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Health care workers express concerns over smallpox immunization plans

Pharmacists in Alabama will be asked to educate patients

The Bush administration's plan to immunize half a million health care workers against the smallpox virus is meeting increasing resistance. As of the last press telebriefing by the Centers for Disease Control and Prevention (CDC) in Atlanta on Feb. 6, the agency had shipped 204,600 doses of vaccine to 40 states or counties that had requested it. The CDC, however, had documentation of fewer than 700 people in 16 jurisdictions being vaccinated in the first two weeks of the program.

The first phase of the president's plan includes vaccinating about 500,000 military and civilian personnel who are or may be deployed in high-threat areas, as well as about 500,000 civilian health care and emergency workers. In the second phase, up to 10 million "first responders," such as health care workers, police officers, firefighters, and emergency medical technicians, will be offered the vaccine. The government expected about half of the people in this category to end up being vaccinated. The plan calls for offering the vaccine to the public at a later date on a volunteer basis.

CDC emphasizes preparedness capacity, not numbers

Compensation is a big stumbling block to the rollout of the program, admits **Julie Gerberding**, MD, MPH, director of the CDC. "We know that many individuals and institutions continue to have questions about compensation. I am confident about our ability to address these issues." She would not discuss details but says she is "optimistic that we will be able to close these gaps."

She also encouraged reporters not to emphasize the numbers of people being vaccinated. "I know it's tempting to concentrate on the number 500,000 and the number 10 million, but I just urge you to understand that our goal is not achievement of a number. Our goal is achievement of a preparedness capacity."

Concern about risk from the vaccine and questions about how to fund an immunization program have kept some health care facilities from

choosing to participate in the program at all. A nationwide survey of state health officials by *The New York Times* in early February found about 350 hospitals that declined to participate. Hundreds more have not yet decided.

State health departments, however, are continuing their vaccination plans. At least in Alabama, pharmacists will play a primary role in preparation. "The pharmacists of the state have been asked to educate themselves about smallpox and the vaccine so they can help educate their patients," says **Charles Thomas**, director of pharmacy for the Alabama Department of Public Health in Montgomery.

Pharmacists and other health care workers will be vaccinated for smallpox in phase 2 of the state's plan. If a smallpox threat did occur and the public would have to be vaccinated, pharmacists would be asked to help in that process, Thomas says. "They would be asked to come to the clinical sites and help vaccinate. They would receive special training for that role."

Alabama was scheduled to start its phase 1 immunization on Feb. 18. ■

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Judge stops Medicare Rx discount program again

Bush administration may turn to Congress next

The Bush administration's latest try at proposing a Medicare drug discount plan was shot down by a federal judge Jan. 29. Now the administration says it may turn to Congress for help.

Judge **Paul L. Friedman** of the United States District Court for the District of Columbia granted an injunction against the program at the request of several pharmacist support organizations. Friedman said the administration did not have the statutory authority to develop and implement the program. The same judge had stopped the administration's original program with an injunction in September 2001.

Pharmacists overwhelmingly cheered the judge's decision. "This flawed program was a false promise, and one that would have cost both pharmacists and our patients," says **John A. Gans**, PharmD, executive vice president of the American Pharmaceutical Association in Washington, DC. "This is a significant victory for the patients we serve."

"We applaud the court's decision," says **Bruce Roberts**, RPh, executive vice president and CEO of the National Community Pharmacists Association in Alexandria, VA. "This proposal would have caused considerable harm to many of the nation's community pharmacies."

The Bush administration isn't down for the count yet; it still seems resolved to offer a discount pharmacy card to Medicare recipients. "There is no question the administration is going to pursue [the issue] legislatively," Medicare administrator Tom Scully told reporters.

Pharmacist groups say they are ready for the challenge. "[This decision] shifts the debate back to Congress, where a number of creative solutions and viewpoints should be considered," says **S. Lawrence Kocot**, senior vice president and general counsel of the National Association of Chain Drug Stores in Alexandria, VA. ■

Diuretic suggested as initial hypertension treatment

Increased use of diuretics could save billions

The largest hypertension trial ever conducted is recommending thiazide diuretics as initial therapy over newer, more costly angiotensin-converting enzyme (ACE) inhibitors or calcium channel blockers. The researchers do say, however, that most patients will need to be prescribed more than one drug to control their blood pressure.

Results of the Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT) were published in the Dec. 18, 2002, issue of *The Journal of the American Medical Association*. The researchers recommended that physicians should consider switching patients who already are being treated with a medication other than a diuretic to a thiazide-type diuretic or adding diuretics to the existing regimen.

> Study participants who took an ACE inhibitor had a higher risk of stroke, heart failure, and coronary revascularization than did those who took a diuretic.

The cost implications of the recommendations are huge. The researchers say diuretic use to treat hypertension fell from 56% in 1982 to 27% in 1992. The switch from diuretics to the more expensive antihypertensive medications cost about $3.1 billion.

ALLHAT was a randomized, double-blind trial conducted from February 1994 through March 2002. It involved 33,357 participants ages 55 and older, and was conducted at 623 clinics and centers in the United States, Canada, Puerto Rico, and the U.S. Virgin Islands. About 7,000 participants were treated at Veterans Affairs clinics. The National Heart, Lung, and Blood Institute, part of the National Institutes of Health, supported the trial.

Participants had hypertension (140/90 mm Hg or higher) and at least one other of the risk factors for heart disease, which include cigarette smoking and Type 2 diabetes.

Almost 50% of the participants were women, 47% were non-Hispanic whites, and 32% were black. Thirty-six percent had diabetes. All participants were followed at three, six, nine, and 12 months after beginning the study and every four months afterward. Participants were followed on average for 4.9 years.

