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DRUG UTILIZATION REVIEW

Pharmaceutical Care Across the Continuum

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Federal court blocks President Bush's prescription discount plan

Decision could derail program for months — or for good

Pharmacy groups received an unexpected gift from a federal court on Sept. 7 — a judge issued an injunction blocking President George W. Bush's plan to offer prescription drug discount cards to senior Americans.

In July, the National Association of Chain Drug Stores and the National Community Pharmacists Association, both in Alexandria, VA, filed suit against Secretary of Health and Human Services (HHS) Tommy Thompson and Centers for Medicare and Medicaid Services Administrator Tom Scully. The suit alleges the following violations in the Medicare Rx Discount Card proposal:

- a lack of legislative authority on the part of the administration;
- violations of the Administrative Procedures Act and the Federal Advisory Committee Act; and
- an unlawful delegation of regulatory power to a private consortium.

Health officials created the plan in "secret meetings," the groups charge.

Judge Paul L. Friedman of the U.S. District Court of the District of Columbia granted the motion for a preliminary injunction, citing a lack of legislative authority on the part of the administration and violations of the Administrative Procedures Act. Friedman also approved a petition filed by the American Pharmaceutical Association (APhA) in Washington, DC, to intervene as a plaintiff in the action.

"Judge Friedman's ruling is positive for our patients because it was a false promise and would have provided minimal discounts, at best," said APhA Executive Vice President **John A. Gans**, PharmD, in a statement after the ruling.

HHS officials told the *Washington Post* that they were reviewing their legal options and had not decided whether they would appeal the injunction. Although the injunction has no time limit, the ruling, at the very least, will postpone the program for months.

"How long [the injunction will last] will depend on whether the government appeals the decision," says **Susan C. Winckler**, RPh, JD,

APhA's group director of policy and advocacy. "For now, things are kind of frozen in place."

To provide "immediate and ongoing relief" to seniors paying full retail prices for prescription drugs, Bush proposed a voluntary prescription "discount card" program for Medicare beneficiaries that would have begun early next year. In the proposed plan, Medicare would endorse and promote a number of qualified, privately administered prescription drug discount cards, to be made available either free of charge or at a nominal, one-time enrollment charge (no more than $25/enrollment).

Administration-endorsed pharmaceutical benefit managers (PBMs) would administer the program. The PBMs would set the rates that participating pharmacies could charge Medicare beneficiaries for medications. The PBMs also would negotiate with drug manufacturers for lower prices, although there is no requirement that the PBMs pass along negotiated savings or manufacturer rebates to the pharmacy or the consumer, nor an explanation of how such rebates would be distributed, according to the APhA. If the PBMs did not pass along any savings to the pharmacy, then the pharmacy may find itself sponsoring the "discount" to the consumer out of its own budget.

"This approach finances the discounts to seniors primarily from community pharmacy, but pharmacies are not the cause of high drug prices," the APhA says.

Community pharmacies would receive most of the traffic from the discount cards, but hospital pharmacies would see them as well, Winckler says. "Many hospital pharmacies also prepare prescriptions for an outpatient population. Certainly seniors or whoever gets these discount cards could bring those into the outpatient pharmacy."

The APhA argues that the program has a misguided focus. "It affects the entire profession because it puts the focus on 'how much of a discount can I get on my medications?' rather than 'am I getting the right medication and do I know how to use that medication?'" Winckler says. Instead of spending time with patients explaining how to use the medication, pharmacists would use part of that time explaining why the pharmacy doesn't participate in the discount card program, or if it does, why the program doesn't yield more of a discount when the government promised them one, she adds.

The discount card program also may disrupt consumer choice, Winckler says. For example, discount card programs may provide enrollees with financial incentives to use one pharmacy provider over another. "Then [pharmacists] have to re-establish relationships with those people who chose to participate in their card program."

To obtain the savings, some of these cards would require some strict formulary compliance, too, she says. "You may spend more time deciding when to change products solely from a financial standpoint because they are covered by the formulary [instead of determining] the clinical appropriateness of making those changes."

Now that the ruling has been made, Gans says it's time to look ahead. "We can focus our energy on a real benefit for Medicare beneficiaries — a benefit that provides coverage for medications and services to make the best use of those medications." ■

Consider conservative stance on Cox-2 inhibitors

Article questions risk of CV events

Arthritis drugs rofecoxib (Vioxx) and celecoxib (Celebrex) may increase the risk of cardiovascular (CV) thrombotic events, according to a recent article published in the Aug. 22/29 issue of the *Journal of the American Medical Association*. But the article has become a lightening rod of controversy, with critics charging faulty analysis on the part of the article's authors.

Rofecoxib and celecoxib are popular COX-2 inhibitors used to treat patients with osteoarthritis and adult rheumatoid arthritis. They were developed to fight the inflammation of arthritis without

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the stomach problems that can be attributed to aspirin and other anti-inflammatory drugs.

To define the cardiovascular effects of COX-2 inhibitors when used for arthritis and musculoskeletal pain in patients without coronary artery disease, authors **Debabrata Mukherjee**, MD; **Steven E. Nissen**, MD; and **Eric J. Topol**, MD, of the Cleveland Clinic Foundation in Ohio studied the results of four clinical trials. These are the Vioxx Gastrointestinal Outcomes Research Study (VIGOR) and the Celecoxib Long-term Arthritis Safety Study (CLASS) — each with more than 8,000 patients — as well as two smaller trials with about 1,000 patients each.

In their analysis of the VIGOR trial, the Cleveland Clinic researchers found that the risk of serious cardiovascular events in the rofecoxib group (111 patients) was 2.2 times higher than in the naproxen group (50 patients). The CLASS trial with celecoxib demonstrated no significant difference in cardiovascular events compared with nonsteroidal anti-inflammatory drugs (NSAIDs). (The event rates are stratified by patients receiving aspirin and those not receiving aspirin.)

The researchers also compared the annualized myocardial infarction (MI) rates for the COX-2 inhibitors in both VIGOR and CLASS with the placebo group of a recent meta-analysis of more than 23,000 patients in aspirin primary prevention trials. In addition, they searched the adverse event reporting system of the U.S. Food and Drug Administration (FDA), which revealed 144 unduplicated thrombotic or embolic cases for celecoxib and 159 cases for rofecoxib.

The authors admit that their analysis has several significant limitations. For example, the increase in cardiovascular events in these trials was unexpected, and evaluation of these endpoints was not prespecified. However, they still say that the available data raise a cautionary flag about the risk of cardiovascular events with COX-2 inhibitors. "Given the remarkable exposure and popularity of this new class of medications, we believe that it is mandatory to conduct a trial specifically assessing cardiovascular risk and benefit of these agents. Until then, we urge caution in prescribing these agents to patients at risk for cardiovascular morbidity."

