SYNOPSIS

INN: FEXOFENADINE

Study number: M016455I/1119

Study title: Pharmacokinetics and pharmacodynamics of oral fexofenadine hydrochloride tablets administered to children from 6 through 11 years of age.

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.

PDF name: Fexofenadine – Study 22

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

Study number M016455I/1119

Title
Pharmacokinetics and pharmacodynamics of oral fexofenadine hydrochloride tablets administered to children from 6 through 11 years of age

Investigator(s), study site(s)
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See Appendix A.2.1 of original Clinical Study Report R2000CLN0431

Study duration and dates
The first subject was enrolled on 25 September 2000 and the last subject completed the study on 20 December 2000.

Phase I

Objectives
Primary objective:
To characterize the pharmacokinetics of oral fexofenadine hydrochloride (HCl) tablets in 6 through 11 year-old pediatric subjects with allergic rhinitis.

Secondary objective:
To characterize the inhibitory effects of oral fexofenadine hydrochloride tablets, on skin wheal and flare induced by histamine, in 6 through 11 year-old pediatric subjects with allergic rhinitis.

Study design
This study was a single center, double blind, single dose, randomized, two period, incomplete block crossover design in pediatric subjects (6 through 11 years of age) with allergic rhinitis. At each period, subjects arrived at the clinic in the morning of Day 1, and were released overnight after the 8-hour blood collection and wheal and flare test. The subjects returned in the morning of Day 2 for the 24, 30, and 34-hour procedures. Subjects returned for a post-study assessment within 3 days of completion of the second study period.

Time data for plasma concentration and wheal and flare, were limited at the request of the ethics committees, to reduce the length and frequency of sampling required in the pediatric subjects.

Population
Children (6 through 11 years of age), with allergic rhinitis, who were candidates for antihistamine therapy or who had tolerated a therapeutic course of antihistamine therapy within the preceding 12 months without adverse effects. Almost all subjects were regular attendees at a hospital based allergy clinic, indicating a considerable degree of atopic disease.

Treatments
Each subject received two of the four following treatments:
Treatment A: Single dose oral administration of 15 mg fexofenadine hydrochloride  
Treatment B: Single dose oral administration of 30 mg fexofenadine hydrochloride  
Treatment C: Single dose oral administration of 60 mg fexofenadine hydrochloride  
Treatment D: Single dose oral administration of placebo  

All subjects received two of the four treatments in a random sequence. Subjects were assigned a subject number at the time they received the first dose of study medication. Each dose was separated by a washout period of at least 7 days.

**Pharmacokinetic data**  
Serial pharmacokinetic blood samples were collected in all subjects prior to (0 hours) and at 1, 2, 3, 8, 24, 30 and 34 hours after administration of each dose. Plasma samples were analyzed for fexofenadine hydrochloride using a validated liquid chromatography-mass spectrometry method.

**Pharmacodynamic data**  
Inhibition of skin wheal and flare responses, induced by a histamine skin prick test, was measured predose (two baseline measurements) and at 1, 3, 8 and 24 hours after each dose. The wheal and flare areas were traced, the tracings transferred to the case report form and subsequently scanned. The areas were obtained from the tracing using a computerized digitizing system.

**Safety data**  
Age-appropriate physical exams, vital signs, 12-lead electrocardiogram (ECG), and clinical laboratory tests were performed at the screening visit and within 3 days following collection of the final pharmacokinetic blood sample. Adverse events were monitored throughout the study.

**Statistical procedures**  
Fexofenadine HCl plasma concentrations were analyzed using noncompartmental techniques. All subjects who completed at least one treatment period were included in the analysis. The pharmacokinetic parameters calculated included maximum plasma concentration (C_{max}), time to maximum plasma concentration (t_{max}), area under the plasma concentration time curve from time=zero until 8 hours postdose [AUC(0-8)], area under the plasma concentration time curve from time=zero until the last measurable plasma concentration time point [AUC(0-z)], area under the plasma concentration time curve from time=zero extrapolated to infinity [AUC(0-\infty)], half-life (t_{1/2}) and apparent oral clearance (Cl_{po}). Pharmacokinetic parameters were summarized descriptively.

