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Drug-resistant bacteria reaching crisis stage

Problem may require more aggressive approach

Pharmacists and other health care professionals must be aggressive in fighting against drug-resistant bacteria — or face serious consequences, infectious disease control specialists say.

A panel of these specialists recently convened in New York to discuss the problem of drug-resistant bacteria. The panelists expressed concern that a growing number of patients have developed bacterial infections that respond poorly, or not at all, to commonly used antibiotics. Particularly troubling are cases of methicillin-resistant *Staphylococcus aureus* (MRSA) and vancomycin-resistant *S. aureus* (VRSA) reported by the Centers for Disease Control and Prevention (CDC). **(For more statistics about drug-resistant bacteria, see story, p. 44.)**

"The potential ramifications [of these infections] are staggering," said panelist **Neil Fishman**, MD, director of the department of health care epidemiology, infection control, and the antimicrobial management program at the University of Pennsylvania Medical Center in Philadelphia. He also was a representative of the Society for Healthcare Epidemiology of America in Mount Royal, NJ.

Panelist **Martin Blaser**, MD, issued a warning. "We can no longer be complacent about the threat posed by antibiotic-resistant bacteria," said the chairman of the department of medicine at New York University School of Medicine and a representative of the Infectious Diseases Society of America in Alexandria, VA. "The fact is, we are simply running out of options. We're already seeing infections that fail to respond to the first or even second antibiotic prescribed. If we continue on this course, we're going to find ourselves back in the Dark Ages, when serious infections had no cure."

Antibiotics should not be used as if they have no impact; instead, their use should be guided by the obvious fact that they do have an impact, says **Michael Rybak**, PharmD, MS, FCCP, president of the Society of Infectious Diseases Pharmacists in Austin, TX, and professor of pharmacy and medicine at the Eugene Applebaum College of

Pharmacy and Health Sciences at Wayne State University in Detroit. Rybak also co-chaired the recent panel. As a pharmacist, he is pleased that he had the opportunity to open the session on such a topic and describe the problem with antibiotic-resistant bacteria before the other panelists commented.

"Unfortunately, antibiotics are not like our laser-guided weapons used in various wars that target one organism and only affect that one organism," he says in later remarks to *Drug Utilization Review*. "When you take an antibiotic and it is absorbed or infused, it goes after that one organism, but it also has activity against many other organisms. Commonly, this is where the problem of resistance occurs; patients now harbor organisms that are potentially resistant to that antibiotic that they received."

The patients then could pass that resistance on to others by transmitting the resistant organism. For instance, a pediatric patient could pass it on to an adult, an immunocompromised patient to other individuals. "This is how resistance spreads from one person to another," Rybak says.

Overprescribing antibiotics and using them improperly has led to bacteria developing resistance to the drugs. But it can be difficult for some clinicians to resist the demands of patients who just want something to help them feel better, even if they have a virus.

The World Health Organization in Geneva, Switzerland, analyzed 10 studies at teaching hospitals worldwide in 2000 and found that 40-91% of antibiotics prescribed were inappropriate. The study also found that health care workers often did not follow basic hygiene practices, such as washing hands and changing gloves between patient visits.

"Like it has always been said, it takes a minute to prescribe an antibiotic, but it takes about 15 minutes not to," Rybak says. "In many cases, we give antibiotics for colds and viruses. They have no activity against those pathogens."

He sees a movement now in health care toward waiting to prescribe an antibiotic, if the patient is not too ill. The patient will improve if he or she has a virus. Clinicians also might take a culture to determine whether the patient has a bacterial or viral infection.

As another way to address the problem, the panel emphasized the need to reinvigorate research on the development of vaccines that may prevent bacterial infections and new antibiotics that kill bacteria using novel mechanisms of action.

Large pharmaceutical companies, though, don't always see the value of developing new antibiotics, Rybak says. "The research that is required to go into antibiotics is high; the cost margin is terrible. It's difficult for them to take a venture into the antibiotic field because the profit margin is small compared to that of chronic drugs."

For this reason, development of new antibiotics often has fallen to smaller companies. However, if the company only has the one antibiotic in development and the U.S. Food and Drug Administration does not end up approving it, the company might not have the resources to try again.

It is important, then, for the government to encourage larger companies to try to develop new antibiotics, because the profits from other drugs can help them survive a drug that does not get approved, Rybak says. "Somehow a

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The role of pharmacists in antimicrobial resistance

Educate patients, prescribers about antibiotics

All pharmacists need to play an active role in the fight against antimicrobial resistance, says **Michael Rybak**, PharmD, MS, FCCP, president of the Society of Infectious Diseases Pharmacists in Austin, TX, and professor of pharmacy and medicine at the Eugene Applebaum College of Pharmacy and Health Sciences at Wayne State University in Detroit. "Education of the prescriber and patient regarding the overuse and abuse of antimicrobials is key to preserving our current armament of antimicrobials to fight another day."

Pharmacists can educate in the community or hospital settings or on a one-on-one basis, he says. They can give lectures to health care providers or communicate to them about the problem in writing. "They have to realize that we are quickly running out of useful antibiotics that we have to fight infections," he says.

Pharmacists have access to many resources, such the Centers for Disease Control and Prevention's "12 Steps to Prevent Antimicrobial Resistance Among Hospitalized Adults," found at www.cdc.gov/drugresistance/healthcare/ha/12steps_HA.htm. Other relevant information can be gathered from sources such as the Society of Infectious Diseases Pharmacists in Austin, TX, and the Infectious Diseases Society of America in Alexandria, VA.

Pharmacists with specialized training in the area of infectious diseases pharmacotherapy can make an especially big difference in the fight against antimicrobial resistance. "Their expert knowledge of antimicrobial action, interaction, and impact on the development of resistance can play a vital role [in helping] the prescriber make the most appropriate choice of an antimicrobial. This includes the choice of drug and the most effective dosage that will eradicate the pathogen in the shortest period of time and have the least amount of undue side effects, as well as the regimen least likely to develop antimicrobial resistance," Rybak says.

"Pharmacists can ensure that the prescribers they work with, as well as their patients, use antibiotics appropriately and rationally," adds **Frank Romanelli**, PharmD, BCPS, assistant professor of pharmacy and clinical specialist in HIV/AIDS at the College of Pharmacy and College of Health Sciences at the University of Kentucky in Lexington. "Prescribers should be aware of resistance patterns and the killing profiles of various antibiotics. More expensive is often equated with better, and that is not always true."

Pharmacists can educate patients by speaking to them, especially patients who are seeking advice on cough-and-cold over-the-counter products, Romanelli says. "I also think it's important for pharmacists to role-model appropriate medication-taking behaviors for both patients and other health care practitioners." ■

partnership with the government needs to encourage that."