The manufacturers respond

The drug companies strongly rebutted the *JAMA* article, calling its analysis flawed and unsound. They said it contained no new clinical information, and was based on an inappropriate re-analysis of several older clinical studies containing data that were not suitable for combination and comparison. For example, patients in these studies had different underlying diseases and different cardiovascular risk profiles.

Both Merck, based in Whitehouse Station, NJ, and Pharmacia, based in Peapack, NJ, said patient experience and other data showed their drugs, Vioxx and Celebrex, respectively, were safe. The manufacturers also previously had requested that the FDA review study results that the companies said indicated that warnings on the drug labels should be removed.

On Feb. 7 and 8, the FDA Arthritis Advisory Committee met to review the study results and to decide if either Celebrex or Vioxx should have the label warnings reduced or if the companies should change the prescribing information. The committee did not recommend any label changes for Celebrex. The committee also advised that a broad warning about ulcers should stay on Vioxx's label, and a warning should exist that says Vioxx users had twice the risk of heart attacks and cardiovascular side effects as naproxen users. The FDA usually follows the recommendations of the committee, but is not required to do so. An FDA spokesperson says a decision should be made sometime this month.

A change of practice?

The drug manufacturers aren't the only ones questioning the analysis of the Cleveland Clinic researchers; some cardiologists also are joining the chorus.

There is a tendency to discount the article on a couple of premises, says **David Roffman**, PharmD, BCPS, associate professor at the University of Maryland in Baltimore. Some physicians tend not to believe anything that they have not encountered in their own experience. Other researchers won't pay attention to the issue without first seeing data from direct-controlled clinical trials that say they should change their current practice. "Both ends of the spectra are clearly there, and I have heard both ends from given individuals."

The article, however, has raised the antennae among the cardiology community, Roffman says. "The article in *JAMA* basically retrospectively identified an issue that was of potential concern to people who are at risk for coronary artery disease or strokes," he says. "But because the data

were retrospective and the studies in and of themselves were not structured to look at this endpoint, the only thing this kind of data can do is let people be aware that this is a potential problem."

He believes that the researchers wanted to raise awareness. "Unless it is pointed out, the potential for something negative will never be investigated," Roffman says. "That is clearly the intention of the release of this kind of data. I think that is a valid approach to something that involves as many people as this potentially does."

A middle approach to this issue sounds reasonable to Roffman at this point. "If you want to manage patients conservatively, you might look at some alternatives rather than just arbitrarily putting patients on COX-2s because [the drugs] have in some cases less gastrointestinal toxicity associated with them."

Instead, he suggests re-evaluating which of the NSAIDs are perhaps a little less risky for people with high risk for coronary disease or patients who already have known coronary disease. "If you have a patient at high risk for coronary disease or patients who already have known coronary disease, and if you feel that GI toxicity is preventable given that a lot of these people are also on proton pump inhibitors for reflux disease, you might just use one of the older agents instead of one of the COX-2 inhibitors. In addition, they are always less costly." ■

Results from recent cardiovascular drug trials

Jury still out on reducing intracranial bleeds

ASSENT 3: Enoxaparin plus tenecteplase significant in treatment of AMI

Heart attack patients who received a new therapy regimen consisting of the single-bolus thrombolytic agent tenecteplase (TNKase / Metalyse) and the low-molecular-weight heparin enoxaparin sodium (Lovenox) injection experienced the most significant clinical efficacy and safety benefits in the ASSENT 3 (ASsessment of the Safety and Efficacy of New Thrombolytic regimens) trial. The treatment regimen also yielded the lowest 30-day mortality rate (5.35%) ever reported in a large-scale clinical trial of acute myocardial infarction (AMI). Results of the study are published in the Aug. 25 issue of *The Lancet*.

ASSENT 3 enrolled 6,095 heart attack patients at more than 500 sites worldwide. Patients were randomized to receive one of three treatments within six hours of the onset of symptoms. Treatment arms included:

- full-dose tenecteplase plus enoxaparin (Group A);
- half-dose tenecteplase plus weight-adjusted, reduced-dose unfractionated heparin (UFH) in combination with a 12-hour infusion of the glycoprotein IIb / IIIa inhibitor abciximab (ReoPro) (Group B);
- full-dose tenecteplase plus weight-adjusted UFH (Group C).

The primary endpoints were the composites of 30-day mortality, in-hospital reinfarction or in-hospital refractory ischemia (efficacy endpoint), and the above efficacy endpoint plus in-hospital intracranial hemorrhage or in-hospital major bleeding complications (efficacy plus safety endpoint).

Results showed that compared with unfractionated heparin, adjunctive therapy with abciximab or enoxaparin reduces ischemic complications of AMI treated with tenecteplase. The enoxaparin regimen, however, had fewer bleeding complications and is easier to administer. One of the investigators of the study also has said that the enoxaparin arm worked out to be less expensive than the abciximab arm.

Gusto V: No significant mortality reduction for half-dose reteplase and abciximab

A large clinical trial has shown that the combination of the glycoprotein IIb / IIIa inhibitor abciximab (ReoPro) and a half-dose of the fibrinolytic agent reteplase (Retavase) failed to show a significant reduction in mortality compared to full-dose reteplase alone. The combination therapy did reduce the numbers of percutaneous coronary interventions and coronary bypass surgeries needed compared to the reteplase group, however, and did not significantly increase intracranial hemorrhage or nonfatal disabling stroke.

The results of GUSTO V (Global Use of Strategies To open Occluded coronary arteries), the first phase III combination trial with heart attack patients, were published in the June 16 issue of *The Lancet*. The largest trial of its kind, GUSTO V involved 16,588 patients suffering

acute myocardial infarction; 1,240 of these patients came from Canada.

At 30 days, the mortality in the combination therapy group was 5.6% (compared to 5.9% in the reteplase patients); this was the lowest mortality rate ever observed in a large clinical trial involving a fibrinolytic agent. Patients treated with the combination therapy also were 34% less likely to experience reinfarction than the patients receiving only reteplase.

One note of caution: Based on the current data, the study did not recommend the combination therapy for the elderly, as patients older than 75 years of age showed an increase in intracranial hemorrhage with the combination.

HERO-2: Bivalirudin reduces reinfarction for AMI patients getting streptokinase

Thrombospecific inhibition by the anticoagulant bivalirudin (Angiomax) may provide advantages over unfractionated heparin for acute MI (AMI) patients getting streptokinase, according to new data presented at the XXIII Congress of the European Society of Cardiology (ESC) in Stockholm, Sweden.

Harvey White, MD, of Green Lane Hospital in Auckland, New Zealand, and principal investigator of the Hirulog Early Reperfusion (HERO-2) trial, reported the results to ESC Congress delegates.

HERO-2 randomized 17,073 AMI patients to unfractionated heparin or bivalirudin, given three minutes before streptokinase administration. All patients also were receiving aspirin. In the trial, bivalirudin reduced the combined incidence of death or investigator-reported second myocardial infarction compared to heparin at 30 days by 1.3% (14.2% in patients treated with heparin vs. 12.9% in patients treated with bivalirudin).

