fluoroquinolones, some microorganisms resistant to other fluoroquinolones may be susceptible to levofloxacin.

Antimicrobial Activity

Levofloxacin has *in vitro* activity against Gram-negative and Gram-positive bacteria.

Levofloxacin has been shown to be active against most isolates of the following bacteria both *in vitro* and in clinical infections as described in *Indications and Usage (1)*:

Aerobic bacteria

Gram-Positive Bacteria

Enterococcus faecalis

Staphylococcus aureus (methicillin-susceptible isolates)

Staphylococcus epidermidis (methicillin-susceptible isolates)

Staphylococcus saprophyticus

Streptococcus pneumoniae (including multi-drug resistant isolates [MDRSP][1])

Streptococcus pyogenes

Gram-Negative Bacteria

Enterobacter cloacae

Escherichia coli

Haemophilus influenzae

Haemophilus parainfluenzae

Klebsiella pneumoniae

Legionella pneumophila

Moraxella catarrhalis

Proteus mirabilis

[1] MDRSP (Multi-drug resistant *Streptococcus pneumoniae*) isolates are isolates resistant to two or more of the following antibiotics: penicillin (MIC ≥2 mcg/mL), 2nd generation cephalosporins, e.g., cefuroxime; macrolides, tetracyclines and trimethoprim/sulfamethoxazole.

Pseudomonas aeruginosa

Serratia marcescens

Other microorganisms

Chlamydophila pneumoniae

Mycoplasma pneumoniae

The following *in vitro* data are available, but their clinical significance is unknown: Levofloxacin exhibits *in vitro* minimum inhibitory concentrations (MIC values) of 2 mcg/mL or less against most (≥90%) isolates of the following microorganisms; however, the safety and effectiveness of LEVAQUIN® in treating clinical infections due to these bacteria have not been established in adequate and well-controlled clinical trials.

Aerobic bacteria

Gram-Positive Bacteria

Staphylococcus haemolyticus

β-hemolytic Streptococcus (Group C/F)

β-hemolytic *Streptococcus (Group G)*

Streptococcus agalactiae

Streptococcus milleri

Viridans group *streptococci*

Bacillus anthracis

Gram-Negative Bacteria

Acinetobacter baumannii

Acinetobacter lwoffii

Bordetella pertussis

Citrobacter koseri

Citrobacter freundii

Enterobacter aerogenes

Enterobacter sakazakii

Klebsiella oxytoca

Morganella morganii

Pantoea agglomerans

Proteus vulgaris

Providencia rettgeri

Providencia stuartii

Pseudomonas fluorescens

Yersinia pestis

Anaerobic bacteria

Gram-Positive Bacteria

Clostridium perfringens

Susceptibility Tests

For specific information regarding susceptibility test interpretive criteria and associated test methods and quality control standards recognized by FDA for this drug, please see: https://www.fda.gov/STIC.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

In a lifetime bioassay in rats, levofloxacin exhibited no carcinogenic potential following daily dietary administration for 2 years; the highest dose (100 mg/kg/day) was 1.4 times the highest recommended human dose (750 mg) based upon relative body surface area. Levofloxacin did not shorten the time to tumor development of UV-induced skin tumors in hairless albino (Skh-1) mice at any levofloxacin dose level and was therefore not photo-carcinogenic under conditions of this study. Dermal levofloxacin concentrations in the hairless mice ranged from 25 to 42 mcg/g at the highest levofloxacin dose level (300 mg/kg/day) used in the photo-carcinogenicity study. By comparison, dermal levofloxacin concentrations in human subjects receiving 750 mg of LEVAQUIN® averaged approximately 11.8 mcg/g at C_{max}.

Levofloxacin was not mutagenic in the following assays: Ames bacterial mutation assay (*S. typhimurium* and *E. coli*), CHO/HGPRT forward mutation assay, mouse micronucleus test, mouse dominant lethal test, rat unscheduled DNA synthesis assay, and the mouse sister chromatid exchange assay. It was positive in the *in vitro* chromosomal aberration (CHL cell line) and sister chromatid exchange (CHL/IU cell line) assays.

Levofloxacin caused no impairment of fertility or reproductive performance in rats at oral doses as high as 360 mg/kg/day, corresponding to 4.2 times the highest recommended human dose based upon relative body surface area and intravenous doses as high as 100 mg/kg/day, corresponding to 1.2 times the highest recommended human dose based upon relative body surface area.

13.2 Animal Toxicology and/or Pharmacology

Levofloxacin and other quinolones have been shown to cause arthropathy in immature animals of most species tested *[see Warnings and Precautions (5.11)]*. In immature dogs (4–5 months old), oral doses of 10 mg/kg/day for 7 days and intravenous doses of 4 mg/kg/day for 14 days of levofloxacin resulted in arthropathic lesions. Administration at oral doses of 300 mg/kg/day for 7 days and intravenous doses of 60 mg/kg/day for 4 weeks produced arthropathy in juvenile rats. Three-month old beagle dogs dosed orally with levofloxacin at 40 mg/kg/day exhibited clinically severe arthrotoxicity resulting in the termination of dosing at Day 8 of a 14-day dosing routine. Slight musculoskeletal clinical effects, in the absence of gross pathological or histopathological effects, resulted from the lowest dose level of 2.5 mg/kg/day (approximately 0.2-fold the pediatric dose based upon AUC comparisons). Synovitis and articular cartilage lesions were observed at the 10 and 40 mg/kg dose levels (approximately 0.7-fold and 2.4-fold the pediatric dose, respectively, based on AUC comparisons). Articular cartilage gross pathology and histopathology persisted to the end of the 18-week recovery period for those dogs from the 10 and 40 mg/kg/day dose levels.

When tested in a mouse ear swelling bioassay, levofloxacin exhibited phototoxicity similar in magnitude to ofloxacin, but less phototoxicity than other quinolones.

While crystalluria has been observed in some intravenous rat studies, urinary crystals are not formed in the bladder, being present only after micturition and are not associated with nephrotoxicity.

In mice, the CNS stimulatory effect of quinolones is enhanced by concomitant administration of non-steroidal anti-inflammatory drugs.

In dogs, levofloxacin administered at 6 mg/kg or higher by rapid intravenous injection produced hypotensive effects. These effects were considered to be related to histamine release.

In vitro and *in vivo* studies in animals indicate that levofloxacin is neither an enzyme inducer nor inhibitor in the human therapeutic plasma concentration range; therefore, no drug metabolizing enzyme-related interactions with other drugs or agents are anticipated.

14 CLINICAL STUDIES

14.1 Nosocomial Pneumonia

Adult patients with clinically and radiologically documented nosocomial pneumonia were enrolled in a multicenter, randomized, open-label study comparing intravenous LEVAQUIN® (750 mg once daily) followed by oral LEVAQUIN® (750 mg once daily) for a total of 7–15 days to intravenous imipenem/cilastatin (500–1000 mg every 6–8 hours daily) followed by oral ciprofloxacin (750 mg every 12 hours daily) for a total of 7–15 days. LEVAQUIN®-treated patients received an average of 7 days of intravenous therapy (range: 1–16 days); comparator-treated patients received an average of 8 days of intravenous therapy (range: 1–19 days).

