

# PharmaNote®

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## Gemifloxacin (Factive®) Dual-Targeting Fluoroquinolone

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### Introduction

Since 1962, when the first quinolone precursor was discovered, fluoroquinolones (FQ) have become an important antibiotic class. Initially, they offered strong coverage against gram-negative bacteria. But with modifications, newer agents offer coverage against both gram-negative and gram-positive organisms. In April 2003, GeneSoft received FDA approval to market gemifloxacin (Factive®). The approved indications include community-acquired pneumonia (CAP) and acute exacerbation of chronic bronchitis (AECB). This article will review some current concepts of FQ resistance, as well as, the pharmacology/pharmacokinetics, dosing, clinical trials, role in therapy, and safety profile of gemifloxacin.

### Fluoroquinolone Resistance

Historically, fluoroquinolones' niche in the infectious disease arena was in the treatment of urinary tract infections. However, with newer agents offering better systemic absorption, the role of fluoroquinolones has expanded. Today, they are commonly used in treating gastrointestinal infections, respiratory tract infections, sexually transmitted diseases, and chronic osteomyelitis<sup>1</sup>. However, inappropriate use of fluoroquinolones in the past decade has led to the development of

bacterial resistance. In a study by Zhang et al., *S. aureus*, *S. epidermidis*, and *E. faecalis* resistance to ciprofloxacin increased by 12.2%, 27.8%, and 23.3%, respectively from 1997-2000.<sup>2</sup> The PROTEKT US study revealed 11 fluoroquinolone resistant pneumococci strains in North America, while the SENTRY study showed that 29% of the *P. aeruginosa* strains in North America were resistant to ciprofloxacin.<sup>3,4</sup>

Fluoroquinolone resistance can be chromosomally mediated with mutations observed in the target genes topoisomerase II and IV. Target genes for topoisomerase II which is also called DNA gyrase, are *gyrA* and *gyrB*, while target genes for topoisomerase IV are *parC* and *parE*. Cross-resistance is high among the fluoroquinolone class as a bacterium develops resistance at either of these sites. Another mode of resistance involves the amount of drug actually accumulating inside the bacteria. This is due to the bacteria developing an impermeable membrane and/or over expressing efflux pump systems.<sup>1,5</sup> More recently, mobile elements have been shown to carry a gene (*qnr*) that confers resistance to fluoroquinolones; this has the potential to introduce a new mode of resistance, one that is plasmid mediated instead of chromosomally mediated.<sup>5</sup>

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**Table 1. Community acquired pneumonia studies evaluating gemifloxacin<sup>a</sup>**

Drug Regimen	Success Rate (%)	Treatment Difference (95% CI)
<b>Study 011</b>		
Gemifloxacin 320 mg x 7 days	88.7	1.1 (-7.3, 9.5)
Amoxicillin/clavulanate 500 mg/125 mg TID x 7 days	86.7	
<b>Study 061</b>		
Gemifloxacin 320 mg x 7 days	91.7	(86.1, 95.2)
<b>Study 267</b>		
Gemifloxacin 320 mg x 7 days	89.9	(84.9-94.7)

<sup>a</sup>All studies used a fixed 7-day antibiotic treatment regimen. CI=confidence interval, TID=three times daily.

### Disease States

Lower respiratory tract infections are a major cause of death. They rank number six as the most common cause of death in the US and have the highest mortality rate of all infections.<sup>6</sup> Community-acquired pneumonia is associated with a mortality rate of ~14% for patients who require hospitalization and a mortality rate of <1% for those who do not.<sup>7</sup> Patients who suffer from chronic obstructive pulmonary disease (COPD) often experience AECB. Viruses are most commonly responsible for these exacerbations, so antibiotic use in this infection is controversial.<sup>8</sup>

The most common pathogens encountered in CAP and AECB are *S. pneumoniae*, *H. influenzae*, *M. catarrhalis*, *C. pneumoniae*, *M. pneumoniae*, and *Legionella* species.<sup>8,9</sup> The 2000 Infectious Diseases Society of America (IDSA) guidelines recommend a fluoroquinolone as first-line treatment/alternative for CAP in almost all patients over 18 years old. On the other hand, the 2003 Antibacterial Selection for CAP (ASCAP) and the Centers for Disease Control and Prevention (CDC) guidelines recommend restricting the use of fluoroquinolones to limit resistant strains from emerging.<sup>7,9,10</sup> Instead they recommend using a third generation cephalosporin along with a macrolide. Furthermore, when an antibiotic is used, it should be in a patient in which an infection has been proven or is strongly suspected to be caused by bacteria that is susceptible to the antibiotic chosen.

