Division of Special Pathogens and Transplant Products

Applications:	20-634/S-043 21-635/S-046 21-721/S-011
Reviewer Name	Kassa Ayalew, M.D
Purpose:	BPCA Summary, DSPTP
Established Name	Levofloxacin
Trade Name	Levaquin®
Therapeutic Class	Fluoroquinolone
Applicant:	Johnson & Johnson Pharmaceutical Research & Development, L.L.C.
Indication	Not requested
Intended Population	Pediatrics

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1 BACKGROUND

Levofloxacin, the L-isomer of ofloxacin, is a synthetic broad-spectrum fluoroquinolone antibacterial agent. The tablet, intravenous (i.v.), and oral solution formulations have been approved by the United States Food and Drug Administration (FDA) for the treatment of : complicated and uncomplicated urinary tract infections, acute pyelonephritis, chronic prostatitis, complicated and uncomplicated skin and skin structure infections, community-acquired pneumonia (CAP, including that due to multi-drug resistant *Streptococcus pneumoniae*), nosocomial pneumonia, acute bacterial sinusitis, and acute bacterial exacerbation of chronic bronchitis and as post exposure prophylaxis against *Bacillus anthracis* in adults (18 years of age and older).

Prior to the submission of the sNDA the applicant had a Written Request for Pediatric Studies that was issued originally on 20 December 2001 and issued in its final, amended form on 16 June 2006. Request for Pediatric Studies, the applicant, Johnson & Johnson Pharmaceutical Research & Development, L.L.C was asked to provide the safety profile, antibacterial activity and pharmacokinetic of levofloxacin in pediatric subjects (≥ 6 months to 17 years of age) with bacterial infections with special attention to short and long term safety of musculoskeletal (MS) adverse events.

The submissions demonstrated consist of safety and efficacy data from Phase 3 studies during which study drug was administered in both active-controlled (Community acquired pneumonia and acute otitis media (AOM) (clinical outcome) and uncontrolled Acute otitis media (bacteriologic outcome) and a long-term surveillance study.

Because of the reduction of the incidence of pneumococcal infection coinciding with widespread use of conjugated pneumococcal infection in children, the company did not request approval for either CAP or AOM. The company included the summary of musculoskeletal safety findings in the labeling. The following review summarizes the studies performed in response to a Written Request and safety data from the two AOM studies.

2 COMMUNITY ACQUIRED PNEUMONIA

2.1 Clinical Study

The study was a randomized, open-label, active-comparator, multicenter, noninferiority, Phase 3 study that was conducted in the United States, Mexico, and various Latin American countries (Argentina, Brazil, Chile, Costa Rica, and Panama).

The primary objective of this study was to establish the efficacy (clinical response [cured vs. not cured] at the Test-of-Cure Visit (10-17 days after last dose) of levofloxacin to be non-inferior to "standard of care" antibiotic therapy in the treatment of community-acquired pneumonia (CAP) in children aged 6 months to 16 years. Secondary objectives included evaluation of clinical response at the Post therapy Visit, evaluation of Microbiologic Response at the Post therapy Visit and Test-of-Cure Visits, evaluation of clinical and microbiologic responses by age group, and determination of steady-state levofloxacin exposure in each age group. Safety was also assessed.

2.2 Study Procedure

Male and female subjects aged 6 months to 16 years with 2 or more clinical signs and symptoms of pneumonia (defined as: fever, shortness of breath, cough, chest pain, abnormal WBC count, and pulmonary consolidation on physical examination) and radiographic evidence of pulmonary infiltrate compatible with acute infection requiring antibiotic therapy were included.

Subjects with CAP who met the above prestudy eligibility criteria were randomized to receive either levofloxacin (intravenous [i.v.], oral suspension, or oral tablet) or a comparator antimicrobial therapy for 10 days followed by posttreatment assessment.

