

Bon Secours Richmond
Pharmacy and Therapeutics Committees
Fluoroquinolones
5/2001

Recommendations:

1. Levofloxacin (Levaquin) the P&T preferred fluoroquinolone is recommended to be automatically substituted for other fluoroquinolones (ciprofloxacin, ofloxacin, gatifloxacin, and moxifloxacin), unless the physician has checked the dispense as written block or when Cipro is being used for osteomyelitis, nosocomial pneumonia, or intra-abdominal infections.
2. Pharmacists will check the drug's indication and patients renal function to ensure appropriate substitution and renal dosing adjustment.
3. Cost savings of approximately \$92,000 annually will be realized for the Richmond System by using levofloxacin in place of ciprofloxacin.

Assessment:

1. The antibiograms for Bon Secours Richmond do not demonstrate significant differences in the spectrums of levofloxacin and ciprofloxacin. Levofloxacin inhibits an equivalent percentage of *Pseudomonas aeruginosa* isolates.
2. Gatifloxacin (Tequin®) is approximately 1.8 times more expensive than levofloxacin and ciprofloxacin is 2.7 times more expensive than levofloxacin (\$17.00, \$31.00, and \$45.58 per day of therapy).
3. Ciprofloxacin has several indications not included in the package insert of the other products (nosocomial pneumonia, osteomyelitis, and intraabdominal infections [with metronidazole]). *Note: the recommended dose of ciprofloxacin is 400 mg q8h for nosocomial pneumonia.*
4. Gatifloxacin and Moxifloxacin are both 8-methoxyflouroquinolones. Gatifloxacin is administered as a racemic mixture, with the disposition and antibacterial activity of the R- and S- enantiomers virtually identical. Moxifloxacin contains an S,S-configured diazabicyclononyl ring moiety at the 7-position differentiating it from Gatifloxacin.
5. Gatifloxacin and levofloxacin are active against pathogens causing community-acquired pneumonia including atypical pathogens (*Chlamydia pneumoniae*, *Legionella pneumoniae*, and *Mycoplasma pneumoniae*). Gatifloxacin is not FDA approved for K. pneumonia in CAP.
6. Moxifloxacin is active against pathogens causing community-acquired pneumonia including some atypical pathogens (*Chlamydia pneumoniae* and *Mycoplasma pneumoniae*) but is not FDA approved for *Legionella pneumophila*.
7. Gatifloxacin and levofloxacin have demonstrated activity against penicillin-resistant pneumococci and produced similar cure and bacteriologic eradication rates in a trial of 417 patients with CAP.
8. Gatifloxacin has lower MICs for MRSA, *Bacteroides* spp. , *Peptostreptococcus* spp, and *Clostridium* spp.
9. Gatifloxacin and levofloxacin are >70% renally excreted unchanged and are indicated for uncomplicated/complicated UTI. Moxifloxacin is not indicated for UTI.
10. Gatifloxacin, levofloxacin, and Moxifloxacin are administered once daily.
11. Gatifloxacin, levofloxacin, and moxifloxacin are well absorbed from the gastrointestinal tract and may be given without regard to food.
12. Gatifloxacin and levofloxacin have high bioavailable allowing the same dose to be administered IV and PO.
13. Gatifloxacin and levofloxacin are supplied as premixed IV formulations.
14. Gatifloxacin, levofloxacin, and moxifloxacin do not interact with warfarin, theophylline, glyburide, cimetidine, midazolam, milk or calcium carbonate, *unlike ciprofloxacin.*
15. Gatifloxacin and moxifloxacin have been associated with QTc interval prolongation. Patients with risk of QTc interval prolongations were not excluded from clinical trials of gatifloxacin. The package insert includes a bolded warning, avoided in patients with known prolongation of the QTc interval and in patients with uncorrected hypokalemia, and patients receiving class Ia (quinidine, procainamide disopyramide) or class III (amiodarone, sotalol) antiarrhythmic agents. Additive effects may be seen with other medications that prolong the QTc interval, such as cisapride, erythromycin, antipsychotics, and tricyclic antidepressants. Caution should be used in patients with ongoing proarrhythmic conditions, clinically import bradycardia, or acute MI. The FDA has required post-marketing testing of gatifloxacin, moxifloxacin and levofloxacin to continue to assess the capability for QTc prolongation.
16. Gatifloxacin requires dosage adjustment with renal insufficiency but moxifloxacin does not.
17. Moxifloxacin (Avelox®) is not recommended for addition to the formulary as it is only available in an oral formulation; is not indicated for uncomplicated/complicated UTI or skin/skin structure infections, and is not FDA approved for *Legionella pneumophila* in Community Acquired Pneumonia.
18. Gatifloxacin (Tequin®) is not recommended for addition to the formulary at this time and will be reconsidered when further clinical data are available. Its indications do not include skin and skin structure infections. It is approximately 80% more expensive than levofloxacin.
19. Fluoroquinolones demonstrate concentration-dependent killing and the area-under-the inhibitor-curve (AUC) or the ratio of peak concentration to minimum inhibitor concentration best predicts efficacy.

