SYNOPSIS

INN : LEVOFLOXACIN

Study number : LOFBO-PHI-110

Study title : An Open-Label Single Oral Dose Study to Evaluate the Safety and Pharmacokinetics of Levofloxacin Suspension Formulation in Infants and Children (≦ 16 Years of Age)

CSR date : 5 March 2001

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.
SYNOPSIS

<table>
<thead>
<tr>
<th>NAME OF SPONSOR/COMPANY:</th>
<th>The R.W. Johnson Pharmaceutical Research Institute</th>
</tr>
</thead>
<tbody>
<tr>
<td>NAME OF FINISHED PRODUCT:</td>
<td>LEVAQUIN®</td>
</tr>
<tr>
<td>NAME OF ACTIVE INGREDIENT:</td>
<td>Levofloxacin</td>
</tr>
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</table>

**Protocol No.:** LOFBO-PHI-110

**Title of Study:** An Open-Label Single Oral Dose Study to Evaluate the Safety and Pharmacokinetics of Levofloxacin Suspension Formulation in Infants and Children (≤16 Years of Age)

**Investigators:** Jeffrey M. Blumer, Ph.D., M.D.; Gregory L. Kearns, Pharm. D.; Thomas G. Wells, M.D.

**Study Centres:** University Hospitals of Cleveland, Cleveland, OH, USA; Children's Mercy Hospital, Kansas City, MO, USA; Arkansas Children's Hospital, Little Rock, AR, USA.

**Publication (Reference):** None

**Studied Period (years):** Clinical Conduct: 8 March 2000 to 22 August 2000

**Number of Subjects (planned and analyzed):** 24 subjects planned (6 per cohort); 28 subjects enrolled, with 24 subjects analyzed for pharmacokinetics and 28 analyzed for safety.

**Methodology:** This was an open-label, nonrandomized, single-dose, multicenter, Phase 1 study involving pediatric subjects aged 6 months to 16 years inclusive with documented, presumed, or at risk for bacterial infections who were undergoing treatment with antibiotics other than quinolones. Subjects were enrolled into one of four cohorts stratified by age (>12 years to 16 years; >5 years to 12 years; >2 years to 5 years; and ≤6 months to 2 years in Cohorts 1, 2, 3, and 4, respectively). All subjects were administered a single oral dose of levofloxacin suspension, 7 mg/kg by body weight (not to exceed 500 mg). Blood and urine samples were collected for up to 48 hours after study drug administration for pharmacokinetic evaluations. Taste acceptability for this oral suspension formulation was also assessed. Safety was assessed based on the incidence and severity of treatment-emergent adverse events, and on changes prestudy to poststudy in physical examination findings, vital sign measurements, and clinical laboratory analyte values.

**Test Product, Dose and Mode of Administration, Batch No.:** Levofloxacin was administered as a single oral dose of 7 mg/kg (not to exceed 500 mg) using a reverse enteric coated suspension formulation (FD # GFI 25213-097-KB-008, Batch # R9691, 25 mg/mL). Subjects were required to fast for two hours before and after study drug administration.

**Duration of Treatment:** Levofloxacin was administered as a single dose.

**Reference Therapy, Dose and Mode of Administration, Batch No.:** Not applicable
Criteria for Evaluation:

**Pharmacokinetics:** Levofloxacin concentrations were determined from plasma and urine samples. Blood samples were obtained immediately prior to study drug administration (0 hour) and at 1, 1.5, 2, 3, 4, 6, 8, 12, and 24 hours after dosing. When possible, blood samples at 36 and 48 hours postdose were collected, and urinary outputs from 0 to 6, 6 to 12, 12 to 24, 24 to 36, and 36 to 48 hours postdosing were collected. Appropriate pharmacokinetic parameters including \( C_{\text{max}} \), AUC, \( T_{1/2} \), CL/F, Vd/F, Ae, and CLr were determined. Taste acceptability was assessed in subjects 4 to 16 years of age by a survey using a 5-point rating scale administered within 15 minutes after dosing.

**Safety:** Safety was evaluated by monitoring treatment-emergent adverse events and changes in clinical laboratory analyze values, vital sign measurements, and physical examination findings.

Statistical Methods:

**Pharmacokinetics:** The sample size was derived from pragmatic considerations and was not based on statistical considerations. No inferential statistics were calculated for this open-label study. The pharmacokinetic parameters were summarized using descriptive statistics.

**Safety:** The incidence and severity of treatment-emergent adverse events were summarized using a standard adverse event dictionary based on WHOART. Changes in clinical laboratory values and vital signs were assessed by descriptive statistics. Clinical laboratory values were also assessed by determining markedly abnormal values. Physical examination findings were listed.

### SUMMARY – CONCLUSIONS

**PHARMACOKINETIC RESULTS:** Of the 28 enrolled subjects, 24 were evaluable for pharmacokinetic analysis, with 4 of these subjects (113, 119, 122, and 303) demonstrating pharmacokinetic profiles different than the majority of subjects. For the majority of subjects (4 outliers excluded), the mean pharmacokinetic estimates, shown below, were quite consistent within each cohort, with the younger subjects (0.5 to 10 years) having a faster elimination, higher clearance, and lower systemic exposure than the older subjects (12 to 16 years).