Overall, in the clinically and microbiologically evaluable population, adjunctive therapy was empirically initiated at study entry in 56 of 93 (60.2%) patients in the LEVAQUIN® arm and 53 of 94 (56.4%) patients in the comparator arm. The average duration of adjunctive therapy was 7 days in the LEVAQUIN® arm and 7 days in the comparator. In clinically and microbiologically evaluable patients with documented *Pseudomonas aeruginosa* infection, 15 of 17 (88.2%) received ceftazidime (N = 11) or piperacillin/tazobactam (N = 4) in the LEVAQUIN® arm and 16 of 17 (94.1%) received an aminoglycoside in the comparator arm. Overall, in clinically and microbiologically evaluable patients, vancomycin was added to the treatment regimen of 37 of 93 (39.8%) patients in the LEVAQUIN® arm and 28 of 94 (29.8%) patients in the comparator arm for suspected methicillin-resistant *S. aureus* infection.

Clinical success rates in clinically and microbiologically evaluable patients at the post-therapy visit (primary study endpoint assessed on day 3–15 after completing therapy) were 58.1% for LEVAQUIN® and 60.6% for comparator. The 95% CI for the difference of response rates (LEVAQUIN® minus comparator) was [-17.2, 12.0]. The microbiological eradication rates at the posttherapy visit were 66.7% for LEVAQUIN® and 60.6% for comparator. The 95% CI for the difference of eradication rates (LEVAQUIN® minus comparator) was [-8.3, 20.3]. Clinical success and microbiological eradication rates by pathogen are detailed in Table 11.

Table 11: Clinical Success Rates and Bacteriological Eradication Rates (Nosocomial Pneumonia)

Pathogen	N	LEVAQUIN® No. (%) of Patients Microbiologic/ Clinical Outcomes	N	Imipenem/Cilastatin No. (%) of Patients Microbiologic/ Clinical Outcomes
MSSA*	21	14 (66.7)/13 (61.9)	19	13 (68.4)/15 (78.9)
P. aeruginosa†	17	10 (58.8)/11 (64.7)	17	5 (29.4)/7 (41.2)
S. marcescens	11	9 (81.8)/7 (63.6)	7	2 (28.6)/3 (42.9)
E. coli	12	10 (83.3)/7 (58.3)	11	7 (63.6)/8 (72.7)
K. pneumoniae‡	11	9 (81.8)/5 (45.5)	7	6 (85.7)/3 (42.9)
H. influenzae	16	13 (81.3)/10 (62.5)	15	14 (93.3)/11 (73.3)
S. pneumoniae	4	3 (75.0)/3 (75.0)	7	5 (71.4)/4 (57.1)

* Methicillin-susceptible *S. aureus*

† See above text for use of combination therapy

‡ The observed differences in rates for the clinical and microbiological outcomes may reflect other factors that were not accounted for in the study

14.2 Community-Acquired Pneumonia: 7–14 day Treatment Regimen

Adult inpatients and outpatients with a diagnosis of community-acquired bacterial pneumonia were evaluated in 2 pivotal clinical studies. In the first study, 590 patients were enrolled in a prospective, multi-center, unblinded randomized trial comparing LEVAQUIN® 500 mg once daily orally or intravenously for 7 to 14 days to ceftriaxone 1 to 2 grams intravenously once or in equally divided doses twice daily followed by cefuroxime axetil 500 mg orally twice daily for a total of 7 to 14 days. Patients assigned to treatment with the control regimen were allowed to receive erythromycin (or doxycycline if intolerant of erythromycin) if an infection due to atypical pathogens was suspected or proven. Clinical and microbiologic evaluations were performed during treatment, 5 to 7 days posttherapy, and 3 to 4 weeks posttherapy. Clinical success (cure plus improvement) with LEVAQUIN® at 5 to 7 days posttherapy, the primary efficacy variable in this study, was superior (95%) to the control group (83%). The 95% CI for the difference of response rates (LEVAQUIN® minus comparator) was [-6, 19]. In the second study, 264 patients were enrolled in a prospective, multi-center, non-comparative trial of 500 mg LEVAQUIN® administered orally or intravenously once daily for 7 to 14 days. Clinical success for clinically evaluable patients was 93%. For both studies, the clinical success rate in patients with atypical pneumonia due to *Chlamydophila pneumoniae*, *Mycoplasma pneumoniae*, and *Legionella pneumophila* were 96%, 96%, and 70%, respectively. Microbiologic eradication rates across both studies are presented in Table 12.

Table 12: Bacteriological Eradication Rates Across 2 Community Acquired Pneumonia Clinical Studies

Pathogen	No. Pathogens	Bacteriological Eradication Rate (%)
H. influenzae	55	98
S. pneumoniae	83	95

Table 12: Bacteriological Eradication Rates Across 2 Community Acquired Pneumonia Clinical Studies

Pathogen	No. Pathogens	Bacteriological Eradication Rate (%)
S. aureus	17	88
M. catarrhalis	18	94
H. parainfluenzae	19	95
K. pneumoniae	10	100.0

Community-Acquired Pneumonia Due to Multi-Drug Resistant *Streptococcus pneumoniae*

LEVAQUIN® was effective for the treatment of community-acquired pneumonia caused by multi-drug resistant *Streptococcus pneumoniae* (MDRSP). MDRSP isolates are isolates resistant to two or more of the following antibacterials: penicillin (MIC ≥2 mcg/mL), 2nd generation cephalosporins (e.g., cefuroxime, macrolides, tetracyclines and trimethoprim/sulfamethoxazole). Of 40 microbiologically evaluable patients with MDRSP isolates, 38 patients (95.0%) achieved clinical and bacteriologic success at post-therapy. The clinical and bacterial success rates are shown in Table 13.

Table 13: Clinical and Bacterial Success Rates for LEVAQUIN®-Treated MDRSP in Community Acquired Pneumonia Patients (Population Valid for Efficacy)

Screening Susceptibility	Clinical Success		Bacteriological Success*	
	n/N†	%	n/N‡	%
Penicillin-resistant	16/17	94.1	16/17	94.1
2nd generation Cephalosporin resistant	31/32	96.9	31/32	96.9
Macrolide-resistant	28/29	96.6	28/29	96.6
Trimethoprim/ Sulfamethoxazole resistant	17/19	89.5	17/19	89.5
Tetracycline-resistant	12/12	100	12/12	100

* One patient had a respiratory isolate that was resistant to tetracycline, cefuroxime, macrolides and TMP/SMX and intermediate to penicillin and a blood isolate that was intermediate to penicillin and cefuroxime and resistant to the other classes. The patient is included in the database based on respiratory isolate.

† n = the number of microbiologically evaluable patients who were clinical successes; N = number of microbiologically evaluable patients in the designated resistance group.

‡ n = the number of MDRSP isolates eradicated or presumed eradicated in microbiologically evaluable patients; N = number of MDRSP isolates in a designated resistance group.

