo administered via a holding chamber with facemask in 167 children with asthma aged 6 to 23 months.

1.3.2 Efficacy

The efficacy data in this supplement do not establish the efficacy superiority of salmeterol xinafoate inhalation aerosol over placebo in children ≤ 4 years of age. The primary source of the efficacy data were the two 4-week clinical studies, Studies SMS30076 and SMS30077, and the primary efficacy endpoint was the change from baseline in daytime asthma symptom scores and nighttime asthma symptom scores during the treatment period. There was no significant difference between the salmeterol treatment groups and placebo with respect to the change from baseline in asthma symptom scores. In addition, the secondary endpoints (peak expiratory flow, asthma symptom-free days, rescue medication use, treatment failures, and subject discontinuations) do not support the efficacy superiority of salmeterol xinafoate inhalation aerosol over placebo.

1.3.3 Safety

The safety data in this supplement show that adverse events (AEs) were more common in children 6 to 23 months of age than in children 24 months to < 4 years of age. Many of the AEs reported were consistent with AEs reported in clinical studies with salmeterol inhalation aerosol in adults and adolescents > 12 years of age. Fever was the most common AE in all treatment groups. AEs reported more frequently in one of the salmeterol treatment groups than in the placebo group included the following: rhinorrhea, rhinitis, irritability, ENT infection, viral URTI, bronchitis, keratitis/conjunctivitis, psychomotor disorders, and pharyngotonsillitis/upper respiratory inflammation/throat irritation.

In general, there were no clinically significant differences between treatment groups in terms of vital signs, ECGs, and laboratories. In the dose ranging studies, Holter monitors were performed at baseline and the end of each treatment period. There was no clinically significant change from baseline in 24 hour heart rates, supraventricular ectopic (SVE) or single ventricular ectopic events between treatment groups. In Study SMS20011, one subject in the salmeterol 25mcg TID treatment group was withdrawn due to abnormal Holter findings (increase from 1 SVE at baseline to 24 SVEs in 23 hours).

Two specific safety assessments are worth noting. Investigators specifically assessed for tremors in all four clinical studies. No tremor was noted in the majority of subjects. In subjects in which tremor was noted, the tremor was generally mild in severity. In one study, tremor was noted more frequently in the salmeterol treatment groups than in the placebo group at Week 4. Dedicated nasopharyngeal examinations were performed in Study SMS30077 at each clinic visit. Overall, there were more subjects in the salmeterol 25mcg treatment group (29%) with a shift from normal to abnormal nasal findings compared to the other groups (16-17%). The majority of changes were related to nasal secretions – quantity, consistency, and color.

1.3.4 Dosing Regimen and Administration

The Applicant does not seek an indication in children < 4 years of age.

1.3.5 Drug-Drug Interactions

There were no important drug-drug interactions noted in the clinical studies in this supplement.

1.3.6 Special Populations

The clinical studies in this submission were performed in children < 4 years of age. There were no additional special population considerations.

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