Patients treated with bivalirudin, however, had a 30% reduction in second myocardial infarction at 96 hours compared to heparin. The reduction in second myocardial infarction also was statistically significant at 30 days, both when the second myocardial infarctions were determined by the treating clinician and when adjudicated by an independent panel of experts.

The overall incidence rate of intracranial hemorrhage was 0.5%; there was not a significant increase in the incidence in patients treated with bivalirudin compared to patients treated with heparin. Furthermore, White said, there was a not a significant increase in other severe bleeding or other blood transfusions in bivalirudin patients compared to heparin patients.

What about the bleeding?

These drug trials are moving toward finding a cardiovascular drug therapy that would have a lower overall incidence of intracranial bleeds, says **David Roffman**, PharmD, BCPS, associate professor at the University of Maryland School of Pharmacy in Baltimore. However, the jury is still out on the results.

"We are talking about huge populations of patients in multiple studies before we can really come to that conclusion," he says. "The incidence of intracranial bleeds is still less than 1%. If it turns out that this [therapy] looks to be the safest, I think this is the way people will tend to go."

The evidence, however, tends to show that primary angioplasty is less risky because it doesn't involve the intracranial hemorrhage issue. That makes the discussion about full-dose vs. half-dose thrombolytic mute, he says. ■

New rules for industry-sponsored articles

Twelve prominent medical journals have joined forces to ensure that clinical trial information published in the peer-reviewed journals has not been influenced by drug-company sponsors.

Data published in these articles are assumed to be gathered and presented in an objective and dispassionate manner, says a joint editorial to be published by all of the journals. Discourse about the data shapes treatment decisions made by physicians and drives public and private health care policy.

In the current intellectual environment, however, drug companies may use the publication of trial information in the journals to market drugs and medical devices for their companies' financial

gain, the editorial states. This is in contrast to patients who may participate in the trials to advance the standard of care. "In the light of that truth," the editorial says, "the use of clinical trials primarily for marketing, in our view, makes a mockery of clinical investigation and is a misuse of a powerful tool."

The editorial's authors denounce contractual agreements that deny investigators the right to examine the data independently or to submit a manuscript for publication without first obtaining the consent of the trial's sponsor. The journals now will routinely require authors to disclose details of their own and the sponsor's role in the study. Many of the journals will ask the responsible author to sign a statement indicating that he or she accepts full responsibility for the conduct of the trial, had access to the data, and controlled the decision to publish. The journals will not review or publish articles based on studies that are conducted under conditions that allow the sponsor to have sole control of the data or to withhold publication.

The joint editorial is signed by editors of the *Annals of Internal Medicine*, the *Journal of the American Medical Association,* the *New England Journal of Medicine*, the *Canadian Medical Association Journal*, the *Journal of the Danish Medical Association, The Lancet, MEDLINE/Index Medicus*, the *New Zealand Medical Journal*, the *Journal of the Norwegian Medical Association*, the *Dutch Journal of Medicine,* the *Medical Journal of Australia,* and the *Western Journal of Medicine*. ▼

Remicade prescribing information updated

Centocor in Malvern, PA, is updating the prescribing information for infliximab (Remicade), a drug used in the treatment of rheumatoid arthritis and Crohn's disease. Developed with the U.S. Food and Drug Administration (FDA), the revised label instructs that patients should be evaluated for latent tuberculosis with a tuberculin skin test in reference to current American Thoracic Society / Centers for Disease Control and Prevention guidelines, and that treatment for latent tuberculosis should be initiated prior to therapy with Remicade. In addition, the revised label strengthens the warnings about the risk of serious infections in general, and has drawn attention to this safety information via a boxed warning.

Many of the serious infections associated with Remicade have occurred in patients on concomitant immunosuppressive therapy that, in addition to their Crohn's disease or rheumatoid arthritis, could hinder further their infection-fighting capabilities.

The new label also addresses the risk of opportunistic infections, including histoplasmosis, listeriosis, and pneumocystis. With respect to the risk for histoplasmosis infection, the revised labeling instructs that the benefits and risks of Remicade therapy should be considered carefully for patients who have resided in a region where histoplasmosis is endemic. ▼

Lilly, Syncor to offer three-hour Xigris delivery

Eli Lilly and Co. in Indianapolis will partner with Syncor International Corp. in Woodland Hills, CA, to provide a three-hour emergency response delivery service for drotrecogin alfa (activated) (Xigris), Lilly's investigational biotechnology compound for the treatment of severe sepsis. Lilly's application to market Xigris is under priority review by the Food and Drug Administration.

"We anticipate most hospitals will stock Xigris through our wholesaler network. However, if a physician needs Xigris, and it is not readily available at the hospital pharmacy, Syncor's emergency response capabilities will ensure that physicians have rapid access," says **Elaine Sorg**, critical care business unit leader for Lilly. ▼

'Filmtab' removed from Gabitril product name

Cephalon in West Chester, PA, is notifying health care professionals that it is removing the word "Filmtab" from the Gabitril (tiagabine HCl) product name. This change is a result of the acquisition of Gabitril by Cephalon from Abbott Laboratories, because the word Filmtab is a registered trademark of Abbott Laboratories. The formulation and manufacturing process of Gabitril tablets have not changed.

The change in the Gabitril product name will be reflected in all related documents (such as prescribing information and packaging material). In addition, the appearance of Gabitril tablets has been changed to replace the Abbott logo with the Cephalon logo. To view Cephalon's "Dear Health Professional" letter, visit the web site www.fda.gov/medwatch/safety/2001/gabitril.htm. ▼

Switching seizure meds may have risks

A study published in the Aug. 28 issue of *Neurology* says that switching epilepsy medications may result in either side effects or loss of seizure control for patients.

The single-dose, two-way crossover study was conducted in 24 healthy patients to determine the effect of a high-fat meal on the pharmacokinetics of generic and brand-name formulations of phenytoin. The impact of switching products on steady-state phenytoin was investigated through simulation using pharmacokinetic data previously obtained from 30 epileptic patients.

The bioavailability (the amount of the medication's active ingredient present in the blood following a given dose) of the generic drug administered with food was 13% lower than what was observed with the brand-name drug. Simulations of substituting the generic drug for the brand-name suggest that the 13% decrease would result in a median 37% decrease in the bioavailability; in 46% of the patients, the levels of the generic drug were below the therapeutic range.

Conversely, the simulations of substituting the brand-name drug for the generic suggested a result of a median 102% increase in the bioavailability, with 84% of patients having phenytoin concentrations above the therapeutic range.