<table>
<thead>
<tr>
<th>Mean (SD) Pharmacokinetic Estimates for the Majority of Subjects</th>
<th>( \geq 0.5-2 ) Years</th>
<th>( &gt;2-5 ) Years</th>
<th>( &gt;5-12 ) Years</th>
<th>( &gt;12-16 ) Years</th>
</tr>
</thead>
<tbody>
<tr>
<td>( C_{\text{max}}, \mu g/\text{mL} )</td>
<td>5.17 (1.10)</td>
<td>4.23 (0.60)</td>
<td>3.81 (0.38)</td>
<td>3.56 (0.58)</td>
</tr>
<tr>
<td>( T_{\text{max}}, \text{h} )</td>
<td>1 (1)</td>
<td>2 (1)</td>
<td>2 (1)</td>
<td>2 (1)</td>
</tr>
<tr>
<td>( T_{1/2}, \text{h} )</td>
<td>4 (0)</td>
<td>4 (1)</td>
<td>5 (0)</td>
<td>7 (3)</td>
</tr>
<tr>
<td>( \text{AUC}_{0-24}, \mu g\cdot\text{h}/\text{mL} )</td>
<td>29.7 (7.6)</td>
<td>26.5 (7.7)</td>
<td>26.0 (4.0)</td>
<td>42.6 (21.7)</td>
</tr>
<tr>
<td>( \text{CL/F}, \text{L/h/kg} )</td>
<td>0.25 (0.07)</td>
<td>0.29 (0.09)</td>
<td>0.27 (0.04)</td>
<td>0.19 (0.06)</td>
</tr>
<tr>
<td>( \text{Vd/F}, \text{L/kg} )</td>
<td>1.46 (0.41)</td>
<td>1.56 (0.23)</td>
<td>1.84 (0.26)</td>
<td>1.74 (0.44)</td>
</tr>
<tr>
<td>( \text{Ae, %Dose} )</td>
<td>not available</td>
<td>73 (20)</td>
<td>62 (20)</td>
<td>55 (23)</td>
</tr>
<tr>
<td>( \text{CLr, L/h/kg} )</td>
<td>not available</td>
<td>0.20 (0.11)</td>
<td>0.21 (0.12)</td>
<td>0.11 (0.05)</td>
</tr>
</tbody>
</table>

Cross-reference: Table 4.
TASTE ACCEPTABILITY RESULTS: Of the 19 subjects surveyed, 10 (53%) rated taste acceptability as really good or good, only 4 (21%) rated taste as bad or really bad, and 5 (26%) were not sure.

SAFETY RESULTS: A single oral dose of levofloxacin suspension, 7 mg/kg by body weight (not to exceed 500 mg), was well tolerated in infants and children from 6 months to 16 years of age. Of the 28 enrolled subjects, 4 (14%) had adverse events during the study. There were no adverse events that were reported more than once. The majority of adverse events were mild to moderate in severity, while three adverse events (hypotension, arrhythmia, and cardiomyopathy) were marked in severity and occurred in the same subject (119). This subject (119) also had the only treatment-emergent serious adverse event (cardiomyopathy). All of the reported adverse events were considered by the investigator not to be related to study medication. There were no deaths during the study, and no subject withdrew from the study due to an adverse event.

There were no clinically significant changes in mean values for serum chemistry, hematology, or urinalysis laboratory tests. Of the 14 subjects with markedly abnormal laboratory values, there were 9 subjects with markedly abnormal chemistry values, 11 subjects with markedly abnormal hematology values, and 2 subjects with markedly abnormal urinalysis values. All of the markedly abnormal chemistry, hematology, and urinalysis values were considered either related to the underlying conditions or not clinically significant. There were no chemistry or urinalysis markedly abnormal values associated with an adverse event. A markedly low hemoglobin level was associated with an adverse event for Subject 123 and was considered by the investigator to be unrelated to study medication. No other markedly abnormal hematology values were associated with an adverse event. There were no treatment-related trends in vital signs during the study. Two subjects (119 and 113) had marked hypotension and mild dyspnea, respectively, that were reported as adverse events and were considered by the investigator to be unrelated to study medication. There were no changes in physical examination findings reported as an adverse event.

CONCLUSION: Following a single oral dose (7 mg/kg by body weight; not to exceed 500 mg) of levofloxacin and using the same suspension formulation, the peak exposure and volume of distribution in infants, children, and adolescents (0.5 to 16 years, $C_{\text{max}} \sim 4-5 \mu\text{g/mL}$ and $V_d/F \sim 1.5-1.7 \text{L/kg}$ with outliers excluded) were quite similar to those observed in adults (18 to 45 years, $C_{\text{max}} \sim 4 \mu\text{g/mL}$ and $V_d/F \sim 2 \text{L/kg}$). Levofloxacin, however, was eliminated nearly twice as fast in infants and children (0.5 to 10 years, $T_{1/2} \sim 4 \text{h}$ and $CL/F \sim 0.3 \text{L/h/kg}$ with outliers excluded) compared with adults ($T_{1/2} \sim 9 \text{h}$, $CL/F \sim 0.16 \text{L/h/kg}$), resulting in a lower systemic exposure in infants and children than in adults ($AUC_{0-\infty} \sim 30 \text{vs. 45 \mu g \text{h/mL}}$). Levofloxacin elimination and total systemic exposure in adolescents (12 to 16 years, with outlier excluded), however, were quite comparable to adults ($T_{1/2} \sim 7 \text{vs. 9 h}$, $AUC_{0-\infty} \sim 43 \text{vs. 45 \mu g \text{h/mL}}$).

Taste was considered good or really good by just over half of the subjects surveyed.

A single oral dose (7 mg/kg by body weight; not to exceed 500 mg) of levofloxacin suspension was well tolerated in infants and children from 6 months to 16 years of age.

Date of the report: 5 March 2001