That possibility leads Rybak to suggest a more aggressive stance in the treatment of drug-resistant bacteria: If health care professionals can rise to the challenge of infectious diseases such as severe acute respiratory syndrome (SARS), maybe the same approach can work with antimicrobial resistance.

"Like SARS, the threat posed by resistant bacteria is scary," Rybak said in his opening remarks at the panel. "Our fear is that we are simply running out of options, and this situation is only going to get worse in the months and years to come if we do not collectively do something about it now."

Leaving aside tuberculosis, in which the patient is isolated immediately when treated in a hospital setting, patients with a drug-resistant organism may not be isolated, depending on the type of organism they have, Rybak says. Instead of being complacent about antibiotic resistance, why don't clinicians put the same effort into treating it that they would invest in a disease like SARS?

Not seeing the immediacy of drug-resistant organisms is a stumbling block, he says. "We just think it's not going to affect us. If we don't see people dropping dead like they might from SARS, we don't concern ourselves."

The goal is to stop the problem before someone gets very sick with no antibiotic working against the infection, he adds. "It's not too long in the distant future before we have organisms that don't respond to anything." ■

Facts about recent upsurge in antimicrobial resistance

The Society of Infectious Diseases Pharmacists in Austin, TX, recently convened a panel with other health care organizations to discuss the recent increase in antibiotic-resistant infections. Here are some facts on the topic compiled from sources such as the Centers for Disease Control and Prevention (CDC) and the U.S. Food and Drug Administration:

- Each year, nearly two million patients in the United States acquire an infection while in a hospital, and 90,000 of these patients die from infections contracted during their stay.
- More than 70% of bacteria that cause hospital-acquired infections are resistant to at least one of the drugs most commonly used to treat them.
- In parts of the United States, up to 30% of infections from the bacteria *Streptococcus pneumoniae* — the most common cause of bacterial pneumonia, meningitis, and ear infections — are no longer vulnerable to penicillin.
- Nearly all strains of *Staphylococcus aureus* are resistant to penicillin, and many are resistant to methicillin and similar antibiotics, the treatments of choice for *S. aureus* infections.
- Up to 100,000 people are hospitalized annually with infections from methicillin-resistant *S. aureus*.
- The CDC has issued two case reports of vancomycin-resistant *S. aureus*. Vancomycin is considered the drug of last resort for many infections.
- Mortality and hospital length of stay are at least doubled for resistant strains of some organisms compared to susceptible ones.
- The more often a drug is used, the more likely bacteria are to develop resistance to it.
- Physicians in the United States and Canada overprescribe antibiotics by 50%.
- Although antibiotics are useless against viruses, nearly 50% of visits to physicians for colds and upper respiratory tract infections are treated with antibiotics.
- Half of all antibiotics produced are used to treat sick animals, as growth promoters in livestock, and to rid foodstuffs of destructive organisms.
- The annual cost of treating antibiotic-resistant infections in United States may be up to $30 billion. ■

SARS gives U.S. practice in fighting new pathogens

Incidence in Asia still a concern

The worldwide outbreak of severe acute respiratory syndrome (SARS) has put pharmacists and other health care professionals on alert. The incidence of SARS cases in the United States seems to be contained, but health officials warn that the threat is still real until Asia is able to control the virus.

On May 8, the World Health Organization (WHO) in Geneva, Switzerland, reported a cumulative total of 7,053 probable SARS cases and 506 deaths in 29 countries. The most deaths were reported in mainland China (224), Hong Kong (208), and Singapore (204). Because of the cases in those areas, the WHO recommends as of May 7 that people consider postponing all but essential travel to several areas of China, namely: Beijing, Hong Kong, Guangdong, Inner Mongolia, Shanxi, Taipei, and Tianjin.

In addition, the WHO has revised its initial estimates of the case fatality ratio of SARS. The revision is based on an analysis of the latest data from Canada, China, Hong Kong, Singapore, and Vietnam. The estimate of case fatality ratio of SARS ranges from 0% to 50% (depending on the age group affected), with an overall estimate of 14-15%.

Broken down by age groups, the case fatality ratio is estimated to be:

- less than 1% in persons ages 24 years or younger;
- six percent in persons ages 25-44 years;
- fifteen percent in persons ages 45-64 years;
- greater than 50% in persons ages 65 years and older.

In contrast to other parts of the world, the United States has contained the outbreak within its borders well, so far. As of May 7, the Centers for Disease Control and Prevention (CDC) reports that a total of 328 SARS cases have been reported from 38 states, of which 265 (81%) were classified as suspect SARS, and 63 (19%) were classified as probable SARS (more severe illnesses characterized by the presence of pneumonia or acute respiratory distress syndrome). Of the 63 probable SARS patients, 42 (67%) were hospitalized, and three (5%) required mechanical ventilation. No SARS-related deaths have been reported in the United States.

Basic information about SARS

The Centers for Disease Control and Prevention (CDC) has provided the following basic information about severe acute respiratory syndrome (SARS):

- **Definition of SARS.** SARS is a respiratory illness that has recently been reported in Asia, North America, and Europe.
- **Symptoms of SARS.** In general, SARS begins with a fever greater than 100.4°F (> 38.0°C). Other symptoms may include headache, an overall feeling of discomfort, and body aches. Some people also experience mild respiratory symptoms. After two to seven days, SARS patients may develop a dry cough and have trouble breathing.
- **How SARS spreads.** The primary way that SARS appears to spread is by close person-to-person contact. Most cases of SARS have involved people who cared for or lived with someone with SARS, or had direct contact with infectious material (for example, respiratory secretions) from a person who has SARS. Potential ways in which SARS can be spread include touching the skin of other people or objects that are contaminated with infectious droplets and then touching your eye(s), nose, or mouth. It also is possible that SARS can be spread more broadly through the air or by other ways that are currently not known. (Some researchers think feces may spread it.)
- **Who is at risk for SARS.** Most of the U.S. cases of SARS have occurred among travelers returning to the United States from other parts of the world with SARS. There have been very few cases as a result of spread to close contacts such as family members and health care workers. Currently, there is no evidence that SARS is spreading more widely in the community in the United States.
- **Possible cause of SARS.** Scientists at the CDC and other laboratories have detected a previously unrecognized coronavirus in patients with SARS. The new coronavirus is the leading candidate for the cause of SARS. ■

Of the 63 probable SARS patients, one (2%) was a health care worker who provided care to a SARS patient, and one (2%) was a household contact of a SARS patient. The remaining 61 (97%) probable SARS patients had traveled to areas with documented or suspected community transmission of SARS during the 10 days before illness onset.