Participants were randomly assigned to receive one of four drugs:

- a diuretic (chlorthalidone, 12.5-25.0 mg/day);
- a calcium channel blocker (amlodipine, 2.5-10.0 mg/day);
- an ACE inhibitor (lisinopril, 10-40 mg/day);
- an alpha-adrenergic blocker (doxazosin). The alpha-adrenergic blocker arm of the study was stopped in March 2000 because those on the drug had increased cardiovascular events and hospitalizations for congestive heart failure as compared to users of the diuretic.

Participants received additional antihypertensive drugs if their doctor thought it necessary to control their blood pressure.

The primary outcome was combined fatal coronary heart disease (CHD) or nonfatal myocardial infarction. The primary outcome occurred in 2,956 participants, with no difference between treatments.

Secondary outcomes were all-cause mortality, stroke, combined CHD, and combined cardiovascular disease. All-cause mortality did not differ between groups. Compared to participants who were taking the diuretic, however, those on the calcium channel blocker had systolic blood pressure that was about 1 mm Hg higher on average, as well as a 38% higher risk of developing heart failure and a 35% higher risk of being hospitalized for the condition.

Compared to participants who were taking the diuretic, those on the ACE inhibitor had:

- systolic blood pressure that was about 2 mm Hg higher on average, and 4 mm Hg higher in African-Americans;
- 15% higher risk of stroke (40% higher risk of stroke for African-Americans);
- 19% higher risk of developing heart failure;
- 11% greater risk of being hospitalized or treated for angina;
- 10% greater risk of having to undergo a coronary revascularization (such as coronary artery bypass surgery).

Some physicians disputed ALLHAT's findings, saying beta-blockers should not have been the add-on therapy for the lisinopril group because

the drugs are not complementary in their actions. In addition, chlorthalidone frequently is used in clinical trials but not in clinical practice. The possibility exists that other thiazide diuretics may not be comparable.

ALLHAT doesn't dramatically change any of the ideas about treating hypertension that have resulted from previous research, such as the reports from the Joint National Committee on Detection, Evaluation and Treatment of High Blood Pressure, says **Daniel Albrant**, PharmD, president of Pharmacy Dynamics, a pharmaceutical consulting company in Arlington, VA. "There are some nuances of difference. There is some support for using diuretics early, which has been known for close to a decade." **(For the challenges of changing physician practice based on research studies, see story at right.)**

It appears now that diuretics and beta-blockers are certainly the way to go to treat hypertension in most people, he says. "In certain subsets, calcium channel blockers may be more appropriate; ACE inhibitors may be more appropriate plus or minus a diuretic." Most important, however, is getting patients on some type of therapy and convincing them to persist with their medications. "Getting them on appropriate therapy, titrating it to the goals, and getting them to persist in their compliance to take the medication — those are the things that make the big outcomes."

ALLHAT's cholesterol study results

In addition to the hypertension trial, ALLHAT included a cholesterol-lowering study that compared the effects of a statin drug (pravastatin) with "usual care." Both groups had a substantial decrease in cholesterol levels. The difference in cholesterol levels between the groups was too small to show a difference in death rates and produced only a small, non-significant decrease in the rates of heart attacks and strokes in the statin group.

ALLHAT's cholesterol study involved 10,355 of ALLHAT participants. At the start of the trial, the participants had moderately elevated blood cholesterol but were judged by their doctors not to need cholesterol-lowering medication.

During the trial, participants in the usual care group were prescribed a cholesterol-lowering drug (not provided by the study) when their doctor felt it was warranted by changes in their condition, such as a heart attack or marked cholesterol increase. Of those in the usual care group, 32% of those who had heart disease at the start of the study and 29% of those without heart disease at the outset used a cholesterol-lowering drug.

After four years, both the statin and usual care groups had reductions in total and low-density lipoprotein cholesterol. Total cholesterol dropped by 17.2% in the pravastatin group and 7.6% in the usual care group.

There were no significant differences between the pravastatin and usual care groups in overall mortality or in mortality from any single cause. There were 631 deaths in the pravastatin group and 641 in the usual care group. ■

Changing physician practice a challenge

Data can take years to influence standard procedure

After reviewing results of the Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT), some physicians predicted that the findings would soon change medical practice in hypertension.

Such a conclusion would ignore human nature, says **Daniel Albrant**, PharmD, president of Pharmacy Dynamics, a pharmaceutical consulting company in Arlington, VA. "It is very hard to change physician practice through research reports. We know for a fact that data take somewhere between eight and 10 years to disseminate into practice." **(For more about the ALLHAT study, see story, p. 19.)**

Claude Lenfant, MD, director of the National Heart, Lung, and Blood Institute (NHLBI) in Bethesda, MD, might agree. Back in 1997, he wrote an article in the Dec. 3 *Journal of the American Medical Association* asking why more physicians weren't heeding the recommendation of the reports of NHLBI's Joint National Committee on Detection, Evaluation, and Treatment of High Blood Pressure (JNC). The JNC had analyzed research results and over the years had issued six reports of the National High Blood Pressure Education Program. The reports included guidelines to improve health care providers' ability to manage hypertension.

JNC reports have little effect on practice

The JNC-V report recommended that traditional agents for treating hypertension, such as diuretics and beta-blockers, be considered as initial therapy because of their proven benefits in reducing mortality. An outside study, however, found that newer agents (such as calcium channel blockers and angiotensin-converting enzyme inhibitors) were being prescribed more frequently than traditional agents. The researchers concluded that the recommendations in the JNC-V reports had had little effect on prescribing patterns in the United States.

> "We know from previous studies that diuretics and beta-blockers should be first-line therapy. That still isn't fully implemented into practice."

After JNC-VI, NHLBI launched a marketing research study to examine physicians' reactions to and use of NHLBI guidelines, which also are issued for management of high blood cholesterol and asthma. The aim of the study was to learn how guidelines could be formatted, organized, and disseminated more effectively. The results then guided the development of the JNC-VI report, although the recommendation for first-line hypertension treatment did not change.

