

# NEW DRUG UPDATE

November 2004

Volume X, Issue 5



West Virginia University • Charleston Division

EDITOR-IN-CHIEF - Kristy Lucas, Pharm.D.

CO-EDITOR - Greg Rosencrance, M.D.

MANAGING EDITOR - Tara White

## Spiriva® HandiHaler® (tiotropium bromide)

**Authors** Norman Montalto, MD  
Associate Professor  
Department of Family Medicine  
West Virginia University - Charleston

### Introduction

Spiriva®, [tiotropium bromide] an inhaled anticholinergic agent for use in Chronic Obstructive Pulmonary Disease (COPD) was approved by the FDA in February 2004. It provides significant, sustained improvement in lung function for a full 24-hours using a single daily dose. Tiotropium acts similarly to ipratropium (Atrovent®) also an inhaled anticholinergic agent with use four times per day. Spiriva® HandiHaler® is indicated for the long term, once daily, maintenance therapy treatment of bronchospasm associated with COPD, including chronic bronchitis and emphysema.

### Therapeutic Recommendation

Tiotropium is recommended as first line maintenance therapy for COPD in the guidelines published by the Global Initiative for Obstructive Lung Disease (GOLD). Tiotropium may be used with long-acting beta agonists to improve lung function in COPD patients, including those with bronchitis and emphysema. It is not recommend for rescue therapy or in asthmatic patients. A single daily 18 mcg dose using the hand-held HandiHaler® system provides significant improvement in forced expi-

ratory volume at one-second (FEV1) when administered in the morning. Peak effects occur within 3 hours of the first dose. In the one year, placebo controlled trials, the main improvement in FEV1 at 30 minutes was 13% with peak improvement of 24% above baseline after the first day. There was additional improvement in FEV1 and forced vital capacity (FVC) by day eight. The mean improvement in FEV1 relative to baseline was 24-31% and this improvement was maintained in the clinical trial, without any evidence of tolerance.

### Dosing and Administration

Tiotropium bromide is available in 18 mcg capsule (placed in a HandiHaler®). This dry powder inhalation, used in the HandiHaler® device is the recommended way to administer this medication. No dosage adjustments required for geriatric, hepatically impaired, or renally impaired patients.

### Contraindications

Tiotropium is contraindicated in patients with a history of hypersensitivity to atropine or its derivatives, including ipratropium, or to any component of this product. This product does contain lactose, as a carrier for taste but no allergic reactions have

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been associated with the small amount contained in this product.

### Cost Comparison

Medication/Dose	Cost*		
	Target	Rite Aid	Kroger
Atrovent®	70.69	72.99	69.39
Spiriva®	127.69	134.99	139.59

\*Cost to patient for a 30 day supply at usual doses

### Warnings

Tiotropium is not indicated for the initial treatment of any acute episode of bronchospasms (i.e. rescue therapy). Immediate hypersensitive reactions, including angioedema, may occur after administration. Any inhaled medicines, including tiotropium may cause paradoxical bronchospasms. If either of these occurs, treatment should be stopped and other treatments considered.

### Special Populations

**Pregnancy:** Tiotropium is rated pregnancy category C however, there are no well-controlled studies in pregnant women. Tiotropium should be used during pregnancy only if potentially benefit justifies the potential risk to the fetus.

**Lactation:** It is not known whether tiotropium is ex-

creted in human milk, but caution should be exercised if tiotropium is administered to nursing women.

**Pediatrics:** Safety and effectiveness of tiotropium in pediatric patients has not been established, because COPD, chronic bronchitis and emphysema are not diseases of children.

**Geriatrics:** No differences in the effectiveness were observed among the elderly population. Rates of dry mouth, constipation and urinary tract infection occurred more than with placebo in clinical trials. However, based on available data, no adjustment of tiotropium dosage in geriatric patients is warranted.

**Hepatic Impairment:** The effects of hepatic impairment on the pharmacokinetics of tiotropium are not well established. Tiotropium is cleared primarily by renal elimination and by simple non-enzymatic ester cleavage to products that do not bind to muscarinic receptors.

**Renal Impairment:** Since tiotropium is excreted renally (approximately 74% in young, healthy volunteers), renal impairment was associated with increased plasma drug concentrations and reduced drug clearance in clinical trials. In COPD patients with moderate to severe renal impairment (CrCl <50 mL/min), intravenous administration resulted in the doubling of the plasma concentration, which was confirmed by plasma concentrations after dry powder inhalation.