Not all isolates were resistant to all antimicrobial classes tested. Success and eradication rates are summarized in Table 14.

Table 14: Clinical Success and Bacteriologic Eradication Rates for Resistant *Streptococcus pneumoniae* (Community Acquired Pneumonia)

Type of Resistance	Clinical Success	Bacteriologic Eradication
Resistant to 2 antibacterials	17/18 (94.4%)	17/18 (94.4%)
Resistant to 3 antibacterials	14/15 (93.3%)	14/15 (93.3%)
Resistant to 4 antibacterials	7/7 (100%)	7/7 (100%)
Resistant to 5 antibacterials	0	0
Bacteremia with MDRSP	8/9 (89%)	8/9 (89%)

14.3 Community-Acquired Pneumonia: 5-day Treatment Regimen

To evaluate the safety and efficacy of the higher dose and shorter course of LEVAQUIN®, 528 outpatient and hospitalized adults with clinically and radiologically determined mild to severe community-acquired pneumonia were evaluated in a double-blind, randomized, prospective, multicenter study comparing LEVAQUIN® 750 mg, IV or orally, every day for five days or LEVAQUIN® 500 mg IV or orally, every day for 10 days.

Clinical success rates (cure plus improvement) in the clinically evaluable population were 90.9% in the LEVAQUIN® 750 mg group and 91.1% in the LEVAQUIN® 500 mg group. The 95% CI for the difference of response rates (LEVAQUIN® 750 minus LEVAQUIN® 500) was [-5.9, 5.4]. In the clinically evaluable population (31–38 days after enrollment) pneumonia was observed in 7 out of 151 patients in the LEVAQUIN® 750 mg group and 2 out of 147 patients in the LEVAQUIN® 500 mg group. Given the small numbers observed, the significance of this finding cannot be determined statistically. The microbiological efficacy of the 5-day regimen was documented for infections listed in Table 15.

Table 15: Bacteriological Eradication Rates (Community-Acquired Pneumonia)

S. pneumoniae	19/20 (95%)
Haemophilus influenzae	12/12 (100%)
Haemophilus parainfluenzae	10/10 (100%)
Mycoplasma pneumoniae	26/27 (96%)
Chlamydophila pneumoniae	13/15 (87%)

14.4 Acute Bacterial Sinusitis: 5-day and 10–14 day Treatment Regimens

LEVAQUIN® is approved for the treatment of acute bacterial sinusitis (ABS) using either 750 mg by mouth × 5 days or 500 mg by mouth once daily × 10–14 days. To evaluate the safety and efficacy of a high dose short course of LEVAQUIN®, 780 outpatient adults with clinically and radiologically determined acute bacterial sinusitis were evaluated in a double-blind, randomized, prospective, multicenter study comparing LEVAQUIN® 750 mg by mouth once daily for five days to LEVAQUIN® 500 mg by mouth once daily for 10 days.

Clinical success rates (defined as complete or partial resolution of the pre-treatment signs and symptoms of ABS to such an extent that no further antibiotic treatment was deemed necessary) in the microbiologically evaluable population were 91.4% (139/152) in the LEVAQUIN® 750 mg group and 88.6% (132/149) in the LEVAQUIN® 500 mg group at the test-of-cure (TOC) visit (95% CI [-4.2, 10.0] for LEVAQUIN® 750 mg minus LEVAQUIN® 500 mg).

Rates of clinical success by pathogen in the microbiologically evaluable population who had specimens obtained by antral tap at study entry showed comparable results for the five- and ten-day regimens at the test-of-cure visit 22 days post treatment (see Table 16).

Table 16: Clinical Success Rate by Pathogen at the TOC in Microbiologically Evaluable Subjects Who Underwent Antral Puncture (Acute Bacterial Sinusitis)

Pathogen	LEVAQUIN® 750 mg × 5 days	LEVAQUIN® 500 mg × 10 days
Streptococcus pneumoniae[*]	25/27 (92.6%)	26/27 (96.3%)
Haemophilus influenzae[*]	19/21 (90.5%)	25/27 (92.6%)
Moraxella catarrhalis[*]	10/11 (90.9%)	13/13 (100%)

[*] Note: Forty percent of the subjects in this trial had specimens obtained by sinus endoscopy. The efficacy data for subjects whose specimen was obtained endoscopically were comparable to those presented in the above table.

14.5 Complicated Skin and Skin Structure Infections

Three hundred ninety-nine patients were enrolled in an open-label, randomized, comparative study for complicated skin and skin structure infections. The patients were randomized to receive either LEVAQUIN® 750 mg once daily (IV followed by oral), or an approved comparator for a median of 10 ± 4.7 days. As is expected in complicated skin and skin structure infections, surgical procedures were performed in the LEVAQUIN® and comparator groups. Surgery (incision and drainage or debridement) was performed on 45% of the LEVAQUIN®-treated patients and 44% of the comparator-treated patients, either shortly before or during antibiotic treatment and formed an integral part of therapy for this indication.

Among those who could be evaluated clinically 2–5 days after completion of study drug, overall success rates (improved or cured) were 116/138 (84.1%) for patients treated with LEVAQUIN® and 106/132 (80.3%) for patients treated with the comparator.

Success rates varied with the type of diagnosis ranging from 68% in patients with infected ulcers to 90% in patients with infected wounds and abscesses. These rates were equivalent to those seen with comparator drugs.

14.6 Chronic Bacterial Prostatitis

Adult patients with a clinical diagnosis of prostatitis and microbiological culture results from urine sample collected after prostatic massage (VB_3) or expressed prostatic secretion (EPS) specimens obtained via the Meares-Stamey procedure were enrolled in a multicenter, randomized, double-blind study comparing oral LEVAQUIN® 500 mg, once daily for a total of 28 days to oral ciprofloxacin 500 mg, twice daily for a total of 28 days. The primary efficacy endpoint was microbiologic efficacy in microbiologically evaluable patients. A total of 136 and 125 microbiologically evaluable patients were enrolled in the LEVAQUIN® and ciprofloxacin groups, respectively. The microbiologic eradication rate by patient infection at 5–18 days after completion of therapy was 75.0% in the LEVAQUIN® group and 76.8% in the ciprofloxacin group (95% CI [-12.58, 8.98] for LEVAQUIN® minus ciprofloxacin). The overall eradication rates for pathogens of interest are presented in Table 17.

Table 17: Bacteriological Eradication Rates (Chronic Bacterial Prostatitis)

	LEVAQUIN® (N = 136)		**Ciprofloxacin (N = 125)**	
Pathogen	**N**	**Eradication**	**N**	**Eradication**
E. coli	15	14 (93.3%)	11	9 (81.8%)
E. faecalis	54	39 (72.2%)	44	33 (75.0%)
S. epidermidis[*]	11	9 (81.8%)	14	11 (78.6%)

[*] Eradication rates shown are for patients who had a sole pathogen only; mixed cultures were excluded.