This shows that infection control practices do work in this country, says **Michael Rybak**, PharmD, MS, FCCP, president of the Society of Infectious Diseases Pharmacists in Austin, TX, and professor of pharmacy and medicine at the Eugene Applebaum College of Pharmacy and Health Sciences at Wayne State University in Detroit.

"The lesson to be learned here is that when there is an outbreak of a communicable disease that can spread rapidly through a population, we seem to be able to put the right people and the right instructions and guidelines into play that contain such an outbreak."

Others also credit good fortune. "I think good fortune in this case is a consequence of a prepared public health system and a prepared clinical community, but also, we have perhaps been fortunate to some extent in that a particularly infectious patient has not slipped through the cracks or had a long period of time to be exposed to others in the home or in the health care setting," **Julie Gerberding**, MD, MPH, director of the CDC, told reporters at a May 6 telebriefing.

Researchers had been concerned that the SARS virus had begun to mutate. That was especially troublesome to clinicians who have worked with infectious pathogens such as HIV. "Any bacteria or virus that divides and mutates is a significant concern," says **Frank Romanelli**, PharmD, BCPS, assistant professor of pharmacy and clinical specialist in HIV/AIDS at the College of Pharmacy and College of Health Sciences at the University of Kentucky in Lexington. "The ability of [the HIV] virus to mutate has made it a very formidable pathogen in terms of drug and vaccine design."

The first major study of the genome of the SARS virus, however, shows that it has not mutated significantly in its spread to different countries. Health officials were both pleased with the news because this might increase the possibility of developing a vaccine, and concerned since SARS seems to stay strong as it continues through successive generations. The study was published in the May 10 edition of the medical journal *Lancet*. ■

NEWS BRIEFS

FDA adds heart benefit to simvastatin (Zocor) label

The U.S. Food and Drug Administration (FDA) has announced changes to the labeling for simvastatin (Zocor), based on the results of the Heart Protection Study (HPS). The new labeling will reflect research showing that simvastatin is effective in reducing risks of fatal and non-fatal heart attacks and strokes, and in reducing the need for bypass surgery and angioplasty. The FDA approved simvastatin in 1991 to lower cholesterol. Merck and Co. manufactures the drug.

HPS was a double-blind, placebo-controlled study conducted in 20,536 patients. Men and women with heart disease or at high risk because of diabetes, peripheral arterial disease, or a history of stroke or other cerebrovascular disease were treated with either simvastatin 40 mg/day or placebo for an average of five years. The average age of patients entering HPS was 64, and the average level at baseline of low-density lipoprotein C, or "bad" cholesterol, was 131 mg/dL. The trial population included a large number of diabetics and elderly patients.

The risk of death from coronary heart disease was reduced by 18% in the patients treated with simvastatin. The risk of having a non-fatal heart attack was reduced by 38% in this group. Simvastatin also reduced the risk of stroke by 25% and the need for undergoing coronary or non-coronary revascularization procedures by 30% and 16%, respectively. ▼

Pharmacists needed for underserved populations

The National Health Service Corps (NHSC) is launching a demonstration project, for this year only, to award loan repayment to a special group of pharmacists and chiropractors who agree to serve underserved populations in primary care health professional shortage areas throughout the United States. A minimum two-year service commitment is required, and applicants must be employed by a primary health care site that has an active NHSC clinician on staff who is authorized to prescribe medications.

Awardees will be part of a three-year trial program that will include an evaluation to determine whether adding chiropractors and pharmacists would enhance the effectiveness of the NHSC. Applications are due by June 30, 2003. For more information, go to http://nhsc.bhpr.hrsa.gov/. ▼

APhA releases bulletin on gabapentin (Neurontin)

The American Pharmacists Association in Washington, DC, has published a New Therapeutics Bulletin on gabapentin (Neurontin) for pharmacists. The U.S. Food and Drug Administration recently approved gabapentin for the management of postherapeutic neuralgia in adults.

The bulletin, supported by an educational grant from Pfizer, provides a comprehensive description of the pharmacokinetics, dosing, administration, efficacy, adverse effects, cautions, use in pregnancy, and drug interactions associated with gabapentin. Postherapeutic neuralgia also is discussed. Additional information about gabapentin is posted on www.pharmacist.com under the link "Drug Information." ■

Smallpox compensation bill becomes law

On April 30, President Bush signed into law the Smallpox Emergency Personnel Protection Act of 2003 (HR 1770). The compromise bill was created to compensate individuals with vaccinia-related injuries. Under the law, people who are permanently disabled are eligible for up to $50,000 annually in lost wages, with no cap on the amount of damages they can collect during their lifetime. Partially disabled recipients also are eligible for up to $50,000 per year in lost wages, with a cap of $262,100. Spouses of recipients killed by the vaccine receive $262,100, while spouses with children choose between a $262,100

lump sum or $50,000 annually until the youngest child turns age 18.

The legislation will be funded by $42 million included in the FY 2003 supplemental appropriations bill.

In addition, the Secretary of the Department of Health and Human Services (HHS) has announced that the department will release $100 million to the states to help them better prepare for a possible smallpox attack and strengthen the public health infrastructure.

The money from HHS' Centers for Disease Control and Prevention will be made available immediately. These funds are in addition to the $1.1 billion in fiscal year 2002 funds sent to states last year, and the $1.4 billion in fiscal year 2003 money. ▼

PhRMA plans to report counterfeit drugs to FDA

The Pharmaceutical Research and Manufacturers of America (PhRMA) in Washington, DC, has announced that it has launched a voluntary program to report counterfeit drugs to the U.S. Food and Drug Administration (FDA).

Under the voluntary program, PhRMA member companies agree to notify the FDA's Office of Criminal Investigations by telephone or in writing within five working days of determining that there is a reasonable basis to believe that a product has been counterfeited. The program also applies to counterfeits discovered in foreign countries if there is clear evidence that the counterfeits are intended for distribution in the United States. The reporting program went into effect on May 1.

The FDA commended PhRMA's announcement. "This formal collaborative agreement will strengthen the FDA's ability to assure the safety and effectiveness of drugs used by Americans," says FDA commissioner **Mark B. McClellan**, MD, PhD. Both the FDA and PhRMA will assess the value of this program at the end of one year. ■

IN THE PIPELINE

• Celgene Corp has announced that its drug CC-5013 (Revimid) received fast-track designation from the U.S. Food and Drug Administration (FDA) for the treatment of **myelodysplastic syndromes**.

• Chiron Corp. has initiated a Phase III trial in the United States for Menjugate, the company's conjugated vaccine for the prevention of **meningococcal C disease**.