The Epilepsy Foundation in Landover, MD, says that all medical rule-making bodies should take note of this research. "The Epilepsy Foundation strongly advises that [they] address the potential adverse effects of changing from one manufacturer's version of an epilepsy medication to another by requiring the prior expressed permission of the treating physician and patient before such medication is dispensed," says **Steven Schachter**, MD, associate professor of neurology at the Harvard Medical School in Cambridge, MA. ▼

Pediatric use of Neumega should be restricted

Wyeth-Ayerst in Philadelphia is notifying health professionals of safety information for oprelvekin (Neumega) use in the pediatric population. Preliminary data from a safety and pharmacokinetic study in 47 children have identified papilledema as a dose-limiting adverse reaction in the pediatric population.

No controlled clinical studies have established a safe and effective dose of Neumega in children. Therefore, the administration of Neumega in children, particularly those younger than 12 years of age, should be restricted to controlled clinical trial settings with closely monitored safety assessments. See the full letter at this web site for further details: www.fda.gov/medwatch/safety/2001/neumega.htm. ▼

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Editorial Questions

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Drug charges rise faster than other medical care

Prescription drug charges have increased at a faster rate than all other medical services, according to the Express Scripts' *2000 Drug Trend Report*. Between 1998 and 1999, charges for prescription drugs increased from 22.9% to 25.3% of the total charges per member per year. The rate of increase in drug spending, however, slowed slightly in 2000 to 16.2%, in part because no new blockbuster drugs were introduced. In 1999, the drug spending increase was 17.4%, primarily because of the introduction of the anti-inflammatory drugs Celebrex and Vioxx.

Factors contributing to the overall prescription drug cost increase were higher prices for existing products, use of more expensive products, stronger dosages, and more units per prescription. New drugs introduced in 2000 accounted for only 0.3% of the overall 1999-2000 trend. However, drugs introduced since 1992 accounted for approximately 47 cents of each dollar spent on prescription drugs in 2000.

The analyses contained in the report are based on claims for prescription medications for a substantial sample of Express Scripts clients. Prescriptions in this database represent drug use for a monthly average of 9.6 million members in 1999 and 8.8 million members in 2000. The report is available at: www.expressscripts.com/other/news_views/outcomes2001/outcomes_conf_2001_news_info_resource.htm. ▼

FDA announces recall of collagenase

The Food and Drug Administration (FDA) recently announced the recall of one lot of collagenase manufactured by Advance Biofactures Corp. and sold as Santyl Ointment. The recalled lot bears the expiration date 11/2002. According to the FDA's Center for Biologics Evaluation and Research, this lot of collagenase has a lower potency than required by product specifications.

Earlier this year, two lots of Santyl Ointment were recalled because they exceeded potency specifications, and last August, one lot was recalled because testing showed it to be unsterile.

Santyl is distributed by Abbot Laboratories, which acquired the product as part of its Knoll Pharmaceuticals Co. acquisition earlier this year. The recall is occurring at the wholesale level. ▼

Aventis Pasteur resumes restrictions on Td toxoids

On Sept. 11, Aventis Pasteur suspended filling orders for tetanus and diphtheria (Td) toxoids in an effort to respond to emergency management officials in New York and Washington, DC.

Aventis Pasteur — now the main U.S. manufacturer of Td's — is accepting orders, but will continue to limit the distribution of Td to urgent-care facilities and hospitals nationwide.

Facilities should order in four-week supply increments to help Aventis Pasteur estimate product need. The company will ship orders from the warehouse closest to the requesting facility to minimize potential fulfillment delays. ■

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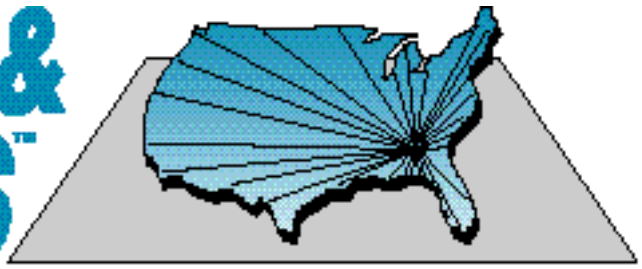

Methylphenidate: New formulations

Prepared by **Brenda Darling**, PharmD
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Introduction

Methylphenidate hydrochloride compounds (Concerta, Methylin, and Metadate ER) are central nervous system (CNS) stimulants. Approval for Concerta 18 mg and 36 mg occurred in August 2000; the 54 mg dose was approved in December 2000. The U.S. Food and Drug Administration (FDA) approved Methylin 10 mg and 20 mg extended-release tablets in May 2000 and Metadate ER 10 mg tablet and Metadate ER 20 mg in October 1999. The newest addition to the methylphenidate "formulation family" is Metadate CD and was approved by the FDA in April 2001. These agents are used for the treatment of attention deficit / hyperactivity disorder (ADHD) and narcolepsy.

Pharmacology

Methylphenidate is a mild central nervous system stimulant. The drug has similar pharmacological properties as the amphetamine CNS derivatives, with predominantly central activity and minimal effects on the cardiovascular system. Although the exact mechanism of action (MOA) is not known, methylphenidate is thought to block the reuptake of norepinephrine and dopamine into the presynaptic neuron and increase the release of these monoamines into the extraneuronal space. This MOA activates the brainstem arousal system, cortex, and subcortical structures, including the thalamus, to produce a significant stimulant effect. However, the specific mode of therapeutic action in ADHD is not known.

Pharmacokinetics

Concerta uses osmotic pressure to deliver methylphenidate HCl at a controlled rate. The system, which resembles a conventional tablet in appearance, comprises an osmotically active trilayer core surrounded by a semipermeable membrane with an immediate-release drug overcoat. The trilayer core is composed of two drug layers containing the drug and excipients, and a push layer containing osmotically active components. There is a precision-laser-drilled orifice on the drug-layer end of the tablet.

In an aqueous environment, such as the gastrointestinal tract, the drug overcoat dissolves within one hour, providing an initial dose of methylphenidate. Water permeates through the membrane into the tablet core. As the osmotically active polymer excipients expand, methylphenidate is released through the orifice. The membrane controls the rate at which water enters the tablet core, which in turn controls drug delivery. The biologically inert components of the tablet remain intact during gastrointestinal transit and are eliminated in the stool as a tablet shell along with insoluble core components.

Following oral administration of Concerta to adults, plasma methylphenidate concentrations increase rapidly, reaching an initial maximum at about 1-2 hours, then increasing gradually over the next several hours. Peak plasma concentrations are achieved at about 6-8 hours, after which a gradual decrease in plasma levels of methylphenidate begins.

No differences in the pharmacokinetics of Concerta were noted following single and repeated qd dosing, indicating no significant drug accumulation. The area under the curve (AUC) and $t_{1/2}$ following repeated qd dosing are similar to those following the first dose of Concerta 18 mg.

Methylin in the ER tablets is more slowly but as extensively absorbed as the regular tablets.

