NEW DRUGS

Generic Lipitor For Lowering Cholesterol

Watson Laboratories and Ranbaxy Laboratories Ltd., a division of Daiichi Sankyo, have gained approval to manufacture generic versions of Pfizer's Lipitor (atorvastatin calcium tablets). Atorvastatin is prescribed along with a low-fat diet to decrease serum low-density lipoprotein-cholesterol (LDL-C) and triglyceride levels.

Watson will be selling an authorized generic version of Lipitor in partnership with Pfizer for the next 5 years. The Ranbaxy tablets will be sold in 10-mg, 20-mg, 40-mg, and 80-mg strengths and will be manufactured by its subsidiary, Ohm Laboratories, in New Brunswick, N.J.

Under federal law providing a period of semi-exclusivity, the two generic versions of Lipitor will be on the market for six months. After that, other generic products will be allowed to enter the marketplace, which should lower prices.

Sources: FDA, November 30, 2011; Bloomberg News, November 18, 2011

NEW FORMULATION

Intermezzo for Middle-of-the-Night Insomnia

Zolpidem tartrate sublingual tablets (Intermezzo, Transcept Pharmaceuticals) have been approved for use, as needed, to treat insomnia characterized by middle-of-the-night waking, followed by difficulty returning to sleep.

Intermezzo should be used only when a person has at least 4 hours of bedtime remaining. It should not be taken if the person has consumed alcohol or any other sleep aid.

Zolpidem was first approved in the U.S. in 1992 as Ambien (Sanofi). Intermezzo, a lower-dose formulation of zolpidem, reduces the risk of drowsiness in the morning. The recommended maximum dosage is 1.75 mg for women and 3.5 mg for men, taken once per night. The dosage is lower for women because zolpidem is eliminated from the body at a faster rate in men.

Intermezzo is a federally controlled substance because it has the potential to be abused and to lead to dependence.

Source: FDA, November 23, 2011

Topical Oxybutynin Gel 3% For Overactive Bladder

Watson Pharmaceuticals, Inc., and Antares Pharma, Inc., have announced the approval of Antares' topical oxybutynin gel 3% product for the treatment of overactive bladder (OAB). The translucent, odorless gel is supplied in a convenient, metered-dose pump. Because the active ingredient is not metabolized by the liver, there are few side effects.

Oxybutynin is an antispasmodic, antimuscarinic agent. It is applied to the thigh, abdomen, upper arm, or shoulder in a dosage of 84 mg (approximately 3 mL), which allows a consistent dose of oxybutynin through the skin over a 24-hour period.

In a phase 3 clinical study, the overall systemic exposure of the drug was not affected by showering 1 hour or later or by applying sunscreen 30 minutes before or after gel application.

Antares Pharma also makes oxybutynin chloride (Gelnique Gel 10%) and oxybutynin transdermal system (Oxytrol) for the treatment of OAB.

Source: Watson/Antares, December 8, 2011.

NEW INDICATION

Isentress for HIV Infection In Pediatric Patients

Raltegravir (Isentress) tablets are now approved for use with other antiretroviral drugs to treat HIV-1 infection in children and adolescents 2 to 18 years of age. The drug was first approved for use in adults in October 2007 under the FDA's accelerated approval program.

An HIV integrase strand transfer inhibitor, raltegravir slows the spread of the virus in the body. The tablets can be taken twice daily with or without food. A chewable form is approved only for children 2 to 11 years of age.

Raltegravir does not cure HIV infection. Patients must continue with HIV therapy to control the infection and decrease HIV-related illnesses.

Source: FDA, December 21, 2011

DRUG NEWS

New Warning Added To Multaq Label

More restrictions were added to the label of Sanofi's dronedarone (Multaq), which is used to treat atrial fibrillation (AF). The warning was added because of the potential for an increased risk of death in patients with "permanent" AF. For those with this form of AF, the normal heartbeat cannot be restored with medications. The FDA recommends that dronedarone not be prescribed for those patients with permanent AF because the drug might double the rate of cardiovascular death, stroke, and heart failure.

Safety concerns arose after the approval of dronedarone in 2009 because an early study had suggested an elevated death rate among patients with advanced heart failure, and a boxed warning was added to the drug's label.

Dronedarone is still indicated for those with "paroxysmal" and "persistent" AF, which can occur intermittently. Patients who are taking dronedarone should receive appropriate antithrombotic therapy and should have an electrocardiogram every 3 months. Dronedarone should be withheld if the patient is in AF, or if it is clinically indicated, the patient should undergo cardioversion.

Early in 2011, Sanofi was instructed to add a warning of liver injury to the label.

Sources: FDA, *The Wall Street Jour-*

nal, Forbes Magazine, Associated Press, December 19, 2011

REMS No Longer Needed For Nplate and Promacta

Although safety risks still exist for romiplostim (Nplate, Amgen) and eltrombopag (Promacta, GlaxoSmithKline), several restrictive requirements of the drugs' REMS (Risk Evaluation and Mitigation Strategies) programs will no longer be necessary to ensure that their benefits outweigh their risks.

The FDA concluded that the long-term safety of romiplostim and eltrombopag can be evaluated by ongoing clinical trials, post-approval studies, and adverse-event reports. Physicians, hospitals, and patients will not need to enroll in the Nplate NEXUS or the Promacta CARES programs to prescribe, use, or receive these drugs, and health care professionals will not have to complete periodic safety forms for patients. The warnings and precautions sections of the prescribing information have been updated accordingly.

Both drugs were approved in 2008 to treat adults with chronic immune thrombocytopenia who did not respond adequately to steroids, immunoglobulins, or removal of the spleen. Since the drugs' approval, the FDA has been monitoring safety risks, including bone marrow changes, blood clots, blood-related cancers, low platelet counts, post-therapy bleeding, and liver injury.

