SYNOPSIS

INN : FEXOFENADINE

Study number : M016455I/1117

Study title : Pharmacokinetics and Pharmacodynamics of Oral Fexofenadine Hydrochloride Suspension Administered to Children from 6 through 11 Years of Age

CSR date : 12 July 2004

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.

PDF name: Fexofenadine – Study 21

EMA request May 2011 – Publication of result-related information on paediatric studies submitted under Article 45 of Regulation (EC) No 1901/2006 (‘Paediatric Regulation’) August 2011
STUDY SYNOPSIS

M016455I/1117

Title
Pharmacokinetics and Pharmacodynamics of Oral Fexofenadine Hydrochloride Suspension Administered to Children from 6 through 11 Years of Age

Investigator(s), study site(s)
Multicenter, three sites participating in the Pediatric Pharmacology Research Unit Network. Greg Kearns, PharmD, Children’s Mercy Hospital
Henry Milgrom, MD, National Jewish Medical and Research Center
Stacie Jones, MD, Arkansas Children’s Hospital

Phase
I

Indication
Not applicable.

Objectives
The primary objective was to characterize the pharmacokinetics of oral fexofenadine suspension in pediatric subjects with allergic rhinitis 6 through 11 years of age. A secondary objective was to characterize the inhibitory effects of oral fexofenadine suspension on skin wheal and flare induced by histamine in pediatric subjects with allergic rhinitis 6 through 11 years of age.

Design
This study was a multi-center, open-label, single-dose, randomized, two-period incomplete block crossover design in male and female pediatric subjects with allergic rhinitis 6 through 11 years of age.

Population
This study was conducted in male and female pediatric subjects with allergic rhinitis, who were in otherwise good health. Subjects were 6 through 11 years of age and were within or close to the 95th percentile for weight by height.

Treatments
Each subject received two of the five following treatments in a random sequence:
Treatment A: single oral dose of 20 mg fexofenadine HCl suspension
Treatment B: single oral dose of 30 mg fexofenadine HCl suspension
Treatment C: single oral dose of 40 mg fexofenadine HCl suspension
Treatment D: single oral dose of 60 mg fexofenadine HCl suspension
Treatment E: single oral dose of 80 mg fexofenadine HCl suspension
Each dosing was separated by a washout period of at least 7 days (and not greater than 21 days).
Pharmacokinetic data
Serial pharmacokinetic blood samples were collected in all subjects prior to and at 1, 2, 3, 6, 12, 24, 30, and 36 hours post-dose.

Pharmacodynamic data
Inhibition of skin wheal and flare responses induced by percutaneous histamine phosphate injection (1 mg/mL and 5 mg/mL) was measured at pre-dose (2 baseline measurements) and at 1, 2, 3, 6, 12, and 24 hours post-dose.

Safety data
Age-appropriate physical exams, vital signs, 12-lead ECGs, and clinical laboratories were performed at the screening visit and within 3 days following collection of the final pharmacokinetic blood sample. Adverse events were monitored throughout study conduct.

Study duration and dates
The study lasted approximately 10 weeks. The first subject was enrolled into this study on 31 July 2000. The last subject completed the study on 08 October 2000.

Statistical procedures
Fexofenadine plasma concentrations were analyzed using noncompartmental techniques. Pharmacokinetic parameters calculated from the single-dose pharmacokinetic data included time of maximum plasma concentration (t_{max}), maximum plasma concentration (C_{max}), area under the concentration-time curve to infinity \( \text{AUC}(0-\infty) \), and apparent oral clearance (Cl_{po}). Pharmacokinetic parameters and plasma concentrations were summarized descriptively.

Fexofenadine wheal and flare inhibition was analyzed using noncompartmental techniques. Wheal/flare inhibition was calculated as the percentage reduction in wheal/flare area from the baseline wheal/flare area measurement obtained prior to each dose administration. Pharmacodynamic parameters calculated from the single-dose pharmacodynamic data included time to maximum wheal/flare inhibition (t_{emax}), maximum wheal/flare inhibition (E_{max}), average wheal/flare inhibition \([E_{avg}(0-6), E_{avg}(0-12), \text{and } E_{avg}(0-24)]\), and area under the wheal/flare inhibition-time curve \([\text{AUEC}(0-6), \text{AUEC}(0-12), \text{and } \text{AUEC}(0-24)]\). Pharmacodynamic parameters, wheal/flare area and wheal/flare inhibition were summarized descriptively.

The frequency of adverse events was tabulated. Baseline, end-of-study, and change from baseline clinical laboratories, vital signs and 12-lead ECGs were summarized.

