



NEW DRUGS

Octaplas

For Coagulation Disorders

Octaplas (OctaPharma, Austria) is now approved for sale in the U.S. for patients with insufficient levels of coagulation factor. Clotting protein deficiencies can cause excessive bleeding or excessive clotting.

The sterile, frozen solution of human plasma is collected from several pretested donors and is treated with a solvent/detergent process to minimize the risk of virus transmission. The product provides an alternative to single-donor fresh frozen plasma.

Octaplas has been used in Europe and other countries. A previous generation of Octaplas was first marketed in 1992, and the current version has been marketed since 2006. More information about Octaplas is presented in this month's Pharmaceutical Approval Update column on page 151.

Source: FDA, January 17, 2013

Seasonal 'Insect Cell' Flu Vaccine

Flublok (Protein Sciences) is the first trivalent influenza vaccine that uses an insect virus (baculovirus) expression system and recombinant DNA technology. The vaccine is approved for preventing seasonal influenza in people 18 through 49 years of age.

Unlike current flu vaccines, Flublok does not use the influenza virus or eggs in its production. Although this technology is new to flu vaccine production, it has been used in some vaccines for preventing other infectious diseases. The technology offers the potential for a faster start-up of the manufacturing process in the event of a pandemic, and it is not dependent on an egg supply or on availability of the influenza virus.

Flublok contains three full-length, recombinant hemagglutinin proteins to protect against two A strains and one

B strain. The shelf life is 16 weeks from the date of manufacture.

Flublok is discussed in the Pharmaceutical Approval Update column, page 151.

Sources: FDA, January 16, 2013; GlobalData, January 18, 2013; Center for Infectious Disease Research and Policy, January 17, 2013, www.cidrap.umn.edu

Three Agents For Type-2 Diabetes

The FDA has approved three related tablets for use with diet and exercise to improve blood glucose control in adults with type-2 diabetes: Nesina (alogliptin), Kazano (alogliptin/metformin HCl), and Oseni (alogliptin/pioglitazone). All three drugs are made by Takeda.

Alogliptin, the new ingredient, is the fourth FDA-approved dipeptidyl peptidase-4 (DPP-4) inhibitor, joining sitagliptin (Januvia, Merck), saxagliptin (Onglyza, Bristol-Myers Squibb/AstraZeneca), and linagliptin (Tradjenta, Boehringer Ingelheim/Eli Lilly).

Takeda first applied for FDA approval in 2007, one year before the agency tightened its standards for new diabetes drugs. The company subsequently resubmitted its application with expanded data. The FDA twice more requested additional information, most recently in April 2012.

The three formulations were studied as monotherapies and in combination with sulfonylureas and insulin. These medications should not be used to treat type-1 diabetes or diabetic ketoacidosis.

Kazano carries a boxed warning for lactic acidosis, which can be associated with metformin. A boxed warning for Oseni mentions the risk of heart failure associated with pioglitazone. The FDA is requiring multiple postmarketing studies for each drug to monitor for cardiovascular problems, liver abnormalities, pancreatitis, and severe hypersensitivity reactions.

Sources: FDA and *MedPage Today*, January 25, 2013

Kynamro Injection For Inherited High Cholesterol

Mipomersen sodium (Kynamro, Genzyme) injection has been approved to treat patients with homozygous familial hypercholesterolemia (HoFH). A rare, inherited condition, HoFH affects about one in one million people in the U.S. Mipomersen is considered an orphan drug. The once-weekly injection works with other lipid-lowering drugs and diet to impair the production of apolipoprotein B-100.

The approval was based primarily on a 6-month, 51-patient trial. In October 2012, an FDA advisory committee had given mipomersen a lukewarm endorsement, voting 9-6 in favor of approval. Panel members had expressed concern about liver toxicity and injection-site reactions.

This is the first antisense oligonucleotide drug for systemic use to be approved by the FDA. Some patients in the drug's clinical trials developed antibodies to mipomersen. There is a theoretical concern that this immunogenicity could also lead to an autoimmune reaction to double-stranded DNA, similar to that seen in lupus.

