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Pharmaceutical Care Across the Continuum

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Be prepared: Anthrax outbreaks may not remain isolated acts, experts say

ASHP recommends following CDC guidelines

You may think you will never see an anthrax case at your hospital. Two experts from the National Institute of Allergy and Infectious Diseases at the National Institutes of Health in Bethesda, MD, say you might be wrong.

"There is no reason to believe this will be an isolated act of bioterrorism. In fact, it is likely that additional attacks involving [*Bacillus*] *anthracis* and perhaps other pathogens will occur," say **H. Clifford Lane**, MD, and **Anthony S. Fauci**, MD, in the Nov. 28 issue of the *Journal of the American Medical Association.*

Each attack will present the health care community with a new set of challenges and a need for rapid dissemination of reliable, up-to-date information, say Lane and Fauci. To successfully deal with these challenges, law enforcement authorities, public health officials, and front-line health care providers must promptly share information, they note. "The alertness, open-mindedness, and sound clinical judgment of physicians and other health care professionals will be critical to the successful public health response to current and future threats."

Treatment guidelines

Since the first announcement on Oct. 4 of the inhalation anthrax case in Florida, information on how to handle the threat has been updated constantly. The Centers for Disease Control and Prevention (CDC) in Atlanta has been in the forefront of providing information. In its Oct. 26 issue of *Morbidity and Mortality Weekly Report*, the CDC released comprehensive guidelines for the treatment of inhalation, gastrointestinal, and cutaneous (skin) anthrax. The recommendations are based on clinical reports and in vitro data.

For example, a 60-day regimen of antibiotics beginning with intravenous ciprofloxacin (Cipro) or doxycycline is recommended to treat inhalation anthrax, along with one or two additional antimicrobials. Treatment can be switched to oral antimicrobial therapy when clinically appropriate. The recommendations are the same for pregnant women

and immunocompromised people.

The American Society of Health-System Pharmacists (ASHP) advises pharmacists to follow the CDC recommendations, but to be alert for potential changes in the recommendations. "Due to limited experience with anthrax, especially when exposure is through these covert actions, it is difficult to establish firm recommendations," says **David R. Witmer**, PharmD, director of ASHP's professional practice and scientific affairs.

American Hospital Formulary Service, ASHP's drug information resource, is fast-tracking new monographs on drugs used in the treatment of several infectious agents. These monographs will be available at the society's Midyear Clinical Meeting Dec. 2-6 in New Orleans.

The Food and Drug Administration (FDA) in Rockville, MD, also issued a *Federal Register* notice on Oct. 30 to clarify that doxycycline and penicillin G procaine currently are approved for use in treating all forms of anthrax infections — cutaneous, inhalation, and gastrointestinal.

The notice includes dosing and other information on the use of these antibiotics to treat anthrax. The currently recommended dosage regimen of doxycycline for severe disease is 100 mg every 12 hours for adults and 1 mg/lb (2.2 mg/kg) every 12 hours for children less than 100 pounds. Although doxycycline and other members of the tetracycline class of antibiotics generally are not recommended for patients younger than age 8 because of negative effects on teeth and bone development, the FDA believes the benefits of doxycycline for the treatment of inhalational anthrax outweigh these risks.

The full-text of the *Federal Register* notice can be found on-line at www.fda.gov/OHRMS/DOCKETS/98fr/110201b.htm.

Addressing the shortage issue

In the initial stages of the anthrax crisis, health care professionals worried that a run on ciprofloxacin (Cipro), which is manufactured by Bayer Corp., would result in a shortage. On Oct. 24, however, Health and Human Services (HHS) Secretary **Tommy G. Thompson** and **Helge H. Wehmeier**, president and CEO of Bayer, announced an agreement for a significant federal purchase of the antibiotic at a substantially lowered price. The ciprofloxacin is expected to be available by year-end.

Under the terms of the agreement (valued at $95 million), HHS will pay 95 cents per tablet for a total initial order of 100 million tablets. This compares with a previously discounted price of $1.77 per tablet paid by the federal government. Bayer said that as part of the agreement, it will rotate the government's inventory to ensure a fresh supply. This inventory rotation adds an additional value of 30% for the government, which is included in the agreement. A $1.6 billion

Mayo Clinic develops rapid anthrax test

Roche is making test available to hospital labs

Mayo Clinic in Rochester, MN, has developed a DNA test that can identify the presence of anthrax in less than one hour, instead of days. Roche Diagnostics is making the test available to public health agencies, hospital laboratories, and reference laboratories in the United States and other countries.

"The first thing people want to know in a case of suspected exposure is whether the agent was in fact anthrax," says **Franklin R. Cockerill III**, MD, the Mayo Clinic biologist who led the research team. The team developed the test using Roche's LightCycler instrument for polymerase chain reaction-based assays.

Some of the test components, which initially would be offered to laboratories for free, were available in November. Mayo Clinic recommends that specimens be tested at the nearest regional location to realize the full advantage of the rapid return of results. ■

COMING IN FUTURE MONTHS

- The problem of fake drugs
- A cost-cutting success story
- Multitasking in community pharmacies
- Drug company mergers squeeze drug availability
- Vending machines dispense drugs

emergency proposal made by President George W. Bush on Oct. 17 includes funds for the purchase.

HHS also is making substantial new purchases of other antibiotics that are effective against anthrax, especially doxycycline.

The purchases will fulfill Thompson's proposal to quickly increase the nation's emergency reserve of antibiotics. Resources to be on hand by January would treat up to 12 million people immediately for anthrax exposure. Treatment would be with a mixture of effective antibiotic products, with ciprofloxacin representing about 10% of the antibiotics on reserve. In October, 18.6 million ciprofloxacin doses were available in the nation's emergency reserve, which would enable immediate treatment of about 2 million people when combined with other antibiotics.

Meanwhile, other drug companies are offering their products to the government. Bioglan Pharma has announced that its doxycycline (ADOXA) tablets are available for treating anthrax. Abbott Laboratories says it would provide supplies of its antibiotics, including clarithromycin (Biaxin), free of charge if requested and approved by the U.S. government. Bristol-Myers Squibb has offered a similar plan for its antibiotic gatifloxacin (Tequin), and GlaxoSmithKline for its amoxicillin (Amoxil) and amoxicillin/clavulanate potassium (Augmentin) drugs. GlaxoSmithKline also says it has submitted a proposal to the government to begin manufacturing smallpox vaccine.