Source: FDA, December 6, 2011

Plan B One-Step Contraceptive Remains Restricted by Age

Plan B One-Step, a single tablet for emergency contraception, will remain behind pharmacy counters for girls younger than 17 years of age, who will still need a prescription. If taken within 3 days of unprotected sexual intercourse, the drug decreases the chance of pregnancy by 89%. It is even more effective when taken within 24 hours. Plan B is available without a prescription to women 17 years of age and older.

Teva Pharmaceuticals had petitioned the FDA to allow stores to put Plan B on shelves after a study showed that girls as young as 12 could understand how to safely use the product. The FDA agreed, but in an unusual action, the Secretary of Health and Human Services, Kathleen Sebelius, overruled the FDA.

Plan B contains 1.5 mg of a synthetic version of the female hormone progesterone that is found in lower doses in daily contraceptive pills. It gradually loses effectiveness, which is why advocates wanted it to be available in stores. The drug prevents ovulation and may make the uterine lining less hospitable to a fertilized egg. Plan B has no effect on established pregnancies. It is not an abortion pill and is not related to RU-486.

Ella (HRA Pharma), sold by prescription only, is also an emergency contraceptive that prevents pregnancy when taken up to 5 days after intercourse.

Although Ms. Sebelius had the legal authority to overrule the FDA, no health secretary had ever publicly done so. FDA Commissioner Dr. Margaret Hamburg stated that it was safe to sell Plan B as a nonprescription item, but Ms. Sebelius countered that the drug's manufacturer had failed to evaluate whether girls as young as 11 years of age could safely use Plan B. Ms. Sebelius concluded that not enough data supported making the tablet available to all girls 16 years of age and younger without the need to consult a health care professional. Advocates of the over-the-counter status claim that emergency contraception would have become available to more people who need it. Many experts agreed that young women would benefit from having easy access to the medication.

On December 12, the FDA denied a petition by a reproductive rights advocacy group that sought to lift all prescription requirements for an older version of the Plan B emergency contraceptive on the eve of a federal court hearing on the issue. The denial came a week after Ms. Sebelius overruled the FDA. In denying the petition, the FDA said it would need to see studies on comprehension for the two-step version of Plan B; the agency also said studies of Teva's single-tablet Plan B would not be transferable to the drug's two-step version.

Sources: *The New York Times*, *The Wall Street Journal*, Medical News Today, December 7, 2011; *The Wall Street Journal,* December 12, 2011

Effectiveness of Drugs for Alzheimer's Disease

Investigators from the REAL.FR study group *(REseau sur la maladie d'Alzheimer FRançais)* conducted a 4-year "real-world" study on the progression of Alzheimer's disease (AD). They observed 686 patients with mild-to-moderate AD. The patients were evaluated twice a year. Outcomes were defined at 4 years according to the following endpoints: an increase in functional incapacity; aggravation of behavioral and psychological symptoms; institutionalization; and death.

Although AD had been diagnosed for a mean of 13 months, many patients were still at a stage of mild cognitive impairment; 54% were independent in performing activities of daily living (ADL); and 88% had at least one behavioral disturbance. Apathy was the most prevalent neuropsychiatric symptom, followed by anxiety, agitation, depression, and irritability. About one-third of the patients had two or more comorbidities.

More than 90% of the patients used cholinesterase inhibitors, indicated for AD, during the 4 years. The proportion of patients who used these drugs alone

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declined from 89% to 70%, and the proportion of those using both cholinesterase inhibitors and memantine (Namenda, Forest) rose from 0% to 26%. The proportion of those who used only memantine increased from 0% to 4%. These patterns reflect current clinical practice guidelines.

At 4 years, 207 patients had completed the study. Although more than half of the patients had been able to perform ADL independently, by the 4th year, ADL scores declined significantly (a mean loss of 2.7 points).

Rates of functional decline were similar from year to year (about 0.7 points per year). Most changes affected patients' ability to bathe and dress (35% of the patients), and incontinence developed in more than 20% of the patients.

Nevertheless, the progression of cognitive changes was slower than it had been before the era of cholinesterase inhibitors. Even after 4 years, 11% of patients had no clinically meaningful decline in mental status scores. Further studies might be able to clarify whether the patients responded to cholinesterase inhibitors or whether they had a slowly progressing form of AD.

High rates of neuropsychiatric symptoms and functional incapacity were associated with disease in the early stages and with increasingly severe cognitive syndromes. Apathy, the most common finding, is now recognized as a behavioral marker of a more aggressive dementia, but it seems to respond to donepezil (Aricept, Eisai/Pfizer).

Of those patients with mild dementia at baseline, 17% did not experience behavior changes or loss of functional capacity during the study, but a high level of variability of disease progression was noted, underscoring the need to assess outcomes at least every 6 months.

Source: *Alzheimers Dement* 2011;7: 579–592

Managing Glucose Helps Vision In Diabetic Patients

Patients with diabetes are at risk for diabetic macular edema (DME), a primary cause of moderate vision loss. Current drug treatments are aimed at inhibiting vascular endothelial growth factor (VEGF), which plays a role in the pathogenesis of DME.

Three therapies used for intravitreal injection—pegaptanib (Macugen, EyeTech), bevacizumab (Avastin, Genentech/Roche), and ranibizumab (Lucentis, Genentech/Roche)—have shown promising results.

Researchers in Turkey evaluated the relationship between glycemic control and outcomes of intravitreal drug injection in DME. Ranibizumab seems to be the most promising of the three anti–VEGF-A drugs, but few studies have addressed its effect on DME. In their study of 65 patients who received ranibizumab, the investigators correlated serum glycosylated hemoglobin (HbA_{1c}) values with changes in best-corrected visual acuity and in the central subfield macular thickness. At baseline, the mean HbA_{1c} was 8.18 (range, 5.7–12.7%).

