SYNOPSIS

INN: FEXOFENADINE

Study number: PJPR0067

Study title: A multicenter, double-blind, randomized, placebo-controlled, parallel study comparing the efficacy and safety of four dosage strengths of fexofenadine HCl (20, 60, 120, & 240 mg BID) in the treatment of chronic idiopathic urticaria

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

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A multicenter, double-blind, randomized, placebo-controlled, parallel study comparing the
efficacy and safety of four dosage strengths of fexofenadine HCl (20, 60, 120, & 240 mg BID) in
the treatment of chronic idiopathic urticaria

Investigator(s), study site(s)
See Appendix C of original Clinical Study Report K-97-0484-C

Study duration and dates
The first subject was enrolled on 26 November 1996 and the last
subject completed the study on 18 June 1997.

Objectives
The primary objective was to determine the efficacy and safety of fexofenadine HCl at oral doses
of 20 mg BID, 60 mg BID, 120 mg BID, and 240 mg BID compared to placebo in the treatment of
chronic idiopathic urticaria (CIU).
Secondary objectives were to:
• assess the pharmacokinetics of fexofenadine using population analyses
• assess the quality of life and work and classroom productivity in subjects with CIU treated
  with fexofenadine HCl 20 mg BID, 60 mg BID, 120 mg BID, and 240 mg BID as compared to
  placebo.

Study design
This was a multicenter, double-blind, randomized, placebo-controlled, parallel study with a
24-hour single-blind placebo lead-in in subjects with CIU. Approximately 400 subjects 12 to
65 years of age, inclusive, were to be included in the study at a total of 35 investigative sites. The
study consisted of three or four visits. Subjects participated in the study for 4 to 6 weeks.
Subjects took study medication at 7:00 AM (±1 hour) and 7:00 PM (±1 hour) daily. Subjects
assessed their urticaria symptoms reflectively (over the previous 12 hours) and recorded them in a
daily diary prior to each dose of study medication. The following four symptoms were assessed by
the subject:
• number of wheals (hives)
• pruritus
• interference with sleep (AM only)
• interference with activities of daily living (PM only)
Visit 1
At visit 1 subjects were screened for entry into the study. A medical history was obtained. Subjects were required to meet the following criteria:

a. history of CIU (diagnosis made or confirmed by the investigator and documented in the CRF)
b. history of wheals (hives) at least 3 days per week for the 6 consecutive weeks prior to visit 1

Subjects meeting criteria a and b above were instructed to assess their urticaria symptoms by reflecting over the previous 12 hours. These assessments were documented in the CRF. In order to qualify for randomization to double-blind study medication, the subjects' assessments must have reflected:

c. presence of at least one wheal (hive), confirmed by the investigator, with a score of 1 or greater

d. pruritus rated by the subject as moderate or greater (a score of 2 or greater)

Note: The sum of the scores from the subjects' assessments of number of wheals (hives) and severity of pruritus became the total symptom score (TSS), which must have been equal to 3 or greater. The investigator was instructed not to advise subjects of qualifications requirements at any time.

Subjects meeting entrance criteria were qualified for randomization. Subjects were given study medication and instructed to take their first dose of study medication at 7:00 PM (±1 hour) the evening of visit 1, and to continue dosing at 7:00 AM (±1 hour) and 7:00 PM (±1 hour) daily during the 2-week treatment period. Subjects were instructed to document all concomitant medications and any adverse events they experienced during the treatment period. Subjects were asked to complete the quality of life and work and classroom productivity questionnaires after randomization and prior to leaving the office.

Subjects who met all entrance criteria, with the exception of criteria c and/or d listed above, or those who used proscribed medications may have been given another opportunity to qualify for entry into the study by returning for visit 1A for reassessment 24 hours to 14 days after visit 1 (see below).

Visit 1A (Second Opportunity to Qualify)
Subjects underwent physical examination and had medical and medication histories updated. Urine pregnancy tests were required of all females, and blood and urine samples for clinical laboratory and drugs of abuse tests were obtained. Subjects continuing to meet all entrance criteria based on these assessments, and also meeting the additional entrance criteria listed in visit 1 above were randomized, given study medication, and proceeded as indicated in visit 1 above. Subjects not meeting all entrance criteria were dismissed.