Pfizer has announced increased production of its doxycycline (Vibramycin) in anticipation of possible future demand. Pfizer says it is discussing with public health authorities the possible use of the company's other human antibiotics, including azithromycin (Zithromax), trovafloxacin (Trovan), and company-produced penicillins, too. ■

Drugs may reduce kidney risk in diabetics

'We really have something,' investigator says

Three recent clinical trials are showing that angiotensin II receptor blockers, used to treat high blood pressure, can slow the progression of renal disease among patients with Type 2 diabetes.

"These studies constitute a major sea change for Type 2 diabetes. We really have something," **Barry M. Brenner**, MD, told the *Washington Post*. Brenner is a kidney specialist at the Brigham and Women's Hospital in Boston, and principal author of one of the studies that featured the angiotensin II receptor blocker losartan. The studies, which were published in the Sept. 20 issue of the *New England Journal of Medicine*, did not test the drugs against angiotensin-converting enzyme (ACE) inhibitors, an omission that some find troubling. **(For more information on this omission, see p. 92.)**

Drugs that can reduce the risk of kidney deterioration in diabetics are welcomed. Forty percent of patients with Type 2 diabetes will develop diabetic kidney disease, the leading cause of kidney failure in the United States, Japan, and Europe. Patients with Type 2 diabetes, hypertension, and kidney disease also are at significant risk of experiencing major cardiovascular events. According to data from the National Institute of Diabetes and Digestive and Kidney Diseases, both the prevalence and the incidence of end-stage renal disease (ESRD) are approximately twice what they were 10 years ago.

Here is a look at the three trials, which were funded by the drug manufacturers.

• The Irbesartan Diabetic Nephropathy Trial (IDNT) compared the effects of the angiotensin II receptor blocker irbesartan (Avapro, Bristol-Myers Squibb, and Sanofi-Synthelabo), the calcium channel blocker amlodipine, and a placebo on a background of antihypertensive therapy. The 1,715 men and women who participated in the trial were between the ages of 30 and 70 and had documented hypertension and proteinuria, with urinary protein excretion of at least 900 mg/24 hours. The mean duration of follow-up was 2.6 years.

The primary composite endpoint was defined as the doubling of baseline serum creatinine and the development of ESRD, indicated by renal transplantation or death from any cause. Treatment of irbesartan was associated with a risk of developing a composite endpoint event that was 20% lower than that in the placebo group, and 23% lower than that in the amlodipine group. The risk of doubling the serum creatinine concentration was 33% lower in the irbesartan group than in the placebo group and 37% lower in the irbesartan group than in the amlodipine group.

Treatment with irbesartan was associated with a relative risk of ESRD that was 23% lower than that found in both other groups. These differences were

not explained by differences in the achieved blood pressures. The serum creatinine concentration increased 24% more slowly in the irbesartan group than in the placebo group and 21% more slowly than in the amlodipine group. There were no significant differences in the rates of death from any cause or in the cardiovascular composite endpoint.

The study researchers concluded that irbesartan is effective in protecting against the progression of nephropathy due to Type 2 diabetes. "Irbesartan is not only an excellent blood pressure drug for patients with diabetes and hypertension, but more importantly, it protects their kidneys from damage independent of its effect on blood pressure," says **Edmund J. Lewis**, MD, director of nephrology at Rush-Presbyterian-St. Luke's Medical Center in Chicago.

• The Irbesartan MicroAlbuminuria Type 2 Diabetes Mellitus in Hypertensive Patients (IRMA 2) trial was a double-blind, placebo-controlled study conducted in 590 patients with hypertension, Type 2 diabetes, and microalbuminuria.

The patients received 150 or 300 mg of irbesartan daily, and were followed for two years. The primary outcome was the time to the onset of diabetic nephropathy, defined by persistent albuminuria in overnight specimens, with a urinary albumin excretion rate that was greater than 200 mcg/min and at least 30% higher than the baseline level. All were treated with antihypertensive therapy.

Ten of the 194 patients in the 300 mg group (5.2%) and 19 of the 195 patients in the 150 mg group (9.7%) reached the primary endpoint, as compared with 30 of the 201 patients in the placebo group (14.9%). The average blood pressure during the course of the study was 144/83 mm Hg in the placebo group, 143/83 mm Hg in the 150 mg group, and 141/83 mm Hg in the 300 mg group. Serious adverse events were less frequent among the patients treated with irbesartan.

The investigators concluded that Irbesartan is renoprotective independently of its blood pressure-lowering effect in patients with Type 2 diabetes and microalbuminuria.

• A total of 1,513 patients were enrolled in Reduction of Endpoints in Non-Insulin Dependent Diabetes Mellitus with the Angiotensin II Antagonist Losartan (RENAAL) trial. The randomized, double-blind study compared the angiotensin II receptor blocker losartan (Cozaar, Merck &, Co.), 50 to 100 mg once daily, with placebo. Both were taken in addition to conventional antihypertensive treatment for a mean of 3.4 years.

The primary outcome was the composite of a doubling of the baseline serum creatinine concentration, ESRD, or death. Secondary endpoints included a composite of morbidity and mortality from cardiovascular causes, proteinuria, and the rate of progression of renal disease.

A total of 327 patients in the losartan group reached the primary endpoint, as compared with 359 in the placebo group (risk reduction 16%). Losartan reduced the incidence of a doubling of the serum creatinine concentration (risk reduction 25%) and ESRD (risk reduction 28%), but had no effect on the rate of death.

The benefit exceeded that attributable to changes in blood pressure. The composite of morbidity and mortality from cardiovascular causes was similar in the two groups, although the rate of first hospitalization for heart failure was significantly lower with losartan (risk reduction, 32%). The level of proteinuria declined by 35% with losartan.

As in the other studies, the investigators concluded that losartan conferred significant renal benefits in patients with Type 2 diabetes and nephropathy, and it was generally well-tolerated. ■

Is politics a part of ACEs' exclusion from studies?

Physician charges drug profit may be a factor

Trials showing that angiotensin II receptor blockers slow renal disease in Type 2 diabetes are promising, but one physician questions the exclusion of angiotensin-converting enzyme (ACE) inhibitors from the studies.