The median value of best-corrected visual acuity was 20/80 (the ability to read 52 letters); the median central subfield macular thickness was 468 µm. Thirty-three patients had pre-proliferative-stage diabetic retinopathy, and 32 patients were in the proliferative stage.

A marked improvement in visual acuity was observed 4 to 6 weeks after one intravitreal injection. The median value of best-corrected visual acuity increased to 20/50 (59.5 letters), and the median central subfield macular thickness dropped to 310 µm—both significant changes. The change in visual acuity was higher (six letters) in patients who had received a previous therapy for DME, compared with those who received no previous treatment (one letter). A total of 29 patients had been treated for DME at least 6 months previously, mostly with intravitreal bevacizumab.

The duration of diabetes was not correlated with changes in either macular thickness or visual acuity; however, changes in the central subfield macular thickness were inversely correlated with serum HbA_{1c} levels. In other studies, glucose regulation had reduced or delayed the incidence and progression of diabetic retinopathy. The initial results in the Turkish trial suggest that patients with lower serum HbA_{1c} levels might need fewer intravitreal anti-VEGF injections.

Source: *J Diabetes Complications* 2011; 25:298–302

Eradicating *H. pylori* To Prevent Atherosclerosis

Many studies have shown a link between *Helicobacter pylori* infection and atherosclerosis in coronary, carotid, or peripheral vessels. Endothelial dysfunction has been called the first step in the response-to-injury hypothesis of atherosclerosis. Researchers in Florida and Israel found that endothelial dysfunction was actually reversed after treatment of *H. pylori* infection was initiated, potentially reducing the risk of atherosclerosis and future cardiovascular events.

Thirty-one patients with documented *H. pylori* infection received triple therapy, consisting of two antibiotics and a proton pump inhibitor (PPI) for 10 days. Three months later, those patients and 11 *H. pylori*–negative control subjects with dyspepsia were re-evaluated. Vascular tests included flow-mediated diameter percent change and the ankle–brachial index (ABI).

Patients with *H. pylori* infection had severe endothelial dysfunction that returned to normal values after the infection was eradicated. By contrast, endothelial dysfunction in the non-infected subjects did not change significantly. The

ABI was not affected by the infection: among infected patients, the ABI was 1.2 both before and after eradication. Among *H. pylori*–negative participants, the ABI rose from 1.25 to 1.31.

Information about markers of systemic inflammation has been inconsistent. In this study, soluble serum interleukin-6 levels were not elevated before or after treatment. The investigators suggest that one reason for the variability of inflammatory markers could be that patients come for health care visits at different stages of the inflammatory response.

Source: *Am J Med* 2011;124:1171–1174

Nexium and Pepcid Work Well With Plavix

Dual antiplatelet therapy with aspirin and clopidogrel (Plavix, Bristol-Myers Squibb/Sanofi) increases the risk of gastrointestinal (GI) bleeding, leading to the need to add gastroprotective proton pump inhibitors (PPIs)—and concerns about the combination's risk of adverse cardiovascular outcomes. However, those concerns may be mitigated by the first head-to-head comparison of a PPI and a histamine-2 (H_2) receptor antagonist—esomeprazole (Nexium, AstraZeneca) and famotidine (Pepcid, Merck)—in terms of their potential interaction with clopidogrel. Neither drug reduced clopidogrel's platelet-inhibiting effect, say researchers in Hong Kong.

Eighty-eight patients with acute coronary syndrome (ACS) or elective percutaneous coronary intervention received aspirin and clopidogrel. The patients were then randomly assigned to receive esomeprazole 20 mg daily or famotidine 40 mg daily. Platelet-reactivity units (PRUs) were measured at baseline and on day 28. No significant difference in PRUs was observed between the two treatment groups.

Fifty-two percent of the esomeprazole group and 43% of the famotidine group showed a poor response to clopidogrel on day 28. However, compared with baseline values, this was equated with only one patient, who was classified as a poor responder in each group.

None of the patients in the esomeprazole group experienced upper GI bleeding, compared with two patients in the famotidine group.

Source: *Am Heart J* 2011;162:870–874

Revised Guidelines To Treat Blocked Arteries

To reduce unnecessary treatment, the American College of Cardiology, the American Heart Association, and the Society for Cardiovascular Angiography and Interventions are suggesting that patients receive advice on treatment options before they undergo surgery or receive a stent to clear clogged arteries.

Patients with the most serious blockages should be evaluated by a surgeon who performs bypass operations and by a cardiologist who implants stents; those with less serious conditions whose clogged arteries have been cleared could see their physician after the diagnosis to review the options.

The new guidance recommends an 81-mg low-dose aspirin daily for heart patients to eliminate the higher-dose range that often led to bleeding. Cardiologists typically are the first health care professionals to evaluate patients and sometimes treat them without reviewing options such as surgery and drug therapy. The use of angioplasty and stents to unblock and hold open arteries has increased, in many cases displacing bypass surgery, which can circumvent the blockage. The three heart groups suggest that patients benefit from a balanced, objective analysis when they receive advice from both a cardiology expert and a surgeon.

Only patients who are able to take aspirin and another drug for a year to prevent blood clots from forming should be given stents.

Genetic tests to identify patients who are resistant to treatment with clopidogrel (Plavix, Bristol-Myers Squibb/Sanofi) may be useful for those with a high risk of clot development. Patients who are found to have a muted response to clopidogrel may be candidates for prasugrel (Effient, Eli Lilly) or ticagrelor (Brilinta, AstraZeneca).

Source: Bloomberg, November 7, 2011

ADHD Drugs Considered Safe for the Heart in Adults

Drugs that are customarily used to treat attention-deficit/hyperactivity disorder (ADHD) have been found to pose no cardiac risk in adults, even though they can increase blood pressure (BP) and heart rates. The results replicate findings in a study of children with ADHD that was published in November by the same researchers.