Visit 2
At this visit, following 15 (±2) days of treatment, subjects' unit dose cards were collected and compliance was assessed. Daily diaries were collected and reviewed for completeness (adverse events and concomitant medication were recorded on the appropriate pages of the CRF). Investigator assessments of urticarial wheals (hives) were performed. A blood sample was drawn for random measurement of plasma fexofenadine; the time of last dose of study medication and the time of the blood draw were recorded on the CRF. Subjects were issued the unit dose cards.
and daily diaries for the next treatment period. Subjects were asked to complete the quality of life
and work and classroom productivity questionnaires.

**Final Visit (or Early Termination)**

At the final visit (following 30 [±4] days of treatment) or early termination visit, subjects' unit
dose cards were collected and compliance was assessed. Daily diaries were collected and
reviewed for completeness (adverse events and concomitant medications were recorded on the
appropriate pages of the CRF). Subjects underwent a physical examination, including assessment
of their urticarial wheals (hives) by the investigator, and had blood samples drawn for clinical
laboratory tests (including a blood draw for fexofenadine levels). All females were to have a urine
pregnancy test performed. Subjects were asked to complete the quality of life and work and
classroom productivity questionnaires and were dismissed from the study.

Subjects who discontinued the study due to intolerable symptoms were encouraged to return to the
study site for their early termination visit before proscribed medications were taken. Any subjects
contacting the site to discontinue the study due to intolerable symptoms (including those subjects
likely to take proscribed medications prior to the early termination visit) were asked to document
their assessment of symptoms at that time on their diary at the next available entry, either AM or
PM, prior to taking any proscribed medication. If the proscribed medication had already been
taken, the subject was instructed to conduct their symptoms assessments only up to the time that
proscribed medication was taken.

**Study drug administration**

At visits 1 (or 1A) and 2, study medication was supplied in unit dose cards. Unit dose cards (two
cards for each 2-week treatment period) contained medication for a total of 15 days plus
2 additional days (136 tablets) for each treatment period. The first unit dose card (Card 1)
contained single-blind placebo tablets for the first 24 hours (two doses). The remainder of study
medication in this card and the study medication in Cards 2, 3, and 4 consisted of one of the five
double-blind treatments: placebo BID, fexofenadine HCl 20 mg BID, fexofenadine HCl 60 mg
BID, fexofenadine 120 mg BID, and fexofenadine HCl 240 mg BID. Subjects were instructed to
take four tablets at 7:00 AM (±1 hour) and 7:00 PM (±1 hour) daily.

**Statistical methods**

In general, continuous variables are summarized by descriptive statistics (n, mean, standard
deviation, and range); categorical variables are summarized in contingency tables (frequency and
percentage in each category).

All statistical tests were two-sided, and differences resulting in P values less than 0.05 are
considered statistically significant.

The analysis of the primary efficacy parameter used an ANCOVA model, adjusting for baseline,
treatment, and investigative site. All secondary analyses were performed using the model from the
primary analysis.

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 476 subjects were randomized to study medication at 39 investigative sites; of these, 461 were exposed to study medication. Of the 461 subjects exposed to study medication, 455 had at least one postbaseline adverse event assessment, qualifying them as safety evaluable. A total of 439 subjects had both baseline and postbaseline MPS scores and were included in the intent-to-treat population, while 309 subjects were included in the protocol-correct population.

Results – Efficacy

The primary assessment of efficacy was the change from baseline in mean MPS over the 4-week treatment period for the intent-to-treat population. The intent-to-treat population consisted of randomized subjects with both baseline and postbaseline MPS data.

There were statistically significant differences among the five treatment groups with respect to mean change from baseline MPS over the 4-week treatment period (P=0.0001), and the test for dose response (linear trend) was also statistically significant (P=0.0001). All four fexofenadine HCl dose groups were statistically superior to placebo (P=0.0001 for all comparisons). There was a larger reduction from baseline in the 60 mg BID group (-1.07) than the 20 mg BID group (-0.88). However, similar reductions were seen in the 60 mg BID, 120 mg BID, and 240 mg BID groups (-1.07, -1.07, and -1.18 units, respectively).