In the past, clinicians have assumed that renin-angiotensin-aldosterone system blockage was of special value in slowing nephropathy related to Type 2 diabetes and have used ACE inhibitors in the hope of attenuating it, says **Thomas H. Hostetter**, MD, of the National Institute of Diabetes and Digestive and Kidney Diseases in Bethesda, MD. His editorial appeared in the Sept. 20 issue of the *New England Journal of Medicine* (NEJM), along with the trial results. "Why, then, were ACE inhibitors not tested in the present studies?" **[For more information about the studies, see p. 91.]**

He suggests that the expense and difficulty of such a trial were primary roadblocks. In a published interview, **Edmund J. Lewis**, MD, director of nephrology at Rush-Presbyterian-St. Luke's Medical Center, Chicago, and the lead investigator of the Irbesartan Diabetic Nephropathy Trial (IDNT), says funding was a problem. In a study published in the Nov. 11, 1993, issue of *NEJM*, his research group reported that the ACE inhibitor captopril (Capoten) prevented kidney disease in patients with Type 1 diabetes. They weren't able to get funding for a similar trial in a Type 2 diabetic population.

"Remarkably, both the NIH and the American Diabetes Association decided that Type 2 diabetic nephropathy, the most common cause for people going on dialysis, wasn't a high enough priority for them to fund, so we had to go back to the industry," he says. The studies were funded by the manufacturers of two of the drugs.

In the *NEJM* article, Lewis and his investigators say that they cannot directly address the issue of whether the effects of ACE inhibitors and angiotensin II receptor blockers would be equivalent in the treatment of patients with nephropathy due to Type 2 diabetes. "It may seem reasonable to assume that agents that primarily reduce the generation or effect of angiotensin II would have similar clinical results," they say. "However, it is important to caution that ACE inhibitors and angiotensin-receptor blockers are distinctly different classes of drugs and that one cannot assume equivalence between them."

Testing multiple agents increases the difficulty of identifying clear differences among them, Hostetter adds. "If ACE inhibitors and angiotensin-receptor blockers are indistinguishable with respect to efficacy, as many previous data predict, decisions about which type of drug to prescribe should be based on side effects and cost." ACE inhibitors have a disadvantage in that they cause a cough in 5-20% of patients.

They are less expensive than the angiotensin II receptor blockers, however. This will not change soon because ACE inhibitors will lose their patent protection sooner. Hostetter suggests that one reason ACE inhibitors were not tested in these trials was because a result of equal effectiveness would reduce the sale of the angiotensin II receptor blockers. He finds the idea troubling.

"We must focus more attention on the regrettable tendency of study sponsors to drop good drugs from important trials when their patents expire and the drugs therefore become less profitable," he says. "The legitimate need to develop and profit from new compounds must be explicitly balanced against the obligation to test established and effective, but cheaper, agents."

Fran Kaufman, MD, president-elect of the American Diabetes Association in Alexandria, VA, won't enter the debate about the study's exclusion of ACE inhibitors. "This study is just comparing a different way to get at angiotensin-converting enzyme inhibition through the receptor vs. the calcium channel blocker — to see whether there is efficacy to either one of those."

These are important studies and may change practice over time, she says. "This may slowly become as widely used a modality as ACE inhibition." She agrees, though, that more research is needed. "Now they maybe need to go head-to-head with an ACE inhibitor and see how [the angiotensin II receptor blockers] compare in efficacy, safety, and cost." ■

Program: 24x7 pharmacist call center support

Review med orders by phone, Internet, or fax

Unable to fill their open pharmacy positions and tightened by budget constraints, many hospitals cannot afford to staff their pharmacies 24 hours a day. But even after pharmacy doors close, physicians continue to write medication orders, and new patients continue to be admitted. The lack of an after-hours pharmacist leaves hospitals more vulnerable to medication errors.

To address this problem, one company is offering health care institutions 24-hour-a-day, seven-day-a-week professional pharmacist call center support, including medication order review and order entry. MedNovations' PharmaCheck After Hours program focuses on being a drug therapy knowledge resource, not just a traditional drug information program where nurses or physicians call if they have a question, says **Kenneth Dandurand**, RPh, MS, president of the Greenbelt, MD-based company.

"We can't wait for the nurse to have a question," he says. "With all of the new drugs being approved by the FDA [Food and Drug Administration] each year, physicians and nurses often don't know the questions to ask because they are not familiar with the drug."

Dandurand sees two primary problems that hospital pharmacies face: medication errors in the hours that the pharmacists are not working, and the significant shortage of pharmacists and nurses. A telepharmacy program allows those hospitals that have trouble filling pharmacy positions to have a support system so their nurses can feel assured that the medications they give are appropriate, he says.

Hospitals are feeling increased pressure to reduce the incidence of medical errors. First, a 1999 Institute of Medicine report targeted medication error as a key contributor to the thousands of deaths every year from medical mistakes in hospitals. Subsequently, accrediting bodies such as the Joint Commission on Accreditation of Healthcare Organizations have identified pharmacists' proactive review of medication errors as a prime method for improving medication safety.

"The majority of the errors are being made in the ordering phase," Dandurand says. "Physicians don't necessarily remember all of the doses that are appropriate."

The PharmaCheck After Hours program gives a hospital off-hours access to a pharmacist with hospital-based, clinical experience. Hospitals can phone in orders, scan them into the computer for the company to see, or fax them. MedNovations also can access hospitals through the Internet or through a virtual private network, such as in a telemedicine model.

"We can access laboratory values, [a list of] the medications a patient is already taking, and the patient's history of allergies," Dandurand explains. "If the computer allows it, we also can enter the prescription information into the system."

If MedNovations receives a fax, the pharmacists review it and verify it. If they find a problem, they contact the appropriate physician from their list of physicians at the hospital or they contact the on-call physician. The turn-around time from receiving the order to acting on it is what hospitals might expect from an in-house pharmacist, Dandurand says.

If the order is correct, the pharmacists fax back a confirmation. "The nurse knows right away that the drug is okay to give to the patient," he says. This can be especially helpful for nurses who work late shifts, he adds, because they are typically less experienced and are operating during those hours without a safety net.

To help nurses initially learn about working with the PharmaCheck After Hours program, MedNovations has provided an orientation about the service. The company also has provided laminated instructions to each nursing unit on how to use the service and how to contact MedNovations.

And at the end of each service day, PharmaCheck After Hours provides a daily pharmacy shift summary report to the pharmacy, documenting all the orders reviewed on the shift, as well as its current status. The in-house pharmacists then can enter their orders.

MedNovations focuses on checking high-risk medications and new admissions. "That is typically where we are going to see a lot of the problems," Dandurand says. Company pharmacists also are available to answer questions from hospital staff. A nurse, for example, may receive approval from PharmaCheck After Hours to administer two drugs. However, she still might not understand how to administer them. The service is available to answer those questions, he says.