ADHD affects about 4% of adults in the U.S.

More than 440,000 adults 25 to 64 years of age who were taking drugs for ADHD had about the same number of heart attacks (1,357), strokes (575), and sudden heart-related deaths (296) as adults who did not use those drugs over a period of up to 20 years. Study participants used the drugs for an average of less than 1 year, but the upper range of use was almost 14 years. There was no sign of increasing vascular risk with longer use.

The study provides encouraging news, given lingering concerns about heart problems and sudden deaths in patients who were using ADHD drugs. The findings support the FDA's decision in 2006 against putting a boxed warning about serious heart events on the labels for ADHD medications.

Sources: *JAMA,* December 28, 2011; *The Wall Street Journal,* December 13; Associated Press, December 12, 2011

Shortages of Nutritional Products Affect Hospital Care

Shortages of chemotherapy and anesthesia drugs have received much attention, but nutritional medications are also in short supply. When patients cannot eat, vitamins, minerals, and substances that are converted to a liquid mixture are delivered by an infusion pump through a catheter implanted in a large vein, often in the chest. Patients undergoing organ transplantation in hospitals also rely on parenteral nutrition after surgery.

The number of reported nutritional drugs affected by shortages rose to 13 in 2010, up from five in 2009. The main cause is production problems at factories.

Texas Children's Hospital has been reducing calcium doses for some infants for months. Children at St. Jude Children's Research Hospital were given gummy vitamins when the hospital could not obtain its liquid multivitamin solution a few months ago. However, one patient was hospitalized with a thiamine deficiency after being unable to tolerate an oral multivitamin.

The C.S. Mott Children's Hospital in Michigan reported a shortage of selenium. The only manufacturer of this supplement, American Regent, said that it expected to start shipping selenium again early next year.

Because of a shortage of a dehydrated alcohol product that is used to kill bacteria in tubes that are delivered from the nutrition machine to the catheter inside the body meant that for several months, there was enough of the solution to clean intravenous feeding lines only twice weekly rather than daily. Consequently, infection rates increased.

Amino acids, lipids, and electrolytes have also been in short supply in hospitals.

Source: *The Wall Street Journal*, December 15, 2011

Who Receives Intensified Cholesterol Therapy?

From a study of patients with cardiovascular disease (CVD), the encouraging news is that 71% achieved their target levels of low-density lipoprotein-cholesterol (LDL-C). However, roughly two-thirds of those with elevated LDL-C levels received no treatment intensification, say researchers at Michael E. DeBakey Veterans Affairs Medical Center in Houston, Texas; Baylor College of Medicine in Houston; Methodist DeBakey Heart and Vascular Center in Houston; and Great Lakes Veterans Affairs Medical Center in Hines, Illinois.

Treatment intensification was defined as initiating or adding a drug to reduce LDL-C levels, increasing the dose of an existing medication, or prescribing the maximum dosage of one or more lipid-lowering medications.

The multicenter study involved 22,888 patients at seven midwestern veterans facilities. Of the 6,538 patients whose LDL-C levels were not controlled, one-third received follow-up care (2,093 with treatment intensification and 11 with a repeated LDL-C assessment without intensification). The most frequent type of treatment intensification was a lipid-lowering drug. Diabetes, hypertension, more lipid panels, and adherence to treatment predicted intensified therapy.

Women with CVD were less likely than men to have controlled LDL-C levels and were somewhat less likely to receive treatment intensification. This could reflect a perception that women have a lower risk of recurrent CVD events. Previous studies had shown sex disparities in hypertension and cholesterol care—an area in need of quality improvement.

Patients between 65 and 75 years of age were more likely to have controlled LDL-C levels, compared with those younger than 65, but they were slightly less likely to receive intensified treatment. By contrast, few patients 75 years of age or older received intensified treatment. Health care professionals tend to believe that treatment intensification is less effective in older patients, especially those with a limited life expectancy. However, older patients have the highest absolute CVD risk. Therefore, the lack of treatment intensification represents a treatment–risk paradox and offers another area for quality improvement.

Patients with CVD who were treated by a non-physician were slightly more likely to have controlled LDL-C levels and were equally likely to receive treatment intensification.

Health care providers more often implemented evidence-based cholesterol-management guidelines in patients who were most likely to benefit. Patients who are more adherent to therapy are more likely to have LDL-C levels under control, and health care providers are more likely to intensify treatment in those patients. Intensifying treatment in nonadherent patients, however, might not work and might even be harmful. Conducting motivational interviews to improve adherence might be a first step before intensified treatment is tried for these patients.

Performance measures that target LDL-C levels provide only a snapshot and don't address whether treatment intensification was provided or whether it actually worked. As a cross-sectional approach, it doesn't allow the longitudinal nature of medical care to be tracked. One possible way to assess adherence is to refer to the patient's refill history in electronic medical records.

The study also showed a positive link between the number of lipid panels and LDL-C treatment intensification. An abnormal lipid profile serves as a reminder to intensify treatment and may also encourage better adherence.

Source: *Am Heart J* 2011;162:725–732.e1

RESEARCH NEWS

Enbrel Benefits Patients With Rare Inflammatory Syndrome

In a study funded by the National Institutes of Health (NIH), etanercept (Enbrel, Amgen/Pfizer) reduced the frequency and severity of symptoms of tumor necrosis factor receptor (TNF)–associated periodic syndrome (TRAPS), a rare inherited inflammatory condition marked by recurrent fevers, abdominal pain, and rashes.