A boxed warning mentions a risk of liver problems. The FDA is requiring four postmarketing studies and a Risk Evaluation and Mitigation Strategy (REMS).

Mipomersen was originally developed by Isis Pharmaceuticals. A competitor agent, lomitapide (Juxtapid, Aegerion), was approved for patients with HoFH in December 2012.

Sources: FDA, January 29, 2013; *Med Page Today*, January 30, 2013

Ravicti for Lethal Urea Cycle Defects

Glycerol phenylbutyrate (Ravicti, Hyperion) has been approved for patients with urea cycle disorders. These rare, potentially deadly hereditary conditions result from a deficiency in the enzymes that help to remove toxic ammonia from



the blood. Glycerol phenylbutyrate aids in the removal of accumulated ammonia, which can cause coma, brain damage, and death.

The drug is given in liquid form three times daily with food. Patients must follow a low-protein diet, sometimes accompanied by dietary supplements. Some studies confirmed that glycerol phenylbutyrate is safe and effective for children 2 years of age and older. The medication was approved in a fast-track program and was given orphan drug status.

Sources: FDA, February 1, 2013; *Med Page Today*, February 2, 2013

Generic Doxorubicin HCl Liposome Injection for Cancer

The FDA has approved the first generic version of Janssen's cancer drug Doxil. Made by Sun Pharma Global FZE, doxorubicin is injected intravenously by a health care professional. Sun's generic product will be available in 20-mg and 50-mg vials.

Doxorubicin HCl liposome injection has been on the FDA's drug shortage list. In February 2012, to address the shortage of this product, the FDA announced that it would exercise its discretion in temporarily importing Sun's Lipodox, an alternative to Doxil, even though it is not approved in the U.S. The FDA also decided to release one lot of Janssen's Doxil, made under an unapproved manufacturing process. For now, the FDA plans to continue importing Lipodox, and limited supplies of Doxil are available. When supplies of Sun's generic doxorubicin are sufficient to meet the projected demand, the FDA expects to stop exercising enforcement discretion for any unapproved doxorubicin HCl liposomal product.

Source: FDA, February 4, 2013

Pomalyst for Advanced Multiple Myeloma

Pomalidomide tablets (Pomalyst, Celgene) are used to treat patients with

multiple myeloma (MM) in patients who have received at least two prior therapies, including lenalidomide (Revlimid, Celgene) and bortezomib (Velcade, Takeda/Millennium).

Pomalidomide is the third drug in a class of immunomodulatory agents that includes lenalidomide and thalidomide (Thalomid, Celgene), and it is the second drug approved recently to treat MM. In July 2012, FDA approved carfilzomib (Kyprolis, Onyx Pharmaceuticals).

Pomalidomide was granted an orphan product designation under an accelerated approval program. A boxed warning mentions the risk of life-threatening birth defects if it is used during pregnancy, as well as a risk of blood clots. Because of the embryofetal risk, the drug is available only through a REMS program. Both lenalidomide and thalidomide have similar REMS programs.

Source: FDA, February 8, 2013

Delzicol for Ulcerative Colitis

Mesalamine (Delzicol, Warner Chilcott) has been approved for the treatment of mildly to moderately active ulcerative colitis and for the maintenance of remission of ulcerative colitis. The new product will be available in 400-mg delayed-release capsules. Mesalamine (5-aminosalicylic acid) is a nonsteroidal anti-inflammatory agent.

For patients with mildly to moderately active ulcerative colitis, the recommended dose in adults is two 400-mg capsules three times daily for 6 weeks. For maintenance of remission, the recommended dose in adults is 1.6 g daily in divided doses. Mesalamine should be taken at least 1 hour before or 2 hours after a meal.

Delzicol is replacing Asacol, Warner Chilcott's tablet for the same indication and its most profitable franchise. The FDA recommended that the company not have two products that might cause confusion to patients. One difference between the two drugs is that Asacol tablets

contain dibutyl phthalate as an inactive ingredient; Delzicol capsules contain dibutyl sebacate.

Other mesalamine agents for ulcerative colitis include Shire's Lialda, approved in 2007, and Pentasa, approved in 2001.