Even with this extra effort, committee members continue to be discouraged that the findings of their report have not been implemented more widely, Albrant says. "We know from previous studies that diuretics and beta-blockers should be first-line therapy. That still isn't fully implemented into practice."

This happens for several reasons, he says. Some physicians don't keep up with the medical literature; they get into a pattern of treating patients a certain way. Others will read the literature, but will glean only what is consistent with their practice — even if the trial is as large and as long-term as ALLHAT. If the recommendations in the literature are contrary to their current practice, the physicians may find a reason to discount the research.

"None of our studies are ever going to be perfect," Albrant says. For example, physicians may say that even though a trial population is huge, it doesn't reflect the patients they treat. "It's really a no-win situation."

Stay current with literature

Good data from a research trial are only pieces in the puzzle, he continues. The next, and more difficult, step is to get physicians to believe the trial's conclusions and to incorporate the new information into their practice.

The role of the pharmacist is to try to stay current on the literature and to interpret it for physicians based on the pharmacist's knowledge of pharmacology. "We say, 'Here is what the literature says what might do best in this patient based on concomitant diseases and age and other factors.'" Pharmacists could develop standard order forms or protocols that make it easier for physicians to order the recommended medications. Once physicians are ordering the medications that pharmacists think are optimal for the patient, pharmacists and physicians can work together to get the patient to stick with the therapy.

"It's a reality check," Albrant concludes. "The data might be great and help us codify what we already know, but the kicker is getting people to fill the prescription initially and then refill it routinely, taking it as we intended and working toward their goals as part of an overall health benefit plan." ■

NEWS BRIEFS

FDA approves new labels for hormone therapy

The Food and Drug Administration (FDA) is advising women and health care professionals about new safety changes to labeling of all estrogen and estrogen with progestin products for use by postmenopausal women.

The FDA says these changes reflect its analysis of data from the Women's Health Initiative study (WHI), a landmark study sponsored by the National Institutes of Health that raised concern about risks of using these products. The Prempro (a combination of estrogens plus a progestin) arm

of the WHI was halted early in July 2002 because the overall health risks, particularly the risks of invasive breast cancer and cardiovascular disease, exceeded the benefits of the drug.

The revisions for the labels of hormones Premarin (containing estrogens), Prempro, and Premphase (containing estrogens with a progestin) build on revisions to the labeling that Wyeth Pharmaceuticals, the products' manufacturer, made in August 2002, shortly after the release of the findings from WHI.

The new boxed warning, the highest level of warning information in labeling, highlights the increased risks for heart disease, heart attacks, strokes, and breast cancer. This warning also emphasizes that these products are not approved for heart disease prevention. FDA also has modified the approved indications for Premarin, Prempro, and Premphase to clarify that these drugs should be used only when the benefits clearly outweigh risks. To minimize the potential risks and to accomplish the desired treatment goals, the new labeling also advises health care providers to prescribe estrogen and combined estrogen with progestin drug products at the lowest dose and for the shortest duration for the individual woman. ▼

USP gives tips to prevent drug errors in children

Medication errors can be especially devastating for children. That's why the United States Pharmacopeia (USP) in Rockville, MD, has announced recommendations for preventing medication errors in children.

USP's Center for the Advancement of Patient Safety created the recommendations after analyzing medication error data from its databases. Before administering the medication, health care providers must consider a child's age, weight, medication dosing frequencies, and a number of other factors to help ensure the safety of young patients.

The recommendations include the following:

• Dosage forms and/or preparations that are compounded, prepared in serial dilutions, and/or extensively manipulated should be prepared in the pharmacy and verified by a pharmacist. Where possible, a second health care professional familiar with dilutions and compounding should verify the product preparation and labeling.

• Policies and procedures should be developed and implemented when automated dispensing machines are being used for pediatric medications, including double independent verification of medications loaded into the machines and the inability to override system safeguards.

• When possible, medications should be prepared and dispensed as "unit-dose" containers for all pediatric medications in all health care facilities.

• The patient's weight, age, and other appropriate dose indicator(s) should be available and clearly identified on all prescriptions and orders before the dose is dispensed and administered.

• Wherever possible, a validated computer algorithm should calculate pediatric dosages as part of an integrated medication order entry system. Calculations, whether computerized or manual, should be independently double-checked by a pharmacist and signed off by at least one other licensed health care professional to confirm accuracy.

• Abbreviations, acronyms, and symbols used throughout an organization should be standardized and readily available. A list of abbreviations, acronyms, and symbols that should not be used also should be available.

• To prevent 10-fold overdoses, a terminal or trailing zero should never be used after a decimal. A leading zero should always precede a decimal expression of less than one.

For a complete list of the recommendations, see www.usp.org. ▼

American Pharmaceutical Association changes name

Members of the American Pharmaceutical Association (APhA) in Washington, DC, have voted overwhelmingly to change the association's name to the American Pharmacists Association.

A name-change amendment to APhA's bylaws required 75% of the votes cast by Dec. 2, 2002. The amendment passed with nearly 90% approval from APhA members. The name change will formally take effect March 29, 2003, at the APhA

Annual Meeting in New Orleans. At the opening session on that date, outgoing president Janet P. Engle, PharmD, will conclude her address by proclaiming the name change and unveiling a new association logo. The association will retain its current abbreviation, APhA. ▼

Consumers still taking risks with OTC painkillers

The ongoing abuse and misuse of over-the-counter (OTC) pain relievers such as ibuprofen and naproxen is a very real problem in the United States, according to the National Consumers League (NCL) in New York.

A Harris Interactive survey of 4,263 adults reveals that many Americans take OTC medications for pain relief, but often they do so without regard for their safety. Of the 84% of survey respondents who have taken an OTC pain reliever within the last year, 44% admitted to exceeding the recommended dose. Many also ignore critical label information. NCL says it released the survey to help educate consumers who take non-steroidal anti-inflammatory drugs about the possible dangers of improper use.