Wheal and flare inhibition were analyzed using noncompartmental techniques. Wheal/flare inhibition was calculated as the percentage reduction in wheal/flare area from the mean baseline wheal/flare area measurement obtained prior to each dose administration. All subjects completing at least one treatment period were included in the analysis. The pharmacodynamic parameters calculated included, time to maximum wheal/flare inhibition (t_{Emax}), maximum wheal/flare inhibition (E_{max}), area under the wheal/flare inhibition-time curve (AUEC(0-8) and AUEC(0-z)), and average wheal/flare inhibition (E_{avg}) over 8 or 24 hours. Pharmacodynamic parameters, wheal/flare area and wheal/flare inhibition were summarized descriptively. Pharmacokinetic-pharmacodynamic relationships were evaluated graphically. No attempt was made to fit the data to a pharmacodynamic model.
The safety analysis included all subjects receiving at least one dose of study medication. The frequency of adverse events was tabulated. Baseline, end-of-study and change from baseline laboratory, vital signs and 12-lead ECGs were summarized. 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 36 subjects were enrolled; all 36 subjects were randomized and received study medication and 35 subjects completed the study. A total of 17 subjects received 15 mg fexofenadine HCl, 18 subjects received 30 mg, 18 subjects received 60 mg and 18 subjects received placebo. Overall, 21 subjects were male (58.3%) and 15 were female (41.7%). All subjects were in the age range 6 through 11 years, with a mean age of 8.4 years and age distribution was similar between treatment groups. Most subjects were described as of white ethnic group (35 subjects, 97.2%) with the remaining subject of black ethnic group (one subject, 2.8%). All 36 subjects receiving fexofenadine HCl were included in the pharmacokinetic, pharmacodynamic and safety analyses.

**Results – Pharmacokinetics**

A proportionate increase in $C_{\text{max}}$ and AUC(0-8) was observed with increasing fexofenadine HCl dose. These observations are consistent with a previous population analysis of fexofenadine pharmacokinetic data collected in pediatric seasonal allergic rhinitis subjects. The following figure illustrates the mean fexofenadine concentration-time profiles by treatment.
Apparent terminal half-life and overall exposure (as expressed by AUC(0–∞)) could not be evaluated in all treatment groups due to the limited sampling requested by the president of the ethics committee. To allow comparison across fexofenadine doses, overall exposure over the 0 to 8 hour collection interval (AUC(0-8)) was calculated. The subsequent table summarizes the key mean fexofenadine pharmacokinetic parameters.

<table>
<thead>
<tr>
<th></th>
<th>Fexofenadine HCl</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>15 mg N = 17</td>
</tr>
<tr>
<td>C_{max} (ng/mL)</td>
<td>Mean (CV%)</td>
</tr>
<tr>
<td>t_{max} (h)</td>
<td>Mean (CV%)</td>
</tr>
<tr>
<td>AUC(0-8) (ng-h/mL)</td>
<td>Mean (CV%)</td>
</tr>
<tr>
<td>AUC(0-∞) (ng-h/mL)</td>
<td>Mean (CV%)</td>
</tr>
<tr>
<td>CL_{po} (L/h)</td>
<td>Mean (CV%)</td>
</tr>
<tr>
<td>t_{1/2} (h)</td>
<td>Mean (CV%)</td>
</tr>
</tbody>
</table>

CV%: percentage coefficient of variation; ND: Could not be determined due to insufficient terminal concentration-time data.

* Unevaluable in one subject

Results – Pharmacodynamics

Fexofenadine administration resulted in the reduction of histamine induced wheal and flare area, which was differentiated from the lack of effect seen following placebo administration for both histamine phosphate concentrations. Median E_{max} for placebo ranged from 4 to 28% inhibition across both wheal and flare. For all fexofenadine doses, across both wheal and flare, median E_{max} in each group ranged from 22 to 67% (15 mg: 22–67%; 30 mg: 28–58%; 60 mg: 31–63%).