Sources: Warner Chilcott, www.wcrx.com/pdfs/pi/pi_delzicol.pdf, February 5, 2013; Reuters, February 8, 2013

NEW INDICATIONS

Botox for Overactive Bladder

Botox (onabotulinumtoxinA, Allergan) has been approved to treat overactive bladder in adults who cannot use or do not adequately respond to anticholinergic agents. Botox is also used to treat facial wrinkles, cervical dystonia, hyperhidrosis, blepharism, spasticity, strabismus, and chronic migraine.

When injected into the bladder, Botox blocks the transmission of nerve impulses to the detrusor muscle and calms contractions, thereby increasing the bladder's storage capacity and reducing episodes of urinary incontinence. The injection is performed via cystoscopy.

In two clinical trials, Botox treatment reduced episodes of incontinence by 50% or more, compared with placebo, after 12 weeks. The product's efficacy in the two studies lasted from 135 to 168 days, compared with 88 to 92 days for placebo.

Adverse effects have included urinary tract infections, painful urination, and urinary retention. Patients with type-2 diabetes who received the injections were more likely to develop urinary retention than nondiabetic individuals.

Candidates for this therapy should be free of any urinary tract infections. The FDA advises taking antibiotics before, during, and for a few days after Botox treatment to lower the risk of infection. The manufacturer and the FDA advise allowing at least 12 weeks between treatments.

Sources: FDA and Allergan, January 18, 2013



Exjade and Diagnostic For Iron Excess Unrelated To Transfusions

Deferasirox (Exjade, Novartis), an iron-chelating agent, was originally approved for treating chronically elevated levels of iron in the blood caused by repeated blood transfusions in patients 2 years of age and older. The expanded use includes patients 10 years of age and older with chronic iron overload resulting from non-transfusion-dependent thalassemia (NTDT), a genetic blood disorder. Individuals with NTDT, a milder form of thalassemia, do not need frequent red blood cell infusions, but over time, some of these patients are still at risk for iron overload, which can damage vital organs.

Deferasirox is intended for patients with NTDT who have liver iron levels of at least 5 mg of iron per gram of dry liver tissue weight.

The FDA also approved FerriScan (Resonance Health, Australia) as a non-invasive diagnostic companion for defer- asirox. This device is used to measure hepatic iron levels via magnetic resonance imaging. The drug's new indication was approved in an accelerated process, and FerriScan data were reviewed in a *de novo* classification process.

Source: FDA, January 23, 2013

Second-Line Avastin For Colorectal Cancer

Bevacizumab (Avastin, Roche/Genentech) is now approved as a second-line therapy for metastatic colorectal cancer. It is used with fluoropyrimidine/irinotecan (Coptosar, Pfizer)-based or fluoropyrimidine/oxaliplatin (Eloxatin, Sanofi)-based chemotherapy when the disease has progressed after a first-line bevacizumab-containing regimen.

Most patients with metastatic colorectal cancer receive bevacizumab plus chemotherapy as their initial treatment. The new use allows patients to be treated a second time with the therapy in com-

bination with a different chemotherapy regimen. The approval was based on a study showing that patients who continued with treatment after disease progression lived longer than patients receiving only chemotherapy.

Sources: California Healthcare Institute and FierceBiotech, January 24, 2013

Gleevec for Children with Acute Lymphoblastic Leukemia

Imatinib (Gleevec, Novartis) is now approved to treat children with newly diagnosed Philadelphia chromosome-positive (Ph+) acute lymphoblastic leukemia (ALL). These children have a genetic abnormality that results in the overproduction of immature white blood cells, leaving less room for healthy white blood cells needed to fight infection.

The safety and effectiveness for this new indication of imatinib were established in a clinical trial conducted by the Children's Oncology Group, sponsored by the National Cancer Institute.

In 2001, imatinib was granted an accelerated approval to treat patients with blast crisis or accelerated-phase or chronic-phase Ph+ chronic myeloid leukemia (CML) who did not respond to interferon-alpha therapy. It was later approved to treat children with newly diagnosed Ph+ CML in 2011. The drug was also approved in 2012 to treat adults after the surgical removal of *kit* (CD117)-positive gastrointestinal stromal tumors (GIST).