• Immusol announced today that the first patient was treated in a Phase I physician-sponsored trial using its investigational new drug, code-named VIT100, to treat **keloids** and **hypertrophic scars**.

• Favrille has expanded its current Phase II clinical trial of the company's investigational agent FavId, a patient-specific anti-lymphoma vaccine, in combination with rituximab (Rituxan), to include patients who have not received prior treatment for their **low-grade or follicular non-Hodgkin's lymphoma**. With this expansion, the study is now enrolling patients who have not received any prior treatment for their lymphoma, as well as those patients who are relapsed or refractory to their prior treatments. Prior treatments may include chemotherapy alone, rituximab alone, or chemotherapy and rituximab used in combination.

• Sucampo Pharmaceuticals has initiated a multicenter safety and efficacy study for the treatment of **constipation-predominant irritable bowel syndrome** with its proprietary agent SPI-0211, a novel chloride channel activator.

• Inhibitex has received FDA clearance to initiate a Phase I clinical trial to assess the safety and tolerability of its second product candidate, Aurexis, a humanized monoclonal antibody. Aurexis is being developed for the prevention and treatment of life-threatening ***S. aureus* infections**. ■

COMING IN FUTURE MONTHS

- ■ A look at off-label drug use
- ■ ASHP strives to improve pharmacy practice
- ■ Maximize your patient counseling opportunities
- ■ The impact of pharmacy on larger clinical trial sizes
- ■ New technological innovations

New FDA Approvals

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

• *Agalsidase beta (Fabrazyme) by Genzyme Corp.* The FDA has approved the first treatment for patients with **Fabry disease**.

The new product, agalsidase beta (Fabrazyme), was produced by recombinant DNA technology to be a synthetic version of a natural human enzyme. It is given intravenously. This replacement of the missing enzyme caused by Fabry disease, alpha-galactosidase A, reduces a particular type of lipid accumulation in many types of cells, including blood vessels in the kidney and other organs. It is believed likely that this reduction of fat deposition will prevent the development of life-threatening organ damage and will have a positive health effect on patients.

Agalsidase beta was approved under an accelerated approval mechanism through the FDA's orphan drugs program. One of the requirements of an accelerated approval is that the sponsor completes a postmarket study verifying that patients will benefit from the product. Genzyme says it will continue conducting an ongoing randomized placebo-controlled trial to verify agalsidase beta's benefit to patients and to assess the drug's effects on the progression of kidney and heart disease and the incidence of strokes.

In addition, Genzyme has set up a patient registry to follow the long-term progress of patients. Enrollment in this registry is voluntary.

In clinical studies of agalsidase beta, the main safety concern in patients receiving the drug was infusion reactions, some of which were severe. These include fever, chest tightness, blood pressure changes, abdominal pain, and headache. Most patients also develop antibodies to the product, and some patients who experience allergic reactions may need to be further evaluated. Because of the potential for these severe reactions, appropriate medical observation and support should be available when agalsidase beta is administered.

• *The NIOX Nitric Oxide Test System by Aerocrine AB, of Sweden.* The FDA has cleared for marketing a first-of-a-kind noninvasive test system to measure the concentration of nitric oxide in exhaled human breath. The test system should help make it easier for doctors to monitor a patient's **asthma**.

The test system combines equipment that detects nitric oxide and equipment that analyzes exhaled breath with a special computer system. To use this new device, patients place a mouthpiece, connected by a breathing tube to the computer, over their mouth. They inhale nitric oxide-free air to total lung capacity, then slowly exhale into the mouthpiece. The nitric oxide concentration is displayed immediately on the computer screen.

The FDA cleared the NIOX system based on clinical studies conducted by the manufacturer of 65 patients, both adults and children ages four years and older, with confirmed diagnoses of asthma. The patients were tested with the NIOX system before they began drug treatment and again two weeks later. The studies were conducted at nine medical centers in the United States. The results showed that most patients had a 30-70% decrease of nitric oxide levels after two weeks of treatment with inhaled steroids. In this study, elevated nitric oxide levels above 30 parts per billion correlated with moderate-to-severe asthma. ■

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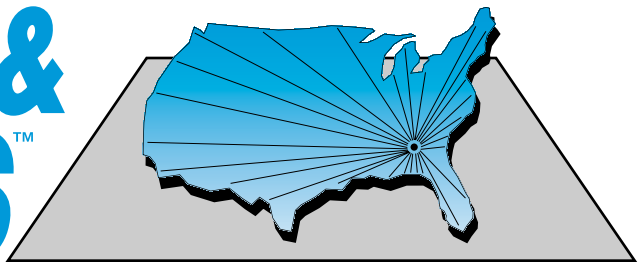

Ramipril formulary evaluation

By **Annie Allen**, PharmD
Written while on clinical rotation with
Auburn University at Huntsville (AL) Hospital

Ramipril (Altace) is a long-acting oral angiotensin-converting enzyme (ACE) inhibitor indicated for the treatment of patients with essential hypertension or congestive heart failure after myocardial infarction. Ramipril also is indicated in cardiovascular risk reduction. Ramipril is the ethyl ester of a non-sulfhydryl ACE inhibitor.[1]

Mechanism of action

Ramipril is a prodrug that is metabolized to the active form ramiprilat. Like other members of the ACE inhibitor class, ramiprilat lowers blood pressure, primarily through the inhibition of ACE. This results in decreased plasma angiotensin II, leading to decreased vasopressor activity, decreased aldosterone secretion, and increased plasma renin activity.[2]

Indications

The Food and Drug Administration (FDA)-approved indications for ramipril include hypertension, congestive heart failure post-myocardial infarction, and cardiovascular risk reduction. Some data suggest that ramipril is more effective than some other ACE inhibitors because it has higher tissue concentrations and thus better inhibition of tissue ACE. However, the data are not conclusive in this area. Other ACE inhibitors thought to have high levels of tissue ACE inhibition include enalapril and fosinopril. The non-prodrug ACE inhibitors, captopril and lisinopril, are not thought to have high tissue concentrations because of their low lipophilicity. The FDA indications for ramipril as compared to the ACE inhibitors included on the Huntsville (AL) Hospital formulary are shown in **Table 1, below**.[3]

Pharmacokinetics

The extent of absorption of ramipril is at least 50-60% and is not significantly influenced by the presence of food in the gastrointestinal tract, although the rate of absorption is reduced. In a trial in which subjects received ramipril capsules or their contents dissolved in water or apple juice or suspended in applesauce, serum ramiprilat levels were essentially unrelated to the use or nonuse of concomitant liquid or food.[2]

During 24-hour continuous ambulatory blood pressure monitoring, at least 50% of the maximal