### Drug Interactions

In clinical trials, intravenous tiotropium tested against cimetidine 400 mg three times a day or ranitidine 300 mg once daily. Administration of cimetidine with tiotropium resulted in a 20% increase in AUC<sub>0-4h</sub>, a 28% decrease in the clearance of tiotropium, and no significant change in the C<sub>max</sub> and amount excreted in urine over 96 hours. Therefore no clinically significant interaction occurred between tiotropium, cimetidine and ranitidine in this limited drug interaction assessment.

### Adverse Reactions

In patients treated with once daily 18 mcg dosing the most common drug reaction was dry mouth. Dry mouth (16% vs. 3% placebo) was usually mild and often resolved during continued treatment.



...A Primary Care  
Physician's Guide to  
Newly Released  
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Departments of Internal Medicine  
and Clinical Pharmacy  
West Virginia University  
Charleston Division

Robert C. Byrd Health Sciences Center  
3110 MacCorkle Ave., SE  
Charleston, WV 25304  
(304) 347-1377

Fax: (304) 347-1350  
E-mail: [klucas@hsc.wvu.edu](mailto:klucas@hsc.wvu.edu)

Visit New Drug Update online at:  
[www.hsc.wvu.edu/charleston/sopc/nduhome.html](http://www.hsc.wvu.edu/charleston/sopc/nduhome.html)

Other side effects, (primarily anticholinergic) included, constipation, increased heart rate, blurred vision, glaucoma, urinary difficulty, and urinary retention. Arthritis, coughing, and influenza-like symptoms occurred at a rate of >3% in the tiotropium group, but were <1% in excess of the placebo group.

### Pharmacology

**Mechanism of Action:** Tiotropium is a long-acting, antimuscarinic agent, which is often referred to as an anticholinergic agent. The primary effect is due to the inhibition of the M3 muscarinic receptor resulting in bronchial smooth muscle relaxation and resultant bronchodilation. The competitive and reversible nature of antagonism in human and in animal studies has been proven. The bronchodilation following inhalation of tiotropium is predominantly a site-specific event.

**Absorption/ Distribution:** Following inhalation of the dry powder in young healthy volunteers, the absolute bioavailability of 19% suggests that the fraction reaching the lungs is highly bioavailable. Tiotropium is poorly absorbed from the GI tract due to the quaternary ammonium compound component. Food is not expected to influence the absorption of tiotropium for that same reason. Maximum tiotropium plasma concentrations occurred five minutes after inhalation. Tiotropium binds significantly to tissues, although it is primarily bound by plasma proteins (72%). Steady state plasma concentrations were 3-4 pg/mL. Local concentrations in the lung are not known, but the mode of administration suggests substantially higher concentrations in the lung.

**Metabolism/Excretion:** Tiotropium is an ester that is nonenzymatically cleaved to the alcohol N-methylscopine and dithienylglycolic acid, neither of which bind to muscarinic receptors. About 25% of tiotropium is metabolized by the cytochrome P450-dependant oxidation and glutathione conjugation CYP2D6 and 3A4. 74% of the (unchanged) drug after an IV dose to young, healthy volunteers is excreted in urine. The terminal elimination half-life of tiotropium is between 5 and 6 days following inhalation. Tiotropium is mainly excreted unchanged in the urine (74%). After inhalation urinary secretion is 14% of the dose, the remainder being mainly non-absorbed drug in the gut which is eliminated via the feces. When administered once daily pharmacokinetic

steady state is reached after 2-3 weeks with no accumulation thereafter.

### Patient Information

1. Tiotropium bromide is to be used only one time per day with the HandiHaler® device.
2. Patients with severe renal impairment should be monitored closely.
3. Capsules should be dumped into the trash without being handled.
4. After use, hand washing is recommended.
5. Be sure the capsule is broken and the contents completely inhaled using the device.
6. Stopping smoking will reduce your risk of worsening Chronic Obstructive Pulmonary Disease, improve quality of life and reduce the risk of lung cancer.
7. The most common side effect is dry mouth, which usually decreases with continued use.

### Reference

1. Spiriva® Handihaler® Product Information. Boehringer Ingelheim. Ridgefield, CT January 2004.
2. Global Initiative for Chronic Obstructive Lung Disease (GOLD), World Health Organization (WHO), National Heart, Lung and Blood Institute (NHLBI). Global strategy for the diagnosis, management, and prevention of chronic obstructive pulmonary disease. Bethesda (MD): 2004. 100 p.