Source: FDA, January 25, 2013

DRUG NEWS

Warning: Liver Injury With Samsca

In a clinical trial involving tolvaptan (Samsca, Otsuka), three cases of serious but reversible increases in hepatic enzymes prompted the FDA to warn of potentially irreversible or fatal liver injury with the drug. Tolvaptan, a selective vasopressin V₂-receptor antagonist, is used to treat hyponatremia.

In the trial, three patients out of approximately 1,400 experienced elevated levels of alanine aminotransferase (ALT) three times above the upper limit of normal (ULN) as well as elevated serum total bilirubin levels above twice the ULN. All three patients improved after the drug was stopped. Therapy should not be restarted unless the cause of liver injury is found to be unrelated to tolvaptan.

Source: *MedPage Today*, January 25, 2013

Bisphosphonates and GI Tract Cancer

Some preclinical studies have shown that bisphosphonates, which are used to treat osteoporosis, have antitumor properties, but other studies have sounded a warning about esophageal cancer. To find out whether adverse effects on the gastrointestinal (GI) tract, such as mucosal irritation, could lead to ulceration and possibly cancer, researchers from the United Kingdom designed a series of nested-control studies using the two largest population databases. They matched patients 50 years of age and older with primary GI tract cancer with up to five controls.

No overall association was found between the use of bisphosphonates and a risk of esophageal, gastric, or colorectal cancer. One database showed a small but significantly increased risk of gastric cancer associated with alendronate (Fosamax, Merck). The risk, which was restricted to short-term users, was nearly double for those who used alendronate for less than 1 year. The researchers say this is unlikely to be a causal relationship because there was no association with long-term use.

The two databases were nearly identical in numbers of cancer cases over a 14-year period. The study group included a higher proportion of patients taking acid-lowering drugs and corticosteroids; these patients are more likely to develop



secondary osteoporosis. An increased rate of upper GI disorders before osteoporosis treatment has also been reported.

Although upper GI disorders and the use of acid-lowering drugs could be important confounders, they might also lie on the causal pathway. Removing these drugs from the adjusted analyses, however, did not noticeably change the results.

Source: *BMJ* 2013;356:f114

Tighter Controls Urged For Pain Drugs

Hydrocodone products accounted for 131 million prescriptions for 47 million patients in the U.S. in 2011. On January 25, an FDA advisory committee voted 19 to 10 in favor of moving hydrocodone combination drugs (e.g., Vicodin, Lortab, and Norco) into the more restrictive Schedule II category of controlled substances. Most of the panelists suggested that the drugs are pharmacologically similar to and as susceptible to abuse as other opioids, such as oxycodone combination drugs like Percocet (Endo), which are in the more tightly regulated class.

Moving the drugs from Schedule III to Schedule II would eliminate a clinician's ability to prescribe up to a 6-month supply of the drugs as well as the ability to simply call in a prescription. For Schedule II drugs, doctors can prescribe for no more than a 3-month supply, and a written prescription is mandatory.

It is not known whether the change will result in lower rates of addiction. Even though oxycodone products are in a more tightly regulated class, they are still subject to abuse. However, hydrocodone often acts as a gateway drug, and so the change may help.

Ultimately, most of the advisory committee decided that a reclassification into Schedule II would be appropriate, but it remains to be seen how the FDA will interpret their conclusions.

Source: *MedPage Today*, January 25, 2013

New Opana Formulation Linked to Blood Disorder

The "abuse-deterrent" version of oxymorphone (Opana ER, Endo) may be related to the development of thrombotic thrombocytopenic purpura (TTP), a blood-clotting disease. Tennessee health officials noted 15 cases of TTP among people who injected the drug since the new formulation of the opioid was launched in February 2012.

The new formulation is designed to inhibit crushing and dissolving tablets. In 2006 the FDA approved Opana ER for oral use only.