Table 1: FDA-approved uses for ACE inhibitors (Ramipril + Huntsville Hospital Formulary ACE inhibitors)[3]

Drug	Approved indication	Data for additional use	Data for mortality benefit
Captopril	HTN, HF, Post-MI, D-Neph	HTN-crisis	Post-MI
Enalapril	HTN, HF, asymptomatic LVD	D-Neph	HF
Enalaprilat	HTN		
Fosinopril	HTN, HF	D-Neph	
Lisinopril	HTN, HF, Post-MI	D-Neph	Post-MI
Ramipril	**HTN, Post-MI, CV Risk ↓**	**HF**	**(see approved indication)**

Key: HTN= hypertension; HF = heart failure; Post-MI = post-myocardial infarction; D-Neph = diabetic nephropathy, LVD = left ventricular dysfunction

Table 2: Pharmacokinetics of ACE inhibitors (ramipril + Huntsville Hospital Formulary ACE inhibitors)[3]

Drug	Route of elimination	Onset of activity (hr)	Peak activity (hr)	Duration of activity (hr)	Food/drug interaction	Dosage adjustment for CrCl < 30 mL/min	T:P ratio	Prodrug
Captopril	Renal	0.25-0.5	1-1.5	6-10	Decrease absorption rate 50%	Yes	25%	No
Enalapril	Renal	1-2	4-6	18-30	None	Yes	40-64%	Yes
Enalaprilat	Renal	0.25	0.5-1	6	None	Yes		No
Fosinopril	Renal (50%) Hepatic (50%)	0.75-1	2-6	24	None	No	64%	Yes
Lisinopril	Renal	2-4	4-6	18-30	None	Yes	30-70%	No
Ramipril	**Renal (70%) Hepatic (30%)**	**2**	**3-8**	**18-24**	**None**	**Yes**	**50-63%**	**Yes**

response of ramiprilat is maintained for 24 hours. Blood pressure was lower by a mean of 6/4 mmHg compared to placebo at the end of the dosing interval.[1] Therefore, ramipril is acceptable for once-daily dosing.

Ramipril is hydrolyzed by hepatic esterases to its active metabolite, ramiprilat. Glucuronidation and hydroxylation reactions are responsible for forming the six other inactive metabolites of ramipril. Plasma ramiprilat concentrations peak at two to four hours after drug intake and then decline in a triphasic manner. The initial rapid decline represents distribution of the drug into a large peripheral compartment and subsequent binding to plasma and tissue ACE with a half-life of two to four hours. The apparent elimination phase corresponds to the clearance of free ramiprilat and has a half-life of nine to 18 hours. The terminal elimination phase has a prolonged half-life (greater than 50 hours) and represents potent binding to ACE with slow dissociation from the enzyme, and does not contribute to accumulation of the drug.[2] About 70% of ramipril and its metabolites are cleared renally, with the remaining 30% eliminated by hepatic mechanisms.[3] About 73% of circulating ramipril and 56% of ramiprilat is bound to plasma proteins; therefore, drug interactions due to protein binding are not expected.

Ramipril's area under the curve (AUC) increases with decreasing renal function. In patients with creatinine clearance of less than 40 mL/min, the AUC is three to four times greater than in patients with normal renal function. Therefore, dose adjustment is required in renal impairment. Plasma ramipril levels in patients with impaired liver function are increased about three-fold. Peak concentrations of ramiprilat are not different from those seen in subjects with normal hepatic function, and the effect of a given dose on plasma ACE activity does not vary with hepatic function.[2]

The pharmacokinetics of ramipril as compared to the ACE inhibitors on the Huntsville Hospital formulary are shown in **Table 2, above**.[3]

Hypertension

All ACE inhibitors have similar efficacy in the treatment of mild-to-moderate hypertension when given in equipotent doses. There are several clinical trials comparing the efficacy of ramipril to that of other ACE inhibitors, and ramipril appears to be as effective as other ACE inhibitors. Ramipril is effective for the treatment of mild-to-moderate essential hypertension as shown by the summary of clinical trials below.

Ramipril was evaluated in 591 patients with essential hypertension in a multicenter, open-label, prospective trial. Patients received 1.25-10 mg of ramipril once daily for eight weeks.[4] Results of the study showed that ramipril reduced mean systolic/diastolic blood pressure by 19.9/14.7 mmHg ($P < 0.001/P < 0.001$) when compared with baseline blood pressure, and ramipril reduced diastolic blood pressure to ≤ 90 mmHg or by at least 10 mmHg in 84.1% of patients. Response rates were similar regardless of age, gender, or race, and no patient stopped ramipril because of an adverse event or experienced an unexpected adverse event. This study shows that ramipril is effective in lowering blood pressure, but the results would be more meaningful if the effects of ramipril were

compared to the effects of a placebo.

In a randomized, double-blind trial, ramipril was compared with placebo in the treatment of 86 patients with mild-to-moderate essential hypertension.[5] A two-week placebo run-in phase was followed by four weeks of treatment. Patients receiving ramipril 5 mg had significantly larger decreases in blood pressure than patients receiving placebo ($P < 0.001$).

A 16-week randomized, double-blind trial in 248 patients showed ramipril once daily to be as effective and well-tolerated as captopril twice daily for the treatment of hypertension.[6] After a four-week placebo run-in period, patients with a supine and standing diastolic blood pressure between 95 and 120 mmHg were randomized to treatment with ramipril 10 mg once daily or captopril 50 mg twice daily. Patients not responding to therapy after six weeks received 50 mg hydrochlorothiazide concomitantly. After six weeks of therapy, mean supine pressure was reduced significantly by both ramipril and captopril. A further reduction of 7/6 mmHg in the ramipril group and 6/6 mmHg in the captopril group occurred with six additional weeks of treatment. Reductions in standing blood pressure were similar. Forty patients in the ramipril group and 36 in the captopril group required the addition of hydrochlorothiazide. After 12 weeks of active treatment, 77% and 83% of patients in the ramipril and captopril groups, respectively, were normotensive. The findings of this study are in agreement with other studies comparing the efficacy of ramipril and another ACE inhibitor in the treatment of hypertension.

The safety and efficacy of ramipril vs. enalapril in the treatment of hypertension was evaluated in a randomized, double-blind, multicenter trial.[7] One hundred fifty-nine patients were enrolled and randomized to receive ramipril 2.5, 5, or 10 mg or enalapril 5, 10, or 20 mg for three to four weeks. Supine and standing blood pressures were reduced by 11.8 and 10.2 mmHg with ramipril 10 mg ($P < 0.001$) and 9.3 and 10.7 mmHg with enalapril 20 mg ($P < 0.001$). At the end of the four-week trial, patients in all six dosage groups had clinically and statistically significant reductions in blood pressure compared with baseline values, and the agents did not differ significantly with respect to their blood-pressure-lowering effects. Only results of comparisons of the ramipril group as a whole vs. the enalapril group as a whole should be considered. However, when comparing individual dosage groups, the sample size was too small to make reliable conclusions based on the results of the comparison.