## Factive® (gemifloxacin)

### Molly Englert, Pharm.D.

Pharmacy Practice Resident

University of Pittsburgh Medical Ctr. – Pittsburgh, PA

### Jeremy J. Taylor, Pharm.D.

Infectious Diseases Pharmacy Resident

Mayo Clinic – Rochester, MN

### Introduction

There are approximately 4 millions cases of Community-Acquired Pneumonia (CAP) diagnosed each year. Of those cases, nearly 25% will develop multi-drug resistance to existing antibiotic regimens. The fluoroquinolone class of antibiotics, which were once reserved for resistant strains of bacteria, have drastically increased in use. As the use of quinolones continues to accelerate, so does the potential for drug resistance. In April of 2003, the FDA approved Fac-

tive® (gemifloxacin [je-mi-FLOX-a-sin]), a new quinolone for multi-drug resistance *Streptococcus pneumoniae* (MDRSP) in CAP and acute exacerbations of chronic bronchitis (AECB). Gemifloxacin's mechanism of action is more specific to the topoisomerase IV inhibition, providing for enhanced gram positive coverage, including *S. pneumoniae*, atypicals, and anaerobes. Gemifloxacin is the first antibiotic approved for these resistant organisms causing CAP.

**Therapeutic Recommendation**

**Current regimens for the treatment of CAP often lack adequate coverage for *S. pneumoniae* as well as a sufficient broad spectrum for coverage of gram positive organisms. Empiric use of antibiotics may lead to cross resistance among drug classes and multi-drug resistant strains. Gemifloxacin provides 30 times more *S. pneumoniae* activity than ciprofloxacin and 4 to 8 times the activity of moxifloxacin in clinical trials. Gemifloxacin has a minimal effect on the cytochrome P450 system, which reduces its potential for drug interactions compared to other classes of antibiotics. Many fluoroquinolones, such as ciprofloxacin and levofloxacin, alter the blood levels of warfarin and impair anti-coagulation. Since gemifloxacin has not been found to interact with warfarin, INR and anticoagulation are not expected to be significantly affected. Gemifloxacin provides broad spectrum coverage while minimizing the potential for drug interactions and coagulation alterations as compared to older quinolones. The incidence of drug-induced photosensitivity and QT interval prolongation were also less likely with gemifloxacin in comparison to other quinolones. Gemifloxacin is active against atypical organisms and is not inhibited by penicillin resistance.**

**Dosing and Administration**

Gemifloxacin is available as a 320 mg tablet. For AECB, the typical dose is 320 mg daily for 5 days. For CAP, the duration of treatment is extended to 320 mg for 7 days.

**Warnings**

QT Interval Prolongation: For patients with a history of arrhythmias, hypokalemia, hypomag-

nesmia, and myocardial infarction, fluoroquinolones as a class should be avoided due to the potential of prolonging the QT interval and inducing fatal arrhythmias. Combined use with tricyclic antidepressants, antipsychotics, erythromycin, and Class 1A and Class III anti-arrhythmics should be avoided due to additive potential of arrhythmias. However in clinical trials, gemifloxacin was not found to prolong QT intervals. Use extreme caution not to combine gemifloxacin with other agents, which may have the potential to prolong QT intervals.

Resistance: Use of gemifloxacin should be reserved for when a susceptible organism has been identified to minimize the potential for resistance. Therefore empiric use should be avoided.

Tendon and Cartilage: Patients should be closely monitored for pain and tenderness in the tendons. Due to the potential weakening of the tendons, which was demonstrated in animal trials, all quinolones, including gemifloxacin, should be avoided in children and during pregnancy and lactation.

**Cost Comparison**

Medication/Dose	Cost *		
	Target	Rite Aid	Kroger
Factive® (Gemifloxacin) 320 mg QD	130.99	179.99	158.79
Cipro® (Ciprofloxacin) 750 mg BID	97.39	119.00	103.80
Levaquin® (Levofloxacin) 500 mg QD	81.99	97.99	88.29
Tequin® (Gatifloxacin) 400 mg QD	67.99	70.99	78.99
Avelox® (Moxifloxacin) 400 mg QD	70.69	82.77	82.09

\*Cost to patient for a 7 day supply

**Precautions**

Electrolyte Imbalances: Patients should drink adequate amounts of fluids to remain hydrated. Dehydration may result in electrolyte imbalances, which can potentiate arrhythmias. Magnesium and potassium levels should be closely monitored.

**Contraindications**

Gemifloxacin is contraindicated in patients that have a known sensitivity to gemifloxacin and other fluoroquinolone antibiotics.