Renal Dosing Per Package Insert				
CrCl (mL/min)	Ciprofloxacin	Gatifloxacin (Tequin)	Levofloxacin	Moxifloxacin (Avelox)
>50	400 mg Q12H	400mg QD	500 mg QD	400mg QD
	\$45.58 IV	\$31.07 IV	\$17.00 IV	IV Not Available
	\$7.20 PO	\$5.71 PO	\$6.31 PO	\$6.81 PO
20-49	400 mg Q12H-24H	200 mg QD	250 mg QD	400mg QD
	\$22.79-45.58 IV	\$15.53 IV	\$9.00 IV	\$6.81 PO
10-19	400 mg QD	200 mg QD	250 mg Q48H	400mg QD
	\$22.79 IV	\$15.53 IV	\$4.50 IV	\$6.81 PO
<10	400 mg QD	200 mg QD	250 mg Q48H	400mg QD
	\$22.79 IV	\$15.53 IV	\$4.50 IV	\$6.81 PO
Hemodialysis	400 mg QD	200 mg QD	250 mg Q48H	400 mg QD
	\$22.79 IV	\$15.53 IV	\$4.50 IV	\$6.81 PO
CAPD	400 mg QD	200 mg QD	250 mg Q48H	400 mg QD
	\$22.79 IV	\$15.53 IV	\$4.50 IV	\$6.81 PO

	Ciprofloxacin	Gatifloxacin	Moxifloxacin	Levofloxacin
Cmax mcg/mL				
200mg PO/IV QD		2.0 / 2.2	1.2	
250mg PO/IV QD				
400mg PO/IV QD	4.4 IV	3.8 / 5.5	2.5	
500mg PO/IV QD				6.4/5.7
500 mg PO BID	3			
AUC mcg/hr/mL				
200mg PO/IV QD		14.2 / 15.9		
250mg PO/IV QD				
400mg PO/IV QD		33.0 / 35.1	27-30	
500mg PO/IV QD				55/48
500 MG PO BID	27.4			
T1/2 hours	5-6	7-14	13	7.6
Bioavailability	70-80%	96%	90%	99%
FEU-Renal	50-70	79-88%	20%	87%
FEU-Bowel		6%	25%	4%
Metabolism	10%	< 1%	52%	5%
Protein Binding	35%	20%	50%	24-38%
Vd (L/kg)	3.4	1.7-2	1.7-3.5	89-112 (Liters)

FDA Approved Indications				
Indications:	Ciprofloxacin	Gatifloxacin	Moxifloxacin	Levofloxacin
Acute Bacterial Exacerbation of Chronic Bronchitis Haemophilus inf & parainfluenzae, Moraxella catarrhalis, Streptococcus pneumoniae, Staphylococcus aureus	+ only M. catarrhalis	+	+ (+) K. pneumoniae	+
Acute Sinusitis Haemophilus influenzae, Moraxella catarrhalis, Streptococcus pneumoniae	+	+ (-) M. cat	+	+
Community Acquired Pneumonia Strep. pneumoniae, Haemophilus inf, Klebsiella pneumoniae, Staph aureus, Mycoplasma pneumoniae, Moraxella catarrhalis, Legionella pneumophila, Chlamydia pneumoniae		+ (-) K. pneumoniae	+ (-) L. pneumophila	+
Complicated Intra-abdominal Infections	+			
Lower Respiratory Tract Infections E.coli, Enterobacter cloacae, Proteus mirabilis, Pseudomonas aeruginosa,	+	-	-	-
Nosocomial pneumoniae H. influenzae or K. pneumoniae	+ 400 mg q8h IV	-	-	-
UTI Uncomplicated Complicated	+	(-) P aer + +		(+) P aer + +
Pyelonephritis Escherichia coli		+		+
Skin and Skin Structure Uncomplicated S. aureus, S. pyogens Complicated/Diabetic Foot	+ E. coli, Proteus mirabilis/vulgaris, Providencia stuartii, Morganella morganii, Citrobacter freundii, Pseudomonas aer., S. epi,	-		+
Bone and Joint Enterobacter cloacae, Serratia marcescens, P. aeruginosa	+			
Chronic Bacterial Prostatitis E.coli, S. saprophyticus	+			
Uncomplicated Gonorrhoea	+	+		

Drug Interactions:

The AUC of Gatifloxacin and Moxifloxacin is significantly decreased when given concurrently with aluminum- and magnesium-containing antacids, zinc-containing products, and products containing divalent and trivalent cations (eg. didanosine). Iron-containing products decreased the C_{max} and AUC of Gatifloxacin by 54% and 35%, respectively, and the C_{max} and AUC of Moxifloxacin by 59% and 39%, respectively, when administered concurrently.