Interim analysis
No interim analysis was performed for this study.

Results - Study subjects and conduct
A total of 40 male and female subjects aged 5–11 years inclusive (mean age of 9 years) were enrolled and completed the study. Subjects included children diagnosed with allergic rhinitis or mild asthma or other associated diseases and were either candidates for antihistamine therapy or required antihistamine therapy in the preceding 12 months. Of the 40 subjects who were enrolled in the study, 22 subjects (55%) were taking ongoing medication for allergies and/or asthma. Twenty-two (55%) of the 40 subjects had mild asthma in addition to allergic rhinitis.

There were no major protocol deviations, except for the use of an incorrect strength of histamine phosphate in 4 subjects during one treatment; these data were excluded from the pharmacodynamic analysis. All other protocol deviations were minor and were not expected to impact the pharmacokinetic, pharmacodynamic, or safety outcomes of the study.
Results

Pharmacokinetics

Descriptive statistics for the 5 dose strengths are presented in the summary table below. Due to assay limitations, the terminal phase concentrations for the lowest dose (20 mg) could not be adequately captured. For all other doses, plasma concentrations could be monitored up to 36 hours post-dose in all subjects.

Peak plasma concentrations were observed between 1 and 3 h post administration of the prototype suspension formulation with less than dose-proportional increases in AUC(0-∞) and C_max values. Mean C_max and AUC(0-∞) estimates for the 40, 60 and 80 mg doses were 1.1, 1.2 and 1.5-fold higher, respectively, than those for the 30 mg dose. Mean terminal half-lives of 11.6, 14.5, 12.5 and 10.2 hours were derived for the 30, 40, 60 and 80 mg doses, respectively, with no evidence of dose dependency.

Summary of fexofenadine pharmacokinetic parameters by treatment

<table>
<thead>
<tr>
<th>Dose</th>
<th>C_max (ng/mL)</th>
<th>t_max (h)</th>
<th>CL_po (L/h)</th>
<th>AUC(0-∞) (ng·h/mL)</th>
<th>t_1/2 (h)</th>
</tr>
</thead>
<tbody>
<tr>
<td>20 mg</td>
<td>Mean 72.6</td>
<td>1.3</td>
<td>ND</td>
<td>ND</td>
<td>ND</td>
</tr>
<tr>
<td></td>
<td>Range 21.3-114.5</td>
<td>1.0-2.2</td>
<td>ND</td>
<td>ND</td>
<td>ND</td>
</tr>
<tr>
<td></td>
<td>CV% 38.2</td>
<td>37.4</td>
<td>ND</td>
<td>ND</td>
<td>ND</td>
</tr>
</tbody>
</table>

| 30 mg| Mean 89.0     | 1.2       | 54.9        | 546                 | 11.6      |
|      | Range 47.3-130.2 | 0.9-2.0  | 33.6-66.5   | 421-833             | 7.0-17.5  |
|      | CV% 29.7      | 34.4      | 25.8        | 32.1                | 41.0      |

| 40 mg| Mean 99.5     | 1.3       | 76.4        | 584                 | 14.5      |
|      | Range 36.3-174.4 | 1.0-3.0  | 32.8-114.0  | 327-1136            | 4.9-22.0  |
|      | CV% 35.3      | 45.9      | 36.3        | 53.2                | 40.5      |

| 60 mg| Mean 110.2    | 1.3       | 94.6        | 653                 | 12.5      |
|      | Range 60.8-162.7 | 1.0-3.0  | 54.4-144.6  | 387-1029            | 7.7-27.5  |
|      | CV% 29.3      | 44.8      | 32.2        | 34.1                | 51.7      |

| 80 mg| Mean 136.3    | 1.4       | 107.3       | 808                 | 10.2      |
|      | Range 64.3-222.3 | 1.0-3.0  | 46.9-178.8  | 417-1590            | 7.3-16.6  |
|      | CV% 33.9      | 50.1      | 39.5        | 43.0                | 28.0      |
Mean plasma profiles of fexofenadine for the various treatment strengths are presented below.

Mean plasma fexofenadine concentration-time profiles following 20, 30, 40, 60 and 80 mg of an oral fexofenadine HCl suspension.

Pharmacodynamics
Mean pharmacodynamic parameters of fexofenadine for the inhibition of wheal and flare responses with the 1mg/mL and 5mg/mL histamine phosphate pricks are presented below.