Eradication rates for *S. epidermidis* when found with other co-pathogens are consistent with rates seen in pure isolates.

Clinical success (cure + improvement with no need for further antibiotic therapy) rates in microbiologically evaluable population 5–18 days after completion of therapy were 75.0% for LEVAQUIN®-treated patients and 72.8% for ciprofloxacin-treated patients (95% CI [-8.87, 13.27] for LEVAQUIN® minus ciprofloxacin). Clinical long-term success (24–45 days after completion of therapy) rates were 66.7% for the LEVAQUIN®-treated patients and 76.9% for the ciprofloxacin-treated patients (95% CI [-23.40, 2.89] for LEVAQUIN® minus ciprofloxacin).

14.7 Complicated Urinary Tract Infections and Acute Pyelonephritis: 5-day Treatment Regimen

To evaluate the safety and efficacy of the higher dose and shorter course of LEVAQUIN®, 1109 patients with cUTI and AP were enrolled in a randomized, double-blind, multicenter clinical trial conducted in the US from November 2004 to April 2006 comparing LEVAQUIN® 750 mg IV or orally once daily for 5 days (546 patients) with ciprofloxacin 400 mg IV or 500 mg orally twice daily for 10 days (563 patients). Patients with AP complicated by underlying renal diseases or

conditions such as complete obstruction, surgery, transplantation, concurrent infection or congenital malformation were excluded. Efficacy was measured by bacteriologic eradication of the baseline organism(s) at the post-therapy visit in patients with a pathogen identified at baseline. The post-therapy (test-of-cure) visit occurred 10 to 14 days after the last active dose of LEVAQUIN® and 5 to 9 days after the last dose of active ciprofloxacin.

The bacteriologic cure rates overall for LEVAQUIN® and control at the test-of-cure (TOC) visit for the group of all patients with a documented pathogen at baseline (modified intent to treat or mITT) and the group of patients in the mITT population who closely followed the protocol (Microbiologically Evaluable) are summarized in Table 18.

Table 18: Bacteriological Eradication at Test-of-Cure

	LEVAQUIN® 750 mg orally or IV once daily for 5 days		**Ciprofloxacin** 400 mg IV/500 mg orally twice daily for 10 days		**Overall Difference [95% CI]**
	n/N	%	n/N	%	LEVAQUIN®-Ciprofloxacin
mITT Population*					
Overall (cUTI or AP)	252/333	75.7	239/318	75.2	0.5 (-6.1, 7.1)
cUTI	168/230	73.0	157/213	73.7	
AP	84/103	81.6	82/105	78.1	
Microbiologically Evaluable Population†					
Overall (cUTI or AP)	228/265	86.0	215/241	89.2	-3.2 [-8.9, 2.5]
cUTI	154/185	83.2	144/165	87.3	
AP	74/80	92.5	71/76	93.4	

* The mITT population included patients who received study medication and who had a positive ($\geq 10^5$ CFU/mL) urine culture with no more than 2 uropathogens at baseline. Patients with missing response were counted as failures in this analysis.

† The Microbiologically Evaluable population included patients with a confirmed diagnosis of cUTI or AP, a causative organism(s) at baseline present at $\geq 10^5$ CFU/mL, a valid test-of-cure urine culture, no pathogen isolated from blood resistant to study drug, no premature discontinuation or loss to follow-up, and compliance with treatment (among other criteria).

Microbiologic eradication rates in the Microbiologically Evaluable population at TOC for individual pathogens recovered from patients randomized to LEVAQUIN® treatment are presented in Table 19.

Table 19: Bacteriological Eradication Rates for Individual Pathogens Recovered From Patients Randomized to LEVAQUIN® 750 mg QD for 5 Days Treatment

Pathogen	Bacteriological Eradication Rate (n/N)	%
Escherichia coli[*]	155/172	90
Klebsiella pneumoniae	20/23	87
Proteus mirabilis	12/12	100

[*] The predominant organism isolated from patients with AP was *E. coli*: 91% (63/69) eradication in AP and 89% (92/103) in patients with cUTI.

14.8 Complicated Urinary Tract Infections and Acute Pyelonephritis: 10-day Treatment Regimen

To evaluate the safety and efficacy of the 250 mg dose, 10 day regimen of LEVAQUIN®, 567 patients with uncomplicated UTI, mild-to-moderate cUTI, and mild-to-moderate AP were enrolled in a randomized, double-blind, multicenter clinical trial conducted in the US from June 1993 to January 1995 comparing LEVAQUIN® 250 mg orally once daily for 10 days (285 patients) with ciprofloxacin 500 mg orally twice daily for 10 days (282 patients). Patients with a resistant pathogen, recurrent UTI, women over age 55 years, and with an indwelling catheter were initially excluded, prior to protocol amendment which took place after 30% of enrollment. Microbiological efficacy was measured by bacteriologic eradication of the baseline organism(s) at 1–12 days post-therapy in patients with a pathogen identified at baseline.

The bacteriologic cure rates overall for LEVAQUIN® and control at the test-of-cure (TOC) visit for the group of all patients with a documented pathogen at baseline (modified intent to treat or mITT) and the group of patients in the mITT population who closely followed the protocol (Microbiologically Evaluable) are summarized in Table 20.

Table 20: Bacteriological Eradication Overall (cUTI or AP) at Test-Of-Cure[*]

	LEVAQUIN® 250 mg once daily for 10 days		**Ciprofloxacin** 500 mg twice daily for 10 days	
	n/N	%	n/N	%
mITT Population[†]	174/209	83.3	184/219	84.0
Microbiologically Evaluable Population[‡]	164/177	92.7	159/171	93.0

[*] 1–9 days posttherapy for 30% of subjects enrolled prior to a protocol amendment; 5–12 days posttherapy for 70% of subjects.

[†] The mITT population included patients who had a pathogen isolated at baseline. Patients with missing response were counted as failures in this analysis.

[‡] The Microbiologically Evaluable population included mITT patients who met protocol-specified evaluability criteria.

14.9 Inhalational Anthrax (Post-Exposure)

The effectiveness of LEVAQUIN® for this indication is based on plasma concentrations achieved in humans, a surrogate endpoint reasonably likely to predict clinical benefit.

LEVAQUIN® has not been tested in humans for the post-exposure prevention of inhalation anthrax. The mean plasma concentrations of LEVAQUIN® associated with a statistically significant improvement in survival over placebo in the rhesus monkey model of inhalational anthrax are reached or exceeded in adult and pediatric patients receiving the recommended oral and intravenous dosage regimens *[see Indications and Usage (1.13) and Dosage and Administration (2.1, 2.2)]*.