Relative bioavailability of the extended-release tablet compared to the immediate-release tablet, measured by the urinary excretion of methylphenidate major metabolite [(alpha)-phenyl-2-piperidine acetic acid] was 105% (range, 49-168%) in children and 101% (range, 85-152%) in adults. The time to peak rate in children was 4.7 hours (range, 1.3-8.2 hours) for the extended-release tablets and 1.9 hours (range, 0.3-4.4 hours) for the tablets. An average of 67% of the extended-release tablet dose was excreted in children as compared to 86% in adults.

Metadate ER in extended-release tablets is more slowly but as extensively absorbed as the regular tablets. Bioavailability of Metadate 20 mg ER tablets was compared to a sustained-release reference product and an immediate-release product. The extent of absorption for the three products was similar, and the rate of absorption of the two sustained-release products was not statistically different.

Based on rate of bioavailability ($AUC_{0 \text{ to } < \text{infinity}}$, T_{max}, and C_{max}), no significant statistical difference was found following single-dose administration, in fasting and fed adults, of two Metadate 10 mg ER tablets or one methylphenidate hydrochloride, USP sustained-release 20 mg tablet. The administration of the extended-release methylphenidate HCl, USP tablets with food resulted in a greater C_{max} and $AUC_{0 \text{ to } < \text{infinity}}$ than when administered in a fasting condition. Pharmacokinetic and statistical analyses for a multiple-dose study demonstrated that three times daily administration of two Metadate 10 mg ER tablets met the requirements for bioequivalence to one methylphenidate hydrochloride, USP sustained-release 20 mg tablet when administered every 8 hours. Pharmacokinetic parameters (i.e., $AUC_{0 \text{ to } < \text{infinity}}$, T_{max}, C_{max}, C_{min}, and C_{av}) demonstrated achievement of steady state following three times daily administration of two Metadate 10 mg ER tablets was confirmed. **(See Table 1, right.)**

Metadate CD is in the form of an extended-release Diffucap capsule containing 30% immediate-release beads and 70% extended-release beads. The dosage released from the immediate-release beads is 6 mg, and a dose of 14 mg is released from the extended-release bead formulation. Within the Diffucap bead-delivery system, one set of beads (immediate-release) consists of a neutral core upon which is layered a mixture of povidone and methylphenidate. The povidone serves as a binding agent for the active drug substance, methylphenidate. An aqueous protective coating is applied over the methylphenidate/povidone layer. The second set of beads (extended-release) contains the same neutral core and layer of povidone/methylphenidate, but it also places an ethylcellulose coating on the top to act as another aqueous protective membrane.

Absorption of this new formulation is presented as a sharp, initial slope similar to a methylphenidate immediate-release tablet, and the second rising portion occurs approximately three hours later. The early peak concentration is reached approximately 1.5 hours after dose intake, and the second peak concentration is reached 4.5 hours after dose intake. The mean terminal half-life is 6.8 hours for Metadate CD, and the terminal half-life for methylphenidate hydrochloride immediate-release tablets and sustained-release tablets is 2.9 hours and 3.4 hours, respectively.

Indications

Concerta is indicated for the treatment of attention deficit/hyperactivity disorder.

Methylin is indicated as an integral part of a total treatment program that typically includes other remedial measures (psychological, educational, and social) for a stabilizing effect in children with a behavioral syndrome characterized by the following group of developmentally inappropriate symptoms: moderate-to-severe distractibility, short attention span, hyperactivity, emotional lability, and impulsivity.

Metadate ER is indicated as an integral part of a total treatment program that typically includes other remedial measures (psychological, educational, and social) for a stabilizing effect in children with a behavioral syndrome characterized by the following group of developmentally inappropriate

Table 1

Mean ± SD Pharmacokinetic Parameters

Parameters	Concerta (18 mg qd) n = 36	Methylphenidate (5 mg tid) n = 35
C_{max} (ng/mL)	3.7 ± 1.0	4.2 ± 1.0
T_{max} (h)	6.8 ± 1.8	6.5 ±1.8
AUC_{0-t} (ng . h/mL)	41.8 ± 13.9	38.0 ± 11.0
$t_{1/2}$ (h)	3.5 ± 0.4	3.0 ± 0.5

symptoms: moderate-to-severe distractibility, short attention span, hyperactivity, emotional lability and impulsivity.

Metadate CD is indicated for the treatment of attention deficit/hyperactivity disorder.

Efficacy and comparative efficacy

Concerta qd minimizes the fluctuations between peak and trough concentrations associated with immediate-release methylphenidate tid. The relative bioavailability of Concerta qd and methylphenidate tid in adults is comparable.

Methylin in ER tablets is more slowly but as extensively absorbed as the regular tablets. Relative bioavailability of the extended-release tablet compared to the immediate-release tablet, measured by the urinary excretion of methylphenidate major metabolite [(alpha)-phenyl-2-piperidine acetic acid] was 105% (range, 49-168%) in children and 101% (range, 85-152%) in adults. The time to peak rate in children was 4.7 hours (range, 1.3-8.2 hours) for the extended-release tablets and 1.9 hours (range, 0.3-4.4 hours) for the tablets. An average of 67% of extended-release tablet dose was excreted in children as compared to 86% in adults.

Metadate ER in extended-release tablets is more slowly but as extensively absorbed as the regular tablets. Bioavailability of Metadate 20 mg ER tablets was compared to a sustained-release reference product and an immediate-release product. The extent of absorption for the three products was similar, and the rate of absorption of the two sustained-release products was not statistically different. Based on rate of bioavailability ($AUC_{0\ to\ <\ infinity}$, T_{max}, and C_{max}), no significant statistical difference was found following single-dose administration, in fasting and fed adults, of two Metadate 10 mg ER tablets, or one methylphenidate hydrochloride, USP sustained-release 20 mg tablet.
The administration of the extended-release methylphenidate HCl, USP tablets with food, resulted in a greater C_{max} and $AUC_{0\ to\ <\ infinity}$ than when administered in a fasting condition.
Pharmacokinetic and statistical analyses for a multiple-dose study demonstrated that three times daily administration of two Metadate 10 mg ER tablets met the requirements for bioequivalence to one methylphenidate hydrochloride, USP sustained-release 20 mg tablet when administered every 8 hours.
Pharmacokinetic parameters (i.e., $AUC_{0\ to\ <\ infinity}$, T_{max}, C_{max}, C_{min}, and C_{av}) demonstrated achievement of steady state following three times daily administration of two Metadate 10 mg ER tablets was confirmed.

Safety and adverse effects

In the four-week, placebo-controlled, parallel-group trial one **Concerta**-treated patient (0.9%; 1/106) and one placebo-treated patient (1.0%; 1/99) discontinued due to an adverse event (sadness and increase in tics, respectively). In uncontrolled Concerta studies lasting as long as 12 months, 6.6% (29/441) of patients discontinued for adverse events. Those events associated with discontinuation of Concerta in more than one patient included the following: twitching (tics, 1.8%); anorexia (loss of appetite, 0.9%); aggravation reaction (0.7%); hostility (0.7%); insomnia (0.7%); and somnolence (0.5%). Overall, headache occurred approximately in 14% of subjects; upper respiratory tract infection, stomachache, anorexia, insomnia, pharyngitis, increased cough, and dizziness occurred in 8-20% of subjects.