Side Effects:

Gatifloxacin - Dizziness and headache (3%), nausea (8%) and diarrhea (4%), vaginitis (6%), and elevated ALT (rare).

Moxifloxacin – Dizziness (3%), headache (2%), nausea (8%) and diarrhea (6%), abdominal pain (2%), and vomiting (2%).

File: Gatifloxacin

Pharmacy and Therapeutics Committee
Memorial Regional Medical Center
Gatifloxacin and Moxifloxacin
5/2000

Recommendations:

1. Levofloxacin (Levaquin®) remains the P&T preferred fluoroquinolone.
2. Gatifloxacin (Tequin®) is not recommended for addition to the formulary at this time and will be reconsidered when further clinical data are available. Its indications do not include skin and skin structure infections. It is approximately 50% more expensive than levofloxacin. It is too early to tell whether any of the unexpected serious adverse effects that have limited use of other fluoroquinolones (grepafloxacin, temafloxacin, trovafloxacin) will occur with the new agents (gatifloxacin, moxifloxacin).
3. Moxifloxacin (Avelox®) is not recommended for addition to the formulary as it is only available in an oral formulation; is not indicated for uncomplicated/complicated UTI or skin/skin structure infections, and is not FDA approved for Legionella pneumophila in Community Acquired Pneumonia.

Assessment:

1. Gatifloxacin and Moxifloxacin are both 8-methoxyflouroquinolones. Gatifloxacin is administered as a racemic mixture, with the disposition and antibacterial activity of the R- and S- enantiomers virtually identical. Moxifloxacin contains an S,S-configured diazabicyclononyl ring moiety at the 7-position differentiating it from Gatifloxacin.
2. Gatifloxacin and levofloxacin are active against pathogens causing community-acquired pneumonia including atypical pathogens (Chlamydia pneumoniae, Legionella pneumoniae, and Mycoplasma pneumoniae). Gatifloxacin is not FDA approved for K. pneumonia in CAP.
3. Moxifloxacin is active against pathogens causing community-acquired pneumonia including some atypical pathogens (Chlamydia pneumoniae and Mycoplasma pneumoniae) but is not FDA approved for Legionella pneumophila.
4. Gatifloxacin and levofloxacin have demonstrated activity against penicillin-resistant pneumococci.
5. Gatifloxacin and levofloxacin are >70% renally excreted unchanged and are indicated for uncomplicated/complicated UTI. Moxifloxacin is not indicated for UTI.
6. Gatifloxacin, levofloxacin, and Moxifloxacin are administered once daily.
7. Gatifloxacin, levofloxacin, and Moxifloxacin are well absorbed from the gastrointestinal tract and may be given without regard to food.
8. Gatifloxacin and levofloxacin have high bioavailable allowing the same dose to be administered IV and PO.
9. Gatifloxacin and levofloxacin are supplied as premixed IV formulations.
10. Gatifloxacin, levofloxacin, and Moxifloxacin do not interact with warfarin, theophylline, glyburide, cimetidine, midazolam, milk or calcium carbonate, *unlike ciprofloxacin*.
11. **Gatifloxacin and Moxifloxacin have been associated with QTc interval prolongation. Patients with risk of QTc interval prolongations were excluded from clinical trials of gatifloxacin. They should be avoided in patients with known prolongation of the QTc interval. Patients with uncorrected hypokalemia, and patients receiving class Ia (quinidine, procainamide disopyramide) or class III (amiodarone, sotalol) antiarrhythmic agents. Additive effects may be seen with other medications that prolong the QTc interval, such as cisapride, erythromycin, antipsychotics, and tricyclic antidepressants. Caution should be used in patients with ongoing proarrhythmic conditions, clinically import bradycardia, or acute MI.**
12. Gatifloxacin requires dosage adjustment with renal insufficiency but moxifloxacin does not.