Levofloxacin pharmacokinetics have been evaluated in adult and pediatric patients. The mean (± SD) steady state peak plasma concentration in human adults receiving 500 mg orally or intravenously once daily is 5.7 ± 1.4 and 6.4 ± 0.8 mcg/mL, respectively; and the corresponding total plasma exposure (AUC_{0-24}) is 47.5 ± 6.7 and 54.6 ± 11.1 mcg.h/mL, respectively. The predicted steady-state pharmacokinetic parameters in pediatric patients ranging in age from 6 months to 17 years receiving 8 mg/kg orally every 12 hours (not to exceed 250 mg per dose) were calculated to be comparable to those observed in adults receiving 500 mg orally once daily *[see Clinical Pharmacology (12.3)]*. LEVAQUIN® Tablets can only be administered to pediatric patients with inhalational anthrax (post-exposure) or plague who are 30 kg or greater due to the limitations of the available strengths *[see Dosage and Administration (2.2)]*.

In adults, the safety of LEVAQUIN® for treatment durations of up to 28 days is well characterized. However, information pertaining to extended use at 500 mg daily up to 60 days is limited. Prolonged LEVAQUIN® therapy in adults should only be used when the benefit outweighs the risk.

In pediatric patients, the safety of levofloxacin for treatment durations of more than 14 days has not been studied. An increased incidence of musculoskeletal adverse events (arthralgia, arthritis, tendinopathy, gait abnormality) compared to controls has been observed in clinical studies with treatment duration of up to 14 days. Long-term safety data, including effects on cartilage, following the administration of levofloxacin to pediatric patients is limited *[see Warnings and Precautions (5.10) and Use in Specific Populations (8.4)]*.

A placebo-controlled animal study in rhesus monkeys exposed to an inhaled mean dose of 49 LD_{50} (~2.7×10^6) spores (range 17 – 118 LD_{50}) of *B. anthracis* (Ames strain) was conducted. The minimal inhibitory concentration (MIC) of levofloxacin for the anthrax strain used in this study was 0.125 mcg/mL. In the animals studied, mean plasma concentrations of levofloxacin achieved at expected T_{max} (1 hour post-dose) following oral dosing to steady state ranged from 2.79 to 4.87 mcg/mL. Steady state trough concentrations at 24 hours post-dose ranged from 0.107 to 0.164 mcg/mL. Mean (SD) steady state AUC_{0-24} was 33.4 ± 3.2 mcg.h/mL (range 30.4 to 36.0 mcg.h/mL). Mortality due to anthrax for animals that received a 30 day regimen of oral LEVAQUIN® beginning 24 hrs post exposure was significantly lower (1/10), compared to the

placebo group (9/10) [P = 0.0011, 2-sided Fisher's Exact Test]. The one levofloxacin treated animal that died of anthrax did so following the 30-day drug administration period.

14.10 Plague

Efficacy studies of LEVAQUIN® could not be conducted in humans with pneumonic plague for ethical and feasibility reasons. Therefore, approval of this indication was based on an efficacy study conducted in animals.

The mean plasma concentrations of LEVAQUIN® associated with a statistically significant improvement in survival over placebo in an African green monkey model of pneumonic plague are reached or exceeded in adult and pediatric patients receiving the recommended oral and intravenous dosage regimens *[see Indications and Usage (1.14) and Dosage and Administration (2.1), (2.2)]*.

Levofloxacin pharmacokinetics have been evaluated in adult and pediatric patients. The mean (± SD) steady state peak plasma concentration in human adults receiving 500 mg orally or intravenously once daily is 5.7 ± 1.4 and 6.4 ± 0.8 mcg/mL, respectively; and the corresponding total plasma exposure (AUC_{0-24}) is 47.5 ± 6.7 and 54.6 ± 11.1 mcg.h/mL, respectively. The predicted steady-state pharmacokinetic parameters in pediatric patients ranging in age from 6 months to 17 years receiving 8 mg/kg orally every 12 hours (not to exceed 250 mg per dose) were calculated to be comparable to those observed in adults receiving 500 mg orally once daily *[see Clinical Pharmacology (12.3)]*. LEVAQUIN® Tablets can only be administered to pediatric patients with inhalational anthrax (post-exposure) or plague who are 30 kg or greater due to the limitations of the available strengths *[see Dosage and Administration (2.2)]*.

A placebo-controlled animal study in African green monkeys exposed to an inhaled mean dose of 65 LD_{50} (range 3 to 145 LD_{50}) of *Yersinia pestis* (CO92 strain) was conducted. The minimal inhibitory concentration (MIC) of levofloxacin for the *Y. pestis* strain used in this study was 0.03 mcg/mL. Mean plasma concentrations of levofloxacin achieved at the end of a single 30-min infusion ranged from 2.84 to 3.50 mcg/mL in African green monkeys. Trough concentrations at 24 hours post-dose ranged from <0.03 to 0.06 mcg/mL. Mean (SD) AUC_{0-24} was 11.9 (3.1) mcg.h/mL (range 9.50 to 16.86 mcg.h/mL). Animals were randomized to receive either a 10-day regimen of i.v. LEVAQUIN® or placebo beginning within 6 hrs of the onset of telemetered fever (≥ 39ºC for more than 1 hour). Mortality in the LEVAQUIN® group was significantly lower (1/17) compared to the placebo group (7/7) [p<0.001, Fisher's Exact Test; exact 95% confidence interval (-99.9%, -55.5%) for the difference in mortality]. One levofloxacin-treated animal was euthanized on Day 9 post-exposure to *Y. pestis* due to a gastric

complication; it had a blood culture positive for *Y. pestis* on Day 3 and all subsequent daily blood cultures from Day 4 through Day 7 were negative.

16 HOW SUPPLIED/STORAGE AND HANDLING

LEVAQUIN® Tablets are supplied as 250, 500, and 750 mg capsule-shaped, coated tablets. LEVAQUIN® Tablets are packaged in bottles in the following configurations:

- 250 mg tablets are terra cotta pink and are imprinted: "LEVAQUIN" on one side and "250" on the other side
  - bottles of 50 (NDC 50458-920-50)
- 500 mg tablets are peach and are imprinted: "LEVAQUIN" on one side and "500" on the other side
  - bottles of 50 (NDC 50458-925-50)
- 750 mg tablets are white and are imprinted "LEVAQUIN" on one side and "750" on the other side
  - bottles of 20 (NDC 50458-930-20)

LEVAQUIN® Tablets should be stored at 15° to 30°C (59° to 86°F) in well-closed containers.

17 PATIENT COUNSELING INFORMATION

Advise the patient to read the FDA-approved patient labeling (Medication Guide).

Serious Adverse Reactions

Advise patients to stop taking LEVAQUIN® if they experience an adverse reaction and to call their healthcare provider for advice on completing the full course of treatment with another antibacterial drug.

Inform patients of the following serious adverse reactions that have been associated with LEVAQUIN or other fluoroquinolone use:

- **Disabling and Potentially Irreversible Serious Adverse Reactions That May Occur Together**: Inform patients that disabling and potentially irreversible serious adverse reactions, including tendinitis and tendon rupture, peripheral neuropathies, and central nervous system effects, have been associated with use of LEVAQUIN® and may occur together in the same patient. Inform patients to stop taking LEVAQUIN® immediately if they experience an adverse reaction and to call their healthcare provider.
- **Tendinitis and Tendon Rupture:** Instruct patients to contact their healthcare provider if they experience pain, swelling, or inflammation of a tendon, or weakness or inability to use one of their joints; rest and refrain from exercise; and discontinue LEVAQUIN® treatment. Symptoms may be irreversible. The risk of severe tendon disorder with fluoroquinolones is

higher in older patients usually over 60 years of age, in patients taking corticosteroid drugs, and in patients with kidney, heart or lung transplants.