According to the survey, 50% of respondents who reported taking an OTC pain reliever within the last year were not concerned about potential side effects. Almost half (45%) agreed that it is more important to control pain regardless of risk. And only 16% (unprompted) reported reading the entire product label.

The survey also shows that consumers overlook the risks of mixing OTC pain medications with other drugs, especially cold remedies with multiple active ingredients, prescription drugs, and alcohol:

• Forty-five percent of the people who reported taking an OTC pain reliever agreed that it is safe to take an OTC pain reliever while also taking another OTC cold or flu medication.

• One-third (34%) agreed it is safe to take an OTC pain reliever while taking a prescription medication.

• Almost 20% agreed it is safe to take an OTC pain reliever while drinking some alcohol.

• An overwhelming majority (80%) have not discussed some of the key risks associated with misusing these products — stomach bleeding or ulcers — with a physician or pharmacist.

Survey results and a free brochure, "OTC Pain Meds: What Helps, What Hurts," are available at www.nclnet.org. The brochure also is available by calling toll-free (866) 216-2316. ■

IN THE PIPELINE

• Amylin Pharmaceuticals and Eli Lilly and Co. have announced the completion of enrollment for the remaining two of three Phase III trials of synthetic exendin-4 (AC2993). One study is evaluating the ability of synthetic exendin-4 to improve glucose control in people with **Type 2 diabetes** not currently achieving target blood glucose levels with sulfonylureas alone. The other is evaluating the ability of synthetic exendin-4 to improve glucose control in people with **Type 2 diabetes** not currently achieving target blood glucose levels with the combination of metformin and sulfonylureas.

• Inhibitex has initiated a Phase II clinical study of Veronate, a human polyclonal immunoglobulin containing elevated levels of antibodies to both *Staphylococcus aureus* and coagulase-negative staphylococci MSCRAMM proteins. Veronate is being developed for the prevention of **staphylococcal infections** in hospitalized premature infants.

• Genelabs Technologies has initiated its confirmatory Phase III clinical trial for prasterone

COMING IN FUTURE MONTHS

- New treatment guidelines issued for Alzheimer's
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(Prestara), the company's investigational drug for **systemic lupus erythematosus**.

• Epimmune has received clearance from the Food and Drug Administration (FDA) to begin Phase I/II clinical trials of its EP-2101 therapeutic, multi-epitope vaccine in **lung and colorectal cancer** patients. Two separate Phase I/II trials will be initiated, one trial for each cancer indication, and will involve an aggregate of approximately 25 patients who have had surgery to remove the majority of the cancer cells.

• Novacea has announced that patient enrollment has begun in a Phase II trial of its lead product, calcitriol (DN-101), for the potential treatment of patients with the blood disorder **myelodysplastic syndromes** (MDS).

• Millennium Pharmaceuticals has initiated a Phase II clinical trial of bortezomib (Velcade) for Injection in patients with stage IIIb (locally advanced) or stage IV (metastatic) **non-small cell lung cancer**.

• RxKinetix has begun patient enrollment in a Phase II clinical trial of its proprietary compound, RK-0202, for **oral mucositis**.

• InterMune has initiated a Phase I clinical study to evaluate PEG-Alfacon, the PEGylated version of Interferon alfacon-1 (Infergen), as a potential new treatment for **chronic hepatitis C virus**.

• Corgentech has announced that the FDA has granted fast-track designation for the company's second product, CGT021. The product will soon enter a Phase I/II clinical trial for the prevention of **arterio-venous graft failure** in end-stage renal disease patients requiring hemodialysis.

• Vion Pharmaceuticals has initiated a new multi-center Phase II trial of its ribonucleotide reductase inhibitor Triapine as a single agent in patients with advanced hormone-refractory **prostate cancer**.

• Antex Biologics has announced that two Phase II clinical trials for the company's Helivax vaccine are scheduled for the first half of 2003. Helivax is an inactivated multivalent whole cell vaccine designed to prevent and treat **infections caused by *Helicobacter pylori***.

• Alexion Pharmaceuticals has completed enrollment in its Phase IIb trial of eculizumab, a humanized monoclonal antibody C5 complement inhibitor, in **rheumatoid arthritis** patients.

• Attenuon LLC has announced a Phase I trial of ATN-161, which is derived from a small fragment of a human protein. The trial is expected to enroll up to 36 patients with **advanced solid tumors** that have not responded to treatments with traditional therapies.

• Vion Pharmaceuticals has initiated a multi-center Phase I trial of VNP40101M in patients with **solid tumors**. VNP40101M is a DNA-damaging alkylating agent that has broad antitumor activity in animal models.

• Micrologix Biotech, in collaboration with Fujisawa Healthcare, has completed patient enrollment in the Phase III clinical trial of MBI 226, a topical, antimicrobial peptide under development for the prevention of **central venous catheter-related bloodstream infections**.

• Aesgen has announced that the FDA granted fast-track designation to the company's investigational new drug, Aesgen-14 (AES-14), for **oral mucositis** associated with cancer chemotherapy.

• Celgene Corp. has announced that CC-5013 (Revimid) received fast-track designation from the FDA for the treatment of **relapsed or refractory multiple myeloma**.