Renal Dosing per Package Insert

CrCl (mL/min)	Gatifloxacin (Tequin)	Levofloxacin	Number of Doses Year to Date	Moxifloxacin (Avelox)	Levofloxacin's Potential Cost Savings per Day
>50	400mg QD	500 mg QD		400mg QD	
	\$31.07 IV	\$21.00 IV	3,336	IV Not Available	\$33,593.52
	\$5.71 PO	\$6.31 PO	2,200	\$6.81 PO	
20-49	200 mg QD	250 mg QD		400mg QD	
	\$15.53 IV	\$15.68 IV	456	\$6.81 PO	\$
10-19	200 mg QD	250 mg Q48H		400mg QD	
	\$15.53 IV	\$7.84 IV		\$6.81 PO	\$
<10	200 mg QD	250 mg Q48H		400mg QD	
	\$15.53 IV	\$7.84 IV		\$6.81 PO	\$
Hemodialysis	200 mg QD	250 mg Q48H		400 mg QD	
	\$15.53 IV	\$7.84 IV		\$6.81 PO	\$
CAPD	200 mg QD	250 mg Q48H		400 mg QD	
	\$15.53 IV	\$7.84 IV		\$6.81 PO	\$

Dosage Recommendation per Package Insert:

	Gatifloxacin		Moxifloxacin		Levofloxacin	
	Dose	Duration	Dose	Duration	Dose	Duration
Acute Bacterial Exacerbation of Chronic Bronchitis	400mg QD	7-10 days	400mg QD	5 days	500mg QD	5-7 days
Acute Sinusitis	400mg QD	10 days	400mg QD	10 days	500mg QD	10-14 days
Community Acquired Pneumonia	400mg QD	7-14 days	400mg QD	10 days	500mg QD	7-14 days
Uncomplicated UTI (cystitis)	400mg	single dose			250mg QD	3 days
	or 200mg QD	3 days				
Complicated UTI	400mg QD	7-10 days			250mg QD	10 days
Acute Pyelonephritis	400mg QD	7-10 days			250mg QD	10 days
Uncomplicated UG in Men; Endocervical and Rectal Gonorrhea in Women	400mg	single dose				
Uncomplicated Skin & Skin Structure	Not indicated			500 mg QD	7-10 days
Complicated SSSI	Not indicated			750 mg QD	7-14 days

Indications:	Gatifloxacin	Moxifloxacin	Levofloxacin
Acute Bacterial Exacerbation of Chronic Bronchitis Haemophilus inf & parainfluenzae, Moraxella catarrhalis, Streptococcus pneumoniae, Staphylococcus aureus	+	+ (+) K. pneumoniae	+
Acute Sinusitis Haemophilus influenzae, Moraxella catarrhalis, Streptococcus pneumoniae	+ (-) M. cat	+	+
Community Acquired Pneumonia Strep. pneumoniae, Haemophilus inf, Klebsiella pneumoniae, Staph aureus, Mycoplasma pneumoniae, Moraxella catarrhalis, Legionella pneumophila, Chlamydia pneumoniae	+ (-) K. pneumoniae	+ (-) L. pneumophila	+
UTI Uncomplicated Complicated	(-) Pseudomonas aer + +		(+) + +
Pyelonephritis Escherichia coli	+		+
Skin and Skin Structure Uncomplicated Complicated/Diabetic Foot	- - -		+ + +
Chronic Bacterial Prostatitis			+
Uncomplicated Gonorrhea	+		

Pharmacokinetics:

	Gatifloxacin	Moxifloxacin	Levofloxacin
Cmax mcg/mL			
200mg PO/IV QD	2.0 / 2.2	1.2	
250mg PO/IV QD			
400mg PO/IV QD	3.8 / 5.5	2.5	
500mg PO/IV QD			6.4/5.7
AUC mcg/hr/mL			
200mg PO/IV QD	14.2 / 15.9		
250mg PO/IV QD			
400mg PO/IV QD	33.0 / 35.1	27-30	
500mg PO/IV QD			55/48
T1/2 hours	7-14	13	7.6
Bioavailability	96%	90%	99%
FEU-Renal	79-88%	20%	87%
FEU-Bowel	6%	25%	4%
Metabolism	< 1%	52%	5%
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Vd (L/kg)	1.7-2	1.7-3.5	89-112 (Liters)

Drug Interactions:

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Side Effects:

Gatifloxacin - Dizziness and headache (3%), nausea (8%) and diarrhea (4%), vaginitis (6%), and elevated ALT (rare).

Moxifloxacin – Dizziness (3%), headache (2%), nausea (8%) and diarrhea (6%), abdominal pain (2%), and vomiting (2%).

File: Gatifloxacin

Dosage Recommendations:

Levofloxacin	Gatifloxacin	Moxifloxacin	
Acute Bacterial Exacerbations of Chronic Bronchitis	400mg QD	400mg QD	500mg QD
Acute Sinusitis QD	400mg QD	400mg QD	500mg
Community-Acquired Pneumonia	400mg QD	400mg QD	500mg QD
Uncomplicated UTI (cystitis)	400mg QD* or 200mg QD**		250mg QD
Complicated UTI			250mg QD
Acute Pyelonephritis	400mg QD		250mg QD
Uncomplicated Urethral Gonorrhea in Men; Endocervical and Rectal Gonorrhea in Women	400mg QD*		

* single dose

** X 3 days