- **Peripheral Neuropathies:** Inform patients that peripheral neuropathies have been associated with levofloxacin use, symptoms may occur soon after initiation of therapy and may be irreversible. If symptoms of peripheral neuropathy including pain, burning, tingling, numbness and/or weakness develop, immediately discontinue LEVAQUIN® and tell them to contact their physician.
- **Central Nervous System Effects** (for example, convulsions, dizziness, lightheadedness, increased intracranial pressure)**:** Inform patients that convulsions have been reported in patients receiving fluoroquinolones, including levofloxacin. Instruct patients to notify their physician before taking this drug if they have a history of convulsions. Inform patients that they should know how they react to LEVAQUIN® before they operate an automobile or machinery or engage in other activities requiring mental alertness and coordination. Instruct patients to notify their physician if persistent headache with or without blurred vision occurs.
- **Exacerbation of Myasthenia Gravis:** Instruct patients to inform their physician of any history of myasthenia gravis. Instruct patients to notify their physician if they experience any symptoms of muscle weakness, including respiratory difficulties.
- **Hypersensitivity Reactions:** Inform patients that levofloxacin can cause hypersensitivity reactions, even following a single dose, and to discontinue the drug at the first sign of a skin rash, hives or other skin reactions, a rapid heartbeat, difficulty in swallowing or breathing, any swelling suggesting angioedema (for example, swelling of the lips, tongue, face, tightness of the throat, hoarseness), or other symptoms of an allergic reaction.
- **Hepatotoxicity:** Inform patients that severe hepatotoxicity (including acute hepatitis and fatal events) has been reported in patients taking LEVAQUIN®. Instruct patients to inform their physician if they experience any signs or symptoms of liver injury including: loss of appetite, nausea, vomiting, fever, weakness, tiredness, right upper quadrant tenderness, itching, yellowing of the skin and eyes, light colored bowel movements or dark colored urine.
- **Diarrhea:** Diarrhea is a common problem caused by antibiotics which usually ends when the antibiotic is discontinued. Sometimes after starting treatment with antibiotics, patients can develop watery and bloody stools (with or without stomach cramps and fever) even as late as two or more months after having taken the last dose of the antibiotic. If this occurs, instruct patients to contact their physician as soon as possible.
- **Prolongation of the QT Interval:** Instruct patients to inform their physician of any personal or family history of QT prolongation or proarrhythmic conditions such as hypokalemia, bradycardia, or recent myocardial ischemia; if they are taking any Class IA (quinidine, procainamide), or Class III (amiodarone, sotalol) antiarrhythmic agents. Instruct patients to notify their physician if they have any symptoms of prolongation of the QT interval, including prolonged heart palpitations or a loss of consciousness.

- **Musculoskeletal Disorders in Pediatric Patients:** Instruct parents to inform their child's physician if the child has a history of joint-related problems before taking this drug. Inform parents of pediatric patients to notify their child's physician of any joint-related problems that occur during or following levofloxacin therapy *[see Warnings and Precautions (5.11) and Use in Specific Populations (8.4)]*.
- **Photosensitivity/Phototoxicity:** Inform patients that photosensitivity/phototoxicity has been reported in patients receiving fluoroquinolones. Inform patients to minimize or avoid exposure to natural or artificial sunlight (tanning beds or UVA/B treatment) while taking fluoroquinolones. If patients need to be outdoors while using fluoroquinolones, instruct them to wear loose-fitting clothes that protect skin from sun exposure and discuss other sun protection measures with their physician. If a sunburn-like reaction or skin eruption occurs, instruct patients to contact their physician.

Antibacterial Resistance

Antibacterial drugs including LEVAQUIN® should only be used to treat bacterial infections. They do not treat viral infections (e.g., the common cold). When LEVAQUIN® is prescribed to treat a bacterial infection, patients should be told that although it is common to feel better early in the course of therapy, the medication should be taken exactly as directed. Skipping doses or not completing the full course of therapy may (1) decrease the effectiveness of the immediate treatment and (2) increase the likelihood that bacteria will develop resistance and will not be treatable by LEVAQUIN® or other antibacterial drugs in the future.

Administration with Food, Fluids, and Concomitant Medications

Patients should be informed that LEVAQUIN® Tablets may be taken with or without food. The tablets should be taken at the same time each day.

Patients should drink fluids liberally while taking LEVAQUIN® to avoid formation of a highly concentrated urine and crystal formation in the urine.

Antacids containing magnesium, or aluminum, as well as sucralfate, metal cations such as iron, and multivitamin preparations with zinc or didanosine should be taken at least two hours before or two hours after oral LEVAQUIN® administration.

Drug Interactions with Insulin, Oral Hypoglycemic Agents, and Warfarin

Patients should be informed that if they are diabetic and are being treated with insulin or an oral hypoglycemic agent and a hypoglycemic reaction occurs, they should discontinue LEVAQUIN® and consult a physician.

Patients should be informed that concurrent administration of warfarin and LEVAQUIN® has been associated with increases of the International Normalized Ratio (INR) or prothrombin time and clinical episodes of bleeding. Patients should notify their physician if they are taking

warfarin, be monitored for evidence of bleeding, and also have their anticoagulation tests closely monitored while taking warfarin concomitantly.

Plague and Anthrax Studies

Patients given LEVAQUIN® for these conditions should be informed that efficacy studies could not be conducted in humans for ethical and feasibility reasons. Therefore, approval for these conditions was based on efficacy studies conducted in animals.

Active Ingredient Made in Japan

LEVAQUIN® Tablets are Manufactured by:

Janssen Ortho LLC, Gurabo, Puerto Rico 00778

Manufactured for:

Janssen Pharmaceuticals, Inc., Titusville, NJ 08560

MEDICATION GUIDE
LEVAQUIN® (Leave ah kwin)
(levofloxacin)
tablets

What is the most important information I should know about LEVAQUIN?

LEVAQUIN, a fluoroquinolone antibiotic, can cause serious side effects. Some of these serious side effects can happen at the same time and could result in death.