Summary of mean pharmacodynamic results for the wheal/flare data

<table>
<thead>
<tr>
<th>Parameter</th>
<th>1 mg/mL Histamine Phosphate</th>
<th>5 mg/mL Histamine Phosphate</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>20 mg</td>
<td>30 mg</td>
</tr>
<tr>
<td>$E_{\text{max}}$ (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>$t_{\text{Emax}}$ (h)</td>
<td>6.4</td>
<td>7.1</td>
</tr>
<tr>
<td>$E_{\text{avg}}(0-12)$ (%)</td>
<td>38.3</td>
<td>34.5</td>
</tr>
<tr>
<td>$E_{\text{avg}}(0-24)$ (%)</td>
<td>31.4</td>
<td>29.7</td>
</tr>
</tbody>
</table>

% Reduction in Wheal Parameters

<table>
<thead>
<tr>
<th>Parameter</th>
<th>1 mg/mL Histamine Phosphate</th>
<th>5 mg/mL Histamine Phosphate</th>
</tr>
</thead>
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<tr>
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</tr>
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</table>
All five doses showed inhibition of wheal and flare areas when compared to their respective baseline areas, with maximal inhibitory responses averaging 70% and 83% for wheal and flare, respectively. Maximal inhibition generally occurred around 6 hours post-dose and appeared to be dose-independent. However, the high degree of variability prevented dose-response inferences at peak levels of inhibition or at the 12- and 24-hour time points. The inhibitory effects at 12 hours post-dose averaged 27% for wheal and 35% for flare areas (range of wheal and flare means: 8 to 53%), and were approximately 20% for both wheal and flare (range of means: -9 to 47%) at 24 hours post-dose. The overall effect ($E_{avg}$) over 12 hours averaged 40% for wheal and 48% for flare with little evidence of dose-related effects. The individual effect-time profiles suggested a trend towards a greater level of inhibition at peak, 12, and 24 hours post-dose with higher doses. However, these results could not be confirmed due to the high degree of variability and less than dose-proportional exposure. The extent of flare inhibition with the 1 mg/mL histamine prick was greater than that with the 5 mg/mL strength whereas wheal inhibition did not appear to be influenced by prick strength.

**Results - Safety**

Overall, 8 (20%) of 40 subjects exposed to study medication reported at least 1 treatment emergent adverse event (TEAE). Of the 8 subjects reporting a TEAE, 4 subjects (50%), reporting 4 TEAEs had the additional diagnosis of asthma. The TEAEs reported occurred in a total of eight system organ classes. The most frequently reported TEAE was viral infection (3 [8%] of 40 subjects) and all 3 subjects with this TEAE were subjects with the concurrent illness of asthma. All other TEAEs each occurred in 1 (3%) of 40 subjects. All TEAEs were mild in intensity. Most adverse events reported during the study were judged by the investigator to be unrelated to the study medication.

One serious adverse event was reported throughout this study in a subject prior to dosing with study medication. No subject withdrew due to an adverse event.

There were 15 occurrences in 9 subjects of predefined change abnormal (PCA) laboratory values. There were 3 PCA increases in platelets; 2 PCA increases each in absolute eosinophils and lactate dehydrogenase; and 1 PCA increase in SGPT. There were 3 PCA decreases in hemoglobin, and 1 PCA decrease each in erythrocytes, hematocrit, absolute lymphocytes, and absolute neutrophils. The PCA increases in absolute eosinophils were both in subjects with the concurrent illness of asthma. None of these changes were judged to be clinically significant by the investigator.

No trends or clinically relevant changes were observed in vital sign data. There was 1 instance in 1 subject of PCA increase in heart rate and there were 3 instances in 3 subjects of increase in systolic blood pressure, but these were not judged to be clinically significant by the investigator.

There were no instances of PCA ECG parameter values.

**Conclusions**

- The fexofenadine HCl oral suspension formulation used in the present study exhibited dose-dependent bioavailability attributable to interaction with the polyol sweetener system used in the formulation. The elimination characteristics were consistent with historic data in adults. Overall, the results point toward the need for further optimization of the qualitative and/or quantitative composition of the oral suspension to achieve comparable bioavailability and bioequivalence with the marketed tablet formulation.

- The pharmacodynamic profile of fexofenadine HCl when administered as oral suspension in subjects 6 to 11 years of age was characterized by inhibition of histamine-induced wheal and flare areas at all dose levels, consistent with the known profile of fexofenadine HCl. However, due to the large variability and less than dose-proportional exposure, dose-related inferences concerning the inhibitory responses could not be confirmed.
• Fexofenadine HCl suspension was safe and well tolerated in pediatric subjects with allergic rhinitis 6 through 11 years of age.