CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS SUMMARY

NDA	20-625 SE8-012 – Allegra® Capsules, Labeling supplement 20-872 SE8-011 – Allegra® Tablets, Labeling supplement 20-786 SE8-014 – Allegra-D® Tablets, Labeling supplement
Drug Substance	Fexofenadine HCl
Drug Product	Allegra®
Strengths	60 mg Capsule; 30, 60 and 180 mg Tablets
Route of Administration	Oral Capsules/Tablets
Sponsor	Aventis Pharmaceuticals
Type of submission	Pediatric exclusivity/Labeling Supplement with clinical Data
Date of submission	11/18/02
OCPB Division	DPE-II
Clinical Division	Pulmonary and Allergy Drug Products (HFD-570)
Reviewer	Shinja R. Kim, Ph.D.
Team Leader	Emmanuel Fadiran, Ph.D.

1. EXECUTIVE SUMMARY

Fexofenadine HCl, the active ingredient of Allegra®, is a selective peripheral histamine H_1-receptor antagonist approved for the treatment of symptoms of seasonal allergic rhinitis (SAR) (60 mg BID or 180 mg QD) and chronic idiopathic urticaria (CIU) (60 mg BID) in patients 12 years and older. Allegra® is also marketed in the United States for the treatment of symptoms of SAR and CIU (30 mg BID) for children 6 to 11 years.

The current application was submitted as labeling supplement and Pediatric Exclusivity Determination request by including the following studies: one Phase I (M016455T/1123), two Phase III (M016455T/3001; M016455T/3002), and two bioavailability studies (PJPROO76; M016455T/1001).

Study T/1123 was a dose- ranging pharmacokinetic study in children from 6 months to <2 years of age using 15 and 30-mg doses of fexofenadine HCl (experimental formulations of fexofenadine). The mean C_{max}, T_{max}, AUC_{0-z}, $AUC_{0-\infty}$ and $t_{1/2}$ following 15 mg were 169 ng/mL, 1.1 hr, 767 ng•h/mL, 804 ng•h/mL, 6.2 hr, respectively. The mean C_{max}, T_{max}, AUC_{0-z}, $AUC_{0-\infty}$ and $t_{1/2}$ following 30 mg dose were 329 ng/mL, 1.1 hr, 1580 ng•h/mL, 1660 ng•h/mL, 7.4 hr, respectively. The mean C_{max}, AUC_{0-z}, and $AUC_{0-\infty}$ values observed in the 30-mg dose group were approximately twice of those in the 15-mg dose group with an average oral clearance (CLpo) of 22 L/h in both dose groups.

In order to determine optimal dose for children 6 months to 2 years of age, a Population PK analysis was performed using the data from pharmacokinetic samples drawn in Study T/1123 combined with data from previous studies in children and adults. The following conclusions were reached from this analysis: (i) administration of 15 mg fexofenadine to children 6 months and older and weighing ≤10.5 kg and administration of 30 mg dose to children 7 to 12 years of age produced exposures (predicted C_{max} and $AUC_{0-\infty}$) comparable to those seen with a dose of 60 mg administered to adults, (ii) administration of 30 mg dose administered to children 2 to 5 years of age produced exposures lower than those seen with a dose of 60 mg administered to adults, (iii) in children 6 months to <2 years of age with body weight >10.5 kg, administration of 15 mg

produced lower exposures, while 30 mg produced higher estimates of exposures in comparison to 60 mg dose in adults.

In addition, two PK studies were conducted to evaluate relative bioavailability of fexofenadine in food vehicles: Study PJPR0076 examined the bioavailability of the content of the fexofenadine marketed immediate-release capsule when co-administered with applesauce, and Study M016455T/1001 examined the bioavailability of fexofenadine when co-administered with other dosing vehicles including Gerber® rice cereal mixed with Similac® infant formula (GS formula). The co-administration of the 60 mg fexofenadine capsule formulation contents mixed with applesauce and GS formula did not affect the AUC but resulted 11.4 and 9.4% increase of C_{max} fexofendaine, respectively.

No labeling changes for pediatric indication or dosing for children less than 6 years old will be made at this time because there are no age appropriate formulations of fexofenadine for these children.

Based on the submitted information, the Office of Clinical Pharmacology and Biopharmaceutics (OCPB) finds this submission acceptable.

1.1 Recommendation

The Office of Clinical Pharmacology and Biopharmaceutics has reviewed the Human Pharmacokinetics and Bioavailability section of the NDA and found that this submission is acceptable. Labeling recommendations should not be sent to the sponsor until age appropriate formulations are available for children less than 6 years of age.

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Shinja R. Kim, Ph.D., DPE II

_____ Emmanuel Fadiran, Ph.D., Team Leader

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/s/

Shinja Kim

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