### Gemifloxacin

Gemifloxacin is one of the only fluoroquinolones that target both topoisomerase II and topoisomerase IV. By doing so, it requires a

stepwise mutation in the bacteria in order for resistance to occur. Initially, *P. aeruginosa* resistance was found to be associated with a mutation at gyrA. However, some highly resistant strains have also shown to possess a mutation at parC.<sup>12</sup> Likewise, some strains of *S. pneumoniae* have shown to possess mutations at both topoisomerase II and IV and are resistant to most fluoroquinolones. However, gemifloxacin can inhibit both enzymes at therapeutically acceptable concentrations rendering some of these double mutant strains susceptible.<sup>11</sup>

### Indications

In April 2003, the FDA approved gemifloxacin for the treatment of mild-to-moderate CAP and AECB. More recently, it was approved to treat mild-to-moderate CAP due to multi-drug resistant *Streptococcus pneumoniae* (MDRSP).

### Pharmacology and Pharmacokinetics

Unlike most fluoroquinolones, gemifloxacin targets both topoisomerase II and IV. These are two enzyme systems involved in the repair and replication of DNA. Topoisomerase II is responsible for the supercoiling of the DNA while topoisomerase IV aids in DNA replication by allowing the DNA strand to separate. The structures of the newer fluoroquinolones have an improved affinity for topoisomerase IV, rendering them more efficacious against gram-positive organisms, yet maintaining their coverage vs. gram-negative bacteria.

Gemifloxacin exhibits linear pharmacokinetics up to a dose of 640 mg, which is twice the daily dose for adults. It is quickly absorbed from the gastrointestinal (GI) tract, with a

**Table 2. AECB Clinical Studies evaluating gemifloxacin vs. alternative antibiotic regimens**

Drug Regimen	Success Rate (%)	Treatment Difference (95% CI)
<b>Study 68</b>		
Gemifloxacin 320 mg x 5 days	86.0	1.2 (-4.7, 7.0)
Clarithomycin 500 mg BID x 7 days	84.8	
<b>Study 70</b>		
Gemifloxacin 320 mg x 5 days	93.6	0.4 (-3.9, 4.6)
Amoxicillin/clavulanate 500 mg/125 mg TID x 7 days	93.2	
<b>Study 212</b>		
Gemifloxacin 320 mg x 5 days	88.2	3.1 (-4.7, 10.7)
Levofloxacin 500 mg x 7 days	85.1	

CI=confidence interval, BID=twice daily, TID=three times daily

bioavailability of 71% and a peak concentration of 0.5-2 hours after administration. Distribution is wide, with concentrations in bronchoalveolar macrophages, epithelial lining fluid, and bronchial mucosa being 90, 2, and 7 times that of plasma, respectively. The volume of distribution is approximately 4.18 L/kg. About 60-70% of the drug is bound to proteins and because it is only metabolized to a limited extent by the liver, CYP450 drug-drug interactions are not expected. Gemifloxacin is mainly excreted in the feces and urine with a half-life of approximately 8 hours.

No dosage adjustments are needed based on a patient's age, hepatic, and/or renal function. However, it should not be given to those <18 yo or in patients with a CrCl <40 ml/min. Gemifloxacin can be taken without regard to meals. Aluminum- and magnesium-containing antacids, ferrous sulfate, MVI with zinc and other metallic cations, sucralfate, and didanosine must be taken two hours prior or three hours following gemifloxacin. Conversely, calcium carbonate does not significantly decrease the AUC when given simultaneously with gemifloxacin. At this time, there are no known clinically significant drug interactions that require dose modifications.

### Clinical Trials

In CAP, there are 3 double-blind, randomized, actively controlled clinical studies, 1 open, actively controlled study, and 2 uncontrolled studies. The studies evaluated patient response to treatment, with success defined as favorable clinical response at follow-up. While all of the studies were suppor-

tive, only one of the double-blind studies and 2 uncontrolled studies used a strict 7-day dosing pattern (Table 1). No *p*-values were provided, only confidence intervals.<sup>11</sup>

Clinical trials for AECB included three double blind, randomized, actively controlled studies. Success rate was again determined by clinical response at follow-up (Table 2).<sup>11</sup>

### Toxicity and Safety

The manufacturer has not provided documentation comparing gemifloxacin's side effect profile to that of placebo. However, common side effects of gemifloxacin compared to other antibiotics are listed in Table 3. Most of the side effects were considered mild to moderate in severity, with rash being the most common especially in females <40 years of age. To lessen the chance of side effects, it is important that gemifloxacin only be used for the recommended length of time.