MedNovations works with automated dispensing and helps the clinical staff when they have difficulty locating a medication, too. "We have a list that tells us exactly what is in [a facility's] automated dispensing," he says. If the list identifies a drug by its brand name, and a nurse knows the drug by its generic name, or vice versa, the company pharmacists can tell the nurse where to find the drug. ■

JAMA: Older antibiotics trump newer ones

Patients treated with new and more expensive antibiotics for acute sinusitis symptoms did not display significant differences in outcomes compared with those treated with older and less expensive antibiotics, according to a study in the Oct. 17 *Journal of the American Medical Association.* Researchers looked at the benefits of 17 older and newer antibiotics; more than 29,000 patients were analyzed. It was determined that cost of care was significantly higher for patients treated with newer antibiotics, yet their outcomes were similar. The average total direct charge for patients receiving

an older antibiotic was $68.98 and a newer antibiotic was $135.17, a difference of $66.19.

"In conclusion, it appears that there is no incremental clinical benefit of newer, more expensive second-line antibiotics over older, less expensive first-line antibiotics for patients with acute uncomplicated sinusitis," the researchers say. "Due to the higher expense and potential for the development of resistant bacteria, physicians should avoid prescribing second-line antibiotics as the initial antibiotic treatment." ▼

Black-box warning added to Xeloda label

The Food and Drug Administration and Roche have added a black-box warning and strengthened the precautions section in the label for capecitabine (Xeloda), indicated for the treatment of colorectal and breast cancer. A clinically important Xeloda-Warfarin drug interaction was demonstrated in a clinical pharmacology trial. Postmarketing reports have shown clinically significant increases in prothrombin time and international normalizing ratio (INR) in patients who were stabilized on anticoagulants at the time Xeloda was introduced. Patients receiving concomitant capecitabine and oral, coumarin-derivative, anticoagulant therapy should have their anticoagulant response (INR or prothrombin time) monitored frequently to adjust the anticoagulant dose accordingly. The Patient Package Insert also was revised to reflect this new safety information. For more information, see www. fda.gov / medwatch / safety / 2001 / safety01.htm. ▼

Centocor issues warning about Remicade

Centocor has alerted health care professionals to new safety information regarding infliximab (Remicade), its drug approved for the treatment of rheumatoid arthritis and Crohn's disease. In a suspended Phase II trial involving 150 patients with moderate-to-severe congestive heart failure (CHF), higher incidences of mortality and hospitalization for worsening heart failure were seen in patients treated with Remicade, especially those treated with the higher dose of 10 mg / kg. Seven of 101 patients treated with Remicade died compared to no deaths among the 49 patients on placebo.

In consultation with the Food and Drug Administration, Centocor mailed a "Dear Doctor" letter communicating these preliminary results to health care professionals nationwide. The letter gives advice about care of patients receiving Remicade who have concomitant CHF. For more information, see www.remicade.com. ▼

'Smart bomb' drugs show promise against cancers

Two new "smart bomb" drugs that target specific proteins needed for tumor growth have produced promising results in clinical trials against a number of cancers, scientists said at a recent American Association for Cancer Research conference in Miami, as reported by Reuters.

AstraZeneca's tablet Iressa and ImClone's

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Editorial Questions

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competing injectable product C225 are the first in a new class of drugs that block the epidermal growth factor receptor (EGFR).

Phase II trial results showed Iressa succeeded in shrinking lung tumors by at least half in 18.7% of seriously ill patients who failed to respond to conventional chemotherapy. In 52.9% of patients the disease stabilized; in 34% the cancer had not grown after four months.

The overall response rate was "much higher" than with standard chemotherapy, while the side effects — primarily diarrhea and skin rash — were minimal, said **Jose Baselga**, MD, of Vall d'Hebron University Hospital in Barcelona, Spain. ▼

Consumers fear vaccine shortage this season

Despite recent reassurances from the Centers for Disease Control and Prevention (CDC), 34% of Americans believe there will be an influenza vaccine shortage this year, according to a national survey conducted by the American Society of Health-System Pharmacists (ASHP). Fifty-eight percent of those surveyed said that they or their family members have already been inoculated or plan to get a flu shot this year, up from 50% who tried to get the vaccination last year.

"Unfortunately, consumers who are concerned about a shortage also are being deluged with a steady stream of media reports about a relatively small number of anthrax infections on the East Coast," says ASHP President **Steven L. Sheaffer**, PharmD, FASHP. "The similarity between flu and anthrax symptoms only confuses matters further."

Public health officials say there will be no shortage of the influenza vaccine this year. The vaccine is distributed in phases that are related to manufacturing capacity. Fifty-six percent of the total supply was available in October; 31% was delivered in November; and 13% will be delivered in December. ■

DRUG CRITERIA & OUTCOMES™

Ticlid/Plavix formulary evaluation

By **Jamie Hayes**, PharmD*

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Platelet aggregation inhibitors

Clopidogrel (Plavix) — Bristol-Myers-Squibb / Sanofi

Ticlopidine (Ticlid) — Roche

Mechanism of action

Both drugs selectively inhibit adenosine diphosphate (ADP)-induced platelet aggregation with no direct effect on arachidonic acid metabolism. Blocking ADP receptors prevents fibrinogen binding at the site and thereby reduces the possibility of platelet adhesion and aggregation.

Pharmacokinetics

The pharmacokinetic profiles of clopidogrel and ticlopidine are shown in **Table 1, below**.

Dosage

Ticlopidine 250 mg bid. Dose adjustment in renal failure patients and possible dose adjustment in the elderly may be necessary. Ticlopidine is contraindicated in hepatic failure patients.

Clopidogrel 75 mg QD. Dose adjustment in renal failure patients or the elderly is not required, but caution is advised in hepatic failure patients. A loading dose of 300 mg is optional.

Indications

Both drugs are used to treat the underlying condition of atherothrombosis, which can manifest clinically in many different ways in any part of the cardiovascular system. There also is significant overlap between disease manifestations in cardiovascular disease. For example, approximately 5% of this population has coronary, peripheral arterial, and cerebrovascular disease.

Clopidogrel

Clopidogrel is approved by the Food and Drug Administration to treat atherosclerotic events, including: myocardial infarction (MI), stroke, and vascular death in patients with atherosclerosis that is documented by stroke, recent MI, or established peripheral arterial disease.

Unlabeled indications for clopidogrel that currently are being investigated include Buerger's disease, acute MI, diabetic nephropathy, ulcers due to venous stasis, and intermittent claudication.