The randomization was stratified by age group (Group I: $\geq$ 6 months to < 5 years; Group II: $\geq$ 5 to 16 years) and country to ensure balance between treatment groups. The subjects were randomized in a 3:1 levofloxacin:comparator ratio in each stratum. Subjects were either hospitalized or outpatients. Due to differences in the microbiologic etiology of pneumonia and differences in drug clearance in children, the comparators, doses, routes of dosing, and dosing regimens differed by age group.

A combination of clinical assessment of clinical cure, chest radiography, microbiologic assessment of sputum and blood, and serology was used to evaluate efficacy. Safety was based on the incidence, relationship to therapy, and severity of treatment-emergent adverse events, and on changes in clinical laboratory values (hematology, chemistry, and urinalysis), vital signs, and physical examination findings.

Safety evaluations for musculoskeletal adverse events were performed during the study and up to 25-35 days after last dose.

Levofloxacin or comparator treatments were given either orally or by i.v. administration. The treatments given were:

> Group I (≥ 6 months to < 5 years of age): Levofloxacin 10 mg/kg oral suspension or IV b.i.d. (up to 500 mg/day).
>
> Group II (≥ 5 to 16 years of age): Levofloxacin 10 mg/kg oral suspension or IV q.d. (up to 500 mg/day); levofloxacin 1-250 mg tablet q.d. (subjects weighing 22.5 to 27.5 kg) or 2-250 mg tablets q.d. (subjects weighing > 45.5 kg);

The comparator treatments were given either orally or by i.v. administration:

> Group I (≥ 6 months to < 5 years of age): amoxicillin + clavulanic acid oral suspension b.i.d. (with dose determined by calculating amoxicillin 22.5 mg/kg, up to 875 mg/day); ceftriaxone 25 mg/kg i.v. b.i.d. (up to 4 g/day);
>
> Group II (≥ 5 to 16 years of age): clarithromycin 7.5 mg/kg oral suspension b.i.d. (up to 250 mg b.i.d.); clarithromycin 250 mg oral tablet b.i.d. (up to 250 mg b.i.d.); ceftriaxone 25 mg/kg i.v. b.i.d. (up to 4 g/day) + erythromycin lactobionate 10 mg/kg i.v. q.6.h (up to 4 g/24 hours).

The study drug was administered for 10 days (minimum of 7 to a maximum of 14 days).

Clinical response (defined as: cured, improved, failure, relapse, or unable to evaluate) and microbiologic response (defined as: eradicated, presumed eradicated, persisted, presumed persisted, persisted with acquisition of resistance, microbiologic relapse, or unknown) were determined at the (posttherapy1-3 days) after last dose and test-of-cure Visits (10-17 days after last dose).

2.3 Results And Analysis

650 planned (488 levofloxacin, 162 comparator), 738 enrolled, 728 randomized (546 levofloxacin, 182 comparator); 539 evaluable for clinical efficacy at the Test-of-Cure Visit (405 levofloxacin, 134 comparator); 208 evaluable for microbiologic efficacy (158 levofloxacin, 50 comparator); 712 evaluable for safety (533 levofloxacin, 179 comparator).

The number clinical cure rate at test-of-cure visit by study population and age group is presented by primary reason in Table 1.

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Table 1: Clinical Cure Rate at Test-of-Cure Visit by Study Population and Age Group

Population by Age Group	Levofloxacin	%	Comparator	%	Diff, 95%CI, p-value
Intention to Treat Analysis	N=546		N=182		
All	442	80.5	146	80.2	0.3, [-6.4, 7.0], 0.93
6 mo- < 5yrs	214/279	76.7	72/94	76.6	0.1, [-9.8,10.0], 0.9
≥ 5 yrs	228/267	85.4	74/88	84.1	1.3, [-7.4, 10.0], 0.8
Modified Intention to Treat Analysis	n=529		n=180		
All	439	83.0	145	80.6	2.4, [-4.2, 9.0], 0.46
6 mo- < 5yrs	211/264	79.9	71/92	77.2	2.8, [-7.1, 12.6], 0.6
≥ 5 yrs	228/265	86.0	74/88	84.1	2.0, [-6.8, 10.7], 0.7
Clinical Evaluable Analysis	n=405		n=134		
All	382	94.3	126	94.0	0.3, [-4.3, 4.9], 0.90
6 mo- < 5yrs	189/205	92.2	59/65	90.8	1.4, [-6.5, 9.4], 0.7
≥ 5 yrs	193/200	96.5	67/69	97.1	-0.6, [-5.3, 4.1], 0.8
Microbiologically Evaluable Analysis	n=143		n=47		
All	134	93.7	42	89.4	4.3, [-5.3, 14.0], 0.32
6 mo- < 5yrs	66/75	88.0	19/23	82.6	5.4, [-10.1, 26.2], 0.5*
≥ 5 yrs	68/68	100	23/24	95.8	4.2, [-2.9, 21.1], 0.2*