Last August, a nephrologist reported three cases of TTP to Tennessee officials. All of these persons were injection-drug users. After a statewide investigation, officials found a total of 15 cases of TTP among injection-drug users; 14 patients reported dissolving and injecting reformulated Opana. There were no deaths. Most of the cases involved women, who are generally at higher risk for TTP than men.

It is not clear how the reformulation might cause TTP. Inactive ingredients not present in the original version of Opana ER include polyethylene oxide (PEO) and polyethylene glycol (PEG). However, reformulated oxycodone (OxyContin, Purdue Pharma) also contains PEO and has not caused these problems. TTP could also be related to methods of preparing the drug for injection.

Adulteration of the product in Tennessee was not considered a probable cause. It is thought that a component of the new formulation, not the drug itself, might be related to endothelial damage.

The Centers for Disease Control and Prevention (CDC) recommends that clinicians treating patients with TTP-like illness with an unknown cause ask them about IV drug abuse, perform a urine drug test to look for oxymorphone, and request a copy of the patient's prescriptions for controlled substances from state

prescription drug-monitoring programs.

Patients who report injecting reformulated Opana ER should be counseled about the risk for recurrent TTP, blood-borne infections, and overdose with continued use.

Endo wants to block generic versions of its drug that do not contain abuse-resistance technology.

Sources: *MMWR* 2013;62(1):1-4; CDC, www.bt.cdc.gov/HAN/han00331.asp; *MedPage Today*, January 12, 2013;

ACE Inhibitors and Hallucinations in the Elderly

Elderly patients with memory problems who take angiotensin-converting enzyme (ACE) inhibitors might need to stop taking them if they suddenly have visual hallucinations. In four case studies, hallucinations experienced by patients with various memory deficits disappeared after they discontinued lisinopril (Zestril, AstraZeneca). The findings were reported from the University of Utah.

Hallucinations are a generally unrecognized adverse effect of ACE inhibitors. Patients in the four cases ranged in age from 92 to 101. They were taking lisinopril for hypertension or heart failure and had some memory impairment. In these four patients, stopping lisinopril resulted in the cessation of hallucinations within 48 hours for two patients and within 7 and 30 days for the third and fourth patients.

One patient who stopped taking hydrochlorothiazide first and then stopped lisinopril experienced recurrent hypertension 12 weeks after stopping the ACE inhibitor. When the patient was given lisinopril again, the hallucinations resumed within a week. The drug was then discontinued.

Seven case reports of visual hallucinations related to ACE inhibitors were published from 1988 to 2001 for cilazapril, enalapril (Vasotec, Merck/Biovail/Valeant), captopril (Capoten, Apothecon/Bristol-Myers Squibb), and quinapril (Accupril, Pfizer). Patient ages ranged



from 49 to 92. Two patients who resumed ACE inhibitor therapy experienced hallucinations again, but these resolved when the medication was discontinued.

In another 14 cases of ACE inhibitor-related hallucinations, four of these involved lisinopril. Other ACE inhibitors were ramipril (Altace, Monarch/King), enalapril, captopril, and perindopril (Aceon, Servier/Solvay/Xoma).

A suggested mechanism of action could be the tendency of these drugs to raise the level of opioid peptides. The data are considered too preliminary to confirm a direct drug-hallucination relationship.

ACE inhibitors are also discussed in this month's Pharmacovigilance Forum column on page 170.

Sources: *J Clin Hypertens*, January 25, 2013 (online); *MedPage Today*, January 30, 2013

A Focus on Treating Early-Stage Alzheimer's Disease

The FDA has issued a proposal designed to help companies develop new therapies for patients with early-stage Alzheimer's disease (AD) before the onset of overt dementia or irreversible damage to the brain. The draft guidance explains how researchers can identify patients with early AD, or those at risk, for participation in clinical trials. In recent years, researchers have tried to identify these patients using criteria based on biological indicators and have tried to develop sensitive measures that can detect subtle mental decline.

For patients with overt dementia, the FDA requires that treatments affect not only their abnormal thinking but also their functioning. The goal of these trials is to ensure that any beneficial effects on thinking are associated with an improvement or a lack of decline in how patients feel or function. However, because patients with early AD have little impairment of global functioning, it is difficult to determine whether a treatment

effect is clinically important.