Table 1. Pharmacokinetics of clopidogrel and ticlopidine

Variable	Clopidogrel	Ticlopidine
Bioavailability	> 50%, unaffected by food	80-90%, increases with food
T_{max}	1 hour	1-3 hours
Half-life	8 hours	Apparent 12.6, terminal 4-5 days
Dosage	250 bid	75 QD with food
Plasma protein binding	98%	98%
Elimination	50% urine; 46% feces	60% urine; 23% feces
Metabolism	Hydrolysis in liver	Extensively in liver
Duration of action	Life of platelet, 7-10 days	Life of platelet, 7-10 days
Formulation	PO	PO
Pregnancy category	B	B
Time to observed effect	2 hours	24-48 hours
Time to reach max effect	3-7 days	3-10 days

Ticlopidine

Ticlopidine is labeled to

reduce the risk of thrombotic stroke (fatal or non-fatal) in patients who have experienced stroke precursors, and in patients who have had a completed thrombotic stroke.

Table 2. Off-label uses of ticlopidine

Condition	Result
Intermittent claudication	Improved maximum walking and pain-free distance
Chronic arterial occlusion	Improved lower extremity ulcer healing, vascular improvement
Subarachnoid hemorrhage	Reduced incidence of neurological deficit
Uremic patients with AV shunts or fistulas	Reduced incidence of vascular occlusion
Open-heart surgery	Preoperative use reduces degree of platelet count drop during extracorporeal circulation
Coronary artery bypass graft	Decreased graft occlusion
Primary glomerulonephritis	Reduced degree of proteinuria and hematuria, improved creatinine clearance
Sickle cell disease	Reduced incidence, duration, and severity of infarctive crisis

Ticlopidine has been used in various other conditions where further study is needed; these unlabeled uses are described in **Table 2, above**.

Both drugs are used after coronary stenting (unlabeled). This indication is being studied actively.

Safety

Ticlopidine has a block-box warning regarding life-threatening hematological adverse reactions, including neutropenia / agranulocytosis and thrombotic thrombocytopenic purpura (TTP). The incidence of ticlopidine-associated TTP is estimated to be 1 per 1,600-5,000 patients.

More than 3 million patients have taken clopidogrel, and approximately 11 cases of TTP have been identified. This rate is similar to background frequency of TTP reported in the general population and approximately 100 times less frequent than ticlopidine-induced TTP. Several of these reports were not believed to be caused by clopidogrel. In 10 of the 11 cases, the effect was seen in less than 14 days. **Table 3, below**, provides a list of common adverse drug reactions and their frequencies.

Monitoring

Ticlopidine requires monitoring for neutropenia and TTP, with baseline and serial complete blood counts every two weeks for the first three months of treatment.

In clinical trials with clopidogrel, neutropenia frequency was no higher than that associated with aspirin. Serial blood tests, therefore, are not required with clopidogrel.

Drug interactions

Clopidogrel inhibits the P-450 CYP2C9 system at high concentrations and, therefore, may interfere with metabolism of other drugs metabolized by this system, requiring dose adjustment. Ticlopidine inhibits the P-450 CYP2C19 system and may require dose adjustment. **Table 4, p. 3**, shows the most important, currently known drug interactions.

Cost and usage

Ticlopidine: $0.88 / d (generic); five days of therapy / month.

Clopidogrel: $2.60 / d; 1,200 days of therapy / month.

Table 3. Adverse drug reactions related to clopidogrel and ticlopidine

Adverse Drug Reaction	Clopidogrel	Ticlopidine
Gastrointestinal	10%	30-40%
Neutropenia	< 0.1%	> 1%
Thrombotic thrombocytopenic purpura	Rare	0.2%
Rash	4%	5%
Pruritus	3.3%	Unknown
Increased liver function tests	Unknown	7.6%
Dizziness	6%	1%
Total cholesterol (increased by 8-10%)	Unknown	1%
Hepatotoxicity	> 3%	Unknown

Clinical trials

Few head-to-head clinical trials prove superior efficacy of ticlopidine vs. clopidogrel. However, three important trials (two of ticlopidine and one of clopidogrel) compare the safety and efficacy of these drugs to aspirin or placebo. The differences in these trials make them very difficult to compare. The CLASSICS trial compared the safety of the two drugs against each

Table 4. Drug interactions with ticlopidine and clopidogrel

Drug	Ticlopidine	Clopidogrel
Cimetidine	Decreases ticlopidine clearance by 50%	No known effect
Aspirin	Possibly increases bleeding	Possibly increases bleeding
Digoxin	Digoxin levels may decrease slightly (–15%)	No known effect
Phenytoin	Elevates phenytoin plasma levels with associated somnolence and lethargy	Possibly increases phenytoin levels
Theophylline	Theophylline elimination half-life increases (significant) with reduction in total plasma clearance	No known effect
Antacids	Decreases ticlopidine plasma levels by 18%	No known effect
Tamoxifen	No known effect	Possibly increases tamoxifen effect
Tolbutamide	No known effect	Possibly increases or decreases either drug's effect
Warfarin	Possibly prolongs bleeding	Prolongs bleeding
Torsemide	No known effect	Possible interaction
Fluvastatin	No known effect	Possible interaction
NSAIDs	Possibly increases bleeding	Increases occult GI blood loss
Heparin	Use caution/possibly increases bleeding risk	Use caution/possibly increases bleeding risk

other, but lacked sufficient power to prove efficacy.

CATS trial

The CATS trial was a multicenter, randomized, placebo-controlled trial designed to assess the effect of ticlopidine (250 mg bid) in reducing the risk of secondary stroke, MI, or vascular events in 1,053 patients who had a recent thromboembolic event.[1] Study results are listed in **Table 5, below**.

P values were not given for actual results. The results demonstrate a trend toward lower event rates with ticlopidine, but significance cannot be assessed. Data were listed in terms of relative risk, which showed a 30.2% reduction in the incidence of stroke, MI, or vascular death associated with the use of ticlopidine (P = 0.006).

Severe adverse events occurred in 8.2% of the ticlopidine group and 2.8% of the placebo group (P < 0.001), including one case of moderate neutropenia in the placebo group and four cases of severe neutropenia in the ticlopidine group.

The CATS trial showed efficacy of ticlopidine and its potential for causing serious adverse events.

Table 5. Results of the CATS trial

Drug	Number of patients	Number of events		
		Stroke	MI	Vascular death
Placebo	528	88 (17%)	12 (2%)	18 (3%)
Ticlopidine	525	53 (10%)	13 (2%)	8 (1.5%)

The study was well-designed and had adequate sample size; however, the absence of P values supporting actual events is a major limitation.