• Immtech International has completed enrollment for its Phase IIa pilot human clinical trial of the oral drug candidate DB 289 for the treatment of ***Pneumocystis carinii* pneumonia**. ■

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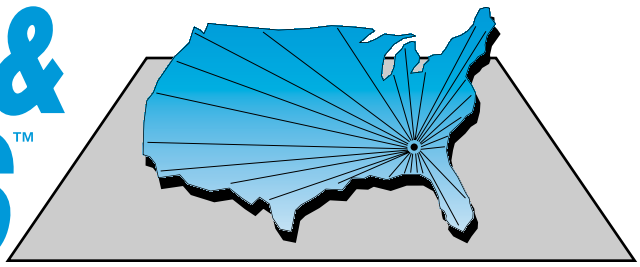

Moxifloxacin IV formulary evaluation

By **Karisa S. Wilks**
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Moxifloxacin (Avelox), a member of the fluoroquinolone class of antibacterial agents, possesses a broad spectrum of bacterial coverage, including both gram-positive and gram-negative microorganisms.[1] Moxifloxacin also offers some coverage against anaerobic bacteria. The methoxy group at the C-8 position enhances the drug's anaerobic activity and allows it to bind to both DNA gyrase and topoisomerase, which is thought to give the drug a low propensity of selective resistance. Gatifloxacin (Tequin), another methoxyquinolone, also offers the above benefits.[2] Moxifloxacin is available as 400 mg film-coated tablets and ready-to-use 250 mL flexible bags containing 400 mg of the drug; both are manufactured by Bayer Pharmaceuticals.

Mechanism of action

Moxifloxacin is an 8-methoxy fluoroquinolone; it is a synthetic, broad-spectrum antibacterial agent for oral and intravenous (IV) administration. The quinolones are the only direct inhibitors of DNA synthesis. These bactericidal antimicrobial agents exert their effects by binding to DNA gyrase (bacterial topoisomerase II), which is required for bacterial DNA replication, transcription, repair, and recombination.

Indications[1]

Moxifloxacin is approved by the Food and Drug Administration (FDA) for the following indications:

- acute bacterial sinusitis caused by *Streptococcus pneumoniae*, *Haemophilus influenzae*, or *Moraxella catarrhalis*;
- acute bacterial exacerbation of chronic bronchitis caused by *S. pneumoniae*, *H. influenzae*, *H. parainfluenzae*, *Klebsiella pneumoniae*, *Staphylococcus aureus*, or *M. catarrhalis*;
- community-acquired pneumonia (of mild-to-moderate severity) caused by *S. pneumoniae*, *H. influenzae*, *Mycoplasma pneumoniae*, *Chlamydia pneumoniae*, or *M. catarrhalis*;
- uncomplicated skin and skin-structure infections caused by *S. aureus* or *Streptococcus pyogenes*.

Table 1, below, provides a list of the indications currently approved for moxifloxacin, levofloxacin, and gatifloxacin.

Moxifloxacin has lower minimum inhibitory concentration (MIC) values than gatifloxacin or

Table 1: Indications approved by the FDA

Indication[3]	Levofloxacin[4]	Moxifloxacin[1]	Gatifloxacin[2]
Lower respiratory tract infection	Yes	Yes	Yes
Acute bacterial sinusitis	Yes	Yes	Yes
Urinary tract infection	Yes	No	Yes
Skin and integument	Yes	Yes	No
Gynecologic and pelvic infections	No	No	Yes

levofloxacin against some gram-positive organisms, such as *Enterococcus faecalis*, *S. aureus*, and *S. pneumoniae*.

Moxifloxacin does not show susceptibility to methicillin-resistant *S. aureus* (MRSA).

The safety and efficacy of moxifloxacin in treating clinical infections due to the following organisms has not been established in adequate and well-controlled trials:[1]

Aerobic gram-positive microorganisms

- *Staphylococcus epidermidis* (methicillin-susceptible strains only)
- *Streptococcus agalactiae*
- *S. pneumoniae* (penicillin-resistant strains)
- *Streptococcus viridans*

Aerobic gram-negative microorganisms

- *Citrobacter freundii*
- *Enterobacter cloacae*
- *Escherichia coli*
- *Klebsiella oxytoca*
- *Legionella pneumophila*
- *Proteus mirabilis*

Table 2: Recommended AUC/MIC ratios

	AUC/MIC ratio[5]
Aerobic gram-negative organisms	125-250
Aerobic gram-positive organisms	> 30
Streptococcus pneumoniae	30-55

Note: Ratio for anaerobes and atypical pathogens not adequately evaluated; AUC/MIC ratios are suggested minimum targets.

Anaerobic microorganisms

- *Fusobacterium* species
- *Peptostreptococcus* species
- *Prevotella* species

The recommended area under the curve (AUC)/MIC ratios to predict clinical and microbiological response to quinolones are listed in **Table 2, above**. **Table 3, below,** presents the AUC/MIC ratios of levofloxacin, gatifloxacin, and moxifloxacin for selected pathogens.

Table 3: AUC/MIC ratios for selected pathogens

	Levofloxacin 500 mg (AUC_{24} = 72.5)	Gatifloxacin 400 mg (AUC_{24} = 51.3)	Moxifloxacin 400 mg (AUC_{24} = 48)
Aerobic gram-positive			
MSSA	145	427	400
MRSA	18*	6*	12*
Streptococcus epidermidis	18*	205	369
Streptococcus pneumoniae	32	102	384
Streptococcus pyogenes	72	102	192
Enterococcus faecalis	72	25*	48
Aerobic gram-negative			
Escherichia coli	604	855	800
Proteus mirabilis	580	205	192
Proteus vulgaris	580	205	96
Salmonella typhi	2416	855	369
Shigella spp.	580	3206	1600
Campylobacter jejuni	NA	205	369
Haemophilus influenzae	2416	1710	1600
Moraxella catarrhalis	1208	1710	1600
Pseudomonas aeruginosa	18*	12*	12*
Neisseria gonorrheae	1208	3206	3000
Klebsiella pneumoniae	290	855	400
Enterobacter cloacae	145	855	800
Klebsiella oxytoca	145	394	800
Providencia rettgeri	NA	102*	96*

*AUC/MIC does not meet suggested minimum target
NA = value not available
(Values calculated using reported MIC and AUC values gathered from Reference 4.)