Nervousness and insomnia are the most common adverse reactions with **Methylin** and **Metadate ER** but usually are controlled by reducing the dosage and omitting the drug in the afternoon or evening. Other reactions include hypersensitivity (including skin rash, urticaria, fever, arthralgia, exfoliative dermatitis, erythema multiforme with histopathological findings of necrotizing vasculitis, and thrombocytopenic purpura); anorexia; nausea; dizziness; palpitations; headache; dyskinesia; drowsiness; blood pressure and pulse changes (both up and down); tachycardia; angina; cardiac arrhythmia; abdominal pain; and weight loss during prolonged therapy. In children, loss of appetite, abdominal pain, weight loss during prolonged therapy, insomnia, and tachycardia may occur more frequently.

Metadate ER should not be prescribed for women of childbearing age unless, in the opinion of the physician, the potential benefits outweigh the possible risks.

The safety and efficacy of Concerta, Methylin, and Metadate ER in children younger than 6 years have not been established. Long-term effects of methylphenidate in children have not been well established.

Drug interactions

Concerta should be used cautiously with pressor agents. Human pharmacologic studies have shown that methylphenidate may inhibit the metabolism of coumarin anticoagulants,

anticonvulsants (e.g., phenobarbital, phenytoin, primidone), and some antidepressants (tricyclics and selective serotonin reuptake inhibitors). Downward dose adjustment of these drugs may be required when given concomitantly with methylphenidate. It may be necessary to adjust the dosage and monitor plasma drug concentrations (or, in the case of coumarin, coagulation times) when initiating or discontinuing concomitant methylphenidate. Serious adverse events have been reported with concomitant use of clonidine, although no causality for the combination has been established. The safety of using methylphenidate in combination with clonidine or other centrally acting alpha-2 agonists has not been evaluated systematically.

Methylin and **Metadate ER** may decrease the hypotensive effect of guanethidine. Use cautiously with pressor agents and MAO inhibitors.

As with Concerta, Methylin and Metadate ER may demonstrate the same drug interactions listed above and caution should be taken to avoid serious adverse events.

Dosing and administration

Concerta is administered orally once daily in the morning with or without food. Concerta must be swallowed whole with the aid of liquids, and must not be chewed, divided, or crushed. The recommended starting dose of Concerta for patients who are not currently taking methylphenidate, or for patients who are on stimulants other than methylphenidate is 18 mg once daily.

Dosage may be adjusted in 18 mg increments to a maximum of 54 mg/d taken once daily in the morning. In general, dosage adjustment may proceed at approximately weekly intervals. **(See Table 2, right.)**

Methylin ER and **Metadate ER**:

Adults: Methylin ER and Metadate ER tablets have a duration of action of approximately 8 hours. Administer in divided doses 2-3 times daily, preferably 30-45 minutes before meals. Average dosage is 20-30 mg daily. Some patients may require 40-60 mg daily. In others, 10-15 mg daily will be adequate. Methylin ER and Metadate ER tablets must be swallowed whole and never crushed or chewed. In patients that have trouble sleeping, the last dose of Methylin or Metadate ER should be administered before 6 p.m.

Children (6 years and older): Methylin or Metadate ER should be initiated in small doses, with gradual weekly increments. Daily dosage above 60 mg is not recommended. ■

Table 2

Recommended Dose Conversion From Methylphenidate Regimens to Concerta

Previous Methylphenidate Daily Dose	Recommended Concerta Dose
5 mg Methylphenidate bid or 5 mg Methylphenidate tid or 20 mg Methylphenidate SR	18 mg q a.m.
10 mg Methylphenidate bid or 10 mg Methylphenidate tid or 40 mg Methylphenidate SR	36 mg q a.m.
15 mg Methylphenidate bid or 15 mg Methylphenidate tid or 60 mg Methylphenidate SR	54 mg q a.m.

Warfarin management: Pearls from a recent MUE

By **Steve McDonald**, PharmD,
Huntsville (AL) Hospital

Fifty patients on warfarin therapy for at least six days of duration were enrolled in a warfarin medication use evaluation (MUE), including patients managed by physicians or the pharmacokinetic service (PKS). Patients were distributed equally with regard to "new" and "chronic" warfarin patients.

The MUE criteria evaluated included warfarin dosage adjustment, drug-drug interaction, disease-state interaction, appropriate PT/INR (prothrombin/international normalized ratio) monitoring and vitamin K usage for reversal of anticoagulation effect. Results were evaluated for opportunities for improvement and differences in the performance of physicians and pharmacists with warfarin management. The following areas were

considered for improvement: initial geriatric dose of warfarin, "hold orders" not carried out correctly and "hold orders" that fell below the desired INR range while on warfarin therapy, use of vitamin K per standard guidelines, use of interacting medications, over-monitoring, and documentation of warfarin education. Performance of both pharmacists and physicians was compared, and opportunities for potential improvement were identified.

• **Disease-related factors.**

Fifty-eight percent of warfarin patients had disease-related factors that could affect warfarin response (such as hypothyroidism, diarrhea, and others).

• **Drug interactions.**

All 50 patients received other drugs that could potentially interact with warfarin in a significant manner. Patients averaged 2.1 potential drug interactions with warfarin. Alternative drugs could have been used to avoid a drug interaction in 25% of cases. Frequently used drugs with a high risk of interaction with warfarin include SMX-TMP, amiodarone, and SSRIs.

• **Clear order writing.**

Orders can be confusing when holding, starting, or re-starting warfarin. Orders should specify clearly the amount to be given the first day (such as warfarin 5 mg this a.m. and 5 mg q p.m. starting tonight). A few extra seconds to write a legible and easily comprehensible order may prevent a medication error.

• **Geriatrics.**

"Start lower and go slower." Geriatric patients often are more sensitive to warfarin than younger patients and often require lower doses. Starting doses generally should be 5 mg or less in geriatric patients; maintenance doses often are less than 5 mg daily. This review indicates that when higher doses are used initially, the INR often becomes supratherapeutic and the dose must be held or decreased. This prolongs the time to reach the desired therapeutic range and could prolong hospitalization.

• **Hold orders.**

Hold orders often are caused by overshooting the goal INR with higher doses, especially in the elderly. In most physician cases, the INR fell below the therapeutic range when holding the dose; the INR often fell below 1.5 (average time of low INR with hold orders was 2.6 days / patient). The risk of thrombotic events increases significantly with INRs below 1.5. Restarting the warfarin dose sooner, albeit at a lower dose, will help minimize or eliminate the subtherapeutic time.