TASS trial

The TASS trial was a multicenter, randomized, triple-blind, controlled trial comparing ticlopidine vs. aspirin for prevention of secondary atherothrombotic stroke or death in 3,069 patients.[2] Patients were randomized to receive ticlopidine 250 mg bid or aspirin 650 mg bid. The primary results of this trial are listed in **Table 6, p. 4**.

Gastrointestinal side effects were the most common adverse drug reaction in both treatment groups. The dose of aspirin was 1,300 mg / d, which is much higher than the typical 325 mg / d dose prescribed today. It was not stated whether the aspirin supplied was enteric-coated. Thus, gastrointestinal safety of ticlopidine in comparison to the lower standard dose of aspirin cannot be assessed. The incidence of diarrhea and rash in the ticlopidine group was twice that of the aspirin group. A total of 13 cases of neutropenia developed in the ticlopidine group; no cases of neutropenia developed in the aspirin group.

The TASS study had a high dropout rate that was similar between treatment groups. The trial was well-designed. Not all P values were given, and most of the data were reported in terms of relative risk. This study did show slightly greater efficacy of ticlopidine compared to aspirin, but ticlopidine also resulted in serious side effects.

CAPRIE trial

The CAPRIE trial was a randomized, blinded, international trial comparing the safety and efficacy of clopidogrel and aspirin for the

Table 6. Primary results of the TASS trial

Endpoint	Ticlopidine	Aspirin	P value
Death from all causes or nonfatal stroke	306 (20%)	349 (23%)	0.048
Fatal or nonfatal stroke	172 (11%)	212 (14%)	0.024
Death from all causes	175 (11%)	196 (13%)	—

prevention of secondary stroke in patients at risk of ischemic events.[3] This study was designed to investigate the risk of a composite outcome cluster of ischemic stroke, MI, or vascular death. The results are summarized in **Table 7, p. 5**.

These results show a consistently lower event rate for clopidogrel vs. aspirin, although statistical significance is unknown. The primary endpoint events, including ischemic stroke, MI, or vascular death, showed a total event rate of 939 (9.8%) in the clopidogrel group and 1,021 (10.7%) in the aspirin group. Therefore, this trial shows a less than 1% difference in the efficacy of clopidogrel and aspirin.

The CAPRIE trial found clopidogrel's safety to be similar to that of a 325 mg aspirin. There was a significantly greater incidence of severe adverse reactions in the clopidogrel group vs. the aspirin group for rash (0.26% vs. 0.10%, P = 0.017) and diarrhea (0.23% vs. 0.11%, P = 0.080), and a greater incidence of severe gastrointestinal discomfort (P = 0.096), intracranial hemorrhage (P = 0.080), and gastrointestinal hemorrhage (P = 0.05) with the aspirin group. It is not known whether the aspirin was enteric-coated. The frequency of neutropenia was 0.1% for clopidogrel and 0.17% for aspirin.

The CAPRIE trial was well-designed; 19,185 patients with parallel demographics were evaluated for 1-3 years. The number of patients discontinuing this study due to adverse events was similar between treatment groups, and the overall safety was comparable between the two drugs. Efficacy was reported as relative risk reduction; no P values for actual events were provided. Differentiation between subgroups cannot be evaluated due to overlapping disease states; 2,144 patients in ischemic stroke and peripheral artery disease had a history of MI. In addition, the trial did not achieve power to detect differences in subgroups. The conclusions of this trial are that clopidogrel is safe and effective.

CLASSICS trial

The CLASSICS trial was a double-blind study comparing the safety of clopidogrel with and without a loading dose and in combination with aspirin vs. ticlopidine in combination with aspirin after coronary stenting. The trial showed the safety and tolerability of clopidogrel to be superior to ticlopidine.[4] Patients were randomized into three treatment groups: 300 mg clopidogrel (loading dose) and 325 mg/d aspirin on day 1, followed by 75 mg/d clopidogrel and 325 mg/d aspirin (days 2-28); 75 mg/d clopidogrel and 325 mg/d aspirin (days 1-28); and 250 mg bid ticlopidine and 325 mg/d aspirin (days 1-28). The 300 mg loading dose of clopidogrel vs. ticlopidine was well-tolerated, with no increase in the risk of bleeding. Difference in efficacy of clopidogrel vs. ticlopidine could not be evaluated in this trial due to insufficient power. Results are listed in **Table 8, p. 6**.

Thrombocytopenia was observed in four clopidogrel patients. These events were reported as transient and without clinical significance. There were no reports in the other treatment groups.

The large sample size and the design of the CLASSICS trial were its strengths. This trial showed safety of clopidogrel with or without a loading dose to be greater than ticlopidine. The loading dose regimen of clopidogrel had a greater statistical significance than the clopidogrel regimen without a loading dose. The limitations of the CLASSICS trial were a short duration (28 days), a lack of statistical power to establish efficacy of one drug vs. the other, and strict inclusion/exclusion criteria that made the results of this trial difficult to apply to the entire cardiovascular disease population. Also, one of clopidogrel's advantages is its faster onset of action; this trial allowed a six-hour time frame to give the study drug. If this trial had demonstrated enough power to prove superior efficacy of either drug, this time frame possibly could affect the results.

Several other studies have been conducted with these two agents in patients undergoing coronary stent placement.[5] With current information, it appears that clopidogrel is associated with a very low rate of stent thrombosis, with efficacy similar to that of ticlopidine, and clopidogrel is better tolerated.

CURE trial

The recently published CURE trial evaluated the efficacy and safety of the antiplatelet agent clopidogrel with aspirin vs. aspirin alone in more

than 12,000 patients with acute coronary syndromes (ACS) without ST-segment elevation.[6]

The trial was a randomized, double-blind, placebo-controlled study enrolling ACS patients who presented within 24 hours following symptom onset; patients received either a clopidogrel 300 mg loading dose followed by 75 mg / d plus aspirin (75-325 mg / d), or placebo plus aspirin for 3-12 months.

The first primary outcome was the composite of death from cardiovascular causes, nonfatal MI, or stroke. The second primary outcome was the composite of the first primary outcome or refractory ischemia.

The secondary outcomes were the need for revascularization, health failure, and severe anemia. The safety outcomes were major and minor bleeding. The triple composite, first primary outcome occurred in 9.3% of the clopidogrel group and 11.4% of the placebo group ($P < 0.001$).

The second primary outcome occurred in 16.5% of the clopidogrel group and 18.8% of the placebo group ($P < 0.001$). All secondary endpoints occurred significantly less often in the clopidogrel group. Major bleeding occurred in 3.7% of the clopidogrel group and 2.7% of the placebo group ($P = 0.001$).