Table 4: Adverse effects of the quinolones

Adverse effect (%)[4,10]	Ciprofloxacin[11]	Levofloxacin[3]	Gatifloxacin[2]	Moxifloxacin[1,12]
Nausea	5	1	3-6	7.2
Vomiting	2	0.2	0.1-3	1-2
Diarrhea	2	1	3-6	5.7-8
Gastrointestinal (GI) distress	0.3	0.1-3	1	
Abdominal pain/cramping	2	0.3 (3.1 constipation)	0.1-3	2
Headache	1	5.4	3	2
Dizziness/vertigo	< 1	0.3	3	3
Nervousness/restlessness/ anxiety	1.1	0.5-1	0.1-3	0.05-1
Insomnia	< 1	0.3		0.05-1
Fatigue		0.1		
Rash	1.1	0.3	0.1-3	0.05-1
Pruritis		0.5	0.1-3	0.05-1
Photosensitivity	< 1	0.03		
Hepatic abnormalities	0.3-1.9	≤ 0.3		
Other		Injection site reaction: 5.6, chest pain: 1.1	Vaginitis: 8, local injection site reaction: 5, taste perversion: 0.1-3	Abnormal liver function test: 1, taste perversion: 1

An AUC/MIC ratio less than the suggested range predicts clinical failure, as with all the compared agents in regard to *P. aeruginosa* and MRSA. A ratio within the suggested range denotes the highest likelihood of a clinical cure; however, a ratio well above the suggested range results in no further improvement in clinical cure rate.

The fluoroquinolones are well-distributed throughout various body tissues. Tissue concentrations often exceed serum values, with the exception of low concentrations of cerebrospinal fluid and aqueous humor. An important characteristic shared by all fluoroquinolones is a high uptake into human phagocytes, which facilitates continued activity against intracellular pathogens.

Contraindications/warnings

Hypersensitivity to moxifloxacin or any other quinolone antimicrobial agent is a contraindication to therapy with this agent. There are several precautions, including the following:

- **Pregnancy:** The quinolones are pregnancy category C. No adequate and well-controlled studies of these agents have been conducted in pregnant women, and quinolones should be used in pregnancy only if the potential benefit outweighs the potential risk to the fetus.
- **Breast-feeding:** There is not a sufficient amount of human data available.
- **Severe hepatic insufficiency:** More pharmacokinetic data are needed before dosage recommendations can be determined in these patients.
- **QT interval prolongation:** The FDA recommends that the package insert contain a statement suggesting that the risk of arrhythmias may be reduced by avoiding their use or administering them with caution in patients with known underlying cardiac conditions, those with known QTc interval prolongation or history of significant cardiac arrhythmia, those

Table 5: Drug interactions

Interacting drug(s)[4,10]	Gatifloxacin[2]	Levofloxacin[3]	Moxifloxacin[1,7,12]
Antacids	C_{max} ⇓ 15-69% AUC ⇓ 17-64%	C_{max} ⇓ 37-65% AUC ⇓ 22-44%	C_{max} ⇓ 40% AUC ⇓ 23-60%
Ferrous sulfate	C_{max} ⇓ 54% AUC ⇓ 35%	C_{max} ⇓ 45% AUC ⇓ 19%	C_{max} ⇓ 59% AUC ⇓ 39%
Sucralfate	ND (recommend use be avoided)	Not significant if given 2 hours before or after sucralfate	ND (recommend use be avoided)
Theophylline	Theo C_{max} and AUC ⇑ 50%	Theo C_{max} and AUC ⇑ 2-11%	NS
Warfarin	NS	NS	NS
Probenecid	AUC ⇑ 42% T½ ⇑ 44%	NS (Cl ⇓ 24-36%)	NS
Phenytoin	ND	ND	ND
Digoxin	NS	NS	NS
Vitamins	Administer 4 hours before if contains zinc, magnesium, or iron	Administer 4 hours before if contains zinc, magnesium, or iron	Administer 4 hours before if contains zinc, magnesium, or iron
QT prolonging drugs or drugs that cause bradycardia (e.g., metoclopramide, erythromycin, classes Ia and III antiarrhythmics, and tricyclic antidepressants)	Avoid or use caution	Avoid or use caution	Avoid or use caution

NS = not significant, ND = no data available

with uncorrected hypokalemia, and those receiving concomitant therapy with agents known to increase the QTc interval or to cause bradycardia (metoclopramide, cisapride, erythromycin, classes Ia and III antiarrhythmics, and tricyclic antidepressants).

Each of the listed precautions applies to levofloxacin, gatifloxacin, ciprofloxacin, and moxifloxacin, with these exceptions:

• It is thought that levofloxacin should not require dosage adjustment in hepatic insufficiency.

• Each of the other drugs besides moxifloxacin requires dosage adjustment in renal insufficiency.

• The labeling in the patient package insert differs in regard to the recommendations on the QT interval prolongation. Currently, moxifloxacin has the strongest warning of these four drugs regarding this potential side effect.[6]

Average QT prolongation for moxifloxacin and comparators:[7]

• Moxifloxacin: 6 ± 26 msec
• Amoxicillin: 4 ± 30 msec
• Doxycycline: 2 ± 34 msec
• Cefuroxime axetil: 2 ± 20 msec
• Clarithromycin: 2 ± 23 msec
• Ofloxacin: 0 ± 81 msec
• Cephalexin: 3 ± 16 msec

No comparative trials have taken place to compare the effects of moxifloxacin, gatifloxacin, and levofloxacin on QT prolongation. The QT prolongation effects of both levofloxacin and gatifloxacin are thought to be slightly less than that of moxifloxacin. A large population has been exposed to levofloxacin, with more than 15 million prescriptions written for the drug in the United States from January 1997 to March 2000, and reporting rates of cardiovascular adverse events are low. Less than one case of QT prolongation or torsades de pointes per million prescriptions has been reported, regardless of whether the condition was attributed to underlying disease or concomitant therapy.