*****Fisher's Exact Test

Of the 712 subjects evaluable for safety, 275 (52%) levofloxacin-treated subjects and 94 (53%) comparator-treated subjects experienced 1 or more adverse event.

Two serious adverse events in levofloxacin-treated subjects resulted in fatal outcomes. The investigator considered this event marked in severity, related to the bronchoscopy procedure, and not related to levofloxacin therapy. Neither death appeared to be related to levofloxacin.

- The first patient was a 13 ½ years old Hispanic female who was diagnosed with multiple foci pneumonia with pneumatocele, fever and respiratory distress who received levofloxacin 250 mg b.i.d. for 3 days. The patient developed cardiorespiratory arrest and died on the third day of the study five minutes after bronchoscopy procedure.

- The second patient was a 2.2-year old, Hispanic male who had completed a ten day course levofloxacin treatment for pneumonia and who was considered to be clinically cured. Patient died after he presented to an emergency room with febrile illness associated with purulent pharyngitis, leukocytosis, airway trapping and respiratory distress.

Adverse events leading to treatment discontinuation occurred in 12 (2%) levofloxacin-treated and 2 (1%) comparator-treated subjects. Serious adverse events were reported in 33 (6%) levofloxacin-treated subjects and 8 (4%) comparator-treated subjects. Most of the serious adverse events were considered doubtfully related or not related to study drug.

Diarrhea was the most frequent adverse event (7% and 11% for levofloxacin and comparator, respectively). Most adverse events were mild or moderate in severity. Seventeen subjects had 23 adverse events of marked severity.The frequency of MS disorders was 2% in levofloxacin-treated subjects and 1% in comparator-treated subjects.

There were no clinically relevant changes in mean laboratory and mean vital sign values or physical examination findings. *S.pneumoniae* and *M. pneumoniae* pathogens isolated from blood and sputum at admission and microbiologic eradication rate at the post therapy visit is summarized below:

Table 2 : *S.pneumoniae* and *M. pneumoniae* pathogens isolated from blood and sputum at admission and microbiologic eradication rate at the post therapy visit in the CAP study: Microbiologically Evaluable Analysis Set

Pathogens	Levofloxacin	Comparator
S.Pneumoniae	17/17 (100%)	5/5 (100%)
M. Pneumoniae	123/138 (89.1%)	39/41(95.1%)

S. pneumoniae was identified in blood at admission in 5 of 17 (29.4%) and 3 of 5 (60%) subjects randomized to levofloxacin and comparator, respectively. *S. pneumoniae* was identified in sputum at admission in 12 (70.6%) and 2 (40%) subjects randomized to levofloxacin and comparator, respectively. *all admission pathogens isolated were susceptible to levofloxacin and the comparator*.

2.4 Conclusion

The overall results of this study suggest that levofloxacin is as effective as the comparator therapies (e.g., amoxicillin, ceftriaxone, clarithromycin) for the treatment of CAP in infants and children. Although there were clinical significant differences between levofloxacin and comparator treated patients in this study, it is very important to address the safety concerns such as musculoskeletal disorders that have been observed in the multicenter, long-term, active-surveillance study of musculoskeletal disorders that is also summarized in this review.