The FDA proposal is part of the U.S. Department of Health and Human Services' efforts under the National Plan to Address Alzheimer's Disease.

Source: FDA, February 7, 2013

Older Cancer Patients Might Not Be Getting Full Treatment

Older adults with stage II or III colorectal cancer have a 25% lower chance of receiving all the treatment they need, according to a study at Boston Medical Center and Boston Veteran's Administration Medical Center.

Standard therapy includes surgical resection of tumor and at least one dose of both chemotherapy and radiation. In the study, 267 patients 71 years of age and older were significantly less likely to have surgery, and only about 50% of these patients received all three modes of therapy versus 115 (66%) younger patients.

Of the patients receiving full treatment, only 56% completed all three modes without a dose reduction, dose withheld, or dose delayed. More patients with stage III disease completed therapy (54%), compared with stage II patients (38%). Half of the patients in each age group received neoadjuvant chemoradiation; these patients were more likely to complete therapy than patients receiving postoperative adjuvant therapy.

One confounding factor could have been the tumor site. In current practice, neoadjuvant chemoradiation is recommended for patients with cancers situated up to 12 cm from the anal verge; however, patients with more proximal cancers are not considered candidates for preoperative radiation. A higher number of older patients had more proximal rectal cancers.

If only 49% of patients 71 years of age and older start all modes of therapy but nearly half do not complete the therapy, then only about 25% complete all standard

therapy at full doses and without delays. This finding is significant, given that the study was conducted at two academic centers with a high awareness of appropriate therapy.

Longstanding reluctance to treat older patients may be behind the poor numbers. Remedies include better education about the benefits of therapy, the long life expectancy of most healthy older adults, and the relatively good tolerance of the types of chemotherapy used for colorectal cancer. Geriatric assessment tools, the researchers suggest, may provide a more scientific basis for predicting toxicity. One practical outcome of the study is that nearly all patients at both centers are now evaluated in a multidisciplinary manner with dedicated oncologic surgery input.

The authors suggested reducing the toxicity of the therapies, for example, by using more neoadjuvant chemoradiation, conformal or intensity-modulated radiation, and less extensive surgery when possible.

Source: *J Geriatr Oncol* 2013;4:90-97

Vitamin B Combo (Metanx) Reduces Diabetic Neuropathy

Increasing vitamin B intake appears to have a beneficial effect on neuropathy and quality of life for patients with diabetes, according to researchers from Louisiana, Nebraska, Alabama, and Texas.

Vitamin B deficiency is common in patients with diabetes and may contribute to neurological deficits. However, current therapies for diabetic neuropathy pose a high risk of adverse effects and do not address the underlying pathology. The researchers theorized that combining L-methylfolate (the biologically active, bioavailable form of folate, which improves vascular function), methylcobalamin (vitamin B₁₂), and pyridoxal-5'-phosphate (vitamin B₆), might improve sensory neuropathy more safely. The vitamin B combination used was Metanx (Pamlab LLC).

The researchers randomly assigned



214 patients to receive Metanx or placebo. The primary endpoint was the effect on vibration perception threshold on the big toe of each foot. Secondary endpoints included scores on neuropathy, pain perception, disability, and quality of life.

The vibration perception threshold did not differ significantly between the two groups and might not have been sensitive enough to detect changes in nerve function attributable to the combination. However, neuropathy symptoms improved in the treated patients, who also experienced less neuropathy-related disability and a modest improvement in quality-of-life measures. Their mental status scores also improved by almost 2 points; by contrast, scores declined in the placebo group. Adverse events were rare and mostly mild to moderate.

From a patient's perspective, symptom relief could be the most important goal of neuropathy management. The clinical change depends on the patient's baseline level of symptoms. Even a small decline from a lower baseline score of 5.7 on the Neuropathy Total Symptom Score (NTSS-6), which measures sensation as well as pain, over a period of 1 year leads to meaningful changes in other parameters of neuropathy.