Table 6: Dosing information

Infection	Daily dose of moxifloxacin[1]	Duration
Acute bacterial sinusitis	400 mg	10 days
Acute bacterial exacerbation of chronic bronchitis	400 mg	5 days
Community-acquired pneumonia	400 mg	10 days
Uncomplicated skin and skin structure infections	400 mg	7 days

Pharmacokinetics[4,8,9]

Oral moxifloxacin is rapidly absorbed with an average T_{max} of 0.75-3.5 hours. The mean C_{max} range is 2.50-4.38 mg/L after the usual therapeutic dose of 400 mg in subjects with normal renal and hepatic function. According to the package insert, plasma concentrations increase proportionately with doses up to the highest tested (1,200 mg single oral dose). Moxifloxacin has excellent oral bioavailability, ranging anywhere from 86-100%. The half-life of oral moxifloxacin ranges from 11-14 hours, and it has a volume of distribution ranging from 2.0-3.5 L/kg. Moxifloxacin is approximately 50% protein-bound. The rate of renal clearance is 12.7-15.2 L/h. Linear increases in C_{max} and AUC also are seen with intravenous infusions of moxifloxacin 100-400 mg. After 400 mg IV moxifloxacin, the C_{max} has been found to be 6.1 mg/L compared to 4.5 mg/L for the equivalent oral dose.

A slight reduction in C_{max} is seen after coadministration of 400 mg moxifloxacin and a standard high-fat meal (mean 2.5 mg/L fed, and 2.8 mg/L fasting). Also, the T_{max} was slightly prolonged (2.5 vs. 1.0 hours). The AUC remains the same for both fed and fasting states. When the standard dose of moxifloxacin is given with yogurt, a modest delay in the T_{max} has been observed (0.88 vs. 2.75 hours). Reductions in mean C_{max} (2.87 vs. 2.44 mg/L, 15.3% decrease) and AUC (33.9 vs. 31.8 mg hr/L, 6.2% decrease) also are seen. These results conclude that moxifloxacin may be administered regardless of food intake.

Information regarding the steady state concentrations of moxifloxacin is limited. A pharmacokinetics study of the drug that involved a 10-day treatment period with 400 mg QD observed a steady state C_{max} and C_{min} of 4.52 mg/L and 0.95 mg/L, respectively. Another multiple-dose study involving a five-day treatment regimen found C_{max} and C_{min} steady states to be 3.24 mg/L and 0.47 mg/L, respectively.

Moxifloxacin undergoes hepatic metabolism by means of sulfate and glucuronide conjugation. Approximately 38% of the dose is converted to the sulfate conjugate, and 14% to the glucuronide conjugate. After single oral and intravenous doses of 400 mg were administered, 96.3% and 98.4% were recovered in the urine and feces respectively as unchanged parent or metabolite. Most of the sulfate conjugate is excreted in the feces, whereas all of the glucuronide conjugate is excreted in the urine.

The major clinical difference in the pharmacokinetics of moxifloxacin, levofloxacin, and

Table 7: Acute bacterial sinusitis

Moxifloxacin, dose and frequency	Comparator, dose and frequency	Treatment Duration	Number of patients	Most commonly isolated pathogens	Clinical cure/ bacterial cure
400 mg QD[13]	Cefuroxime axetil 250 mg BID	10 days	457	*S. pneumoniae* *H. influenzae* *M. catarrhalis* *S. aureus*	90% moxifloxacin 89% cefuroxime
400 mg QD[14]	Trovafloxacin 200 mg QD	10 days	590	*S. pneumoniae* *H. influenzae* *M. catrrahalis* *S. aureus*	88% moxifloxacin 89% trovafloxacin

Table 8: Acute bacterial exacerbations of chronic bronchitis

Moxifloxacin, dose and frequency	Comparator, dose and frequency	Treatment duration	Number of patients	Most commonly isolated pathogens	Clinical cure/ bacterial cure
400 mg QD[15]	Clarithromycin 500 mg BID	5-10 days	926	*S. pneumoniae* *H. influenzae* *M. catarrhalis* *S. aureus* *K. pneumoniae* *H. parainfluenza*	89% moxifloxacin (5) 91% moxifloxacin (10) 91% clarithromycin/ 89% moxifloxacin (5) 91% moxifloxacin (10) 85% clarithromycin
400 mg QD[16]	Clarithromycin 500 mg BID	5-7 days	649	*H. influenzae* *S. pneumoniae* *M. catarrhalis*	89% moxifloxacin 88% clarithromycin/ 77% moxifloxacin 62% clarithromycin
400 mg QD[17]	Azithromycin 500 mg X 1D, then 250 mg X 4D	5 days	567	*H. influenzae* *S. pneumoniae* *M. catarrhalis*	97% moxifloxacin 96% azithromycin/ 89% moxifloxacin 86% azithromycin

gatifloxacin is the elimination profile. Both gatifloxacin and levofloxacin are excreted primarily by the kidneys, whereas moxifloxacin undergoes a high percentage of hepatic elimination. This difference would account for the different recommendations for hepatic and renal dosage adjustment among the agents. This difference may account for moxifloxacin not achieving renal/urine concentrations as high as those achieved by gatifloxacin and levofloxacin, but no clinical studies of moxifloxacin for treatment of urinary tract infection (UTI) have yet been done to confirm this.

Adverse effects

The side-effect profiles of the above agents do not have any major differences. Moxifloxacin has a slightly greater incidence of gastrointestinal side effects than levofloxacin and gatifloxacin. Moxifloxacin also has a stronger warning regarding QTc interval prolongation than the other two agents. **Table 4 on page 3** lists the more common adverse effects association with quinolones.

Drug interactions

Table 5 on page 4 presents the interaction profiles of gatifloxacin, levofloxacin, and moxifloxacin.

Dosage

Table 6 on page 5 lists the doses of moxifloxacin and the duration of therapy for the given indications.

Moxifloxacin IV should be administered by intravenous infusion over a period of 60 minutes by direct infusion or through a Y-type intravenous infusion set that may already be in place.

