BPCA CLINICAL SUMMARY

APPLICATION:	NDA 20-625 SE8-012 11/18/02 NDA 20-786 SE8-014 11/18/02 NDA 20-872 SE8-011 11/18/02	**TRADE NAME:**	Allegra® Capsules Allegra-D ® Tablets Allegra® Tablets
APPLICANT:	Aventis Pharmaceuticals, Inc. Bridgewater, New Jersey 08807-0890	**GENERIC NAME:**	Fexofenadine hydrochloride
MEDICAL OFFICER:	Charles E. Lee, M.D.		
SECONDARY REVIEWER:	Badrul A. Chowdhury, M.D., Ph.D.	**CATEGORY:**	Antihistamine
DUE DATE:	14 May 2003	**ROUTE:**	Oral
REVIEW DATE:	7 May 2003	**FORMULATION:**	(b)(4)------- powder

1. RECOMMENDATIONS

1.1. Recommendations on approvability

From a clinical perspective, this reviewer recommends an approval action. The sponsor has submitted information that supports the addition of new safety data to labeling for Allegra® Capsules and Allegra® Tablets. Language describing PK data and dose in children <6 years of age should not be added to the label until the sponsor has a marketable formulation for this population.

1.2. Recommendations on Phase 4 studies and risk management steps

No Phase 4 studies or risk management steps are recommended.

2. SUMMARY OF CLINICAL FINDINGS

2.1. Brief overview of clinical program

This application is a pediatric labeling supplement submitted to NDAs for Allegra® Tablets (fexofenadine HCl, NDA 20-625), Allegra® Capsules (fexofenadine HCl, NDA 20-872), and Allegra® D Tablets (fexofenadine HCl/pseudoephedrine HCl, NDA 20-786).

The pivotal studies in the application were performed in response to a Written Request for pediatric studies, dated April 23, 2001, and amended on November 6, 2001. The sponsor met all specifications of this Written Request, and was granted pediatric exclusivity on January 27, 2003. There were three pivotal studies in this application, Studies M106455T/1123, M106455T/3001 and M106455T/3002. Study M106455T/1123 was a Phase 1 study to characterize the pharmacokinetics of fexofenadine HCl in children ≥6 months to <2 years of age after a single oral dose of 15-mg and 30-mg. The sponsor

found it necessary to perform two safety and tolerability studies in children ≥6 months to <2 years of age to meet the specifications of the Written Request. Two studies were necessary because pharmacokinetic data indicated a smaller dose of fexofenadine was appropriate for children ≤ 10.5 kg in weight. These two safety and tolerability studies were Study M106455T/3001 and M106455T/3002. Study M106455T/3001 was a Phase 3 multicenter study designed to compare the safety and tolerability of fexofenadine HCl 15 mg BID to placebo in children with allergic rhinitis ≥6 months to <2 years of age and ≤10.5 kg in weight. Study M106455T/3002 was a Phase 3 multicenter study designed to compare the safety and tolerability of fexofenadine HCl 30 mg BID to placebo in children with allergic rhinitis ≥6 months to <2 years of age and >10.5 kg in weight. The sponsor also included information in their safety analysis from the previously reviewed safety and tolerability study M106455I/3112. This study evaluated the safety and tolerability of fexofenadine HCl in children ≥2 to <6 years of age.

There were two supportive clinical pharmacology studies in this application, Study PJPR0076, and Study M016455T/1001. PK data from these studies were used to determine an acceptable vehicle for fexofenadine (b)(4)------ powder in the pivotal studies.

2.2. Efficacy

The sponsor's clinical studies did not focus on the assessment of efficacy. The disease course and pathophysiology of allergic rhinitis and chronic idiopathic urticaria and the drug's effect are substantially similar in children and in adult patients. The sponsor's pharmacokinetic studies provide for an appropriate dose of fexofenadine for children from ≥6 months to <6 years of age. Extrapolation of efficacy could be considered if the sponsor had a marketable pediatric formulation. The sponsor has not developed a marketable pediatric formulation, however. The studies in this application were performed using 15 mg and 30 mg of fexofenadine(b)(4)------- powder administered in applesauce or rice cereal, and the sponsor has not s----------emistry, manufacturing, and controls data to support the 15-mg and 30-mg doses. Until such time as a marketable pediatric formulation has been developed, an allergic rhinitis or chronic idiopathic urticaria indication for fexofenadine in children ≥6 months to <6 years of age cannot be supported.

2.3. Safety

The sponsor supported the safety of the drug in children of this age group with integrated safety data from pediatric safety studies, an evaluation of worldwide spontaneous adverse event reports in children <12 years of age, and a review of published literature related to safety in the pediatric age group.

A total of 415 children with allergic rhinitis ≥6 months to <6 years of age were exposed to fexofenadine in pediatric studies M106455T/3001, M106455T/3002, and M106455I/3112. Adverse events were fairly common and occurred at similar frequencies for placebo (49.3%, 212/430), fexofenadine 15 mg (40.0%, 34/85), and fexofenadine 30 mg (45.2%, 149/330). Adverse events occurring at a rate of ≥3.0% in any group and more

commonly in fexofenadine than placebo included vomiting, otitis media, increased cough, rhinitis, sore throat/pharyngitis, accidental injury, diarrhea, rash, and gastroenteritis. The differences between fexofenadine and placebo in frequencies of these adverse events are likely to be due to chance. There were no meaningful differences between treatment groups in adverse events leading to withdrawal from the studies. Vital signs, physical examinations, laboratory studies, and ECGs revealed no safety signal. The sponsor's search of the their global pharmacovigilance database and their review of the medical literature provided no evidence of a new safety signal. In summary, there is no evidence of a safety signal in this application. The sponsor's clinical safety data supports the use of their product in children ≥6 months to <6 years of age.

2.4. Dosing and administration

The pivotal studies in this application in children ≥6 months to <2 years in age and those previously performed in children (2 years to <6 years of age used fexofenadine (b)(4)------ powder. The b)(4)---------powder is identical to the contents of the approved and marketed 60-mg fexo----------psules. The (b)(4)--------powder was administered in either (b)(4)----------applesauce or in (b)(4)----r----------ixed with either (b)(4)---- or ----------as. The sponsor does not have a marketable formulation for children from ≥6 months of age to <6 years of age.

2.5. Special populations

This application is a pediatric labeling supplement with clinical data. Use in the elderly was not addressed and is not relevant to this application. The percentages of male and female patients who experienced adverse events in pediatric safety studies M106455T/3001, M106455T/3002, and M106455I/3112 were comparable between treatment groups. No particular adverse event was identified that occurred more frequently in female or male patients. The majority of patients in pediatric safety studies M106455T/3001, M106455T/3002, and M106455I/3112 were of Caucasian race. No particular adverse event was noted that appeared to be more frequent in patients of a particular race.

Reviewed by:

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