<table>
<thead>
<tr>
<th></th>
<th>Placebo BID</th>
<th>Fexofenadine HCl BID</th>
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</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>20 mg</td>
<td>60 mg</td>
<td>120 mg</td>
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<tr>
<td>MPS</td>
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<td>90</td>
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<tr>
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<tr>
<td>N</td>
<td>88</td>
<td>91</td>
<td>84</td>
<td>88</td>
</tr>
<tr>
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<tr>
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<tr>
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<td>MTSS</td>
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</table>

* P values, adjusted means (LSMEANS), and adjusted standard errors are from an ANCOVA model with baseline, treatment, and site for the overall changes from baseline.

† P values are from the above ANCOVA and for comparing fexofenadine HCl dose and placebo.
### Results – Safety

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

**Table 2 – Number (%) subjects with TEAEs (safety-evaluable population)**

<table>
<thead>
<tr>
<th>Type of TEAE</th>
<th>Placebo (N = 93)</th>
<th>20 mg (N = 95)</th>
<th>60 mg (N = 89)</th>
<th>120 mg (N = 93)</th>
<th>240 mg (N = 85)</th>
<th>Total (N = 362)</th>
</tr>
</thead>
<tbody>
<tr>
<td>All</td>
<td>61 (65.6)</td>
<td>67 (70.5)</td>
<td>51 (57.3)</td>
<td>60 (64.5)</td>
<td>50 (58.8)</td>
<td>228 (63.0)</td>
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<tr>
<td>Serious</td>
<td>0 (0.0)</td>
<td>0 (0.0)</td>
<td>1 (1.1)</td>
<td>0 (0.0)</td>
<td>0 (0.0)</td>
<td>1 (0.3)</td>
</tr>
<tr>
<td>Leading to discontinuation</td>
<td>5 (5.4)</td>
<td>4 (4.2)</td>
<td>4 (4.5)</td>
<td>3 (3.2)</td>
<td>1 (1.2)</td>
<td>12 (3.3)</td>
</tr>
</tbody>
</table>

The system organ class with the highest incidence of TEAEs was nervous system disorders. The most common TEAE was headache, and was reported in 70 (19.3%) fexofenadine HCl subjects and 17 (18.3%) placebo subjects.

Following the current ICH guidelines for reporting of serious TEAEs, 1 subject in the fexofenadine HCl group had a serious TEAE. This subject was in the fexofenadine HCl 60 mg BID group and was hospitalized for nausea and vomiting secondary to a hiatal hernia.

TEAEs leading to discontinuation were reported in 3.3% (12/362) of subjects receiving fexofenadine HCl and 5.4% (5/93) of subjects receiving placebo. The most common TEAEs leading to discontinuation were headache and nausea, which were each reported in 3 (0.8%) of subjects receiving fexofenadine HCl and 0 (0.0%) subjects receiving placebo. The frequencies for all other specific TEAEs leading to discontinuation of study medication were only 1 or 2 subjects in each treatment group.

Changes in laboratory values and vital signs were similar between the treatment groups, and no pattern indicating a safety concern was observed.

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.

### Conclusions

The results of the analysis of mean pruritus score (MPS) and mean number of wheals (MNW) demonstrated that fexofenadine HCl, administered orally in doses of 20 mg BID, 60 mg BID, 120 mg BID, and 240 mg BID for 4 weeks, was statistically superior to placebo in reducing signs and symptoms of chronic idiopathic urticaria. In addition, there was a statistically significant dose response for the four fexofenadine HCl doses. For both MPS and MNW, the 60 mg dose showed a larger treatment effect than the 20 mg dose and was similar to the 120 mg and 240 mg dose groups.

Fexofenadine HCl was safe and well-tolerated in all 4 doses. The recoding of adverse event data did not change the safety profile of fexofenadine HCl.