If you have any of the following serious side effects while you take LEVAQUIN, **you should stop taking LEVAQUIN immediately and get medical help right away.**

1. **Tendon rupture or swelling of the tendon (tendinitis).**
   - **Tendon problems can happen in people of all ages who take LEVAQUIN.** Tendons are tough cords of tissue that connect muscles to bones. **Some tendon problems include**:
     - pain
     - swelling
     - tears and swelling of tendons including the back of the ankle (Achilles), shoulder, hand, or other tendon sites.
   - The risk of getting tendon problems while you take LEVAQUIN is higher if you:
     - are over 60 years of age
     - are taking steroids (corticosteroids)
     - have had a kidney, heart or lung transplant.
   - Tendon problems can happen in people who do not have the above risk factors when they take LEVAQUIN.
   - Other reasons that can increase your risk of tendon problems can include:
     - physical activity or exercise
     - kidney failure
     - tendon problems in the past, such as in people with rheumatoid arthritis (RA)
   - Stop taking LEVAQUIN immediately and get medical help right away at the first sign of tendon pain, swelling or inflammation. Avoid exercise and using the affected area.
   - The most common area of pain and swelling is the Achilles tendon at the back of your ankle. This can also happen with other tendons. You may need a different antibiotic that is not a fluoroquinolone to treat your infection.
   - Tendon rupture can happen while you are taking or after you have finished taking LEVAQUIN. Tendon ruptures can happen within hours or days of taking LEVAQUIN and have happened up to several months after people have finished taking their fluoroquinolone.
   - Stop taking LEVAQUIN immediately and get medical help right away if you get any of the following signs or symptoms of a tendon rupture:
     - hear or feel a snap or pop in a tendon area
     - bruising right after an injury in a tendon area
     - unable to move the affected area or bear weight
2. **Changes in sensation and possible nerve damage (Peripheral Neuropathy)**. Damage to the nerves in arms, hands, legs, or feet can happen in people who take fluoroquinolones, including LEVAQUIN. Stop taking LEVAQUIN immediately and talk to your healthcare provider right away if you get any of the following symptoms of peripheral neuropathy in your arms, hands, legs, or feet:
   - pain
   - numbness

- burning
- tingling
- weakness

The nerve damage may be permanent.

3. **Central Nervous System (CNS) effects**. Seizures have been reported in people who take fluoroquinolone antibacterial medicines, including LEVAQUIN. Tell your healthcare provider if you have a history of seizures before you start taking LEVAQUIN. CNS side effects may happen as soon as after taking the first dose of LEVAQUIN. Stop taking LEVAQUIN immediately and talk to your healthcare provider right away if you get any of these side effects, or other changes in mood or behavior:

- seizures
- hear voices, see things, or sense things that are not there (hallucinations)
- feel restless
- tremors
- feel anxious or nervous
- confusion
- depression
- trouble sleeping
- nightmares
- feel lightheaded or dizzy
- feel more suspicious (paranoia)
- suicidal thoughts or acts
- headaches that will not go away, with or without blurred vision

4. **Worsening of myasthenia gravis (a problem that causes muscle weakness)**. Fluoroquinolones like LEVAQUIN may cause worsening of myasthenia gravis symptoms, including muscle weakness and breathing problems. Tell your healthcare provider if you have a history of myasthenia gravis before you start taking LEVAQUIN. Call your healthcare provider right away if you have any worsening muscle weakness or breathing problems.

What is LEVAQUIN?

LEVAQUIN is a fluoroquinolone antibiotic medicine used in adults age 18 years or older to treat certain infections caused by certain germs called bacteria. These bacterial infections include:

- nosocomial pneumonia
- community acquired pneumonia
- skin infections, complicated and uncomplicated
- chronic prostate infection
- inhalation anthrax germs
- plague
- urinary tract infections, complicated and uncomplicated
- acute kidney infection (pyelonephritis)
- acute sinus infection
- acute worsening or chronic bronchitis

Studies of LEVAQUIN for use in the treatment of plague and anthrax were done in animals only, because plague and anthrax could not be studied in people.

LEVAQUIN should not be used in patients with uncomplicated urinary tract infections, acute bacterial exacerbation of chronic bronchitis, or acute bacterial sinusitis if there are other treatment options available.

LEVAQUIN Tablets is also used to treat children who weigh at least 66 pounds (or at least 30 kilograms) and may have breathed in anthrax germs, have plague, or been exposed to plague germs.

It is not known if LEVAQUIN is safe and effective in children under 6 months of age.

The safety and effectiveness in children treated with LEVAQUIN for more than 14 days is not known.

Who should not take LEVAQUIN?

Do not take LEVAQUIN: if you have ever had a severe allergic reaction to an antibiotic known as a

fluoroquinolone, or if you are allergic to levofloxacin or any of the ingredients in LEVAQUIN. See the end of this leaflet for a complete list of ingredients in LEVAQUIN.

Before you take LEVAQUIN, tell your healthcare provider about all of your medical conditions, including if you:

- have tendon problems; LEVAQUIN should not be used in people who have a history of tendon problems.
- have a problem that causes muscle weakness (myasthenia gravis); LEVAQUIN should not be used in people who have a known history of myasthenia gravis.
- have central nervous system problems such as seizures (epilepsy).
- have nerve problems; LEVAQUIN should not be used in patients how have a history of a nerve problem called peripheral neuropathy.
- have or anyone in your family has an irregular heartbeat, especially a condition called “QT prolongation.”
- have low blood potassium (hypokalemia).
- have bone problems.
- have joint problems including rheumatoid arthritis (RA).
- have kidney problems. You may need a lower dose of LEVAQUIN if your kidneys do not work well.
- have liver problems.
- have diabetes or problems with low blood sugar (hypoglycemia).
- are pregnant or plan to become pregnant. It is not known if LEVAQUIN will harm your unborn child.
- are breastfeeding or plan to breastfeed. It is not known if LEVAQUIN passes into your breast milk. You and your healthcare provider should decide if you will take LEVAQUIN or breastfeed. You should not do both.

Tell your healthcare provider about all the medicines you take, including prescription and over-the-counter medicines, vitamins, and herbal supplements.

LEVAQUIN and other medicines can affect each other causing side effects.

Especially tell your healthcare provider if you take:

- a steroid medicine.
- an anti-psychotic medicine.
- a tricyclic antidepressant.
- a water pill (diuretic).
- certain medicines may keep LEVAQUIN from working correctly. Take LEVAQUIN either 2 hours before or 2 hours after taking these medicines or supplements:
    - an antacid, multivitamin, or other medicines or supplements that have magnesium, aluminum, iron, or zinc
    - sucralfate (Carafate®)
    - didanosine (Videx®, Videx® EC)
- a blood thinner (warfarin, Coumadin, Jantoven).
- an oral anti-diabetes medicine or insulin.
- an NSAID (Non-Steroidal Anti-Inflammatory Drug). Many common medicines for pain relief are NSAIDs. Taking an NSAID while you take LEVAQUIN or other fluoroquinolones may increase your risk of central nervous system effects and seizures.
- theophylline (Theo-24®, Elixophyllin®, Theochron®, Uniphyl®, Theolair®).
- a medicine to control your heart rate or rhythm (antiarrhythmics).

Ask your healthcare provider if you are not sure if any of your medicines are listed above.

Know the medicines you take. Keep a list of your medicines and show it to your healthcare provider and pharmacist when you get a new medicine.

How should I take LEVAQUIN?