3 LONG-TERM SURVEILLANCE STUDY

3.1 Clinical Study

This was a prospective, long-term, comparative, multicenter, observational study conducted in the United States, Argentina, Brazil, Chile, Costa Rica, Israel, Mexico, and Panama. Pediatric subjects who took at least 1 dose of levofloxacin or comparator as part of a prior Phase 3 levofloxacin study to treat an acute bacterial infection (community acquired pneumonia and acute otitis media and uncontrolled Acute otitis media) were eligible to participate in this long-term surveillance study.

The primary objective of this study was to evaluate and compare the overall incidence of musculoskeletal (MS) disorders defined by protocol as (tendinopathy, arthritis, arthralgia or gait abnormality) in pediatric subjects that occurred during the 60-day period after the first dose of levofloxacin with that of 'standard' non-fluoroquinolone therapy (comparator) for an acute bacterial infection.

Secondary objectives included assessment of 1) overall incidence of MS disorders including impaired growth in the 1-year period after the first dose, 2) incidence of each MS disorder that occurred at weight- and nonweight-bearing joints in the 30-day, 60-day and 1-year periods after the first dose, and 3) incidence of each MS disorder including impaired growth (1-year only) in the 30-day, 60-dayand 1-year periods after the first dose.

3.2 Study Procedure

Male and female subjects aged 6 months to 16 years who took at least 1 dose of levofloxacin or comparator as part of a Phase 3 levofloxacin study to treat an acute bacterial infection.

The primary endpoint was the overall incidence of MS disorders (tendinopathy, arthritis, arthralgia, and gait abnormality) during the 60-day period after the first dose of study drug (levofloxacin or comparator).

Secondary endpoints included the overall incidence of MS disorders (including impaired growth) during the 1-year period after the first dose, incidence of each MS disorder at weight- and nonweight-bearing joints (30-day, 60-day and 1-year periods), and incidence of each individual MS disorder (30-day, 60-day and 1-year periods) including impaired growth (1-year only). Safety was also evaluated by monitoring MS and serious adverse events (SAE) and changes in physical examination findings.

The incidence, severity, and relationship to study drug of MS and SAEs were summarized by treatment using a standard adverse event MedDRA dictionary.

3.3 Results

A total of 2,233 male and female subjects, 6 months to 16 years of age, who took at least 1 dose of levofloxacin or comparator as part of a Phase 3 clinical study were eligible to be enrolled in this trial. A total of 2003 (90%) subjects (89% levofloxacin and 90% comparator) completed the study. 141 (11%) of patients in the levofloxacin and 89 (10%) patients in the comparator group were withdrawn from the study. The primary cause for discontinuation was "Lost to follow-up" (9% in each treatment group).

The primary efficacy endpoint was the overall incidence of MS disorders as defined in the protocol (tendinopathy, arthritis, arthralgia or gait abnormality) within 60 days after the first dose of study medication (Table 3).

Table 3: Incidence of Musculoskeletal Disorders in the 60-Day Period After the First Dose

MS disorder	Levofloxacin (N=1340)		Comparator (N=893)		Total N=2233	P-value[b]
	n (%)	95%CI[a]	n (%)	95%CI[a]	n (%)	
60-Day Period						
Any MS disorder	28 (2.1)	(1.4; 3.0)	8 (0.9)	(0.4; 1.8)	36 (1.6)	0.038
Tendinopathy	1 (0.1)	(0.0; 0.4)	1 (0.1)	(0.0; 0.6)	2 (0.1)	>0.999
Arthritis	5 (0.4)	(0.1; 0.9)	0	(0.0; 0.4)	5 (0.2)	0.164
Arthralgia	22 (1.6)	(1.0; 2.5)	7 (0.8)	(0.3; 1.6)	29 (1.3)	0.088
Gait abnormality	2 (0.1)	(0.0; 0.5)	0	(0.0; 0.4)	2 (0.1)	0.520

Levofloxacin had a significantly higher incidence of disorders than the comparator group (2.1% vs. 0.9%, pvalue: 0.038). The most frequently occurring MS disorder in both groups was arthralgia (levofloxacin – 22/1340 [1.6%] subjects; comparator – 7/893 [0.8%] subjects).