TRAPS is associated with mutations in the gene that codes for the TNF receptor 1 (TNF-R1) molecule, which plays a critical role in the reception of inflammatory signals in the body's immune system. Etanercept blocks TNF, a protein that has been implicated in the harmful inflammation in TRAPS, as well as in some rheumatic diseases, including rheumatoid arthritis.

The initial study enrolled 15 patients with TRAPS. Each patient kept a daily diary of attacks, symptom severity, and the use of additional medications. Periodic blood tests were conducted to measure acute-phase reactants (proteins that fight infection and serve as markers of inflammation). During etanercept treatment, patients reported fewer symptoms and more symptom-free days each week. Attacks still occurred, but they were less severe and were of short duration. Between attacks, patients were relatively symptom-free. Etanercept also reduced levels of acute-phase reactants, particularly during asymptomatic periods.

To determine whether etanercept was effective over the long term, the researchers contacted all 15 patients 7 to 9 years after the initial study period. Despite the overall beneficial effects of etanercept, most patients had stopped taking the drug during the follow-up period because of a perceived lack of efficacy or painful injection-site reactions, which might have been related to the skin manifestations of the disease. The three patients who continued etanercept therapy reported benefits, suggesting that for some individuals, etanercept might be a long-term treatment option.

The more recent study did not show whether etanercept could prevent the long-term consequences of TRAPS, mainly amyloidosis.

Sources: *Arthritis Rheum* October 17, 2011 (online); NIH, October 25, 2011

Progesterone Lowers Risk of Preterm Delivery

An analysis of five studies has uncovered new evidence of the effectiveness of progesterone, a naturally occurring female hormone, in reducing the rate of preterm births among a high-risk category of pregnant women—those with a short cervix. Preterm infants, born 3 weeks or more before a full 40-week term, are at increased risk for death in the first year of life, as well as for breathing problems, cerebral palsy, learning disabilities, blindness, and deafness.

A previous study funded by the NIH had indicated that progesterone helped to reduce rates of preterm births. In their meta-analysis, researchers found that the treatment tested in the earlier studies substantially reduced the risk of delivery in the 27th to 34th weeks of gestation. For example, preterm deliveries were decreased by 50% before week 28.

The team analyzed studies testing vaginal progesterone formulations in doses ranging from 90 to 200 mg/day. They concluded that even if the delivery occurs before full term, progesterone can reduce the likelihood that the infant will die (by 43%), have respiratory distress syndrome (by 52%), weigh less than 3.5 pounds (by 45%), need intensive care (by 25%), or require mechanical ventilation (by 34%).

The researchers recommended that doctors screen pregnant patients with ultrasound of the cervix routinely at 19 to 24 weeks of gestation. If a short cervix (10 to 20 mm) is detected, progesterone 90 mg/day is recommended between weeks 20 and 37.

Preterm delivery also raises the risk of a preterm birth in subsequent pregnancies. However, women with a short cervix who previously had given birth preterm benefited from progesterone as much as women without a history of preterm delivery. The original studies did not have sufficient data to compare results for infants born before week 32.

Sources: *Am J Obstet Gynecol* 2011; NIH, December 14, 2011

Vaccine Attacks Breast Cancer in Mice

Researchers at the University of Georgia and the Mayo Clinic in Arizona have developed a vaccine that reduced tumors in a mouse model by almost 80% and elicited a strong immune response.

When cells become cancerous, the sugars on their surface proteins undergo distinct changes that set them apart from healthy cells. For decades, scientists have tried to enable the immune system to recognize those differences to destroy cancer cells rather than normal cells. Because cancer cells originate within the body, however, the immune system doesn't usually recognize them as foreign and therefore doesn't mount an attack.

The researchers used mice developed by Dr. Sandra Gendler at the Mayo Clinic. Like humans, the mice develop tumors that overexpress a protein, MUC1, on the surface of their cells. Tumor-associated MUC1 proteins are adorned with shortened carbohydrates that set them apart from the proteins in healthy cells. Dr. Gendler said this is the first time that a vaccine has been designed to train the immune system to identify and kill cancer cells based on the sugar structures on proteins, such as MUC1.

MUC1 is found on more than 70% of all lethal cancers. Most breast, pancreatic, and ovarian cancers and multiple myeloma express MUC1 with its shortened carbohydrates.

In cancer, MUC1 is overexpressed, promoting tumor formation. A vaccine directed against MUC1 has the potential to prevent the development of tumors or to reduce the risk of recurrence. The vaccine could also be used with standard therapy (e.g., chemotherapy). MUC1 is overexpressed in 90% of patients who do not respond to hormonal therapy, such as tamoxifen (Nolvadex, AstraZeneca), aromatase inhibitors, or trastuzumab (Herceptin, Genentech).

Therapeutic vaccines received renewed attention last year when the FDA approved Dendreon's sipuleucel-T (Provenge) for metastatic prostate cancer. When using sipuleucel-T, clinicians isolate immune cells from the patient and send the cells to a lab to be linked to a protein that stimulates the immune system. The cells are then returned to the patient's treating physician, who infuses the drug over three treatments, usually two weeks apart.

The breast cancer vaccine is simpler; it consists of an immune system booster that triggers the production of T-helper cells and a carbohydrate-linked peptide molecule that directs the immune response to cells bearing MUC1 proteins with shortened carbohydrates. The team is currently testing the vaccine's effectiveness against human cancer cells in culture. If all goes well, the researchers anticipate that phase 1 clinical trials could begin by late 2013.

Sources: *Proc Natl Acad Sci;* Medical News Today, www.medicalnewstoday.com/articles/239115.php

New Breast Cancer Studies

BOLERO-2: Afinitor and Aromasin

In the Breast Cancer Trials of Oral Everolimus–2 (BOLERO-2), disease progression was slowed in postmenopausal women with advanced hormone receptor-positive breast cancer when they took the hormone-blocking drug exemestane (Aromasin, Pfizer) along with a kidney cancer drug and molecular target of rapamycin (mTOR) inhibitor, everolimus (Afinitor, Novartis). BOLERO-2 involved patients who had previously received a nonsteroidal aromatase inhibitor (AI). Patients receiving the combination remained progression-free an average 4.1 months longer than patients receiving exemestane alone.