- Take LEVAQUIN exactly as your healthcare provider tells you to take it.
- Take LEVAQUIN at about the same time each day.
- Drink plenty of fluids while you take LEVAQUIN.
- LEVAQUIN can be taken with or without food.
- If you miss a dose of LEVAQUIN, take it as soon as you remember. Do not take more than 1 dose in 1 day.
- Do not skip any doses of LEVAQUIN or stop taking it, even if you begin to feel better, until you finish your prescribed treatment unless:
    - you have tendon problems. See "**What is the most important information I should know about LEVAQUIN?**".
    - you have a nerve problem. See "**What are the possible side effects of LEVAQUIN?**".
    - you have a central nervous system problem. See "**What are the possible side effects of LEVAQUIN**?".
    - you have a serious allergic reaction. See "**What are the possible side effects of LEVAQUIN?**".
    - your healthcare provider tells you to stop taking LEVAQUIN.

Taking all of your LEVAQUIN doses will help make sure that all of the bacteria are killed. Taking all of your LEVAQUIN doses will help you lower the chance that the bacteria will become resistant to LEVAQUIN. If your infection does not get better while you take LEVAQUIN, it may mean that the bacteria causing your infection may be resistant to LEVAQUIN. If your infection does not get better, call your healthcare provider. If your infection does not get better, LEVAQUIN and other similar antibiotic medicines may not work for you in the future.

- If you take too much LEVAQUIN, call your healthcare provider or get medical help right away.

What should I avoid while taking LEVAQUIN?

- LEVAQUIN can make you feel dizzy and lightheaded. **Do not** drive, operate machinery, or do other activities that require mental alertness or coordination until you know how LEVAQUIN affects you.
- Avoid sunlamps, tanning beds, and try to limit your time in the sun. LEVAQUIN can make your skin sensitive to the sun (photosensitivity) and the light from sunlamps and tanning beds. You could get severe sunburn, blisters or swelling of your skin. If you get any of these symptoms while you take LEVAQUIN, call your healthcare provider right away. You should use a sunscreen and wear a hat and clothes that cover your skin if you have to be in sunlight.

What are the possible side effects of LEVAQUIN?

LEVAQUIN may cause serious side effects, including:

- See **"What is the most important information I should know about LEVAQUIN?"**
- **Serious allergic reactions.**

Allergic reactions can happen in people taking fluoroquinolones, including LEVAQUIN, even after only 1 dose. Stop taking LEVAQUIN and get emergency medical help right away if you have any of the following symptoms of a severe allergic reaction:

- hives
- trouble breathing or swallowing
- swelling of the lips, tongue, face
- throat tightness, hoarseness
- rapid heartbeat
- faint
- skin rash

Skin rash may happen in people taking LEVAQUIN, even after only 1 dose. Stop taking LEVAQUIN at the first sign of a skin rash and immediately call your healthcare provider. Skin rash may be a sign of a more serious reaction to LEVAQUIN.

- **Liver damage (hepatotoxicity)**: Hepatotoxicity can happen in people who take LEVAQUIN. Call your healthcare provider right away if you have unexplained symptoms such as:
    - nausea or vomiting
    - stomach pain
    - fever
    - weakness
    - abdominal pain or tenderness
    - itching
    - unusual tiredness
    - loss of appetite
    - light colored bowel movements
    - dark colored urine
    - yellowing of your skin or the whites of your eyes

Stop taking LEVAQUIN and tell your healthcare provider right away if you have yellowing of your skin or white part of your eyes, or if you have dark urine. These can be signs of a serious reaction to LEVAQUIN (a liver problem).

- **Intestine infection (Pseudomembranous colitis)**

  Pseudomembranous colitis can happen with many antibiotics, including LEVAQUIN. Call your healthcare provider right away if you get watery diarrhea, diarrhea that does not go away, or bloody stools. You may have stomach cramps and a fever. Pseudomembranous colitis can happen 2 or more months after you have finished your antibiotic.

- **Serious heart rhythm changes (QT prolongation and torsades de pointes)**

  Tell your healthcare provider right away if you have a change in your heart beat (a fast or irregular heartbeat), or if you faint. LEVAQUIN may cause a rare heart problem known as prolongation of the QT interval. This condition can cause an abnormal heartbeat and can be very dangerous. The chances of this happening are higher in people:

    - who are elderly
    - with a family history of prolonged QT interval
    - with low blood potassium (hypokalemia)
    - who take certain medicines to control heart rhythm (antiarrhythmics)

- **Joint Problems**

  Increased chance of problems with joints and tissues around joints in children can happen. Tell your child's healthcare provider if your child has any joint problems during or after treatment with LEVAQUIN.

- **Changes in blood sugar**

  People who take LEVAQUIN and other fluoroquinolone medicines with oral anti-diabetes medicines or with insulin can get low blood sugar (hypoglycemia) and high blood sugar (hyperglycemia). Follow your healthcare provider's instructions for how often to check your blood sugar. If you have diabetes and you get low blood

sugar while taking LEVAQUIN, stop taking LEVAQUIN and call your healthcare provider right away. Your antibiotic medicine may need to be changed.

- **Sensitivity to sunlight (photosensitivity**)

  See "**What should I avoid while taking LEVAQUIN?**"

  The most common side effects of LEVAQUIN include:

  - nausea
  - headache
  - diarrhea
  - insomnia
  - constipation
  - dizziness

In children 6 months and older who take LEVAQUIN to treat anthrax disease or plague, vomiting is also common.

LEVAQUIN may cause false-positive urine screening results for opiates when testing is done with some commercially available kits. A positive result should be confirmed using a more specific test.

These are not all the possible side effects of LEVAQUIN.

Call your doctor for medical advice about side effects. You may report side effects to FDA at 1-800-FDA-1088.

How should I store LEVAQUIN?

- Store LEVAQUIN at room temperature between 59°F to 86° F (15°C to 30°C).
- Keep LEVAQUIN in a tightly closed container.

General information about the safe and effective use of LEVAQUIN.

Medicines are sometimes prescribed for purposes other than those listed in a Medication Guide. Do not use LEVAQUIN for a condition for which it is not prescribed. Do not give LEVAQUIN to other people, even if they have the same symptoms that you have. It may harm them.

This Medication Guide summarizes the most important information about LEVAQUIN. If you would like more information about LEVAQUIN, talk with your healthcare provider. You can ask your healthcare provider or pharmacist for information about LEVAQUIN that is written for healthcare professionals.

What are the ingredients in LEVAQUIN?
Active ingredient: levofloxacin
Inactive ingredients: crospovidone, hypromellose, magnesium stearate, microcrystalline cellulose, polyethylene glycol, polysorbate 80, titanium dioxide.
LEVAQUIN 250 mg Tablets also contain synthetic red iron oxide.
LEVAQUIN 500 mg Tablets also contain synthetic red iron oxide and synthetic yellow iron oxide.
Manufactured by:
Active Ingredient Made in Japan
Finished Product Manufactured by:
•Janssen Ortho LLC, Gurabo, Puerto Rico 00778
Manufactured for:
•Janssen Pharmaceuticals, Inc., Titusville, NJ 08560

For more information, go to www.levaquin.com or call 1-800-526-7736

This Medication Guide has been approved by the U.S. Food and Drug Administration Revised: 07/2018