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Proprietary Drug Name: ALLEGRA®	**INN:** fexofenadine HCl capsules and tablets	**Therapeutic area and FDA approved indications:** for the relief of symptoms associated with seasonal allergic rhinitis in adults and children 6 years of age and older. Symptoms treated effectively were sneezing, rhinorrhea, itchy nose/palate/throat, itchy/watery red eyes. ALLEGRA is also indicated for treatment of uncomplicated skin manifestations of chronic idiopathic urticaria in adults and children 6 years of age and older. It significantly reduces pruritus and the number of wheals.
Name of Sponsor/Company:	Aventis Pharmaceuticals, Inc.. Member of the sanofi-aventis group.	

Title of Study: (M016455A/4121) A phase IIIa, multicenter, randomized, double-blind, parallel-group, placebo-controlled study on the efficacy and safety of fexofenadine HCl 180 mg once daily in chronic idiopathic urticaria.

Principal Study Investigators: Allen P. Kaplan, MD and Sheldon L. Spector, MD.

Study centre(s): 40 US centers

Publication: Kaplan AP, Spector SL, Meeves S, Liao Y, Varghese ST, Georges G. Once-daily fexofenadine treatment for chronic idiopathic urticaria: a multicenter, randomized, double-blind, placebo-controlled study. *Ann Allergy Asthma Immunol.* 2005 Jun;94(6):662-9.

Studied period (years): 29 July 2002 to 24 November 2003	**Phase of development:** Phase IIIa
Objectives: The primary objective of this study was to determine the efficacy and safety of fexofenadine HCl 180 mg once daily (QD) compared to placebo in the treatment of chronic idiopathic urticaria (CIU). Secondary objectives included the examination of health-related quality of life and pharmacokinetic variables (results to be reported elsewhere).	
Methodology: This multicenter, randomized, double-blind, parallel group, placebo-controlled study consisted of 6 or 7 visits. It included a single-blind placebo run-in period of 2-5 days beginning at visit 1 or visit 1A (if a 2nd opportunity to qualify was required), followed by a 28±4 day double-blind treatment period (visits 2 through 6).	
Number of patients (planned and analyzed): A total of 240 subjects were to be enrolled in a 2:1 ratio of fexofenadine to placebo. 483 patients were screened, 358 were enrolled into the single-blind placebo-run-in phase. Of these, 259 were randomized to receive either placebo (n=92) or fexofenadine HCl 180 mg tablet (n=167). The intention-to-treat (ITT) population was composed of 255 patients (92 in the placebo group and 163 in the fexofenadine group). The safety-evaluable population consisted of 259 patients (92 in placebo group, and 167 in fexofenadine group).	
Diagnosis and main criteria for inclusion: Male or female subjects 12 years of age or older with a diagnosis of CIU, a history of urticarial wheals for at least 3 days per week for the 6 consecutive weeks prior to visit 1 or 1A, and an assessment of urticaria reflective over the previous 12 hours. In addition, an assessment of the subject's urticaria was to be completed by the investigator or study staff.	

Test product, dose and mode of administration, batch number:

one fexofenadine HCl 180 mg oral tablet once daily (QD). Batch # L0001254

Duration of treatment: single-blind placebo run-in period of 2-5 days, followed by a 28±4 day double-blind treatment period.

Reference therapy, dose and mode of administration, batch number:

One placebo oral tablet once daily (QD). Batch # KH2001044

Criteria for evaluation:

Efficacy: The primary efficacy assessments were the change from baseline in patients' mean daily number of wheals (MNW score) and mean daily severity of pruritus (itching) score during the 28-day double blind treatment period. MNW score was rated on a scale of 0 to 4 in which 0 = zero wheals; 1 = 1-10 wheals; 2 = 11-20 wheals; and 3 indicated > 20 wheals. Pruritus severity was rated on a scale from 0 to 4 in which 0 indicates none; 1 = mild, not annoying or troublesome; 2 = moderate, annoying and troublesome, may interfere with normal daily activity and sleep; 3 = severe, very annoying and troublesome, substantially interfering with sleep and daily activities; 4 = very severe, warrants a visit to the physician. These variables were recorded in the patients' daily diaries the morning before dosing and 12 hours later as reflective evaluations of symptom severity during the previous 12 hours.

Safety: Safety was evaluated by adverse event reporting throughout the study; 12-lead electrocardiography, clinical laboratory tests, including hematologic analysis, urine analysis, and clinical chemistry measurements; and physical examinations. All of these assessments were performed at visit 1 or 1A and at the final visit (visit 6).

Statistical methods: The study was powered to test 2 end points:

1. The difference in change from baseline in the number of wheals between the fexofenadine and placebo groups
2. The difference in change from baseline in pruritus severity scores between groups.

We required 128 and 64 patients to be randomized to receive fexofenadine and placebo respectively (2:1 randomization). This sample size was calculated to provide at least 90% power to detect differences in both end points at 0.05 significance level, assuming an underlying difference of 0.56U and a common SD of 1.03U. The efficacy study population evaluated was the intention-to-treat (ITT) population, defined as patients who took the study medication and had baseline and at least 1 post-baseline measure. The safety analysis was performed on all randomized patients who received at least 1 dose of study medication. The primary efficacy variables were analyzed using an analysis of covariance model.

SUMMARY – CONCLUSIONS

EFFICACY RESULTS:

1. **Wheal score (MNW score):** Baseline MNW score was 1.9 (0.67) for the placebo group, and 1.9 (0.74) for the fexofenadine group. During the 28-day treatment period, patients treated with fexofenadine experienced a significant decrease in the mean daily number of wheals (MNW score) compared with patients who received placebo (- 0.78 vs - 0.40; $P < 0.001$)
2. **Pruritus score:** Baseline mean pruritus score was 2.2 (0.55) for the placebo group and 2.3 (0.58) for the fexofenadine group. During the 28-day treatment period, patients treated with fexofenadine experienced a significant decrease in the pruitus severity score compared with patients who received placebo (- 1.04 vs - 0.57; $P < 0.001$)

SAFETY RESULTS:

There were no significant differences in the frequency of treatment-emergent adverse events (TEAEs) reported between placebo (37%) and fexofenadine (31%) groups. The most commonly reported TEAE was headache: 3% in the placebo group and 5% in the fexofenadine group. Headache was the most common event considered to be possibly related to study medication (0% and 2% in the placebo and fexofenadine groups respectively). All TEAEs that were evaluated as possibly related to study medication were rated as mild to moderate in intensity. One serious TEAE was reported in the fexofenadine group. In this case, the patient experienced asthma that required hospitalization; however, the asthma was not considered related to the study drug. No clinically relevant changes from baseline to the end of treatment were observed in either group with respect to clinical laboratory data, vital signs, or electrocardiograms.

Date of the report: April 7, 2004.