The studies above reflect the results of the majority of similar studies conducted. The conclusions of these trials demonstrate that ramipril lowers blood pressure in hypertensive patients, has a long duration of action suitable for once-daily administration in most patients, and is well-tolerated. These results also demonstrate that ramipril is as effective as the other ACE inhibitors.

Heart failure post-myocardial infarction

Several ACE inhibitors on the Huntsville Hospital formulary are FDA-approved for use after a myocardial infarction. ACE inhibitors reduce afterload, preserve electrolytes, and reduce the ventricular enlargement that ensues in some patients after myocardial infarction. Ramipril also is FDA-approved for the treatment of stable patients who have demonstrated clinical signs of congestive heart failure within the first few days after sustaining acute myocardial infarction (AMI).

In a multicenter, double-blind, randomized, placebo-controlled study, ramipril was evaluated in 2,006 patients with AMI and clinical evidence of heart failure.[8] Patients were randomly allocated to treatment with either placebo or ramipril on day three to day 10 after AMI. Patients with severe heart failure resistant to conventional therapy, and for whom the use of an ACE inhibitor was considered mandatory, were excluded. Follow-up was continued for a minimum of six months and an average of 15 months. Mortality from all causes was significantly lower for patients randomized to receive ramipril (170 deaths; 17%) than for those randomized to receive placebo (222 deaths; 23%). The observed risk reduction was 27% ($P = 0.002$). Analysis of prespecified secondary outcomes revealed a risk reduction of 19% for the first event in an individual patient — namely, death, severe/ resistant heart failure, myocardial infarction, or stroke ($P = 0.008$). This trial shows the survival benefit of ramipril use after AMI and is representative of other similar trials conducted with ramipril in this patient population.

Cardiovascular risk reduction

Most of Huntsville Hospital's ACE inhibitors on formulary show some data for mortality benefit. Captopril and lisinopril have been shown to decrease mortality post-myocardial infarction, and enalapril has been shown to decrease mortality in patients with heart failure. Ramipril, however, is

the only ACE inhibitor shown to reduce the risk of cardiovascular events including death in those at high risk for these events, regardless of whether they have heart failure.

The Heart Outcomes Prevention Evaluation (HOPE) study was a large, multicenter, randomized, placebo-controlled, 2x2 factorial design, double-blind study.[2] It was conducted in 9,541 patients who were age 55 years or older and considered at high risk of developing a major cardiovascular event because of a history of coronary artery disease, stroke, peripheral vascular disease, or diabetes that was accompanied by at least one other cardiovascular risk factor. Patients were either normotensive or under treatment with other antihypertensive agents, and they were excluded if they had clinical heart failure or were known to have a low ejection fraction. This study was designed to examine the long-term effects of ramipril on the combined endpoint of myocardial infarction, stroke, or death from cardiovascular causes. The study results showed that ramipril 10 mg daily significantly reduced the rate of myocardial infarction, stroke, or death from cardiovascular causes, as well as the rates of the three components of the combined endpoint **(see Table 3, above)**.

Table 3: Incidence of the primary outcome of the HOPE study (%)[2]

Outcome	Ramipril (n = 4,645)	Placebo (n = 4,652)	P value
Combined endpoint	14	17.8	0.0001
Component endpoint			
Death from CV causes	6.1	8.1	0.0002
Myocardial infarction	9.9	12.3	0.0003
Stroke	3.4	4.9	0.0002
Death from any cause	10.4	12.2	0.005

The secondary endpoints of this study also showed significant benefit for those receiving ramipril therapy. The ramipril group had significantly fewer revascularizations and complications related to diabetes. The group also had lower incidences of heart failure, cardiac arrest, worsening angina, and new diagnosis of diabetes. The study showed that ramipril is beneficial in a broad range of patients without evidence of left ventricular systolic dysfunction or heart failure who are at high risk for cardiovascular events.

This landmark study also demonstrates that ACE inhibitor therapy decreases the incidence of death and cardiovascular events in patients who are at high risk for these events but who do not have heart failure. Results of other studies have proven ACE inhibitors to be effective in preventing death in those with heart failure.

The magnitude of the benefit of treatment with ramipril was at least as large as that observed with other proven secondary measures, such as treatment with beta-blockers, aspirin, and lipid-lowering agents. In addition, the rapid and sustained response to ramipril and the continuing divergence in results between the ramipril group and the placebo group indicate that treatment for longer periods of time may yield even better results. The benefits of ramipril were observed among patients who were already taking a number of effective treatments, such as aspirin, beta-blockers, and lipid-lowering agents, indicating that inhibition of ACE offers an additional approach to the prevention of atherothrombotic complications. Only a small part of the benefit could be attributed to a reduction in blood pressure, because the majority of patients did not have hypertension at baseline, and the mean reduction in blood pressure with treatment was extremely small.[9] The results of this study can be reliably used to make conclusions about ramipril therapy because of the study's strong design. A significant weakness is that the baseline demographics of the treatment groups were not compared statistically, so there might have been differences in the treatment groups from the start of the study.

Congestive heart failure

The ACE inhibitors on the Huntsville Hospital formulary are FDA-approved for use in heart failure. These provide both hemodynamic and symptomatic improvement by decreased ventricular remodeling, anti-ischemic processes, and blunting of neurohormonal activation. Although ramipril is not FDA-approved for the treatment of heart failure, several studies suggest that it also may be beneficial in this disease state.

In a randomized trial, 15 patients with grade III New York Heart Association congestive heart failure were assigned to treatment with either captopril or ramipril.[10] Both groups were similar with respect to baseline hemodynamic measurements. The group receiving ramipril showed

Table 4: Ramipril: Frequency of adverse events (%)[2]

	Ramipril (n = 651)	Placebo (n = 286)
Headache	5.4	5.9
Dizziness	2.2	3.1
Asthenia	2.0	0.7
Nausea/vomiting	1.1	1.0

hemodynamic changes comparable to the group receiving captopril on the seventh day of treatment. The stroke volume index increased by 20% vs. 21%, respectively, and the total peripheral resistance decreased by 13% vs. 20%, respectively. Hemodynamic improvement was more pronounced and comparable in both groups during exercise. The study concluded that ramipril is equally effective compared with captopril in the treatment of patients with severe congestive heart failure. However, this study was only for a short period of time with a small sample size, and no reliable conclusions can be drawn from these results. Most of the published trials comparing the efficacy of ramipril in the treatment of heart failure to other ACE inhibitors concluded that ramipril is equal in efficacy to the other ACE inhibitors, but they were limited by small sample sizes.