Musculoskeletal disorders were reported more frequently in levofloxacin subjects than in comparator-treated subjects over the 1-year period. This difference was statistically significant (p-value: 0.025). At each of the 3 evaluation periods (30-Day, 60-Day and 1-Year) there was a greater incidence of MS disorders at weight-bearing joints than nonweight-bearing joints for both treatment groups. This difference was significant at the 60-Day period (p-value: 0.025), and the 1-Year period (p-value: 0.047).

A total of 134 subjects (90 levofloxacin, 44 comparator) reported serious adverse events. The most frequently reported event category was infections and infestations (3% in each treatment group). Only pneumonia and surgery were reported by ≥1% of subjects. Abnormal coordination (1 levofloxacin and 1 comparator subject each) and hypotonia (1 levofloxacin subject) were the only nervous system disorders reported.

3.4 CONCLUSION:

Pediatric subjects treated for an acute bacterial infection with levofloxacin showed a significantly higher incidence of MS disorders (tendinopathy, arthritis, arthralgia, and gait abnormality) compared to 'standard' non-fluoroquinolone therapy (comparator) (p-value: 0.038) at the 60-day period after the first dose. The results of this study indicate that levofloxacin is likely to cause Musculoskeletal disorders in children when compared with comparator. Based on the review of the above study report, we recommend adding the safety concerns related to musculoskeletal disorders to the label.

4 ACUTE OTITIS MEDIA (CONTROLLED STUDY)

4.1 Clinical Study

This was a randomized, evaluator-blinded, active-comparator, non-inferiority, multicenter, Phase 3 study conducted in the United States and several Latin American countries (Argentina, Brazil, Chile, Costa Rica, and Panama). The study was not requested in the Written Request but was provided because of safety data.

The primary objective of this study was to demonstrate non-inferiority of levofloxacin compared with amoxicillin + clavulanic acid with respect to the clinical response (cured versus not cured) at the end of therapy (Visit 3, 2 to 5 days after last dose) in infants and children who had recurrent and/or persistent acute otitis media (AOM).

Secondary objectives were to assess the efficacy of levofloxacin based on the clinical cure rate at Visit 4 (10 to 17 days after the last dose), the clinical success rate (cured or improved versus failed) at Visit 3 and Visit 4, the clinical failure rate at Visit 2 (4 to 6 days after the first dose), and persistence of middle ear effusion at Visit 3. Safety was also assessed.

4.2 Study Procedure

Outpatient pediatric subjects (aged ≥ 6 months to < 5 years) who had recurrent and/or persistent acute otitis media and met the prestudy eligibility criteria were randomized to receive either levofloxacin amoxicillin + clavulanic acid (comparator) oral suspension twice daily (b.i.d.) for 10 days followed by post treatment assessment. Levofloxacin 10 mg/kg oral suspension b.i.d. (up to 500 mg/day), Amoxicillin + clavulanic acid (14:1) 45 mg/kg (amoxicillin) oral suspension b.i.d. (up to 3,600 mg/day). The duration of treatment was 10 days.

Subjects were randomized to the treatment groups in a 1:1 levofloxacin: comparator ratio. Male and female subjects aged ≥ 6 months to < 5 years who had clinical signs and symptoms of recurrent and/or persistent acute otitis media (defined as: middle ear effusion and 1or more indicators of acute inflammation [defined as ear pain within 24 hours, including unaccustomed tugging or rubbing of ear; marked redness of the tympanic membrane; distinct fullness or bulging of the tympanic membrane; or acute purulent otorrhea of less than 48 hours duration not due to otitis externa]).

Efficacy was based on the comparison of the clinical cure rate in levofloxacin-treated subjects with the cure rate in comparator treated subjects. Clinical response (defined as: cured, improved, failure, or unable to evaluate) was determined at Visits 3 and 4.

Safety was based on the incidence, relationship to therapy, and severity of treatment-emergent adverse events, and on changes in clinical laboratory values (hematology, chemistry, and urinalysis), vital signs, and physical examination findings. Supplementary safety evaluations for musculoskeletal (MS) adverse events were performed throughout the study. A Data Safety Monitoring Committee (DSMC) reviewed serious and MS adverse events on an ongoing basis.

