NEW DRUGS

Combined Hypertension/Cholesterol Tablet Available

Pfizer’s Caduet® (amlodipine besylate, Norvasc®; atorvastatin calcium, Lipitor®) is the first prescription tablet that combines two medications to treat hypertension or angina as well as high cholesterol levels. Approved in early 2004, Caduet® is now available. It should be used along with diet and exercise.

Overall, 55% percent of people with high blood pressure also have hypercholesterolemia, and 43% with high cholesterol levels have hypertension.

(Source: American College of Cardiology, March 7, 2004; American Heart Association; Centers for Disease Control and Prevention; Pfizer, June 23, 2004.)

Oral Rifaximin Tablets for Travelers’ Diarrhea

The Food and Drug Administration (FDA) has approved the antibiotic rifaximin (Xifaxan™, Salix) 200 mg to treat travelers’ diarrhea in patients 12 years of age and older. In clinical trials, the drug helped to shorten the duration of diarrhea for the most common cause of this disease, namely, noninvasive strains of Escherichia coli.

Rifaximin should not be used for diarrhea that is complicated by fever or blood in the stool or for diarrhea caused by pathogens other than E. coli. It should be discontinued if diarrhea symptoms worsen or last more than 24 to 48 hours.

The product is expected to be available in August 2004.


Generic Cipro Approved

Israeli drugmaker Teva Pharmaceutical Industries has received approval from the FDA to market ciprofloxacin tablets in strengths of 250, 500, and 750 mg. This is the generic equivalent of Bayer’s antibiotic Cipro® Tablets.

(Author: Teva, June 10, 2004.)

Azacitidine Fights Bone Marrow Illness

The Pharmion Corporation has announced the approval of azacitidine for injectable suspension (Vidaza™) to treat a cancer-like, bone-marrow illness that sometimes progresses to leukemia.

Vidaza™ is used to treat myelodysplastic syndromes, a collection of disorders in which the bone marrow does not make enough normal blood cells. Pharmion will have as much as a seven-year monopoly on treating the disease because Vidaza™, which has been granted orphan-drug status by the FDA, combats a relatively rare condition.


NEW INDICATION
Paricalcitol Injection for Parathyroid Problems in Children

The FDA has approved paricalcitol injection (Zemplar®, Abbott Labs) for children and adolescents with secondary hyperparathyroidism who are undergoing hemodialysis. Zemplar® was initially introduced in 1998.

Because patients with kidney failure do not produce the active form of vitamin D, they have vitamin D deficiency and secondary hypoparathyroidism, in which the parathyroid glands produce excess amounts of parathyroid hormone (PTH).

Approximately 1,400 American children between ages 5 and 19 undergo hemodialysis.

Secondary hyperparathyroidism can lead to weak and brittle bones, anemia, and cardiac and neurological problems. Because bones and other organs are still developing in children, and because children are typically patients for longer periods of time, the disease can be more difficult to treat than in adults. Left untreated, secondary hyperparathyroidism can be a factor in growth retardation.

Zemplar® was tested in a 12-week randomized, double-blind, placebo-controlled study of 29 pediatric hemodialysis patients with chronic renal failure. Nearly all patients had received a form of vitamin D therapy before the study. Sixty percent of the Zemplar® patients showed two consecutive 30% decreases in PTH levels; only 21% of the placebo patients did. Fewer Zemplar® patients (23%) than placebo patients (31%) experienced elevated serum calcium levels.

The overall percentage of serum calcium measurements (defined as 10.3 mg/dl or greater) was 7% in the Zemplar® group and 7% in the placebo group. Hypercalcemia did not occur in either group during the study.


DRUG NEWS

Letrozole May Reduce Cancer Recurrence

Researchers have noted a 40% reduction in the rate of cancer recurrence in other parts of the body in postmenopausal women with breast cancer who took letrozole (Femara®, Novartis) after standard therapy. These findings were presented at the American Society of Clinical Oncology meeting in New Orleans, June 3–8, 2004.

Femara®, an aromatase inhibitor, has already been approved as a first-line treatment of metastatic breast cancer in postmenopausal women.

In a study of 5,200 women at Princess Margaret Hospital in Toronto, the drug boosted the survival rate after 2.5 years in women whose cancer had already spread to their lymph nodes at the time of diagnosis. Before being enrolled in

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the study, the women had undergone surgery and had taken the drug tamoxifen for five years. At that point, patients usually discontinue medication; in this study, however, the women received either Femara® or a placebo.