• **Over-monitoring.**

Cases of over-monitoring were observed in this review; daily monitoring continued after the patient's dosage had been stabilized. Unnecessary monitoring adds additional work, time, and expense to patient management.

• **Vitamin K administration.**

Higher doses than recommended by the current literature guidelines were administered in two cases (i.e., 20-25 mg SQ). Subsequently, once the warfarin was resumed, these two patients both exhibited a prolonged period of resistance with subtherapeutic INR values for 8 and 13 days. These high vitamin K doses caused prolonged warfarin resistance and likely contributed to extended hospitalization. National guidelines now recommend lower vitamin K doses if the patient is not bleeding (i.e., 1-5 mg orally in many cases). Overuse of vitamin K will cause warfarin resistance, extended subtherapeutic times, and possibly prolonged hospitalization.

• **Education.**

Fewer than 50% of physicians' new warfarin patients had warfarin education documented in the chart. Education is important for good patient compliance and self-management at home. Warfarin education by a pharmacist in the hospital is not automatic, and a specific physician order for warfarin education is necessary. Remember to include patient teaching well in advance of discharge.

• **Adverse reactions.**

One warfarin-related adverse drug reaction was observed in the 50 patients. Bleeding occurred in a patient with heparin-induced thrombocytopenia (platelet count dropped to 70,000) who was receiving both danaparoid and warfarin.

• **Atrial fibrillation.**

A separate survey showed that 35% of atrial fibrillation patients at Huntsville Hospital were receiving warfarin. Many patients had justifiable reasons for not receiving warfarin, such as recent history of GI bleed, poor prognosis, high fall risk, or psychological / situational issues. However, approximately 20% of patients were not receiving warfarin and potentially could have. Studies have demonstrated a significant stroke risk reduction in atrial fibrillation patients, but appropriate patient selection is critical.

Summarizing the results of physician-pharmacist comparative data for "new" warfarin patients, physicians ordered higher initial doses (especially in geriatric patients), achieved the goal INR value

more rapidly, had more supratherapeutic INR values and more resulting hold orders, and documented less patient warfarin education. For "chronic" warfarin patients, physicians ordered less INR monitoring, had more subtherapeutic days related to hold orders, had fewer overall percent therapeutic INR days, and documented less patient warfarin education.

Pearls for warfarin management

In conclusion, here are some "pearls" gathered from the warfarin MUE.

• **Disease factors.**

Be aware of situations that can affect warfarin response and make adjustments as needed.

• **Drug interactions.**

Potential interactions are common in warfarin patients. Maintain awareness, avoid interacting drugs when possible, and make adjustments as needed.

• **Order writing.**

Take a few extra seconds to write clearly understandable orders — it may prevent a medication error.

• **Geriatrics.**

Geriatric patients generally require lower doses, often 5 mg or less daily. The elderly are at risk for "over-shooting" the goal INR.

• **Hold orders.**

Hold orders often are due to supratherapeutic INR. Try to avoid falling to a subtherapeutic INR by restarting warfarin at a lower dose as the INR approaches goal range.

• **Over-monitoring.**

Once the INR has been stabilized, daily INR monitoring is not necessary.

• **Vitamin K.**

New guidelines recommend much lower doses for supratherapeutic INR if the patient is not bleeding.

• **Education.**

Pharmacist warfarin education should be specifically ordered well in advance of the planned day of discharge.

• **Adverse reactions.**

Bleeding is more likely to occur in risk patients (on other antiplatelet / anticoagulation drugs, thrombocytopenia, history of bleed, etc.).

• **Atrial fibrillation.**

Warfarin demonstrates significant stroke risk reduction in atrial fibrillation patients; patient selection is critical. ■

Results of the second Warfarin-Aspirin Re-Infarction Study (WARIS II) suggest that the combination of warfarin and aspirin is superior to either agent alone in reducing death and recurrent events after MI.

WARIS II was a long-term secondary prevention study. The results of the 20 Norwegian hospitals participating in the trial were presented at the XXIII Congress of the European Society of Cardiology in Stockholm, Sweden, by Principal Investigator **Harald Arnesen**, MD, PhD, of Ullevaal University Hospital in Oslo, Norway.

The trial aimed to investigate whether there was a benefit in addressing both the activated platelets and fibrin that make up coronary thrombus in patients who had already had an MI, Arnesen said. "In the WARIS II trial, the combined treatment of warfarin with a mean INR of 2.2, together with aspirin in a dose of 75 mg a day, was significantly more efficient in reducing the combined endpoint of death, nonfatal MI and stroke than aspirin alone," Arnesen concluded. Warfarin also was more effective than aspirin but to a lesser degree than the combination.

Arnesen indicated that he believed these findings — along with the rationale of what is known about how coronary thrombus is constituted of platelets and fibrin — are sufficient to change practice in this large population of patients. He pointed out that the level of anticoagulation in this study was 2.0-2.5, the same as is now recommended for warfarin treatment as stroke prophylaxis in patients with atrial fibrillation.

Cost also will be an important factor, Arnesen said. In this study, INRs were managed on an outpatient basis according to the standard practice of the hospitals involved. But that may be changing, too. "The tradition of anticoagulation may be changed because today, it's more and more common that patients monitor their own INR, as the diabetics do with their blood sugar. It shouldn't be too dramatic to make that change."

Physicians, however, might not be so quick to change their practice because of this trial, preferring instead to continue using long-term clopidogrel. ■

In the Pipeline

• Novartis has submitted an application to the Food and Drug Administration (FDA), seeking marketing authorization for zoledronic acid for injection (Zometa) in the treatment of **bone metastases associated with a broad range of tumor types**. These include prostate and lung cancer, for which no bisphosphonate therapy currently is approved, as well as breast cancer and multiple myeloma. Zometa is a new generation intravenous

bisphosphonate that received FDA approval on Aug. 20 for the treatment of hypercalcemia of malignancy (HCM). Novartis has received marketing clearances for Zometa in the treatment of HCM in more than 30 countries.

• Repligen Corp. announced that the FDA has granted fast-track designation for secretin for the treatment of **pediatric autism**. In April, Repligen completed a Phase II clinical trial that evaluated three doses of secretin or a placebo in 126 children, 3-6 years of age, with moderate-to-severe symptoms of autism and reported gastrointestinal symptoms.

• NeoTherapeutics has added four additional clinical trial locations to its Neotrofin Phase II **Parkinson's disease** trial. New participants include Memorial Hospital of Rhode Island (Providence), Rush Presbyterian-St. Luke's Medical Center (Chicago), The Parkinson's Institute (Sunnyvale, CA), and Oregon Health & Science University (Portland). Ten patients currently are receiving either Neotrofin or placebo, including seven patients at the Parkinson's and Movement Disorder Institute at Long Beach (CA) Memorial Hospital. Patients in this trial will receive doses of Neotrofin escalating from 250 mg to 1,000 mg twice per day for 12 weeks.