### Dosing and Administration

Gemifloxacin will be supplied as a 320 mg oral tablet in five- and seven-day dose packs. It is dosed once daily for seven days for CAP and once daily for five days for AECB. Gemifloxacin should be taken with plenty of liquid and can be taken without regard to meals. Dosing adjustments are only required in patients whose CrCl is <40 ml/min or those undergoing dialysis; the dose for these patients should be 160 mg per day. This drug should not routinely be used and has not been approved for use in patients younger than 18 years of age or pregnant/lactating women.<sup>11</sup>

**Table 3. Comparison of side effects of gemifloxacin to other oral antibiotics**

Side Effect	Gemifloxacin 320 mg (% patients)	Oral Antibiotic Comparators* (% patients)
Diarrhea	3.6	4.6
Rash	2.8	0.6
Nausea	2.7	3.2
Headache	1.2	1.5
Abdominal Pain	0.9	1.1
Vomiting	0.9	1.1
Dizziness	0.8	1.5
Taste Perversion	0.3	1.9

\* included  $\beta$ -lactam, macrolide, and other fluoroquinolone antibiotics

## Cost

The retail cost of gemifloxacin was not available at the time this article was prepared.

## Summary

Since the discovery of fluoroquinolones, their use has played a major role in combating infections. However, with their extensive use has come misuse that has led to resistance at target genes within bacteria<sup>5</sup>. Gemifloxacin is the newest addition to this class. It works at both topoisomerase II and IV and has demonstrated to be effective in the treatment of both CAP and AECB.

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# What practitioners should know about the new JNC 7 hypertension guidelines

John M. Tovar, Pharm.D.

## Introduction

Hypertension affects approximately 50 million individuals in the United States and over 1 billion worldwide.<sup>1</sup> The relationship between blood pressure and risk of cardiovascular disease (CVD) is well-established with numerous clinical studies demonstrating that blood pressure is a continuous, consistent, and independent risk factor of CVD.

The benefits of lowering blood pressure are also well-established. In clinical trials, antihypertensives have been shown to decrease the incidence of stroke (35-40%), myocardial infarction (20-25%), and heart failure (50%). Unfortunately, blood pressure control rates are far below the Healthy people 2010 goal of 50%. The National Health and Nutrition Examination Survey (NHANES) for the 1999-2000 period reported that although 68.9% of people were aware of their hypertension, only 58.4% were treated and hypertension was controlled in only 31% of individuals.<sup>2</sup>

## JNC 7

Since the "Sixth Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure (JNC 6)" was released in 1996, many large-scale clinical trials have been published. Therefore, the National High Blood Pressure Education Program (NHBPEP) and the National Heart, Lung, and Blood Institute (NHLBI) deemed necessary the publication of a new set of guidelines that would simplify the classification of blood pressure as well as provide new, clear, and concise recommendations for the management of hypertension.<sup>1</sup>

In order to facilitate its implementation, the "Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure (JNC 7)" will be presented in 2 separate publications. The first or "Express," which is a succinct and practical guide for the busy practitioner, was released in May of 2003. This will be followed by a more comprehensive report that will contain a detailed review of the current recommendations and is expected to be released sometime in the Fall of 2003.<sup>3</sup>

## Key Messages

1. In persons older than 50 years, systolic blood pressure greater than 140 mmHg is a much more important CVD risk factor than diastolic

**Table 1. Classification and management of blood pressure for adults\***

BP Classification	SBP* (mmHg)	DBP* (mmHg)	Lifestyle Modification	Initial Drug Therapy	
				Without Compelling Indication <sup>§</sup>	With Compelling Indications <sup>§</sup>
Normal	<120	and <80	Encourage	No antihypertensive indicated.	Drugs for compelling indications. <sup>‡</sup>
Prehypertension	120-139	or 80-89	Yes	No antihypertensive indicated.	Drugs for compelling indications. <sup>‡</sup>
Stage 1 Hypertension	140-159	or 90-99	Yes	Thiazide-type diuretics for most. May consider ACEI, ARB, BB, CCB, or combination.	Drug(s) for the compelling indications. <sup>‡</sup> Other antihypertensive drugs (diuretics, ACEI, ARB, BB, CCB) as needed.
Stage 2 Hypertension	=160	or =100	Yes	Two-drug combination for most <sup>†</sup> (usually thiazide-type diuretic and ACE, ARB, BB, or CCB).	Drug(s) for the compelling indications. <sup>‡</sup> Other antihypertensive drugs (diuretics, ACEI, ARB, BB, CCB) as needed.