Approximately 30% of women with breast cancer experience a recurrence after five years. The trial, sponsored by Novartis, suggests that Femara® might be the first hormonal therapy to demonstrate a survival advantage in the extended period following standard therapy with tamoxifen. (It is not considered safe to continue taking tamoxifen for more than five years.)

A cautionary note: almost 7% of women who received Femara® were more likely to develop osteoporosis, compared with a rate of 5.5% for patients taking placebo. (Source: The Wall Street Journal, June 9, 2004.)

Simvastatin for MS

Statins, customarily used to lower cholesterol levels, may have another newly discovered benefit. A multicenter study suggests that their newly identified immunomodulatory effects might be the key in treating relapsing–remitting multiple sclerosis (MS).

Researchers enrolled 30 patients who had not taken interferon or glatiramer in the previous three months or corticosteroids within the previous 30 days. They monitored the patients for three months and assessed magnetic resonance images of the brain each month. If the scans picked up at least one gadolinium-enhancing lesion during that phase, oral simvastatin 80 mg/day was prescribed for six months. The brain scans were repeated at the fourth, fifth, and sixth months of treatment.

Simvastatin reduced the number and volume of gadolinium-enhancing lesions by 44% and 41%, respectively. Mean total cholesterol values dropped from 5.0 mmol/liter at baseline to 3.5 mmol/liter at the sixth month. Low-density cholesterol (LDL) values declined from 3.1 to 1.8 mmol/liter.

(Source: Lancet 2004;363:1607–1608.)

New Help for Hep C

When interferon-based treatment does not appear to be working in patients with hepatitis C virus (HCV) infection, a new once-daily, antiviral oral treatment might be the answer. NM283 (Idenix Pharmaceuticals), which passed its first human clinical trial with flying colors, metabolizes to a form that inhibits HCV RNA polymerase.

In a multicenter trial, 82 patients completed treatment; 68 patients received NM283 and 14 received placebo. All of the patients had chronic HCV infection (genotype 1 strain) and either had not received previous treatment or had not responded to interferon-based therapy.

The groups receiving antiviral therapy were divided into cohorts of 12 patients each. In each group, two received placebo and 10 received the drug at 50, 100, 200, 400, or 800 mg once daily, and one group received 200 mg twice a day.

Tolerance of higher daily doses was studied in two more cohorts: one patient initially received NM283 at 100 mg/day, advancing progressively to 800 mg/day for the second week of the clinical trial. The second cohort initially received NM283 at 400 mg/day, advancing progressively to 800 mg/day for the second week of the clinical trial. Antiemetic treatment was given together with NM283 at 400 mg/day for the first two days and for one day in conjunction with each of the two dose escalations.

NM283 consistently reduced serum HCV RNA in a dose-related manner. Patients who had the highest cumulative dose over 15 days experienced the greatest antiviral effect, with a mean HCV RNA reduction of 92%. In this dosing group, HCV RNA decreased in all 10 patients, by 79% to 99%. Nine of the 10 patients had not responded to earlier interferon-based therapies.

For the three highest-dose groups in the clinical trial, antiviral responses over the 15 days of treatment exceeded the average reduction in serum viral level observed in hepatitis C patients who respond to treatment with the current standard of therapy, ribavirin plus pegylated interferon.

At the higher doses, some patients had mild-to-moderate gastrointestinal side effects, but these usually appeared in the first two days of treatment and typically resolved quickly. None of the patients changed or stopped treatment because of side effects.

NM283 was well absorbed during treatment. There was no significant drug accumulation; drug levels on the 15th day were comparable to those of the first day.

The once-daily 800-mg cohort is ongoing. The next clinical trial will evaluate NM283 combined with pegylated interferon over four weeks. Longer-term trials of NM283 are expected later this year. (Source: Idenix, May 18, 2004, PR Newswire.)

Do Statins Prevent Colon Cancer?

At the conference of the American Society of Clinical Oncology in June 2004, researchers revealed that people who took statins for at least five years appeared to cut their risk of colon cancer by 50%.

Earlier work with statins had shown reductions in breast and prostate cancer as well as general cancer risk. However, the evidence is still too weak to recommend that everyone take statins for cancer prevention alone. A carefully controlled experiment that would be designed specifically to show a reduced
risk is needed. So far, the data pertain largely to patients who take statins for reasons other than cancer.

