Contract Implementation Guidance
Workhorse Fluoroquinolone

VHA Pharmacy Benefits Management Strategic Healthcare Group and the Medical Advisory Panel

The following recommendations are based on current medical evidence and expert opinion from clinicians. The content of the document is dynamic and will be revised as new clinical data becomes available. The purpose of this document is to assist practitioners in clinical decision-making, to standardize and improve the quality of patient care, and to promote cost-effective drug prescribing. The clinician should utilize this guidance and interpret it in the clinical context of the individual patient situation.

Introduction

Effective January 15, 2004 a joint DoD/VA open class contract was awarded to gatifloxacin (Tequin®) for a workhorse quinolone. This contract includes only oral formulation s of this agent, gatifloxacin 200 and 400 mg tablets. It is a one-year contract with four additional option years. This drug class will remain "open", which means that VISN are permitted to add additional products within the drug class on their VISN formularies. The contract does not mandate that patients currently receiving a course of oral fluoroquinolone therapy be switched to gatifloxacin.

Current formulary status of Fluoroquinolones in the VA

The VA National Formulary includes:

Ciprofloxacin IV and PO

Gatifloxacin IV and PO

The MAP and VISN Formulary Leaders removed Levofloxacin from the VA National Formulary in January 2004. This will not affect VISN Formulary status of the agent unless the VISN level Formulary Committee makes a decision.

Patient Selection

If a patient has a medical necessity to use a fluroquinolone, agent selection should be based on patient specific parameters such as, renal function, comorbidities, previous antibiotic therapy, concurrent medications, possible infections agents and/or susceptibility testing. Several consensus guidelines are available to aid the clinician in selection.

Acute sinusitis: The March 2001 American College of Physicians position paper on appropriate antibiotic use for acute sinusitis in adults states that most cases of sinusitis do not require antibiotic treatment. The position paper recommends patients with severe or persistent moderate symptoms and specific findings of bacterial sinusitis should be treated with narrow-spectrum antibiotics such as amoxicillin, doxycycline or trimethoprim/sulfamethoxazole as first-line agents. Broader spectrum antibiotics, like the fluoroquinolones, should be reserved for second-line therapy or for persons with severe symptoms.

Community-Acquired Pneumonia (CAP): The 2003 Infectious Disease Society of America (IDSA) CAP Guidelines recommend use of erythromycin, azithromycin, clarithromycin, and doxycycline as initial antibiotic treatment in outpatients with no recent antibiotic use and no co-morbidities. In patients recently treated with other antibiotics or with co-morbidities a fluoroquinolone (gatifloxacin, levofloxacin, or moxifloxacin) may be appropriate. Inpatients with CAP should receive an agent active against penicillin-resistant *S. pneumoniae*. This generally entails the use of a β-lactam agent such as ceftriaxone or cefotaxime or the use of a respiratory fluoroquinolone such gatifloxacin, levofloxacin or moxifloxacin. Gatifloxacin is not active against *P. aeruginosa* and thus should not be relied upon in patients with severe structural lung disease (e.g., bronchiectasis), cystic fibrosis, or recent hospitalization with receipt of antimicrobials (especially if in an Intensive Care Unit). Please refer to **Table 1** for the IDSA statement regarding CAP.

Acute exacerbations of chronic bronchitis: Gatifloxacin has been approved for the treatment of acute bacterial exacerbation of chronic bronchitis. The NHLBI/WHO Workshop summary for the treatment of acute exacerbations of chronic bronchitis conclude the antibiotics are only effective when patients with worsening dyspnea and cough also have increased sputum volume and purulence. Similar principles pertain to the selection of antimicrobial therapy for acute exacerbations of chronic bronchitis as for the outpatient treatment of CAP.

Urinary Tract Infections: Gatifloxacin has been approved for the treatment of uncomplicated and complicated urinary tract infections including pyelonephritis due to *Enterobacteriaceae*. Gatifloxacin is not effective in the treatment of urinary tract infections due to *P. aeruginosa*.

Safety concerns with fluroquinolone therapy involve the use of these agents in specific populations.