There was a tendency to greater reduction of wheal and flare areas following the two higher fexofenadine HCl doses of 30 and 60 mg, and this was most evident at 8 and 24 hours postdose. This tendency was also seen in E_{avg} (0–8) and was supported by E_{avg} (0–z) and AUECs. The dose differentiation was clearer in response to the higher histamine phosphate concentration. The median E_{avg} (0–z) in the placebo group ranged from –40 to –14%, reflecting an increased skin response in the absence of antihistamine treatment that contributed to a significant baseline drift. In the 15 mg group the median E_{avg} (0–z), for inhibition of wheal and flare ranged from –16 to +15%. The median E_{avg} (0–z), ranged from –3 to 15% for the 30 mg group, and from 2 to 23% for the 60 mg group, both indicating a decrease in the skin response. The 30 and 60 mg doses of fexofenadine HCl had similar maximal and average activity, whereas the efficacy of the 15 mg fexofenadine HCl was less sustained.

Results – Pharmacokinetics and pharmacodynamics

The relationship between a pharmacodynamic response (percent reduction in wheal or flare size) and fexofenadine concentrations was evaluated graphically. Across doses, maximum wheal and flare inhibition levels generally occurred at later time points relative to the time of peak plasma
fexofenadine concentrations. The decline in plasma fexofenadine concentrations was more rapid than the decline in wheal and flare inhibition, indicating hysteresis.

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>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Placebo (N = 18)</td>
</tr>
<tr>
<td>All</td>
<td>5 (27.8)</td>
</tr>
<tr>
<td>Serious</td>
<td>0 (0.0)</td>
</tr>
<tr>
<td>Leading to discontinuation</td>
<td>0 (0.0)</td>
</tr>
</tbody>
</table>

The system organ class with the highest incidence of TEAEs was gastrointestinal disorders. The most common TEAE was abdominal pain NOS, and was reported in 6 (16.7%) subjects while on fexofenadine HCl treatment and in 0 (0.0%) subjects while on placebo.

Following the current ICH guidelines for reporting of serious TEAEs, there were no serious TEAEs reported. There were no TEAEs leading to discontinuation.

A total of six (17.1%) subjects had at least one laboratory value that met the criteria for predefined change abnormal (PCA) at the end of study. These included an increase in eosinophils to a clinically noteworthy value, an increase in lymphocytes, two decreases in leukocytes and three decreases in neutrophils. Five subjects (13.9%) had one or more PCAs for vital signs. Two of these subjects, and one further subject, had clinically noteworthy abnormal vital signs. One PCA was related to heart rate (decreased), two to systolic blood pressure (one increase, one decrease) and two to diastolic blood pressure (one increase, one decrease). The vital signs clinically noteworthy abnormal laboratory values were high systolic blood pressure, high diastolic blood pressure and low diastolic blood pressure in one subject each. There were no findings of clinical relevance in overall ECG data. No subjects had QT interval corrected for heart rate (using Bazett's formula) (QTc) values above the upper limit of normal for age of 440 msec. Two subjects (Subject 0001/00011 (fexofenadine HCl 30 and 15 mg) and Subject 0001/00021 (fexofenadine HCl 60 and 30 mg)) had increases in QTc of ≥30 but ≤60 msec (32 and 42 msec, respectively) with minor changes in heart rate (>0 to ≥10 bpm). These changes in QTc were not considered clinically significant.

Evaluation of safety shows neither an overall difference between fexofenadine HCl-treated subjects and placebo-treated subjects, nor any dose-dependent effect. The results of this study are consistent with the current product label and do not raise any new safety concerns.

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

- Administration of single oral doses of 15 mg, 30 mg and 60 mg fexofenadine HCl to pediatric patients (6-11 years of age) resulted in dose proportional increases in Cmax and AUC(0-8).
- All fexofenadine HCl doses caused inhibition of histamine induced wheal and flare areas, whereas placebo did not. However, large variability in the baseline and treatment responses limited quantitative inferences of the pharmacodynamic effect. Overall, it appears that 15 mg may not be as effective as the two higher doses.
- All 3 doses of fexofenadine HCl were safe and well tolerated.
- The recoding of adverse event data did not change the safety profile of fexofenadine HCl.