A team from the University of Michigan, working in Israel, studied more than 1,608 patients with colorectal cancer and 1,734 matched patients without colon cancer and noted a 50% reduced risk of this malignancy in the statin patients. However, this was an observational study of patients’ prescription records.

Most of the participants took either pravastatin (Pravachol®, Bristol-Myers Squibb) or simvastatin (Zocor®, Merck). Adjusting for other factors (e.g., health habits) did not change the strong link between statins and a lowered risk. Patients taking other types of cholesterol drugs had no cancer protection.

Some experts suggest that statins can reduce inflammation or block the functions of some cancer-causing genes. Physicians are concerned that exposing people to statins, when there is no definitive proof of their immediate worth with cancer, might lead to possible side effects, such as muscle pain, liver problems, and blood clots.


**Antidepressant Not Available**

Sales of the antidepressant nefazodone (Serzone®) were scheduled to cease as of June 14, 2004, according to Bristol-Myers Squibb, the drug’s manufacturer. Generic sales of versions of the drug will continue. However, the watchdog group Public Citizen is suing the FDA to ask that all versions of the drug be taken off the market.

Serzone® and its generic equivalents appear to unpredictably cause serious, sometimes fatal, liver damage in some patients. The product must carry a “black box” warning on its label mentioning the potential for life-threatening liver damage. Short of an outright ban, this is the FDA’s strongest message on the drug’s health risks to consumers.

The FDA has received reports of at least 55 cases of liver failure, including 20 deaths. Serzone® has been available since 1994.

(Sources: Associated Press, May 21, 2004; WebMD Medical News, May 20, 2004.)

**Aspirin and Breast Cancer Risk**

Aspirin, often used to help prevent heart attacks and strokes, also appears to reduce the risk of the most common type of breast cancer—that is, tumors whose growth was fueled by estrogen or progesterone. Approximately 70% of women with breast cancer have the hormone receptor–positive type.

The women who used aspirin at least four times a week for at least three months were almost 30% less likely to develop hormone-related breast cancer than women who used no aspirin. Aspirin had no effect on the risk for hormone receptor–negative tumors.

Researchers believe that aspirin works by interfering with the body’s production of estrogen.

Many studies have relied on subjects’ recollections of how often they took aspirin. A more rigorous study has linked the use of low-dose aspirin and a reduced risk of growths that can eventually turn into colon cancer. That study involved randomly assigning patients to take aspirin or placebos, the gold-standard method.

For now, it is not recommended that all women take aspirin, because it can cause side effects such as stomach bleeding. Although the findings are exciting, more research is needed before doctors recommend aspirin to prevent breast cancer.


**COX-2 Drugs and GI Bleeding**

In Canada, when the Ontario government began paying for a new generation of supposedly safer arthritis drugs, the number of hospital admissions for stomach bleeding rose.

The unexpected finding runs counter to expectations that these widely prescribed drugs, called cyclooxygenase (COX-2) inhibitors, would relieve pain and inflammation with little risk of stomach upset and irritation. This analysis, however, is based on a retrospective look at health data for elderly people rather than on a more rigorous trial.

The COX-2 inhibitors, part of a class of drugs known as NSAIDs, have become blockbusters. For many doctors, managing the risk of stomach bleeding seemed worth the price, as that is a major drawback of the older NSAIDs, such as ibuprofen and aspirin, which sell for pennies a day.

The authors of the Canadian report could not trace each bleeding case to the use of a specific NSAID. Nevertheless, the report suggested that the increased use of COX-2 inhibitors and gastrointestinal (GI) bleeding are directly related.

Researchers believe that the use of COX-2 inhibitors, including rofecoxib (Vioxx®, Merck), celecoxib (Celebrex® (Pfizer), and meloxicam (Mobic®, Boehringer Ingelheim), has resulted in more stomach bleeding because more patients have been encouraged to use the newer drugs. In fact, a group of 90,000 people who had not been taking any NSAIDs started taking COX-2 drugs after the Ontario government began paying for them. Afterward, hospital admissions for GI bleeding increased by 10% out of a pool of 1.3 million elderly patients in Ontario.

Other factors, such as the increased use of over-the-counter NSAIDs, might explain the study results.
(For more on this topic, see the cover story on page 454 of this issue of P&T.)