- Patients with a history of long QT syndrome, hypokalemia or who are receiving Class Ia or class III antiarrhythmic agents (quinidine, disopyramide, procainamide, sotalol, amiodarone, dofetilide, ibutilide) are predisposed to development of Torsades or other cardiac arrhythmias. These arrhythmias have been reported with levofloxacin, gatifloxacin and moxifloxacin. These fluoroquinolones should be avoided in this patient population.

- Diabetic patients receiving oral hypoglycemic agents or insulin and a fluoroquinolone appear to be at increased risk for dysglycemic events, although these events are rare. Patients receiving glyburide, glipizide or insulin may be those most at risk for developing dysglycemias. In these patients, hypoglycemia appears to occur more frequently in the first 2-3 days of therapy. Hyperglycemia appears to occur later in a course of therapy. Elderly patients who may have unrecognized diabetes, age related decrease in renal function, underlying medical problems, and/or are taking concomitant medications associated with hyperglycemia may also be at particular risk for serious hyperglycemia. Dysglycemic events have been reported more frequently with gatifloxacin than with other fluoroquinolones, however the true difference in incidence is unknown and all fluoroquinolones increase the risk of dysglycemia.

- All fluoroquinolones should be used with caution in the diabetic population. All diabetic patients treated with any fluoroquinolone should be counseled regarding the possibility of hypo- or hyperglycemia during fluoroquinolone treatment. Patients may require increased home glucose testing to monitor this. Patients and/or caregivers should be reminded of the symptoms of both hypo and hyperglycemia, when to seek additional medical care and how to monitor their course of therapy.

- Patients with compromised renal function require dosage adjustment for most quinolones. Moxifloxacin is an exception to this since it is not renally excreted. The following summarizes the dose adjustments for levofloxacin and gatifloxacin. Failure to adjust the dosage in renal impairment may predispose the patient to other adverse effects such as dysglycemias.

Renal dose adjustment for gatifloxacin- all doses are given once daily

	Urinary Tract Infection		*All other Indications*	
Creatinine Clearance	*Initial gatifloxacin dose*	*Subsequent dose*	*Initial gatifloxacin dose*	*Subsequent dose*
≥ 40 ml/min	200 mg	200 mg	400 mg	400 mg
<40 ml/min	200 mg	200 mg	400 mg	200 mg
Hemodialysis	200 mg	200 mg	400 mg	200 mg
CAPD*	200 mg	200 mg	400 mg	200 mg

* chronic ambulatory peritoneal dialysis

Renal Dose adjustment for levofloxacin- doses are given once daily unless otherwise noted

	Urinary Tract Infection, Pyelonephritis		*AECB, SSI, Prostatitis, CAP, Acute sinusitis*		*Complicated SSI, nosocomial pneumonia*	
Creatinine Clearance	*Initial levofloxacin dose*	*Subsequent dose*	*Initial levofloxacin dose*	*Subsequent dose*	*Initial levofloxacin dose*	*Subsequent dose*
≥50 ml/min	250 mg	250 mg	500 mg	500 mg	750 mg	750 mg
≥20 ml/min	250 mg	250 mg	500 mg	250 mg	750 mg	750 mg QOD
≥10 ml/min	250 mg	250 mg QOD*	500 mg	250 mg QOD	750 mg	500 mg QOD
Hemodialysis	250 mg	250 mg QOD	500 mg	250 mg QOD	750 mg	500 mg QOD
CAPD[@]	250 mg	250 mg QOD	500 mg	250 mg QOD	750 mg	500 mg QOD

Hospital acquired pneumonia * every other day [@] chronic ambulatory peritoneal dialysis

Contract Prices:

Gatifloxacin (Tequin®) Price Information					
Strength	**Dosage Form**	**NDC**	**Package Size**	**Price per Package**	**Price per Tablet**
200mg	Tablet	00015-1117-50	30	$40.50	$1.35
400 mg	Tablet	00015-1177-60	50	$67.50	$1.35
200 mg	Tablet	00015-1117-80	100	$135.00	$1.35
400 mg	Tablet	00015-1177-80	100	$135.00	$1.35
400 mg	Tablet	00015-1177-21	3 Teq-paqs (5 tabs ea)	$20.25	$1.35

Current FSS prices for Cipro are 250 mg- $2.68, 500 MG $2.74 AND 750 MG $3.33

Economic Impact of the Contract:

We do not have definitive price information at this time, but the price of levofloxacin is expected to increase to the FSS price of $5.26 per tablet on 31 January 2004. **Table 3** shows the range of potential cost savings that can result from using gatifloxacin instead of levofloxacin.