### Special Populations

**Race and Age:** Pharmacokinetics are not affected

**Gender:** Females tend to have a higher AUC; however, this does not necessitate dosage adjustment.

**Renal Impairment:** Patients with renal impairment have a higher AUC. For CrCl > 40 ml/min, no adjustment is needed. For CrCl < 40 ml/min, the recommended dosage adjustment is 160 mg every 24 hours.

**Hepatic Impairment:** No changes in dosage for hepatic impairment are necessary.

**Pediatrics:** Not yet established. Gemifloxacin is not approved for use in children under the age of 18 years.

**Pregnancy and Lactation:** Not yet established. Gemifloxacin is Pregnancy Category C.

### Drug Interactions

Avoid combining gemifloxacin with agents that increase the QT interval such as tri-cyclic antidepressants, antipsychotics, erythromycin, and Class IA and III anti-arrhythmics. Antacids including both divalent and trivalent cations containing aluminum and magnesium may decrease the concentrations of gemifloxacin. Iron and multiple vitamin supplements may also decrease blood levels. Sucralfate may decrease absorption of gemifloxacin. Probenicid may increase blood levels of gemifloxacin. Gemifloxacin may be taken at least 2 hours before or 4 hours after an agent that may alter the drug level concentration to avoid this interaction.

### Adverse Effects

Gemifloxacin is generally well tolerated. Side effects are minimal and include GI upset (including nausea, vomiting, and diarrhea), rash, abdominal pain, dizziness, and taste perversion.

### Pharmacology

**Mechanism of Action:** Gemifloxacin is a fluoroquinolone that inhibits DNA gyrase. It is a more selective topoisomerase IV inhibitor, which displays a post-antibiotic effect and enhances its activity compared to the older quinolones.

**Absorption/Distribution:** Gemifloxacin is rapidly absorbed in the GI tract. Peak concentration is

achieved in 0.5 to 2 hours. Absorption is not limited by food and the bioavailability is about 71%. Approximately 60-70% of the drug is protein bound. The volume of distribution in the tissue is 4.18 L/kg.

**Metabolism/Excretion:** Gemifloxacin is metabolized to a minimal extent by the liver. It does not undergo CYP 450 metabolism to a clinically important extent. The half-life is approximately 7 hours, which is not altered by hepatic or renal impairment. Approximately 65% of the drug is excreted unchanged. Urine excretion is 36% while fecal excretion is 61%. Renal clearance is 9.06 L/h.

### Patient Information

1. Gemifloxacin is an antibiotic used to treat a bacterial infection and should NOT be used for viruses.
2. Make sure your physician is aware of your medical history, including kidney problems, heart attacks, irregular heart beats, seizures, and/or drug allergies.
3. This medicine should be taken once a day with or without food. DO NOT crush, cut, or chew the tablet. Make sure to drink plenty of fluids.
4. If you take an antacid, calcium or iron supplement, or a multivitamin, take your dose of gemifloxacin at least 2 hours before or 4 hours after these products.
5. Contact your doctor if you notice an irritation rash or persistent muscle or joint pain and tenderness.
6. As with any medication, do not operate machinery or an automobile until you are aware of how you will react to it.

### Reference

1. Gemifloxacin (Factive®) Package Insert. Genesoft Pharmaceuticals, April 2003.
2. Lowe M, Lamb H. Gemifloxacin. *Drugs* 2000;59:1137-47.
3. Hong CY. Discovery of gemifloxacin (Factive, LB203304a): a quinolone of a new generation. *II Farmaco* 2001;56:41-4.
4. <http://www.pslgroup.com/dg/23795E.htm> [accessed 8/26/03]

## Welcoming New Faculty

Listed are new faculty members in the West Virginia University Department of Medicine, Charleston Division. Please join us in welcoming them to our institution.

Charin Hanlon, MD  
Internal Medicine/Psychiatry

Alfred Pfister, MD  
Professor  
Internal Medicine

Prasuna Jami, MD  
Assistant Professor  
Internal Medicine

Rajeeve Thachil, MD  
Associate Professor  
Section Chief  
Critical Care/Pulmonology

Joel Levien, MD  
Associate Professor  
Section Chief  
Gastroenterology

Tanya Warwick, MD  
Assistant Professor  
Neurology

Rathi Narayan, MD  
Assistant Professor  
Gastroenterology

Brent E. Watson, MD  
Assistant Professor  
Internal Medicine/Pediatrics

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Departments of Internal Medicine  
and Clinical Pharmacy  
WVU - Charleston Division  
Robert C. Byrd Health Sciences Center  
3110 MacCorkle Ave., SE  
Charleston, WV 25304

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