In this trial, 724 women with cancer that was resistant to the AIs letrozole (Femara, Novartis) and anastrozole (Arimidex, AstraZeneca) received exemestane plus placebo or exemestane plus everolimus, which blocks the mTOR protein. Cancer growth was delayed in more patients who received exemestane and everolimus, and for a longer time, compared with women who received exemestane and placebo. After 1 year, compared with exemestane and placebo, the everolimus/exemestane combination increased the median progression-free interval from 3.2 months to 7.4 months.

Sources: *Internal Medicine News,* December 7, 2011; http:/connection.asco.org

CLEOPATRA: Omnitarg and Herceptin

Investigators looked at preventing drug resistance in breast cancer in which tumor growth is driven by Her-2/neu, a protein that occurs in about 25% of breast cancers. Trastuzumab (Herceptin, Genentech/Roche) attacks the Her-2/neu protein and shuts down cancer growth. In CLEOPATRA, 808 women were given standard therapy plus placebo or standard therapy plus an experimental drug, pertuzumab (Omnitarg, Genentech), which binds to a different part of the Her-2 protein. The median progression-free survival in women receiving standard therapy was 12.4 months; in women taking pertuzumab, the cancer didn't start to grow again until six months later on average. This degree of improvement was considered uncommon.

Sources: *N Engl J Med*; *The Wall Street Journal*, December 8, 2011

Solving the 'Superbug' Mystery

The treatment of infections caused by *Staphylococcus aureus* is complicated by the development of antibiotic resistance. Seriously ill patients, who are especially vulnerable to infections, can face an additional risk if antimicrobial agents become less effective in fighting infections.

Using whole-genome DNA sequencing of strains obtained from patients with bloodstream infections, researchers at the University of Melbourne, Australia, have discovered how *S. aureus* can make one small change to its DNA and then develop resistance to the last-line-of-defense antibiotic, vancomycin (Vancocin, ViroPharma). The organism can easily become resistant to vancomycin by acquiring a single mutation in its DNA. When the bacteria mutate, they reprogram themselves and change their cell walls to resist the action of the antibiotic.

The team expressed concerns about the implications of this discovery, because the mutation causes *S. aureus* to be more resistant to another last-line antibiotic, daptomycin (Cubicin, Cubist). Last-line therapies are thought to be more toxic and to cause additional side effects in already compromised patients.

Sources: *PLoS Pathogens* and *R&D Magazine*, November 11, 2011

Suboxone May Help to Reduce Addiction to Pain Drugs

People who are addicted to prescription pain medications have been able to reduce their opioid abuse when they received sustained treatment with bupren-

orphine plus naloxone (Suboxone sublingual film, Reckitt Benckiser). A study conducted by the National Institute on Drug Abuse (NIDA) was the first randomized, large-scale clinical trial to use a drug as therapy for prescription opioid abuse.

Pain medications are beneficial when used as prescribed, but they have a significant abuse liability, especially when they are taken for non-medical reasons. Suboxone combines buprenorphine (to reduce opioid craving) plus naloxone, which causes withdrawal symptoms in those addicted to opioids if Suboxone is taken by a route other than orally, as prescribed. This combination was developed to prevent opioid abuse and diversion.

Most studies of opioid dependence have involved heroin-addicted patients at methadone clinics, and little information is available on addiction to prescription pain drugs. To address this issue, a study was conducted in 2007. More than 600 treatment-seeking outpatients addicted to prescription opioids received Suboxone along with brief standard medical management. Half of the participants also received addiction counseling, provided by trained professionals.

Approximately 49% of participants were able to decrease their addiction to prescription pain drugs during extended Suboxone treatment of at least 12 weeks, but this rate dropped to 8.6% when Suboxone was discontinued.

Patients who received counseling did not show better outcomes compared with those who did not receive it.

Sources: *Arch Gen Psychiatry*, November 7, 2011; NIH, November 8, 2011

A Protein May Spur Metastasis

Scientists from Nova Scotia have identified a key mechanism of metastasis that could help block tumor growth. Lead researcher David Waisman, PhD, at Dalhousie University, explained how macrophage cell-surface protein S100A10 enables macrophages to move to the site of tumor growth, a process that is essential to tumor development.

Scientists had thought that cancer cells were the only key cells in a tumor. They now suggest that other cells might work with cancer cells to allow the cancer cells to evolve into metastatic cells. This change is what leads to a poor prognosis.

Dr. Waisman and his team discovered that tumors could not grow without the help of macrophages. To move into the tumor site and combine with the cancer cells, the macrophages "chewed" their way, like a scissors, through the tissue that forms a barrier around the growing tumor. On the outside surface of the macrophage, S100A10 allowed the macrophage to remove the tissue barriers that prevent migration to the tumor site.

Theoretically, blocking either the macrophages or S100A10 can stop tumor growth. Identifying drugs that might inhibit the protein's activity might help to prevent the movement of macrophages to the tumor site.

Source: *Cancer Res,* November 1, 2011

Eyedrops to Prevent Pinkeye

Scientists have developed eyedrops (Adenovir Pharma AB) for the most common form of pinkeye to eradicate the infecting virus before it enters and inflames the eye. Epidemic keratoconjunctivitis is a contagious disease caused by the adenovirus family. Currently, treatment is available only for the less common bacterial form of conjunctivitis.