Table 3. Potential Cost Savings with Gatifloxacin Contract				
Drug (Oral formulations only)	Cost/day	Cost savings/day with gatifloxacin	Cost/ 10-day course of therapy	Cost savings/10-day course of therapy with gatifloxacin
Levofloxacin	$2.01 to $5.26/day	$0.65 to $3.91/day	$20.00 to $52.60/ 10 day course	$6.50 to $39.10/ 10 day course
Gatifloxacin	$1.35/day		$13.50/ 10 day course	

References

1. Package insert Tequin®. Bristol Meyers Squibb Company, Princeton, NJ. 2003

2. Package insert Cipro® Bayer Corporation. West Haven, CT, 2003.

3. Package insert Levaquin®. Ortho Mc-Neil Pharmaceutical, Inc. Raritan NJ. 2003.

4. Maeda N, Tamagawa T, Niki I, et al. Increase in insulin release from rat pancreas islets by quinolone antibiotics. Br J Pharmacol 1996 Jan;117(2):372-376.

5. Gajjar DA, LaCreta FP, Kollia GD, et al. Effect of multiple dose gatifloxacin and ciprofloxacin on glucose homeostasis and insulin production in patients with non insulin dependent diabetes mellitus maintained with diet and exercise. Pharmacotherapy 2000;20(6 part 2):76S-86S.

6. Zunker BJ, Wos Maria. Effects of lomefloxacin and norfloxacin on pancreatic B-cell ATP-sensitive K channels. Life Sciences 2003.

7. Data on file, Bristol Meyers Squibb Company

8. Data on file, Bayer Corporation.

9. Data on file, Ortho McNeil Pharmaceuticals.

10. Unpublished data and personal communication, Richard Frothingham M.D.

11. Unpublished data, VA Center for Medication Safety

12. Frothingham R. Rates of Torsades de pointes associated with ciprofloxacin, ofloxacin, levofloxacin, gatifloxacin and moxifloxacin. Pharmacotherapy 21(12);1468-1472, 2001.

13. Curtis LH, Ostbye T, Sendersky V, et al. Prescription of QT prolonging drugs in a cohort of about 5 million outpatients. Am J Med 2003;114(2).

14. Noel GJ, Natarajan J, Chien S, et al. Effects of three fluoroquinolones on QT interval in healthy adults after single doses. Clin Pharmacol Ther 2003;73:293-303.

15. Mandell LA, Bartlett JG, Dowell SF, File TM, Jr., Musher DM, Whitney C. Update of practice guidelines for the management of community-acquired pneumonia in immunocompetent adults. Clin Infect Dis. 2003; 37:1405-33.

16. Pauwels RA, Buist AS, Calverley PM, Jenkins CR, Hurd SS. Global strategy for the diagnosis, management, and prevention of chronic obstructive pulmonary disease. NHLBI/WHO Global Initiative for Chronic Obstructive Lung Disease (GOLD) Workshop summary. Am J Respir Crit Care Med. 2001; 163:1256-76.

17. Snow V, Mottur-Pilson C, Hickner JM. Principles of appropriate antibiotic use for acute sinusitis in adults. Ann Intern Med. 2001; 134:495-7.

Table 1. Initial empiric therapy for suspected bacterial community-acquired pneumonia (CAP) in immunocompetent adults.