Cancer Rates Fall in Adults

The incidence of lung cancer has begun to drop for the first time ever in American women after decades of smoking-fueled increases, and overall survival rates are improving for most types of tumors among both men and women. However, minorities still are more likely than whites to die from cancer. Much of the disparity reflects minorities’ lack of access to cancer prevention and early detection services.

A study, co-sponsored by the National Cancer Institute and the American Cancer Society, also found that survival rates for other types of cancers (i.e., colon and kidney) are improving for both men and women. The latest annual overview covered the period from 1975 to 2001; however, from 1992 to 2001, the decline in death rates was more dramatic in men than in women.

Overall, death rates from cancer in general have dropped by 1.1% a year since 1993, and that decline continued in 2001. Rates of new cases are also declining about 0.50 percent per year.

(Sources: Cancer, June 3, 2004; The Wall Street Journal/Associated Press, June 3, 2004; www.lifeclinic.com.)

Fighting Cancer with Placebos?

Sure to be controversial is a plan to give promising new cancer drugs to some patients in clinical trials and to give placebos to other patients.

Some cancer researchers strongly oppose the use of placebos. Placebo trials have not generally been used in life-threatening diseases such as cancer, because it has been considered unethical to give placebos when any kind of effective therapy might be available. However, some companies, including Bayer, Pfizer, and Genentech, are adding placebo arms to their trials in an effort to speed promising new drugs to market. Because placebo trials make it easier to verify results, the strategy can reduce the need for additional studies and lead to faster regulatory approval.

Many in the cancer community maintain that this approach denies desperately ill people a last best hope. The M.D. Anderson Cancer Center in Houston and the University of Michigan Cancer Center in Ann Arbor have refused to put patients in clinical trials that use placebos. Patient-advocacy groups have urged companies to change their minds about running trials with placebo arms.

It has become difficult to get patients to participate in cancer-drug studies in the first place. One reason is that patients fear getting a placebo; patients receiving placebos have died sooner than those receiving drug therapy.

Some pharmaceutical companies say that the very nature of these new cancer drugs makes it imperative to have a placebo arm for comparison. Unlike traditional chemotherapy, which is designed to shrink or eradicate tumors, many of these drugs aim to stop or slow tumors’ growth and allow some patients to live with their cancer. This makes it difficult to measure whether it is the drug that is working or whether the tumor is simply less aggressive.

(Source: The Wall Street Journal, June 8, 2004.)

NEW MEDICAL DEVICES

By Marvin M. Goldenberg, PhD, RPh, MS

Name: Quick ELISA™ Anthrax-PA Kit
Manufacturer: Immunetics, Inc., Boston, MA
Approval Date: June 4, 2004
Use Classification: The test is used to detect 100% of the Bacillus anthracis (anthrax) organism in a patient’s blood specimen, with less than a 1% chance of false-positive results.

Description: The test can detect antibodies to a key component of the anthrax bacillus, which forms part of the toxin responsible for its deadly effects. Test results have been positive for individuals with either inhalational or cutaneous anthrax.

Purpose: The FDA has approved the kit for the direct detection of anthrax in blood specimens.

Benefit: This standardized test kit benefits people who might have been exposed to the dangers of a suspected bioterrorism attack. The kit can be made widely available in the event of terrorism emergencies.


Name: RAMP® Cardiac Marker Test
Manufacturer: Response Biomedical Corporation, Vancouver, BC
Approval Date: May 25, 2004
Use Classification: The test detects creatine kinase (CK–MB) in patients to assist in the rapid diagnosis of heart attack or acute myocardial infarction (AMI). CK–MB is one of three forms of the enzyme CK and occurs mostly in heart muscle. Levels rise when heart muscle cells are diseased or damaged in any way.

Description: This high-sensitivity test detects troponin I, recognized as the cardiac marker of choice, allowing increased sensitivity and specificity in diagnosing AMI. The approval by the FDA recognizes the fluorescence-based RAMP Reader for general clinical use and three RAMP Cardiac Marker Tests for detecting troponin I, myoglobin, and CK–MB.

Purpose: RAMP provides a quantitative result in approximately 15 minutes, in contrast to the several hours of turn-
patients with a history of known hypersensitivity to avian proteins. It is not indicated for breast augmentation or for implantation into bone, tendon, ligament, or muscle. It should not be injected into blood vessels because it might clog the vessels, restricting blood flow and killing tissue by embolization or infarction.

