

Bon Secours Richmond
Pharmacy & Therapeutics Committees
Cipro XR
7/2004

Recommendations

- Cipro XR is not recommended for formulary inclusion as efficacy is equivalent to the immediate release formulation, but cost is 20-30 times more per day of therapy.
- Ciprofloxacin immediate release will be autosubstituted and will be given twice daily providing the same total daily dose at MRMC and SMH.

Dosage Equivalence for MRMC and SMH	
Ordered	Dispense
Cipro XR 500 mg QD	Ciprofloxacin 250 mg BID
Cipro XR 1000 mg QD	Ciprofloxacin 500 mg BID

- Levaquin once daily will be auto substituted for Cipro XR at RCH

Dosage Equivalence for RCH		
Dispense	Ordered	Ordered
Levaquin 250 mg QD	Cipro XR 500 mg QD	Ciprofloxacin 250 mg BID
Levaquin 500 QD	Cipro XR 1000 mg QD	Ciprofloxacin 500 mg BID

Findings

- Indication: Cipro XR is indicated for treatment of urinary tract infections (complicated and uncomplicated) and acute uncomplicated pyelonephritis.
- Dose:
 - Uncomplicated UTI: 500mg po q 24 h for 3 days
 - Complicated UTI: 1000mg po q 24 h for 7 to 14 days
 - Acute Complicated Pyelonephritis: 1000mg po q 24 h for 7 to 14 days
- Contraindications: Hypersensitivity to ciprofloxacin or any member of the quinolone class
- Warnings:
 - No safety or efficacy data for persons <18 years-old, pregnant women, and nursing women
 - Convulsions, increased intracranial pressure, and toxic psychosis
 - Use with caution in patients with a known lowered seizure threshold
 - CNS events: dizziness, confusion, tremors, hallucinations, depression, and possible suicidal thoughts/acts.
 - Concurrent administration of theophylline and ciprofloxacin may result in serious and fatal reactions such as:
 - Cardiac arrest, seizure, status epilepticus, and respiratory failure
- Drug Interactions
 - Concurrent use of ciprofloxacin with theophylline: increased serum concentrations of theophylline
 - Concurrent use of ciprofloxacin with caffeine: decreased clearance of caffeine and prolonged half-life of caffeine
 - Concurrent use of ciprofloxacin with multivalent cation-containing products: decreases serum and urine levels of ciprofloxacin
 - Concurrent use of ciprofloxacin with warfarin: enhanced effects of warfarin may be seen

Package Insert Data						
	Levaquin 250 mg qd	Levaquin 500 mg qd	Cipro 250mg bid	Cipro XR 500mg	Cipro 500 mg bid	Cipro XR 1000 mg
Half-life (hr)		7.6	4.8	6.6	5.66	6.3
Tmax (hr)		1.1	1.0	1.5	2	2
Cmax (mg/L)		5.7	1.14	1.59	2.06	3.11
AUC (mg*h/L)		47.5	8.25	7.97	17.04	16.83
% Excreted Unchanged		87%	35%	35%	35%	35%
Urine Concentration (Average)						
<= 4 hours post dose				300 mcg/ml		300 mcg/ml
12-24 post dose				27 mcg/ml		58 mcg/ml
Indications						
Uncomplicated UTI	+		+	+		
Complicate UTI	+				+	+
Acute Uncomplicated Pyelonephritis	+				+	+
Chronic Prostatitis		+			+	

Indications per Package Insert			
	Levofloxacin	Cipro immediate release	Cipro XR
UTI	E. coli, K. pneumoniae, S. saprophyticus,	E. coli, K. pneumoniae, E. cloacae, S. marcescens, P. mirabilis, P. rettgeri, M. morgannii, C. diversus, C. freundii, P. aeruginosa, S. epidemidis, S. saprophyticus, E. faecalis	E. coli, P. mirabilis, E. faecalis, S. saprophyticus
Complicated UTI	E. faecalis, E. cloacae, E. coli, K. pneumoniae, P. mirabilis, P. aeruginosa	E.coli	E. coli, K. pneumoniae, E. faecalis, P. mirabilis, or P. aeruginosa
Pyelonephritis	E. coli	E.coli	E.coli
Chronic Prostatitis	E. Coli, E. faecalis, S. epi.	E.coli, P. mirabilis	

Clinical Trial Data from Package Insert Data		
Uncomplicated urinary Tract Infections		
	Cipro 250 mg BID x 3 days	Cipro XR 500 mg QD x 3 days
N	453	452
Per Protocol Patients	223	199
Bacteriologic Eradication	93.7% (209/223)	94.5% (188/199)
Clinical Response	91.5%	95%
Complicated Urinary Tract Infections		
	Cipro 500 mg BID	Cipro XR 1000 mg QD
N	521	521
Randomized	521	521
Per Protocol Patients	229	206
Bacteriologic Eradication	81.4%	89.2%
Acute Uncomplicated Pyelonephritis		
Bacteriological Eradication	98.1%	87.5%
Clinical Cure	96.2%	97.5%

* No statistically significant difference was found between Cipro and Cipro XR.