• AstraZeneca has initiated a clinical trial to examine the ability of the beta-blocker metoprolol succinate (TOPROL-XL) extended-release tablets to reverse the cardiac remodeling associated with **left ventricular (LV) systolic dysfunction**. REVERT (Reversal of Ventricular Remodeling with TOPROL-XL) will involve some 300 patients diagnosed with asymptomatic heart failure (NYHA Class I) who have a reduced ejection fraction of less than 40%. The study will be conducted at 45 centers across the United States. TOPROL-XL recently was approved by the FDA for the treatment of stable, symptomatic (NYHA Class II or III) heart failure of ischemic, hypertensive or cardiomyopathic etiology.

• OraPharma has started a Phase I clinical trial of OC-1012 for the prevention of **mucositis**, following the FDA's recent clearance of the Investigational New Drug (IND) application for this agent. In the double-blind, placebo-controlled trial, OC-1012 will be administered to patients undergoing bone marrow transplants at the University of Washington, Fred Hutchinson Cancer Research Center.

• Ribozyme Pharmaceuticals Inc. (RPI) has started a new Phase I clinical trial relating to the safety and pharmacokinetics of its compound HERZYME, an anti-Human Epidermal growth factor Receptor type 2 (HER2) ribozyme being developed through RPI's collaboration with Elan Corp. (Medizyme Pharmaceuticals Ltd.). Elan and RPI plan to develop HERZYME for treatment of **breast and ovarian cancer** in conjunction with Elan's proprietary MEDIPAD Drug Delivery system.

• Adolor Corp. has dosed the first group of normal volunteers in a Phase I clinical trial of ADL 10-0116, an orally available peripherally restricted kappa opioid receptor agonist designed to relieve **inflammatory pain** associated with acute and chronic inflammatory diseases, such as rheumatoid arthritis. This Phase I study will assess the compound's safety. ADL 10-0116 is the second in a series of kappa agonists that Adolor is evaluating in clinical trials.

• Keryx Biopharmaceuticals announced that the FDA has designated its compound, sulodexide (KRX- 101) for the treatment of **diabetic nephropathy**, as a fast-track product. The company is discussing with the FDA preparations to initiate a Phase III study.

• Cubist Pharmaceuticals has completed patient enrollment in the first of two Phase III trials investigating the safety and efficacy of daptomycin for injection (Cidecin) in the treatment of **community-acquired pneumonia** requiring hospitalization. This first study (CAP1), which is an international, randomized, prospective, double-blind study, has 729 enrolled patients.

• Immunex Corp. and Wyeth-Ayerst Laboratories will sponsor a 10,000-patient **rheumatoid arthritis** study. The Rheumatoid Arthritis DMARD Intervention and Utilization Study (RADIUS) is designed to gain more comprehensive knowledge regarding current treatment for the disease.

• RxKinetix has initiated a Phase IB trial with its first lead drug candidate, RK-0202, in treatment of **oral mucositis**. The study, which is being conducted under its collaboration with Elan Corp., will enroll a small number of patients at two major U.S. transplant centers and is designed to assess the safety and tolerability of the compound and finalize the formulation.

• MedImmune has begun dosing **rheumatoid arthritis** patients with the antibody Vitaxin in a Phase I clinical trial. The randomized, double-blind, placebo-controlled, dose-escalation trial will be conducted at eight U.S. and Canadian sites.

• Pharmacyclics has completed patient enrollment in a Phase II clinical trial to evaluate its lead investigational product, motexafin gadolinium

(Xcytrin) for the potential treatment of **glioblasoma mulltiforme** (GBM). Twenty-four newly diagnosed GBM patients were enrolled at eight leading medical centers in this single-arm study designed to evaluate the safety and pharmacokinetics of a six-week treatment course of Xcytrin combined with a standard six-week course of radiation therapy.

• Neurobiological Technologies announced that Forest Laboratories is conducting a second large-scale, multicenter, double-blind, placebo-controlled trial to assess the safety and efficacy of Memantine in the treatment of **diabetic neuropathy**.

• Tanox has opened enrollment in a Phase I clinical trial of a monoclonal antibody TNX-355 (formerly known as Hu5A8) being developed for a new approach to the treatment of **HIV**. The dose-escalation study will evaluate the safety and tolerability of single intravenous infusions of TNX-355 in patients infected with HIV who have failed two courses of a highly active antiretroviral therapy (HAART). ■

New FDA Approvals

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

• *Capecitabine (Xeloda) by Roche in combination with docetaxel (Taxotere) by Aventis.* The FDA has approved a combination of the cancer drugs Xeloda and Taxotere for treating patients with **metastatic breast cancer** whose cancer has progressed after treatment with an anthracycline-containing cancer therapy (such as Adriamycin and doxorubicin). Xeloda, an oral cancer therapy initially was approved for breast cancer on April 30, 1998. Taxotere, an intravenous product, was approved for treating advanced breast cancer on May 15, l998.

• *Verteporfin for injection (Visudyne) by Novartis Ophthalmics and QLT.* The FDA has approved Visudyne therapy for the treatment of predominantly classic **subfoveal choroidal neovascularization** (CNV) due to pathologic myopia (severe nearsightedness) and presumed ocular histoplasmosis. Visudyne is the only drug treatment approved for these eye conditions. Visudyne was approved in April 2000 in the United States and since has been launched in almost 50 countries for the treatment of predominantly classic CNV caused by age-related macular degeneration.

• *Nesiritide (Natrecor) by Scios.* Natrecor has been approved by the FDA for the intravenous treatment of patients with **acutely decompensated congestive heart failure** who have shortness of breath at rest or with minimal activity. Natrecor is a recombinant form of human B-type natriuretic peptide (hBNP), a naturally occurring hormone secreted by the ventricles. It is the first of this drug class to be made available as a therapeutic for human disease in the United States. Scios anticipates launching the drug in U.S. hospitals by the end of August.

• *Acetaminophen and tramadol HCl (Ultracet) by Ortho-McNeil Pharmaceutica.* Ultracet (37.5 mg tramadol hydrochloride / 325 mg acetaminophen tablets) has been approved by the FDA for the short-term (five days or less) management of **acute pain**. This medication is a centrally acting analgesic that controls pain through different mechanisms of action than nonsteroidal anti-inflammatory drugs (NSAIDs), the most commonly used pain medications. As a result, Ultracet is not associated with the side effects that can result from NSAID use, such as gastrointestinal ulcers or bleeding.

• *Granisetron Solution (Kytril) by Hoffmann-La Roche.* Kytril been approved for the prevention of **nausea and vomiting** associated with initial and repeat courses of cancer therapy, including high-dose cisplatin, and nausea and vomiting associated with radiation, including total body irradiation and fractionated abdominal radiation. Kytril is currently available in both tablet and injection formulations. ■