Researchers in Sweden determined that the adenovirus responsible for conjunctivitis enters the eye through receptor molecules, called sialic acid, located on the surface of corneal cells. They constructed molecular structures (liposomes), which have numerous sialic-acid residues projecting from the surface that scoop up or aggregate adenoviruses, preventing them from binding to the receptor molecules.

The compound, when given as eyedrops, inhibited the corneal cells from being infected by adenoviruses. No adverse effects were reported in animals. The risk of viral resistance is low because the compound acts outside of human cells.

The eyedrops may help to reduce symptoms of infections and may also be used to prevent the virus from spreading. The drops will be tested in humans starting next year.

Sources: *J Med Chem* 2011;54:6670–6675; *The Wall Street Journal,* October 18, 2011

DEVICES IN THE NEWS

Supplemental Test For Chagas Disease

The FDA has approved the first adjunctive test of human serum or plasma found to be positive for antibodies to *Trypanosoma cruzi (T. cruzi)*. This parasite causes Chagas disease, a serious and potentially fatal infection.

The Abbott ESA Chagas (*T. cruzi* [*Escherichia coli*, Recombinant] Antigen) is an *in vitro* enzyme-strip assay that detects antibodies to *T. cruzi*. Two donor screening tests are currently licensed for this purpose, but this is the first test that enables health care professionals to counsel donors with positive screening results.

Chagas disease is spread mainly by blood-sucking insects infected with *T. cruzi*. The disease can also be spread through blood transfusions, by organ transplants, and from mother to unborn child.

More than 5,000 donors with positive test results have been identified since national screening of the blood supply was instituted in early 2007.

Source: FDA, November 21, 2011

First Rechargeable Device For Pain Relief

Boston Scientific Corp. has announced the FDA's approval of the Infinion 16 Percutaneous Lead for its Precision Plus Spinal Cord Stimulator System. The leads are designed to deliver electrical pulses from an implantable pulse generator to the spinal cord to mask pain signals to the brain.

Until now, percutaneous leads have offered a maximum of eight stimulating contacts. By providing twice the number of contacts as before, the Infinion device offers more coverage of the spinal cord to relieve chronic pain. The 16 contacts can be inserted through a single, small needle with only one placement.

Source: Medical Daily, www.medicaldaily.com; December 8, 2011

Hand-Held Device Detects Skull Bleeding

The Infrascanner Model 1000, made by Infrascan, Inc., has been approved by the FDA to aid in detecting life-threatening intracranial hematomas. Near-infrared spectroscopy is used to identify patients with a head injury who need an immediate brain-imaging study.

Intracranial hematomas occur when blood from a ruptured blood vessel collects within the brain or between the skull and the brain, causing compression.

Near-infrared light can penetrate the skull bones and surrounding tissue. The scanner detects differences in light absorption and transmits the information wirelessly to a display on a hand-held computer. By comparing the optical density from a series of scans of specific areas on both sides of the skull, the clinician can use the information to determine the likelihood of an intracranial hematoma and the need for further diagnostics.

The FDA reviewed data through the *de novo* classification process, a regulatory pathway for low- to moderate-risk devices that are not comparable to a legally marketed device.

The Infrascanner Model 1000 is not a substitute for computed tomography.

Source: FDA, December 13, 2011

Cardiac-Assist Device for Children With Heart Failure

The Excor Pediatric System (Berlin Heart) helps to keep children with heart failure alive until a donor for a heart transplant can be found. The mechanical pulsatile device fits children ranging in size from newborns to teenagers.

Previous adult heart-assist devices were too large to be used in critically ill children. The Excor system consists of one or two external pneumatic (driven by air) blood pumps, tubes to connect the blood pumps to heart chambers and the great arteries, and the driving unit.

Heart failure in children is less common than in adults, and fewer pediatric donor hearts are thus available for transplantation in children. This limits the use of the surgery in children and prolongs the waiting period for a donor heart. In infants, the median waiting time for a donor heart is 119 days. From 12% to 17% of children and 23% of infants have died while on the waiting list for a heart.

In a group of 48 patients, the device improved survival to transplantation when compared with extracorporeal membrane oxygenation (ECMO). Even though ECMO is the current standard of care, it is not FDA-approved.

The Excor system was designated as a Humanitarian Use Device by the FDA's Office of Orphan Products Development.

There is a potential risk of stroke with this device.

Source: FDA, December 16, 2011

OraQuick HCV Test Waiver

The FDA has granted a waiver to OraSure Technologies under the Clinical Laboratory Improvement Amendments of 1988 (CLIA) for its OraQuick HCV Rapid Antibody Test for use with fingerstick and venous whole-blood specimens.

This is the first FDA-approved rapid (20-minute) test for the detection of antibodies to the hepatitis C virus (HCV). With this waiver, the test can be used at more than 180,000 sites to identify persons who are at risk for HCV infection or who have signs or symptoms of hepatitis. The CLIA-waived tests can be performed in outreach clinics, community organizations, and physicians' offices. OraSure will be collaborating with Merck on the development and promotion of the test.

Source: *The Wall Street Journal*, November 29, 2011

MelaFind Detects Melanoma

MelaFind (Mela Sciences) is an optical device that helps to identify melanoma among atypical skin lesions. The hand-held attachment emits light that penetrates below the surface of the skin. A computer is used to compare these images to a database of 10,000 archived images and to suggest whether a biopsy is needed. MelaFind can be used if a dermatologist prefers to obtain additional data on atypical skin lesions when deciding whether to perform a biopsy. The device is approved for use only by dermatologists and only for growths that do not show obvious signs of cancer but may display one or two worrisome signs.

Adverse effects associated with the device may include incorrect test results or interpretations, which could lead to incorrect diagnoses and, subsequently, improper patient management. False-negative results may lead to delays in diagnosis and treatment, and false-positive results may lead to unnecessary biopsies or more frequent screening.