The rate of the first primary outcome was lower with clopidogrel within the first 30 days, and clopidogrel's benefit was apparent within the first few hours after randomization. Study drug was discontinued permanently in 21.1% and 18.8% of clopidogrel and placebo patients, respectively.

The CURE study demonstrates the benefit of the clopidogrel-aspirin combination in the trial population, as well as an increased risk of bleeding.

Other selected studies

In another trial on patients undergoing coronary artery stenting, 243 study patients were randomized to ticlopidine 500 mg / d with and without aspirin 100 mg / d.[7] The primary endpoint was the absence of death, cardiac events, and vascular access-site complications during hospitalization.

Follow-up clinical exams and angiography were performed at three months. Stent thrombosis occurred in two combined-treatment patients and in none in the monotherapy group. No significant differences in the primary endpoint were demonstrated between the two groups. There are several important weaknesses with this study, and the results need to be confirmed in larger multicenter trials.

In a randomized, unblended trial in 700 patients undergoing coronary stenting, patients received either clopidogrel 75 mg / d or ticlopidine 250 mg bid for 30 days, with no loading doses. Both regiments included aspirin 100 mg / d.[8]

Glycoprotein IIb / IIIa receptor blockers were administered in 7% and 11% of the ticlopidine and clopidogrel patients, respectively. The primary endpoint was the incidence of noncardiac events at 30 days (i.e., noncardiac death, stroke, leukopenia / thrombocytopenia, hemorrhage, or vascular complication or

Table 7. CAPRIE trial intention-to-treat analysis — primary and secondary outcome clusters

Outcome event cluster and treatment group		First outcome events			Event rate per year	Relative risk reduction	P value
		Nonfatal	Fatal	Total			
Ischemic stroke, MI, or vascular death (primary cluster)	Clopidogrel	631	308	939	5.32%	8.7%	0.043
	Aspirin	700	321	1,021	5.83%		
Ischemic stroke, MI, amputation, or vascular death	Clopidogrel	677	302	979	5.56%	7.6%	0.076
	Aspirin	737	314	1,051	6.01%		
Vascular death	Clopidogrel		350	350	1.90%	7.6%	0.29
	Aspirin		378	378	2.06%		
Any stroke, MI, or death from any cause	Clopidogrel	643	490	1,133	6.43%	7.0%	0.081
	Aspirin	720	487	1,207	6.90%		
Death from any cause	Clopidogrel		560	560	3.05%	2.2%	0.71
	Aspirin		571	571	3.11%		

Table 8. Summary of data on primary (safety) endpoint

Outcome event	Ticlopidine	Clopidogrel 75 mg QD	Clopidogrel 300/75 mg QD	Clopidogrel total
Composite (of all events)	31 (9.1%)	21 (6.3%)	10 (2.9%)	31 (4.6%)
Major peripheral or bleeding complications	4 (1.2%)	4 (1.2%)	5 (1.5%)	9 (1.3%)
Neutropenia	1 (0.3%)	0	0	0
Thrombocytopenia	0	2 (0.6%)	2 (0.6%)	4 (0.6%)
Early discontinuation due to noncardiac event	28 (8.2%)	17 (5.1%)	7 (2%)	24 (3.5%)
Skin disorder	9 (2.6%)	3 (0.9%)	2 (0.6%)	5 (0.7%)
Gastrointestinal disorder	9 (2.6%)	8 (2.4%)	1 (0.3%)	9 (1.3%)
Allergy	4 (1.2%)	0	0	0
Other	6 (1.8%)	6 (1.8%)	4 (1.2%)	10 (1.5%)

P values for the composite of primary endpoints:
P = 0.005 for ticlopidine vs. clopidogrel combined (both clopidogrel groups combined)
P = 0.001 for ticlopidine vs. 300/75 mg QD clopidogrel
P = 0.194 for ticlopidine vs. 75 mg QD clopidogrel
P = 0.043 for 300/75 mg QD clopidogrel vs. 75 mg clopidogrel

intolerance). Occurrence rates were 4.5% for clopidogrel and 9.6% for ticlopidine (P = 0.01).

The secondary endpoint of cardiac-related events at 30 days (i.e., thrombotic stent occlusion, target vessel revascularization, nonfatal MI, and cardiac death) was lower with ticlopidine (1.7% vs. 3.1%) but did not prove to be statistically significant. The authors proposed that a clopidogrel loading dose might be beneficial.

Several nonrandomized, observational studies indicate that clopidogrel may be similar in efficacy to ticlopidine but causes fewer adverse effects when used as prophylaxis with coronary stent thrombosis, when both drugs are combined with aspirin.[9-11] Investigators recommend large controlled trials be done to study these issues.

Clopidogrel doses of either 50 mg, 75 mg, or 100 mg daily or ticlopidine 250 mg bid were started the day following coronary artery bypass surgery in 62 patients studied.[12] At postoperative day 9, clopidogrel did not significantly inhibit platelet aggregation vs. baseline, but ticlopidine exerted a significant antiplatelet effect. At 28 days post-op, all three clopidogrel doses demonstrated a significant antiplatelet effect, and short-term outcomes were similar in both groups. The authors speculated that a clopidogrel loading dose may be necessary in this population.

Summary

The CAPRIE, TASS, and CATS trials showed both drugs to be effective. The CLASSICS trial showed clopidogrel to have a better safety profile than ticlopidine. Although neutropenia and TTP are less common with clopidogrel than ticlopidine, these reactions can occur. Patients and health care providers need to be aware and watchful for signs and symptoms of these adverse events. Both drugs have demonstrated efficacy with coronary stent placement.

Clopidogrel has a number of advantages over ticlopidine, including once-daily dosing, better safety and tolerability, no serial blood testing required, and faster onset of action. Ticlopidine recently has become available as a generic drug, thus decreasing the cost significantly; however, the cost of laboratory monitoring may offset these savings. These characteristics give clopidogrel an advantage over ticlopidine, along with the fact that prescribing practices have trended toward clopidogrel (five patient therapy days / month of ticlopidine use vs. 1,200 patient therapy days / month of clopidogrel use). Ticlopidine has no significant advantage over clopidogrel, other than possibly cost; therefore, clopidogrel can be recommended as the formulary "workhorse drug." Considering the current prescribing trend, this interchange will be relatively simple.