DBP=diastolic blood pressure; SBP=systolic blood pressure

Drug abbreviations: ACEI=angiotensin converting enzyme inhibitor; ARB=angiotensin receptor blocker; BB=beta-blocker; CCB=calcium channel blocker.

\* Treatment determined by highest BP category.<sup>§</sup> For compelling indications refer to Table 2.

<sup>†</sup> Initial combined therapy should be used cautiously in those at risk for orthostatic hypotension.

<sup>‡</sup> Treat patients with chronic kidney disease or diabetes to BP goal of <130/80 mmHg.

**Table 2. Compelling indications for individual drug classes**

Compelling Indication*	Recommended Drugs†					
	Diuretic	BB	ACEI	ARB	CCB	Aldo ANT
Heart Failure	X	X	X	X		X
Postmyocardial infarction		X	X			X
High coronary disease risk	X	X	X		X	
Diabetes	X	X	X	X	X	
Chronic kidney disease			X	X		
Recurrent stroke prevention	X		X			

\* Compelling indications for antihypertensive drugs are based on benefits from outcome studies or existing clinical guidelines; the compelling indication is managed in parallel with the BP.

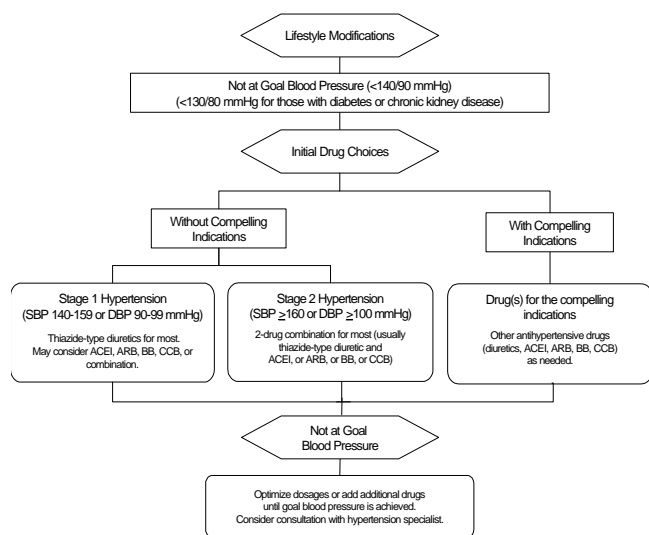
† Drug abbreviations: BB=beta-blocker; ACEI=angiotensin converting enzyme inhibitor; ARB=angiotensin receptor blocker; CCB=calcium channel blocker; Aldo ANT=aldosterone antagonist.

blood pressure.

- The risk of CVD begins at 115/75 mmHg and doubles with each increment of 20/10 mmHg.
- Individuals who are normotensive at age 55 have a 90% lifetime risk of developing hypertension.
- The classification of blood pressure has been simplified (Table 1), with prehypertensive patients requiring health-promoting lifestyle modifications to prevent CVD.
- Thiazide-type diuretics should be used for most patients with uncomplicated hypertension, either alone or combined with drugs from other classes. Certain high-risk conditions are compelling indications (Table 2) for the initial use

of other antihypertensive drug classes (angiotensin converting enzyme inhibitors, angiotensin receptor blockers, beta-blockers, calcium channel blockers).

- Most patients with hypertension will require two or more antihypertensive medications to achieve goal blood pressure (<140/90 mmHg, or <130/80 mmHg for patients with diabetes or chronic kidney disease).
- If blood pressure is >20/10 mmHg above goal, consideration should be given to initiating therapy with two agents, one of which usually should be a thiazide-type diuretic.
- The most effective therapy prescribed by the most careful clinician will control hypertension only if patients are motivated. Motivation improves when patients have positive experiences with, and trust in, the clinician. Empathy builds trust and is a potent motivator.



**Figure 1. Algorithm for the treatment of hypertension.**

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