Source: www.fda.gov/cdrh/mda/docs/p030032.html.

Name: Elecsys® Troponin T STAT Test
Manufacturer: Roche Diagnostics, Basel, Switzerland
Approval Date: May 21, 2004
Use Classification: The test aids in the differential diagnosis of acute coronary syndrome, in evaluating risk in these patients, and in assessing cardiac risk in patients with chronic renal failure. It may also help physicians select more intensive therapy and interventions in patients with elevated levels of troponin T.

Description: The test measures concentrations of troponin T, a cardiac-specific protein that is released into the blood when heart cells die.

Purpose: Patients with increased troponin T levels have a five-fold increase in cardiac risk over patients with non-elevated troponin T concentrations. Troponin T helps to identify patients with acute coronary syndrome who might benefit from antithrombotic therapy.

According to the U. S. Renal Data System, cardiac disease is the leading cause of mortality among kidney dialysis patients. In patients with renal failure and detectable concentrations of troponin T, physicians should initiate a plan to manage aggressive risk factors.

Benefit: Cardiologists and nephrologists can use this test to evaluate cardiac risk in patients with kidney disease.


Name: SurePath™ Liquid-Based Pap Test
Manufacturer: TriPath Imaging, Inc., Burlington, NC
Approval Date: June 4, 2004
Use Classification: This liquid-based Pap test is a thin-layer cell preparation process used in the screening and detection of cervical cancer, precancerous lesions, atypical cells, and other cytological categories. It has received FDA approval for expanded labeling claims to include the use of a brush/plastic spatula combination collection device with the company’s liquid-based cytology system.

Description: The test pack consists of a test, a sample collection vial, a proprietary preservative solution, and a sample collection device.

Purpose: An endocervical brush/spatula combination is as effective as the currently approved broom-type collection device in transferring representative cervical material from the sampling device to the preservative fluid.

Benefits: There are several advantages of this method over conventional Pap smears:

• There is a 64.4% increased detection of positive high-grade squamous intraepithelial lesions, a precancerous condition.
• The sample-collection process ensures that 100% of collected cells are sent to the laboratory for testing.
• A thin-layer, cell-enrichment preparation process reduces obscuring of the collected cells and offers greater clarity for diagnosis.
• The liquid-collection method allows the laboratory access for repeated and ancillary testing from the residual cell solution, thus providing more effective patient management.


around time needed with traditional laboratory testing.

Benefit: The RAMP System provides physicians with laboratory-quality information in minutes to accurately diagnose heart attacks at the point of care. RAMP has the capability to reduce health care costs associated with unnecessary hospital admissions of patients with symptoms that are often mistaken for cardiac arrest.

Sources: www.stargeek.com/item/136643.html.

Name: Hylan-B Gel (Hylaform®)
Manufacturer: Inamed Corporation, Fremont, CA, and Genzyme Corporation, Cambridge, MA
Approval Date: May 25, 2004
Use Classification: Hylaform® gel, a hyaluronic acid-based dermal filler, is indicated for injection into the mid to deep dermis to correct moderate-to-severe facial wrinkles and folds, such as in the nasolabial area.

Description: Hylaform® is a sterile, colorless viscoelastic gel, made of hyaluronic acid. The treatment’s composition is based upon a naturally occurring substance, hyaluronan, which is found in human skin and throughout the body. This substance helps to keep the skin smooth and elastic. Hylaform® is derived from roosters’ combs. The gel is gradually absorbed by the body.

Purpose: The gel temporarily adds volume to facial tissue and restores a smoother appearance to the face. After the initial treatment, “touch-ups” may be needed to achieve optimal skin smoothing.

Benefit: The gel helps to smooth facial wrinkles and folds for approximately 12 weeks.

Cautions: Side effects include bruising, redness, swelling, pain, tenderness, and raised bumps of skin (nodules). Hylaform® should not be used in patients with a history of known hypersensitivity to avian proteins. It is not indicated for breast augmentation or for implantation into bone, tendon, ligament, or muscle. It should not be injected into blood vessels because it might clog the vessels, restricting blood flow and killing tissue by embolization or infarction.

Source: www.fda.gov/cdrh/mda/docs/p030032.html.

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