General recommendations

1. Patients entering the hospital on ticlopidine should be changed to clopidogrel, if there are no contraindications.

2. Patients prescribed one of these drugs while in the hospital should be started on clopidogrel.

3. Educate clinicians and patients on clopidogrel-induced TTP and neutropenia, which occurs with low frequency. Although no specific laboratory monitoring is required for clopidogrel, practitioners should be watchful for signs and symptoms of TTP and neutropenia.

Interchange doses

Ticlopidine (Ticlid) 250 mg bid ➥ clopidogrel (Plavix) 75 mg QD

Steps: Initiating clopidogrel into pharmacy

1. Establish pharmacist interchange for these antithrombotic agents.
2. Educate on clopidogrel formulary interchange program prior to implementation.
3. Evaluate program once in place to assess problems, compliance, and outcomes.
4. Address any problems that arise and re-educate, as needed.

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IN THE PIPELINE

• Protein Design Labs will start a Phase II clinical trial to evaluate its humanized antibody to interleukin-4 in **asthma**. The randomized, double-blind, placebo-controlled study will be conducted in the United States in 120 symptomatic asthma patients who are not being treated with controller medications, including inhaled steroids, leukotriene modifiers, or long-acting beta agonists. The primary goals of the study are to determine safety, tolerability, and preliminary efficacy.

• SkyePharma PLC and Sanofi-Synthelabo have announced that an "approvable letter" has been received from the Food and Drug Administration (FDA) for the once-daily formulation of alfuzosin (UroXatral) for the symptomatic treatment of **benign prostatic hyperplasia**. The formulation uses SkyePharma's proprietary oral drug delivery technology, GEOMATRIX. The New Drug Application for UroXatral was submitted in December 2000 in the United States.

• Amylin Pharmaceuticals has announced that the FDA has completed its review of the New Drug Application for SYMLIN (pramlintide acetate) and has determined that SYMLIN is approvable for both **Type 1 and insulin-using Type 2 diabetes**. However, approval will require additional clinical work, the specific requirements of which will be determined following discussions with the FDA.

• Following an end-of-Phase II meeting with the FDA, Amylin Pharmaceuticals has reiterated its plans to initiate its Phase III program for synthetic exendin-4 (AC2993) before the end of 2001. AC2993 is a 39-amino acid peptide being studied for the treatment of **Type 2 diabetes**.

• Atrix Laboratories has completed enrollment of its first Phase III study for dapsone topical gel in SMP technology (Atrisone), for the treatment of **acne**. The results of the trial are expected to be analyzed and available by April 2002.

• Transgene has initiated a Phase II clinical

trial of its immunotherapeutic MVA-HPV-IL2 product candidate for the treatment of **cervical cancer**. The trial will be conducted in Mexico and will include up to 57 women with varying stages of HPV 16 cervical cancer, each of whose cancer either is resistant to radiotherapy or has recurred after radiotherapy.

• Genaissance Pharmaceuticals has initiated its second clinical study, STRENGTH II, to extend its efforts in developing new therapeutic approaches to lowering **cholesterol**, one of the country's top public health issues. The STRENGTH (Statin Response Examined by Genetic HAP Markers) Studies are designed to link Genaissance's proprietary markers of human gene variation, HAP Markers, to clinical response for the development of novel diagnostic and therapeutic products.

• Novartis has submitted a supplementary New Drug Application (sNDA) to the FDA, seeking marketing authorization for its drug imatinib mesylate (Gleevec) for the treatment of patients with **unresectable (inoperable) and/or metastatic malignant gastrointestinal stromal tumors**.

• Cell Genesys has initiated a Phase II clinical trial of GVAX vaccine in patients with **pancreatic cancer** who have undergone surgical resection of their tumors. This trial will evaluate the safety and efficacy of GVAX cancer vaccine used in combination with surgical resection of pancreatic cancer followed by standard adjuvant radiation and chemotherapy. The study is being conducted at the Johns Hopkins Oncology Center and will enroll up to 60 patients.

• SLIL Biomedical Corp. has announced that the FDA has completed its review of the Investigational New Drug application (IND) for SLIL's candidate drug, SL11047. Phase I human clinical trials, aimed at **AIDS-lymphoma** patients, will be undertaken by Dr. Lawrence Kaplan at the University of California San Francisco.

• Novartis has announced that zoledronic acid for injection (ZOMETA) has been designated a priority review by the FDA in the treatment of **bone complications** (metastases) associated with a broad range of tumor types. These included patients with prostate cancer, lung cancer, and other tumor types for which no intravenous bisphosphonate therapy is currently approved for treatment, as well as patients with breast cancer and multiple myeloma.

• Immuno-Designed Molecules, S.A. (IDM), and its Canadian subsidiary, IDM-Biotech Ltd., has announced approval from the Canadian health authorities to begin Phase III clinical trials for the treatment of **ovarian cancer** using IDM's Cell Drug known as IDM-1.

• Oculex Pharmaceuticals has begun to enroll patients suffering from **persistent macular edema** (PME) as part of its Phase II clinical trial for Posurdex. Posurdex, a biodegradable, micro-sized drug delivery system designed to provide continuous drug therapy for approximately one month inside the eye. ■

New FDA Approvals

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

• *Mixed salts of a single-entity amphetamine product (ADDERALL XR) by Shire Pharmaceuticals Group.* The FDA has approved mixed salts of a single-entity amphetamine product (ADDERALL XR) for the treatment of **attention deficit/hyperactivity disorder** (ADHD). ADDERALL XR, an extended-release formulation of Shire's ADHD treatment ADDERALL, is designed to provide symptom control in the morning and throughout the day with just one morning dose.

• *New indication for celecoxib capsules (Celebrex) by Pharmacia Corp. and Pfizer.* The FDA has approved the use of celecoxib capsules (Celebrex) for the management of **acute pain** and **primary dysmenorrhea** in adults. This new indication provides patients the benefit of being able to take an additional dose if needed for individualized relief of acute pain.

• *Reformulation of prednisolone tablets USP, 5 mg, by Lannett Co.* The FDA has approved the reformulated version of the Lannett's existing Abbreviated New Drug Application for prednisolone tablets USP, 5 mg, indicated for the **anti-inflammatory** treatment caused by organ disorders.

• *New indication for gatifloxacin by Bristol-Myers Squibb Co.* Gatifloxacin (TEQUIN), a broad-spectrum fluoroquinolone antibiotic, has been approved by the FDA for short-course (5-day) regimen in the treatment of **acute bacterial exacerbation of chronic bronchitis** (ABECB). TEQUIN already is approved for ABECB, acute sinusitis, and community-acquired pneumonia. ■