Sources: FDA, November 1, 2011; *The Denver Post*, November 2, 2011

Pocket Mobile ECG System

CardioDefender (Everist Genomics) is an automated "smart-phone" electrocardiographic (ECG) system that provides physicians and patients with high-quality heart rhythm monitoring outside the hospital. It delivers mobile monitoring and automated reporting by combining analytical smart-phone software with a Bluetooth device and electrodes. Up to 3 months of data can be analyzed. Symptomatic and asymptomatic arrhythmias are reported to the physician.

Conventional monitoring has included hospital-based ECG systems, portable ECG recorders, and Holter monitors, but observation periods with those devices can be limited. Since its FDA approval and European CE Mark registration last year, CardioDefender has been used in more than 150 medical facilities in the U.S. for post-approval commercial evaluation. The device is sold in the U.S. and in Europe as PocketECG.

Sources: www.everistgenomics.com; www.telecomlead.com, November 12, 2011

A More Prominent Role for Women in Medical Device Trials

The FDA has issued draft guidance to address the historic underrepresentation of women in clinical studies. Intended for medical device developers and manufacturers, the guidance lists the FDA's recommendations for designing and conducting studies of devices that may expand the enrollment of women.

Women may respond differently to some devices compared with men, possibly because of basic differences in genetics, hormones, body size, diet, and sociocultural status. These variables may also affect the safety and effectiveness of the device for each sex.

In a 2001 report by the Government Accountability Office, women represented 52% of enrollees, but 30% of the study documents did not mention outcomes by sex and 40% of the documents did not report enrollment demographics.

The guidance addresses the evaluation of sex differences, data analysis, and reporting in both premarket and postmarketing clinical studies. Devices intended for men only or women only would not be expected to address potential sex differences. The FDA is seeking input on this draft guidance during a 90-day public comment period.

Source: FDA, December 16, 2011

NEW MEDICAL DEVICES

Marvin M. Goldenberg, PhD, RPh, MS

Name: Sapien Transcatheter Heart Valve

Manufacturer: Edwards Lifesciences, Irvine, Calif.

Approval Date: November 2, 2011

Purpose: The Sapien valve is used for patients who are considered to be too ill for open aortic valve replacement.

Description: The valve is made of cow tissue, which is attached to a stainless steel mesh frame with a polyester wrap. During transcatheter aortic valve replacement, the valve is crimped onto the catheter-based transfemoral delivery system, which is inserted into the body through a small incision in the leg. When the Sapien valve is delivered to the site of the diseased valve, the new valve is expanded with a balloon and immediately replaces the patient's native valve and facilitates proper blood flow.

Benefit: A diseased aortic valve can be replaced without traditional open-heart surgery while the heart continues to beat, thereby eliminating the need for cardiopulmonary bypass. The Society of Thoracic Surgeons and the American College of Cardiology are working with the FDA and the Centers for Medicare and Medicaid Services to create a registry for continued evaluation of this device and future transcatheter devices.

Precaution: The Sapien valve is not approved for patients who can undergo open-heart surgery. In the Placement of Aortic Transcatheter Valves (PARTNER) trial, the Sapien valve patients experienced 2.5 times more strokes and eight times as many vascular and bleeding complications compared with patients who did not receive the implant. However, the Sapien patients were more likely to survive 1 year after surgery compared with those receiving an alternative treatment, such as balloon valvuloplasty (69% vs. 50%, respectively).

Sources: www.edwards.com; www.fda.gov.

Name: Ovation Abdominal Stent-Graft System

Manufacturer: TriVascular Inc., Santa Rosa Calif.

Approval Date: November 1, 2011

Purpose: The Ovation system provides patients who have small arteries with the option of less invasive surgery to repair potentially life-threatening abdominal aortic aneurysms (AAAs). The FDA approved the system for patients with iliac or femoral artery access of less than 7 mm and an aorta with an inner diameter of between 15.5 and 17.4 mm. This Humanitarian Use Device is intended to treat fewer than 4,000 people in the U.S. each year.

Description: A portion of the metal stent is replaced with ring-shaped channels. After the device is in place in the aorta, the channels are injected with a polymer, expanding the endograft against the aorta to create a seal.

Benefit: The Ovation 20-mm system uses a narrow delivery system (4.7 mm in diameter vs. 7 mm in diameter for typical delivery catheters). The 20-mm system thus enables some patients with small blood vessels to be treated via minimally invasive surgery, an option not previously available.

Precaution: The Ovation system is

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contraindicated in patients with an infection that threatens to affect the graft, those who are allergic to the device materials, and those who are unable to undergo necessary imaging studies.

Adverse events may include problems with the blood, lungs, lymphatic system, heart, and gastrointestinal and genitourinary tracts. Investigators plan to track patients for complications and adverse events for 5 years.

Sources: www.trivascular.com; www.fda.gov

Device Recall

On October 18, 2011, Drager Medical issued a class 1 recall for its Infinity Acute Care System Monitoring Solution (M540), Catalog No. MS25510. All serial numbers are affected.

Made from March 1, 2011 through September 30, 2011, the device was distributed only to the Rush University Medical Center in Chicago from July 1, 2011, through September 30, 2011.

The system is used to monitor the patient's vital signs and therapy, to control alarms, to review Web-based diagnostic images, and to access patient records. The recall was initiated because of a potential for incorrect weight-based drug dosage calculations. There might also be a 5- to 10-second delay between the electrocardiogram and blood pressure curves at the device, possibly resulting in serious adverse health consequences, including death.

On October 17, the company advised Rush University Medical Center that users should enter the patient's weight via the administration/demographics screen to ensure the correct drug dosage calculation. Clients should follow the instructions for use and should use the bedside monitor for patients in bed.

The Infinity Central station is to be used only for remote assessment of the patient's status.

Source: FDA, December 6, 2011, www.fda.gov ■