The primary efficacy endpoint, clinical cure rate (cured versus not cured) at Visit 3, was compared overall and by age group (≤ 2 years, > 2 years), sex, race, and for US versus Non-US subjects.

A 2-sided 95% confidence interval (CI) for the difference in clinical cure and clinical success rates between the 2 treatments (comparator minus levofloxacin) was performed to assess therapeutic non-inferiority. To claim noninferiority, the upper bound of the 95% CI (comparator minus levofloxacin) was to remain below a non-inferiority margin of 10%.

The incidence of treatment-emergent adverse events was compared by treatment, severity, relationship to study drug, age group, sex, and race using a standard adverse event dictionary based on the World Health Organization Adverse Reaction Terminology (WHOART). Musculoskeletal adverse events were compared by treatment and diagnosis and classified as 1 of the following MS disorders as defined by the protocol: tendinopathy, arthritis, arthralgia, or gait abnormality. Changes in clinical laboratory tests and vital signs were reported.

4.3 Results And Analysis

1,650 planned (to achieve 660 clinically evaluable levofloxacin subjects and 660 clinically evaluable comparator subjects); 1,678 screened; 1,650 randomized (827 levofloxacin, 823 comparator); 1,305 evaluable for clinical efficacy at Visit 3 (630 levofloxacin, 675 comparator); 1,607 evaluable for safety (797 levofloxacin, 810 comparator).

For the primary efficacy analysis (clinical cure rate at Visit 3 [2 to 5 days after the last dose of study drug] in the Clinically Evaluable Analysis Set), the clinical cure rate was 72.4% in the levofloxacin group and 69.93% in the comparator group. For the Modified Intent-to-Treat Analysis Set (defined as all subjects who were randomized, took at least 1 dose of study drug, provided efficacy information, and who had a confirmed diagnosis of recurrent and/or persistent AOM) the corresponding cure rates were 65.4% and 63.6%. For both analysis sets and age groups (≤ 2 years, > 2 years), the upper limits of the CIs were less than the non-inferiority margin of 10% indicating that levofloxacin treatment is

non-inferior to comparator treatment overall and in both younger and older children (Table 4)

Table 4: Clinical cure rates at Visit 3 (2 to 5 days after the last dose of study drug) are summarized for the Clinically Evaluable and MITT Analysis Sets.

Analysis Set Age Group	N	Levofloxacin Cured (%)[a]	N	Comparator Cured (%)[a]	Difference[b]	95% CI [c]
Clinically Evaluable						
All Subjects	630	456 (72.4)	675	472 (69.9)	-2.5	(-7.3, 2.4)
2 Years	357	246 (68.9)	394	261 (66.2)	-2.7	(-9.3, 4.0)
>2 Years	273	210 (76.9)	281	211 (75.1)	-1.8	(-8.9, 5.2)
Modified Intent-to-Treat						
All Subjects	705	461 (65.4)	745	474 (63.6)	-1.8	(-6.6, 3.1)
2 Years	406	249 (61.3)	441	262 (59.4)	-1.9	(-8.5, 4.6)
>2 Years	299	212 (70.9)	304	212 (69.7)	-1.2	(-8.4, 6.1)

[a]Cured = cured response category only.
[b]Difference in % clinical cure rates: comparator minus levofloxacin [c]Two-sided 95% CI around the difference in the % clinical cure rates using normal approximation to binomial probability without continuity correction. Upper confidence limit of <10% indicates that levofloxacin is non-inferior to comparator. Numbers in parentheses represent percentages.

Persistence of middle ear effusion at Visit 3 occurred in 16% of subjects in the levofloxacin group and in 20% of subjects in the comparator group. Clinical success rate (cured or improved) at Visit 3 was 94.0% in the levofloxacin group and 90.8% in the comparator group. Less than 1% of levofloxacin-treated subjects (0.32%) and 1.04% of comparator-treated subjects were clinical failures at 4 to 6 days after the start of study drug.

