SYNOPSIS

INN : FEXOFENADINE

Study number : PJPR0056

Study title : Comparison of Fexofenadine (60 mg BID) versus Loratadine (10 mg QD) in Seasonal Allergic Rhinitis

CSR date : 15 December 2003

The study results and synopsis are supplied for informational purposes only.

Not all of the study results have necessarily been reviewed by the Regulatory Authorities.

The decision to prescribe and take a product should always be made on the basis of the most recent version of the product information and product package insert in the country of prescription.
STUDY SYNOPSIS

Study number 016455PR0056 (PJPR0056)

Title
Comparison of fexofenadine (60 mg BID) versus loratadine (10 mg QD) in seasonal allergic rhinitis

Investigator(s), study site(s)
See Appendix C of original Clinical Study Report L-97-003-C.

Study duration and dates
The first subject was enrolled on 22 April 1996 and the last subject completed the study on 13 August 1996.

Objectives
The objectives of this study were to compare the efficacy of fexofenadine 60 mg BID and loratadine 10 mg QD as measured by Total Symptom Score and to compare the safety profiles and health economic profiles of the drugs when used in patients with seasonal allergic rhinitis.

Study design
This was a two-arm, parallel, double-blind, randomized, multicenter study with a seven day placebo Baseline period followed by a two week treatment period. The duration of the study for a given subject was approximately three weeks during which he/she was seen by the investigator on four occasions: two screening/Baseline visits (Weeks 1 and 2), and two treatment visits (Weeks 3 and 4). Subjects first entered into a six to eight day single-blind placebo lead-in period to qualify for the study and establish their Baseline allergy symptoms. Subjects who met study criteria were then randomized to double-blind study medication (fexofenadine HCl 60 mg BID or loratadine 10 mg QD) and treated for two weeks.

Efficacy was determined by Total Symptom Score (TSS) which was the sum of subject reported symptom severity scores for the following items: sneezing; rhinorrhea; itchy nose, palate, or throat; and itchy, watery, and red eyes. TSS was recorded to determine the onset of action of the first dose and at the time of daily peak blood levels for the duration of the study. In addition, trough blood level TSS were recorded daily along with a daily reflective (past 12 hours) measurement.

The primary efficacy parameter was: change from Baseline in average 7 PM Reflective TSS.

The secondary efficacy parameters included the following:
- Onset of action using the instantaneous TSS assessments on Day 1 of Visit 2;
- Median percent reduction in 7 PM (trough) Reflective TSS;
- Change from Baseline in average 7 PM (trough) Instantaneous TSS;
- Change from Baseline in average Bedtime (peak) Instantaneous TSS;
- Change from Baseline in average 7 PM (trough) Reflective Individual Symptom Scores;
- Change from Baseline in average 7 PM (trough) Instantaneous Individual Symptom Scores;
- Change from Baseline in average Bedtime (peak) Instantaneous Individual Symptom Scores;
- Physician's overall assessment of effectiveness;
- Weekly analyses for TSS and Individual Symptom Scores at each time and reference period.

Using subject questionnaires, health economic analyses provided between group comparisons of subject productivity impairment (work, school). Additionally, assessments were made of subject preference for the relief and improvement of specific allergy symptoms and conditions, of the significance each allergy symptom had to subject impairment, and of subjects' usual utilization of allergy medication.

The comparative safety of fexofenadine and loratadine treatment was based on the following parameters: Adverse Events, Vital Signs, 12-lead ECG, Physical Examination, Concomitant Medication.

### Study drug administration

Placebo capsules were administered to each subject every 12 hours during the Baseline period after which subjects were randomized to either fexofenadine or loratadine. Fexofenadine subjects took a 60 mg capsule each morning (7 AM ± 1 hr) and a 60 mg capsule each evening (7 PM ± 1 hr). Loratadine subjects took a placebo capsule each morning (7 AM ± 1 hr) and a 10 mg loratadine capsule each evening (7 PM ± 1 hr).