The IV form is compatible with the following intravenous solutions at ratios from 1:10 to 10:1:

- 0.9% NaCl injection, USP;
- 1M NaCl injection;
- 5% dextrose injection, USP;
- sterile water for injection;
- 10% dextrose for injection;
- lactated Ringer's for injection.

Clinical trials

Few head-to-head trials among the fluoroquinolones have taken place. The trials presented in **Tables 7-9 on pp. 5-7** show results of the major trials that have been completed to date. Each of these trials were well-structured, with relatively large numbers of patients. The inclusion and exclusion criteria were similar among the different trials and the comparator drug was given at a dose comparable to that of moxifloxacin for the given indication.

There also has been a randomized, double-blind, controlled clinical trial involving 401 patients conducted in the United States comparing the efficacy of moxifloxacin 400 mg once daily for 7 days with cephalexin 500 mg three times a day for 7 days for the treatment of uncomplicated skin and skin-structure infections.[22] The clinical

Table 9: Community-acquired pneumonia

Moxifloxacin, dose and frequency	Comparator, dose and frequency	Treatment duration	Number of patients	Most commonly isolated pathogens	Clinical cure/ bacterial cure
400 mg QD[18]		10 days	196	*C. pneumoniae* *M. pneumoniae* *S. pneumoniae* *H. influenzae*	93%/94%
400/400 mg QD (IV/PO)[19]	Alatrofloxacin 200/200 mg (IV/PO) Levofloxacin 500/500 mg (IV/PO)*	IV for at least 3 days before switch to PO. Mean length of total treatment = 11 days.	507		67% moxifloxacin, 67% comparator
400 mg QD (IV/PO)[20]	Amoxicillin/ clavulanate (IV/PO) 1.2 g /625 mg TID clarithromycin (IV/PO) 500 mg BID	IV for at least 3 days before BIDswitch to PO. Total = 7-14 days.	538	*S. pneumoniae* *H. influenzae* *M. pneumoniae* *C. pneumoniae* *L. pneumophila*	93.4% moxifloxacin, 85.5% comparator/ 93.7% moxifloxacin, 81.7% comparator
400 mg QD[21]	Clarithromycin 500 mg BID	10 days	382	*C. pneumoniae* *M. pneumoniae* *H. influenzae* *S. pneumoniae*	91% moxifloxacin, 92% clarithromycin/ 97% moxifloxacin, 96% clarithromycin

*Alatrofloxaxin was switched to levofloxacin after concerns arose regarding alatrofloxacin hepatotoxicity

success rates in evaluable patients were 89% (108/122) for moxifloxacin and 91% (110/121) for cephalexin.

Economic issues

Bayer Corp. recently introduced a new pricing structure for acute care hospitals that includes both oral and IV formulations of ciprofloxacin and moxifloxacin. Pricing structures also are being developed for those hospitals that do not place the full lines of ciprofloxacin and moxifloxacin on the formulary.

Bayer Corp. is marketing moxifloxacin for the treatment of gram-positive infections and ciprofloxacin for the treatment of gram-negative infections. The probability of reaching tier 1 (90-100% of quinolone market share with ciprofloxacin/ moxifloxacin) for lowest pricing with ciprofloxacin IV is low, and even at that point the daily cost of ciprofloxacin would be significantly more than gatifloxacin. Therefore, the cost savings benefit of this pricing structure would not surpass the current savings for many hospitals. Currently, the cost savings resulting from a switch from levofloxacin to gatifloxacin would be approximately $30,000-40,000 per year.

Summary

Gatifloxacin should continue to be the primary formulary quinolone. Gatifloxacin has been studied in several areas that moxifloxacin has not, such as UTIs and bone and joint infections. Both of these infections are seen regularly in the hospital, and information regarding the use of moxifloxacin in these infections is lacking. Several studies currently are in progress concerning the use of IV/PO moxifloxacin in the areas of complicated skin and soft-tissue infections, complicated hospital-acquired pneumonia, community-acquired pneumonia, and intra-abdominal infections. After the results of these studies are available, it may be necessary to review the use of moxifloxacin once again.

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New FDA Approvals

These drugs recently received final approval from the U.S. Food and Drug Administration (FDA):

• *New indication for lamotrigine (Lamictal) tablets by GlaxoSmithKline.* The FDA has approved lamotrigine (Lamictal) tablets as add-on therapy in **partial seizures** in children ages 2 years and older. This new indication expands the already-approved indications for adjunctive use in adults with partial seizures, and for the generalized seizures of Lennox-Gastaut Syndrome in children two years of age and older.

Because the rate of serious rash is greater in pediatric patients than in adults, it bears emphasis that Lamictal is approved only for use in pediatric patients younger than age 16 who have partial seizures or seizures associated with the Lennox-Gastaut syndrome.

• *Interferon beta-1a (Avonex) by Biogen.* The FDA has approved Interferon beta-1a (Avonex) to include treatment of patients with a first **multiple sclerosis** (MS) attack if brain MRI scan abnormalities characteristic of MS are shown.

Interferon beta-1a should be used with caution in patients with depression or other mood disorders and in patients with seizure disorders. Pregnant women should not use the drug. Patients with cardiac disease should be closely monitored. Patients also should be monitored for signs of hepatic injury. Routine periodic blood chemistry and hematology tests are recommended during treatment with Avonex. Rare cases of anaphylaxis have been reported.

• *Adalimumab (Humira) by Abbott Laboratories.* The FDA has approved adalimumab (Humira) for treatment of **rheumatoid arthritis**. Adalimumab is produced by recombinant DNA technology; it is a human-derived antibody that binds to human tumor necrosis factor-alpha (TNF-alpha). The drug can be used alone or in combination with methotrexate or other anti-rheumatic drugs.

Adalimumab is administered as a single subcutaneous injection every other week. The package insert carries a bolded warning stating that serious, sometimes fatal, infections (including cases of tuberculosis and sepsis) have been reported with the use of TNF-blocking agents including adalimumab. ■