Safety wise, there were no deaths. Serious adverse events were reported in 10 (1%) levofloxacin-treated subjects and 13 (2%) comparator-treated subjects. Most of the serious adverse events were considered doubtfully related or not related to study drug. Adverse events leading to treatment discontinuation occurred in 31 (4%) levofloxacin-treated and 22 (3%) comparator-treated subjects. The most frequent adverse events leading to treatment discontinuation was gastrointestinal system disorders (vomiting, diarrhea, abdominal pain, nausea) that occurred in 21 of 31 patients in the levofloxacin treated patients and 14 of the 22 subjects in the comparator group.

Of the 1,607 subjects evaluable for safety, 448 (56%) levofloxacin-treated subjects and 475 (59%) comparator-treated subjects experienced 1 or more adverse event up to Visit 4. Diarrhea was the most frequent adverse event (14% and 20% for levofloxacin and comparator, respectively). Most adverse events were mild or moderate in severity (97% levofloxacin; 96% comparator). Fifty-one subjects had 69 adverse events of marked severity.

Twenty-three MS adverse events were reported by the investigators before the database lock. Analysis of the data showed that the incidence of MS adverse events was higher in levofloxacin-treated subjects (2%) than in comparator-treated subjects (<1%), and the difference between treatment groups was significant overall (p value = 0.02) for the preferred term 'arthralgia' (p value = 0.03). The most common adverse event was arthralgia occurred in 11 of 17 levofloxacin treated subjects as compared to 3 of the 6 patients who were treated with the comparator treatment.

There were no treatment-related trends or clinically relevant changes in laboratory tests and mean vital sign values or physical examination findings.

4.4 Conclusion

The results of this study demonstrate that levofloxacin is not inferior to standard-of-care therapy (e.g., amoxicillin + clavulanic acid) for the treatment of recurrent and/or persistent AOM in infants and children aged 6 months to < 5 years as defined by protocol-stated criteria of non-inferiority.

Levofloxacin 10 mg/kg b.i.d. (up to 500 mg/day) for 10 days was well tolerated in infants and children. However, musculoskeletal occurred more frequently in association with levofloxacin than the comparator treatment (amoxicillin + clavulanic acid).

5 ACUTE OTITIS MEDIA (UNCONTROLLED)

5.1 Clinical Study

The study was a multicenter, nonrandomized, open-label study conducted in the United States, Argentina, Costa Rica, and Israel. The study for this indication was not requested in the Pediatric Written Request and was provided because of the safety data.

Pediatric subjects (>6 months to <5 years of age) with clinical signs and symptoms of AOM who were at high risk for difficult-to-treat AOM. Patients who met the prestudy eligibility criteria were enrolled and received levofloxacin 10 mg/kg oral suspension twice daily for 10 days followed by post treatment assessment.

The primary objective of this study was to assess the rate of eradication of bacteria from the middle ear fluid (MEF) at Visit 2 (Study Days 4 to 6) in infants and children who had acute otitis media (AOM) and were at high risk for difficult-to-treat infections caused by *S. pneumoniae* or *H.influenzae*.

Secondary objectives were to assess the efficacy of levofloxacin based on clinical cure rate, clinical success (cured plus improved) rate, and microbiologic responses at 2 to 5 and 10 to 17 days after the last dose; and the clinical failure rate at Visit 2. Safety was also assessed.

5.2 Study Procedure

Male and female subjects aged ≥6 months to <5 years who had signs and symptoms of AOM (middle ear effusion, acute inflammation of the ear, acute purulent otorrhea) and who were at high risk for difficult-to-treat AOM (recurrent or persistent AOM).

186 planned; 205 enrolled; 42 evaluable for PK; 93 evaluable for microbiologic efficacy at Visit 2 (37 evaluable for *S. pneumoniae*, and 54 evaluable for *H. influenzae)*;163 evaluable for clinical efficacy; 204 evaluable for safety.