### Statistical methods

To analyze the primary efficacy variable, an analysis of covariance (ANCOVA) model was used in which the Baseline average TSS was the covariate and investigative site and treatment were included as independent classification variables. Both the site by treatment interaction and the covariate by treatment interaction were separately assessed for inclusion in the model. These interaction terms were considered for inclusion in the final model if significant at an \( \alpha = 0.10 \). If the treatment by Baseline interaction was included in the model, then the treatment comparison was to be assessed at the average Baseline value. If the assumptions underlying these analyses were not satisfied, a rank ANCOVA was to be used (ANCOVA after ranking across the sample for the change from Baseline and the covariate).

Secondary endpoints were analyzed with similar methods.

With the exception of Percent of Work Time Missed and Percent of Classroom Time Missed, the model used to analyze the primary efficacy variable was also used for these variables. Because the Percents of Work Time Missed and Classroom Time Missed did not satisfy the basic statistical assumptions, another approach was taken. A Cochran-Mantel-Haenszel procedure was used to compare the percentage of subjects whose percents deteriorated during the course of the double-blind treatment. Preferences with respect to relief of specific symptoms and importance of fatigue and physical limitations as well as feeling thermometer data were described using summary statistics (e.g. mean, standard deviation, etc.).

Adverse events were coded using the Medical Dictionary for Regulatory Activities (MedDRA) Version 5.1.

### Interim analysis

No interim analysis was performed for this study.
**Results – Study subjects and conduct**

A total of 569 subjects were screened for entry into the study at 19 investigative sites. One hundred and seven (107) subjects were Screening Failures and 462 subjects were randomized to receive either fexofenadine 60 mg BID or loratadine 10 mg QD. Three (3) randomized subjects discontinued the study prior to receiving double-blind medication. The Intent-to-Treat and Safety subject populations consisted of the 459 subjects who were exposed to double-blind medication (fexofenadine 229; loratadine 230). The Protocol Correct subject population consisted of 431 randomized subjects who completed the study without any major protocol violations (fexofenadine 213; loratadine 218).

**Results – Efficacy**

Both study treatments showed similar effects in the reduction of tree/grass seasonal allergy symptoms. The change from Baseline of the Average Daily 7 PM Reflective TSS was similar between treatment groups where the TSS change from Baseline in the fexofenadine was \(-1.83 \pm 0.162\) and \(-1.87 \pm 0.163\) in the loratadine group (p=0.8273). The Protocol Correct analysis fully supported the Intent-to-Treat analysis where treatment groups were similar (p=0.9031). All secondary and supporting analyses confirmed these findings.

**Results – Safety**

Overall frequencies of treatment-emergent adverse events (TEAEs) are summarized below.

<table>
<thead>
<tr>
<th>Type of TEAE</th>
<th>No. (%) of subjects in treatment group</th>
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</thead>
<tbody>
<tr>
<td></td>
<td>Fexofenadine HCl 60 mg BID (N = 229)</td>
</tr>
<tr>
<td>All</td>
<td>52 (22.7)</td>
</tr>
<tr>
<td>Serious</td>
<td>0 (0.0)</td>
</tr>
<tr>
<td>Leading to discontinuation</td>
<td>3 (1.3)</td>
</tr>
</tbody>
</table>

The system organ class with the highest incidence of TEAEs was nervous system disorders system organ class. The most common TEAE was headache, and was reported in 13 (5.7%) fexofenadine HCl subjects and 10 (4.3%) loratadine subjects.

There were no serious TEAEs reported.

TEAEs leading to discontinuation were reported in 3 subjects receiving fexofenadine HCl and no (0.0%) subject receiving loratadine. The frequencies for specific TEAEs leading to discontinuation of study medication were only 1 subject each. No specific TEAE or system organ class could be identified as a major reason for discontinuation.

There were no statistically significant findings for the mean change from Baseline for vital signs (diastolic blood pressure, systolic blood pressure, heart rate) or ECG parameters.
The recoding of adverse events data in MedDRA did not change the safety profile of fexofenadine HCl, and the nature of adverse events reported remain consistent with those reported in the original study report.

**Health economics report**

Results from the Health Economics Study are provided in the original study report.

**Conclusions**

The results of this study demonstrate that twice daily fexofenadine 60 mg BID is a safe, effective and well tolerated medication in the therapy of seasonal allergic rhinitis.

The efficacy and safety profile of fexofenadine 60 mg BID is equivalent to that of loratadine 10 mg QD.

The recoding of adverse event data did not change the safety profile of fexofenadine HCl.