	Bon Secours Cost Per Day of Therapy	
Levaquin 250 mg QD	Ciprofloxacin 250 mg BID	Cipro XR 500 mg QD
\$6.49	\$0.2058	\$6.17
Levaquin 500 mg QD	Ciprofloxacin 500 mg BID	Cipro XR 1000 mg QD
\$7.43	\$0.2938	\$7.03

Comparison of once-daily extended-release ciprofloxacin and conventional twice-daily ciprofloxacin for the treatment of uncomplicated urinary tract infection in women

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Clin Ther. 2002 Dec;24(12):2088-104.

Background: Trimethoprim/sulfamethoxazole (TMP/SMX) is currently the first choice for empiric therapy of acute uncomplicated urinary tract infection (UTI) in women. In areas where resistance to TMP/SMX is known to be high, ciprofloxacin and other fluoroquinolones are recommended as first-line choices for the empiric therapy of UTI. **Objective:** This study compared the efficacy and safety profile of once-daily extended-release ciprofloxacin 500 mg (referred to hereafter as ciprofloxacin QD) with those of conventional ciprofloxacin 250 mg BID, each administered orally for 3 days, in the treatment of uncomplicated UTI in women. **Methods:** In this multicenter, prospective, randomized, double-blind, double-dummy, Phase III trial, adult women with clinical signs and symptoms of acute uncomplicated UTI, pyuria, and a positive pretherapy urine culture ($\geq 10^5$ colony-forming units/mL) received ciprofloxacin QD or ciprofloxacin BID. Bacteriologic and clinical outcomes were assessed at the test-of-cure visit (4–11 days after completion of therapy) and the late follow-up visit (25–50 days after completion of therapy). Exclusion criteria: asymptomatic infection, suspicion of complicated UTI, symptoms of UTI within the last 4 weeks, 3 or more previous UTI within the past year, evidence of predisposing factors to UTI, history of fluoroquinolone hypersensitivity, history of tendinopathy associated with the use of fluoroquinolones, immunosuppression, use of systemic antimicrobial agent within 48 hours before enrollment, ingestion of sucralfate or cation-containing antacid less than 6 hours before or less than 2 hours after administration of study drug, serum creatinine greater than or equal to 3.0 mg/dL or creatinine clearance less than 30, and liver impairment. **Results:** The intent-to-treat population consisted of 891 patients (444 ciprofloxacin QD, 447 ciprofloxacin BID); 422 patients were evaluable for efficacy (199 ciprofloxacin QD, 223 ciprofloxacin BID). At the test-of-cure visit, bacteriologic eradication was achieved in 94.5% (188/199) of the ciprofloxacin QD group and 93.7% (209/223) of the ciprofloxacin BID group (95% CI, –3.5 to 5.1). Clinical cure was achieved in 95.5% (189/198) of the ciprofloxacin QD group and 92.7% (204/220) of the ciprofloxacin BID group (95% CI, –1.6 to 7.1). Bacteriologic and clinical outcomes at the late follow-up visit were consistent with the test-of-cure findings. The rate of eradication of *Escherichia coli*, the most prevalent organism, was >97% in each treatment group. Rates of drug-related adverse events were similar with the once- and twice-daily ciprofloxacin regimens (10% and 9%, respectively). **Conclusion:** Extended-release ciprofloxacin 500 mg given once daily for 3 days was as effective and well tolerated as conventional ciprofloxacin 250 mg given twice daily for 3 days in the treatment of acute uncomplicated UTI in women.

Extended-release ciprofloxacin (Cipro XR) for treatment of urinary tract infections.

Talan DA, Naber KG, Palou J, Elkharrat D.

Int J Antimicrob Agents. 2004 Mar;23 Suppl 1:S54-66.

Symptomatic urinary tract infections (UTIs) constitute a major health problem throughout the Western world. In the USA, UTIs are responsible for 7-8 million outpatient visits each year and for over one-third of all hospital-acquired infections. Empiric antimicrobial therapy for UTIs, which are primarily caused by *Escherichia coli*, is increasingly being complicated by the emergence of resistance to the most widely used agents. Recent studies indicate that the prevalence of *E. coli* resistance to trimethoprim/sulphamethoxazole (TMP/SMX), the current first-line therapy for UTIs, exceeds 20% in many North American regions. Importantly, antibiotic resistance often translates into clinical failure. The use of antibiotics with favourable pharmacokinetic/pharmacodynamic profiles and convenient dosing schedules, which effectively increase bacterial eradication and patient