Patient variable	Preferred treatment options
Outpatient	
Previously healthy	
No recent antibiotic therapy	A macrolide[a] or doxycycline
Recent antibiotic therapy[b]	A respiratory fluoroquinolone[c] alone, an advanced macrolide[d] plus high-dose amoxicillin,[e] or an advanced macrolide plus high-dose amoxicillin-clavulanate[f]
Comorbidities (COPD, diabetes, renal or congestive heart failure, or malignancy)	
No recent antibiotic therapy	An advanced macrolide[d] or a respiratory fluoroquinolone
Recent antibiotic therapy	A respiratory fluoroquinolone[c] alone or an advanced macrolide plus a β-lactam[g]
Suspected aspiration with infection	Amoxicillin-clavulanate or clindamycin
Influenza with bacterial superinfection	A β-lactam[g] or a respiratory fluoroquinolone
Inpatient	
Medical ward	
No recent antibiotic therapy	A respiratory fluoroquinolone alone or an advanced macrolide plus a β-lactam[h]
Recent antibiotic therapy	An advanced macrolide plus a β-lactam or a respiratory fluoroquinolone alone (regimen selected will depend on nature of recent antibiotic therapy)
ICU	
Pseudomonas infection is not an issue	A β-lactam[h] plus either an advanced macrolide or a respiratory fluoroquinolone
Pseudomonas infection is not an issue but patient has a β-lactam allergy	A respiratory fluoroquinolone, with or without clindamycin
Pseudomonas infection is an issue[i]	Either (1) an antipseudomonal agent[j] plus ciprofloxacin, or (2) an antipseudomonal agent plus an aminoglycoside[k] plus a respiratory fluoroquinolone or a macrolide
Pseudomonas infection is an issue but the patient has a β-lactam allergy	Either (1) aztreonam plus levofloxacin,[l] or (2) aztreonam plus moxifloxacin or gatifloxacin, with or without an aminoglycoside
Nursing home	
Receiving treatment in nursing home	A respiratory fluoroquinolone alone or amoxicillin-clavulanate plus an advanced macrolide
Hospitalized	Same as for medical ward and ICU

NOTE. COPD, chronic obstructive pulmonary disease; ICU, intensive care unit.

[a] Erythromycin, azithromycin, or clarithromycin.

[b] That is, the patient was given a course of antibiotic(s) for treatment of any infection within the past 3 months, excluding the current episode of infection. Such treatment is a risk factor for drug-resistant *Streptococcus pneumoniae* and possibly for infection with gram-negative bacilli. Depending on the class of antibiotics recently given, one or other of the suggested options may be selected. Recent use of a fluoroquinolone should dictate selection of a nonfluoroquinolone regimen, and vice versa.

[c] Moxifloxacin, gatifloxacin, levofloxacin, or gemifloxacin (oral gemifloxacin only, which was approved by the US Food and Drug Administration on 4 April 2003 and which is the only fluoroquinolone approved for multidrug-resistant *S. pneumoniae;* not yet marketed).

[d] Azithromycin or clarithromycin.

[e] Dosage, 1 g po t.i.d.

[f] Dosage, 2 g po b.i.d.

[g] High-dose amoxicillin, high-dose amoxicillin-clavulanate, cefpodoxime, cefprozil, or cefuroxime.

[h] Cefotaxime, ceftriaxone, ampicillin-sulbactam, or ertapenem; ertapenem was recently approved for such use (in once-daily parenteral treatment), but there is little experience thus far.

[i] The antipseudomonal agents chosen reflect this concern. Risk factors for *Pseudomonas* infection include severe structural lung disease (e.g., bronchiectasis), and recent antibiotic therapy or stay in hospital (especially in the ICU). For patients with CAP in the ICU, coverage for *S. pneumoniae* and *Legionella* species must always be assured. Piperacillin-tazobactam, imipenem, meropenem, and cefepime are excellent β-lactams and are adequate for most *S. pneumoniae* and *Haemophilus influenzae* infections. They may be preferred when there is concern for relatively unusual CAP pathogens, such as *Pseudomonas aeruginosa, Klebsiella* species, and other gram-negative bacteria.

[j] Piperacillin, piperacillin-tazobactam, imipenem, meropenem, or cefepime.

[k] Data suggest that elderly patients receiving aminoglycosides have worse outcomes [47].

[l] Dosage for hospitalized patients, 750 mg q.d.

Update of Practice Guidelines for the Management of Community-Acquired Pneumonia in Immunocompetent Adults

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