The clinical trials included above are only a few of the many published trials involving ramipril. This evaluation contains a representative sample of the ramipril trials available.

Adverse events

Ramipril has been evaluated for safety in more than 4,000 patients with hypertension. Of these, 1,230 patients were studied in U.S. controlled trials, and 1,107 were studied in foreign controlled trials. Almost 700 of these patients were treated for at least one year. The overall incidence of reported adverse events was similar in ramipril and placebo patients. The most frequent clinical side effects (possibly or probably related to study drug) reported by patients receiving ramipril in U.S. placebo-controlled trials were headache (5.4%), dizziness (2.2%), and fatigue or asthenia (2.0%), but only the last was more common in ramipril patients than in patients given placebo. Generally, the side effects were mild and transient, and there was no relation to total dosage within the range of 1.25 to 20 mg. Discontinuation of therapy because of a side effect was required in approximately 3% of U.S. patients treated with ramipril. The most common reasons for discontinuation were cough (1.0%), dizziness (0.5%), and impotence (0.4%). The side effects considered possibly or probably related to study drug that occurred in more than 1% of patients treated with ramipril are shown in **Table 4, at left**.[2]

In placebo-controlled trials, there also was an excess of upper respiratory infection and flu syndrome in the ramipril group. As these studies were carried out before the relationship of cough to ACE inhibitors was recognized, some of these events may represent ramipril-induced cough. In a later one-year study, increased cough was seen in almost 12% of ramipril patients, with about 4% of these patients requiring discontinuation of treatment.[2]

In the Acute Infarction Ramipril Efficacy (AIRE) study, which evaluated the use of ramipril in patients after myocardial infarction, there were fewer patients with reported serious adverse events on ramipril (58%) than placebo (64%). Serious adverse events included the endpoints of the trial (death, progression to severe/resistant heart failure, reinfarction, and stroke), as well as possible adverse effects of treatment.[1] Adverse reactions considered possibly/probably related to study drug that occurred in more than 1% of patients with heart failure treated with ramipril are shown in **Table 5, p. 6**.[2]

Safety data in the HOPE trial, which evaluated cardiovascular risk reduction with ramipril, were collected as reasons for discontinuation or temporary interruption of treatment **(see Table 6, p. 6)**. The incidence of cough was similar to that seen in the AIRE trial. The rate of angioedema was the same as in previous clinical trials.

Side effects with ramipril are usually mild or transient. Cough is the most common adverse event reported in patients taking ACE inhibitors. It is a class effect, with no dose-response relationship.[3] The incidence of cough with ramipril is comparable to that of the other ACE inhibitors. The adverse effect profiles of the ACE inhibitors are not significantly different enough to favor one ACE inhibitor over another.[3] The results of the previously mentioned trials showed the overall frequency of adverse events to be similar in patients treated with ramipril and in those treated with placebo. In the AIRE trial, renal failure occurred with a similar frequency in the two groups. Angina, which was thought to worsen in some patients prescribed an ACE inhibitor,

was reported as an adverse event in 18% of patients taking ramipril and 17% of patients taking placebo. This shows that ramipril also is generally well-tolerated.

Contraindications

Ramipril is contraindicated in patients who are hypersensitive to this product and in patients with a history of angioedema related to previous treatment with an ACE inhibitor.[6] Like other ACE inhibitors, ramipril is contraindicated in pregnancy.

Drug interactions

Drug interactions with the ACE inhibitors are associated mostly with the class as a whole.[4] Like the other ACE inhibitors, ramipril interacts with diuretics, especially potassium-sparing diuretics, potassium supplements, and lithium, and demonstrates a drug interaction profile similar to those of the other ACE inhibitors.

Dosing

• **Use in hypertension.** The dosing of ramipril as compared to the ACE inhibitors included on the Huntsville Hospital formulary is shown in **Table 7, p. 7**.

Table 5: Patients with adverse events possibly/probably related to study drug (%)[2]

Adverse Event	Ramipril (n = 1004)	Placebo (n = 982)
Hypotension	10.7	4.7
Cough increased	7.6	3.7
Dizziness	4.1	3.2
Angina pectoris	2.9	2.0
Nausea	2.2	1.4
Postural hypotension	2.2	1.4
Syncope	2.1	1.4
Heart failure	2.0	2.2
Severe/resistant heart failure	2.0	3.0
Myocardial infarct	1.7	1.7
Vomiting	1.6	0.5
Vertigo	1.5	0.7
Headache	1.2	0.8
Kidney function	1.2	0.5
Abnormal chest pain	1.1	0.9
Diarrhea	1.1	0.4
Asthenia	0.3	0.8

Table 6: Ramipril safety data from the HOPE trial (%)[2]

	Ramipril (n = 4,645)	Placebo (n = 4,652)
Discontinuation at any time	34	32
Permanent discontinuation	29	28
Reasons for stopping		
Cough	7	2
Hypotension or dizziness	1.9	1.5
Angioedema	0.3	0.1

• **Use in heart failure post-myocardial infarction.** The recommended starting dose of ramipril is 2.5 mg twice daily. A patient who becomes hypotensive at this dose may be changed to 1.25 mg twice daily, but all patients should then be titrated toward a target dose of 5 mg twice daily.

• **Use in cardiovascular risk reduction.** Ramipril should be given at an initial dose of 2.5 mg once a day for one week, 5 mg once a day for the next three weeks, and then increased as tolerated to a maintenance dose of 10 mg once a day. If the patient is hypertensive or recently post-myocardial infarction, ramipril also can be given as a divided dose.

• **Use with diuretics.** In patients currently receiving a diuretic, symptomatic hypotension can occur following the initial dose of ramipril. To reduce the likelihood of hypotension, the diuretic should be discontinued two to three days prior to beginning therapy with ramipril, if possible. Then, if blood pressure is not controlled with ramipril alone, diuretic therapy should be resumed. If the diuretic cannot be discontinued, an initial dose of 1.25 mg ramipril should be used to avoid excess hypotension.