A combination of clinical assessment and microbiologic assessment of MEF and blood was used to evaluate efficacy. Safety was based on the incidence, relationship to therapy, and severity of treatment-emergent adverse events, and on changes in clinical laboratory values (hematology, chemistry, and urinalysis), vital signs, and physical examination findings.

The primary endpoint was the eradication rate of the admission pathogens (isolated from MEF) at Visit 2 (Study Day 4 to 6), with special emphasis on pathogens of interest: *S. pneumoniae* and *H. influenzae.* Secondary endpoints included post treatment (Visits 3 and 4 [2 to 5 and 10 to 17 days after the last dose, respectively]) clinical cure and clinical success rates, Visit 2 clinical failure rates, and post treatment microbiologic response rates. Safety was evaluated by monitoring treatment-emergent adverse events (with special emphasis on MS adverse events) and changes in clinical laboratories, vital signs, and physical examination findings.

5.3 Results And Analysis

Table 5 summarizes the microbiologic eradication rates in subjects with admission pathogens in middle ear fluid at Visit 2:

Table 5: Microbiologic Eradication Rates in Subjects with Admission Pathogens in Middle Ear Fluid at Visit 2 (Study LOFBO-OTMD-001: Microbiologically Evaluable Analysis Set)

Pathogen By pathogens of interest	N	Levofloxacin Eradication (%)a	95% CIb
All pathogens	93	83 (89.25)	(82.95, 95.54)
S. pneumoniae	37	31 (83.78)	(71.91, 95.66)
H. influenzae	54	54 (100.0)	(100.00, 100.00)

aEradication = documented eradication and presumed eradication
b 95% confidence interval
c Subjects who had both H. influenzae and S. pneumoniae infections were included in the number of subjects and eradication rates for both pathogens.
N = number of subjects

The microbiologic eradication rate at Visit 4 (10 to 17 days after completing therapy) was 75% for subject's infection, 67% for infections due to *H. influenzae,* and 73% for infections due to *S. pneumoniae.*

The clinical cure rate at Visit 3 was 83% and at Visit 4 was 68%. The clinical success rate (clinical cure or improvement) at Visit 3 was 94% and at Visit 4 was 72%.

30% of children with Penicillin Resistant *S. pneumoniae* (PRSP) and 9% children with Penicillin Susceptible *S. pneumoniae* (PSSP) who were classified as clinical non failures had microbiologic persistence..

Safety wise, Of the one hundred twenty-two subjects (60%) reported at least 1 adverse event up to Visit 4, twenty-nine (14%) of those subjects reported episodes of AOM as adverse events that were considered new infections. There were no deaths. Seven subjects (3%) experienced 8 serious adverse events.

Vomiting was the most common treatment-limiting adverse event and occurred in 4% (8/204) of subjects. Other common adverse events were diarrhea (9%), upper respiratory tract infection (8%), rash (7%), and fever (6%). Seven subjects (3%) reported 8 serious adverse events. In 2 subjects (maculo-papular rash, dehydration) relationship to study therapy was considered possible and in a third subject with bloody diarrhea, the relationship was considered very likely. Six (1.47%). patients experienced MS events. The MS events were limping, knee pain, leg pain, dislocated elbow, broken wrist, ankle pain.

For serum chemistry, hematology, and urinalysis laboratory tests, there were no clinically relevant changes in mean values. There were no treatment-related trends or clinically relevant changes in mean vital sign values or physical examination findings.

5.4 Conclusions:

The study was open-label and uncontrolled. Therefore, interpretation of the data should be made with caution.

6 RECOMMENDATION

Fluoroquinolones have been associated with musculoskeletal adverse events in adults, children and animals.

Consistent to the findings seen in adults, children and animals, the results from the reviewed study suggest that the use of levofloxacin in children is likely to be associated with increasing incidence of MS disorders and adverse events when compared with other antimicrobial agents used in the study.

The supplement contains sufficient data to support the proposed label changes and provides important safety information about the use of levofloxacin in children as stated in the Written Request. Due to increasing incidence of MS disorders associated with the use of levofloxacin in children, we recommend the current labeling be changed.

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/s/

Leonard Sacks
6/15/2007 05:06:50 PM