compliance, can help to curb the current epidemic of resistance and reduce the rate of clinical failure associated with resistance. Fluoroquinolones have well-established efficacy in the treatment of multiple bacterial infections and, over the years, the rates of resistance to these antibiotics have remained very low. Fluoroquinolones are currently recommended for therapy of uncomplicated UTIs when the local incidence of TMP/SMX resistance is $\geq 10\text{-}20\%$, as well as for the treatment of complicated UTIs and acute pyelonephritis. Ciprofloxacin, one of the most widely used fluoroquinolones, has a potent bactericidal effect across the full spectrum of uropathogens, as well as a long and excellent efficacy and safety record in the management of UTI and other infections. A recently developed extended (modified)-release formulation of ciprofloxacin (Cipro XR or Cipro XL) provides higher maximum plasma concentrations with lower inter-patient variability than the conventional, immediate-release, twice-daily formulation. Additionally, therapeutic drug levels with extended-release ciprofloxacin are achieved rapidly and maintained over the course of 24 h, allowing once-daily dosing. Clinical trials in patients with cystitis and those with complicated UTIs or acute uncomplicated pyelonephritis indicate that extended-release ciprofloxacin is at least as effective as the immediate-release formulation. These studies have also confirmed good tolerability and safety of extended-release ciprofloxacin, similar to the immediate-release formulation. Therefore, extended-release ciprofloxacin is a convenient, well-tolerated and effective therapy for UTIs that may improve patients' compliance with treatment and thus decrease the risk of treatment failure and the spread of antibiotic resistance.

Novel pharmacokinetic-pharmacodynamic model for prediction of outcomes with an extended-release formulation of ciprofloxacin.

Meagher AK, Forrest A, Dalhoff A, Stass H, Schentag JJ.

Antimicrob Agents Chemother. 2004 Jun;48(6):2061-8

The pharmacokinetics of an extended-release (XR) formulation of ciprofloxacin has been compared to that of the immediate-release (IR) product in healthy volunteers. The only significant difference in pharmacokinetic parameters between the two formulations was seen in the rate constant of absorption, which was approximately 50% greater with the IR formulation. The geometric mean plasma ciprofloxacin concentrations were applied to an in vitro pharmacokinetic-pharmacodynamic model exposing three different clinical strains of *Escherichia coli* (MICs, 0.03, 0.5, and 2.0 mg/liter) to 24 h of simulated concentrations in plasma. A novel mathematical model was derived to describe the time course of bacterial CFU, including capacity-limited replication and first-order rate of bacterial clearance, and to model the effects of ciprofloxacin concentrations on these processes. A "mixture model" was employed which allowed as many as three bacterial subpopulations to describe the total bacterial load at any moment. Comparing the two formulations at equivalent daily doses, the rates and extents of bacterial killing were similar with the IR and XR formulations at MICs of 0.03 and 2.0 mg/liter. At an MIC of 0.5 mg/liter, however, the 1,000-mg/day XR formulation showed a moderate advantage in antibacterial effect: the area under the CFU-time curve was 45% higher for the IR regimen; the nadir log CFU and 24-h log CFU values for the IR regimen were 3.75 and 2.49, respectively; and those for XR were 4.54 and 3.13, respectively. The mathematical model explained the differences in bacterial killing rate for two regimens with identical AUC/MIC ratios.

J Urol. 2004 Feb;171(2 Pt 1):734-9.

Once daily, extended release ciprofloxacin for complicated urinary tract infections and acute uncomplicated pyelonephritis.

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PURPOSE: We assessed the efficacy and safety of 1,000 mg extended release ciprofloxacin orally once daily vs conventional 500 mg ciprofloxacin orally twice daily, each for 7 to 14 days, in patients with a complicated urinary tract infection (cUTI) or acute uncomplicated pyelonephritis (AUP). **MATERIALS AND METHODS:** In this prospective, randomized, double-blind, North American multicenter clinical trial adults were stratified based on clinical presentation of cUTI or AUP and randomized to extended release ciprofloxacin or ciprofloxacin twice daily. Efficacy valid patients had positive pretherapy urine cultures (10⁵ or greater cFU/ml) and pyuria within 48 hours of study entry. Bacteriological and clinical outcomes were assessed at the test of cure visit (5 to 11 days after therapy) and the late followup visit (28 to 42 days after therapy). **RESULTS:** The intent to treat population comprised 1,035 patients (extended release ciprofloxacin in 517 and twice daily in 518), of whom 435 were efficacy valid (cUTI in 343 and AUP in 92). For efficacy valid patients (cUTI and AUP combined) bacteriological eradication rates at test of cure were 89% (183 of 206) vs 85% (195 of 229) (95% CI -2.4%, 10.3%) and clinical cure rates were 97% (198 of 205) vs 94% (211 of 225) (95% CI -1.2%, 6.9%) for extended release vs twice daily ciprofloxacin. Late followup outcomes were consistent with test of cure findings. Eradication rates for *Escherichia coli*, which accounted for 58% of pathogens, were 97% or greater per group. Drug related adverse event rates were similar for extended release and twice daily ciprofloxacin (13% and 14%, respectively). **CONCLUSIONS:** Extended release ciprofloxacin at a dose of 1,000 mg once daily was as safe and effective as conventional treatment with 500 mg ciprofloxacin twice daily, each given orally for 7 to 14 days in adults with cUTI or AUP. It provides a convenient, once daily, empirical treatment option