• **Use in patients with renal impairment.** In patients with creatinine clearance of less than 40 mL/min doses, only 25% of those normally used should be expected to induce full therapeutic levels of ramiprilat. For patients with hypertension and renal impairment, the recommended initial dose is 1.25 mg once daily. The dose may be titrated upward until a maximum total daily dose of 5 mg is obtained. Those with heart failure and renal impairment should be started at 1.25 mg once daily. The dose may be increased to 1.25 mg

Table 7: Dosing of ACE inhibitors (Ramipril + Huntsville Hospital Formulary ACE inhibitors)[3]

ACE inhibitor	Initial dose	Usual dose	Maximum dose
Captopril	6.25 mg bid/tid	25-50 mg bid/tid	150 mg bid/100 mg tid
Enalapril	2.5-5 mg qd	10-40 mg qd	40 mg qd
Fosinopril	10 mg qd	20-40 mg qd	40 mg qd
Lisinopril	10 mg qd	20-40 mg qd	40 mg qd
Ramipril	**2.5-5 mg qd**	**10-20 mg qd**	**20 mg qd**

twice daily, and up to a maximum dose of 2.5 mg twice daily depending upon clinical response and tolerability.[2]

Cost

The cost to the hospital of oral ACE inhibitor therapy ranges from approximately $2.75 to $6.75 per week for most regimens, depending on drug and dose.[11] Ramipril costs to the hospital are in the middle of this range. Enalapril and fosinopril are slightly more expensive than ramipril in equivalent doses, while lisinopril and quinapril are slightly less expensive. Captopril tends to cost considerably less than the other drugs in this class.

Conclusions and recommendations

Captopril, enalapril/enalaprilat, fosinopril, and lisinopril are the current formulary ACE inhibitors at the Huntsville Hospital System.

• Captopril was chosen because it is a non-prodrug useful in patients with severe liver disease. It has indications for hypertension, heart failure, post-myocardial infarction, and diabetic nephropathy. Data also exist to support its use in hypertensive crisis. A mortality benefit is seen post-myocardial infarction. Captopril is the most rapid-acting oral agent, is inexpensive, and has an adverse effect profile similar to that of other ACE inhibitors.

• Enalapril was chosen because it is FDA-approved for hypertension, heart failure, and asymptomatic left ventricular dysfunction, with additional benefit data concerning diabetic nephropathy. Mortality benefit is shown in heart failure patients. Enalapril has an unlabeled use for hypertensive crisis and is the only ACE inhibitor available in IV form. Dosing can be both once and twice daily, and the adverse effect profile is similar to that of the other ACE inhibitors.

• Fosinopril was chosen because it is FDA-approved for hypertension and heart failure, with benefit data concerning diabetic nephropathy. A dual route of elimination that is compensatory allows for use in renal dysfunction without a dosage alteration. Fosinopril is comparably priced, has once-daily dosing, and has a similar adverse effect profile to the other ACE inhibitors.

• Lisinopril was chosen because it is FDA-approved for hypertension, heart failure, and post-myocardial infarction, with additional data suggesting benefit in patients with or at risk for diabetic nephropathy. A mortality benefit is seen in patients with heart failure. Lisinopril is comparably priced and is a non-prodrug, allowing for use in patients with severe liver impairment.[3]

Based on the evidence provided in this formulary evaluation, ramipril should be added to the formulary. Ramipril is the only ACE inhibitor shown to be beneficial in a broad range of patients without evidence of left ventricular systolic dysfunction or heart failure who are at high risk for cardiovascular events. Ramipril has been shown to reduce the risk of cardiovascular events in high-risk patients; this information currently is unavailable for the other ACE inhibitors. Most patients are in the hospital for a short time, so the ACE inhibitor they receive during their stay is not likely to impact long-term therapeutic effects; however, many patients are discharged on the ACE inhibitor that they received during their hospital stay. This warrants the need for ramipril to be added to the formulary. The adverse effect profile and drug interaction profile are comparable to that of other ACE inhibitors on formulary; the cost is slightly higher.

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New FDA Approvals

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

• *Gefitinib (Iressa) by AstraZeneca LP.* The FDA has approved gefitinib (Iressa) tablets as a single-agent treatment for patients with **advanced non-small cell lung cancer** (NSCLC). Gefitinib is being approved as a treatment for patients whose cancer has continued to progress despite treatment with platinum-based and docetaxel chemotherapy, two drugs that are the standard of care for this disease.

Gefitinib was reviewed and approved under the FDA's accelerated approval program. As required by the accelerated approval regulations, gefitinib's developer will perform additional studies to verify the drug's clinical benefit.

Gefitinib was developed to block growth-stimulatory signals in cancer cells. These signals are mediated in part by enzymes called tyrosine kinases. Gefitinib blocks several of these tyrosine kinases, including the one associated with epidermal growth factor receptor.

The FDA based the approval on the results of a study of 216 patients with NSCLC, including 142 patients with refractory disease. The response rate (defined as at least 50% tumor shrinkage lasting at least one month) was about 10%. There were more dramatic responses in some patients, and the median duration of response was seven months.

There appeared to be substantial differences in response rates in subsets of patients, with higher response rates for women (about 17%) and patients with adenocarcinoma, and lower response rates seen in men (about 5%) and smokers.

Common side effects reported with gefitinib in clinical trials were nausea, vomiting, diarrhea, rash, acne, and dry skin. Gefitinib may cause fetal harm when administered to pregnant women. A concern also has been raised about the occurrence of serious and sometimes fatal interstitial lung disease in patients treated with gefitinib. The FDA researched those reports and decided that this rare but serious toxicity of gefitinib does not outweigh the benefits demonstrated in patients with advanced NSCLC.

• *Gemifloxacin (Factive) by GeneSoft Pharmaceuticals.* The FDA has approved gemifloxacin (Factive), a fluoroquinolone antibiotic, for the treatment of **mild-to-moderate community-acquired pneumonia** (CAP) and **acute bacterial exacerbation of chronic bronchitis** (AECB).

Gemifloxacin has been tested in global clinical trials in nearly 10,000 people. AECB trials have shown that five days of gemifloxacin is as effective as other marketed products. In CAP trials, gemifloxacin given for seven days is effective treatment for patients.

Gemifloxacin should be used only to treat infections that are proven or strongly suspected to be caused by bacteria. The most common side effects include diarrhea, rash, nausea, and headache. Rash is generally mild-to-moderate in nature and is more likely to occur if taken for longer than the recommended course.

• *New indication for sirolimus (Rapamune) by Wyeth Pharmaceuticals.* The FDA has approved a new indication for the immunosuppressant agent sirolimus (Rapamune). Sirolimus was approved in 1999 for the prophylaxis of organ rejection in renal transplant patients in combination with cyclosporine and corticosteroids. The new indication provides for withdrawal of cyclosporine from the immunosuppressive regimen two to four months after **renal transplantation in patients at low-to-moderate immunologic risk**. The safety and efficacy of cyclosporine withdrawal in high-risk patients have not been adequately studied and is therefore not recommended for these patients. Rapamune is available in both 1 mg and 2 mg tablet formulations.