In this study, patients had only mild symptoms on the NTSS-6, with a mean baseline score of 3.6, or three to four mild symptoms or one to two moderate symptoms at baseline. The observed 1-point decrease over the 6 months of the study suggests that at least one mild symptom was completely eliminated or that one moderate symptom could be classified as mild.

Metformin (Glucophage, Bristol-Myers Squibb) was associated with less improvement in NTSS-6 scores. Metformin interferes with the absorption of cobalamin, which leads to progressive deterioration of nerve tissue, frequently misdiagnosed as diabetic peripheral neuropathy, according to the researchers.

They add that the negative association between NTSS-6 scores and metformin use suggests that methylcobalamin might have corrected a vitamin B₁₂ deficiency.

Source: *Am J Med* 2013;126:141-149

Potential Reversal Antidote For Factor Xa Inhibitors

Several drug companies are collaborating to test an agent that would reverse the anticoagulant effect of a new generation of factor Xa inhibitors. Portola Pharmaceuticals plans to work on a phase 2 trial of PRT 4445 with Bayer and Janssen, co-developers of rivaroxaban (Xarelto). Portola, Bristol-Myers Squibb, and Pfizer plan to collaborate on another phase 2 trial designed to test PRT 4445 against apixaban (Eliquis).

PRT 4445 is a recombinant protein designed to reverse the anticoagulant activity of any factor Xa inhibitor in the case of uncontrolled major bleeding or the need for emergency surgery. Similar to native factor Xa, it acts as a "decoy" for factor Xa inhibitors in the blood, preventing them from blocking the activity of native factor Xa. As a result, native factor Xa is available to participate in coagulation and restore normal clotting.

Reversal agents are available for heparin and the vitamin K antagonists but not for rivaroxaban and apixaban. Health care professionals are concerned about the lack of an antidote for reversing excess bleeding with the recently approved FXa inhibitors.

In the trials, PRT 4445 passed phase 1 testing in 32 healthy volunteers in the U.S. with no apparent safety problems. The phase 2 trial will test various doses of PRT 4445 for its ability to reverse the anticoagulation activity of rivaroxaban. The trial is expected to be completed later this year.

The newer-generation oral anticoagulants are discussed on page 173.

Source: *MedPage Today*, February 6, 2013

ACE Inhibitor Improves Walking Time in Patients With PAD

In a clinical trial reported from Australia, walking duration and pain-free walking improved significantly in patients with claudication after they were treated with ramipril (Altace, Monarch/King), an angiotensin-converting enzyme (ACE) inhibitor. The average pain-free walking time increased by more than 60%, and maximum walking time more than doubled after 6 months of treatment.

Most secondary outcomes improved with ramipril, compared with placebo, including ankle-brachial index, a scale specific to peripheral arterial disease (PAD), and health-related quality of life.

ACE inhibitors are not specifically recommended for relieving intermittent claudication. This appears to be the first adequately powered, randomized trial showing that ramipril was associated with improved walking on a treadmill in patients with PAD.

About one-third of patients with PAD have intermittent claudication, characterized by pain during walking that is relieved by rest. Therapy for PAD is focused on reducing cardiovascular risk and improving function and quality of life. Medical therapy usually has only a modest effect on walking distance. The only drugs approved for PAD in the U.S. are pentoxifylline (Trental, Sanofi-Aventis) and cilostazol (Pletal, Otsuka), which increase walking distance by 15% to 25%.

After a pilot study of ramipril showed improvement, investigators extended the evaluation in a larger, randomized, placebo-controlled trial of 212 patients with symptomatic PAD. The patients received either daily ramipril or matching placebo for 24 weeks. Patients underwent treadmill assessments before randomization and at the end of the trial.

Half of the patients had hypertension, about 28% had never smoked, and about 25% of the patients had diabetes.

The baseline mean pain-free walking



time was 140.3 seconds with ramipril and 144.2 seconds with placebo. At the completion of the trial, the treated patients reported improved pain-free walking time and they had better walking distance, walking speed, stair climbing, and physical well-being.

The results should be interpreted cautiously because of possible differences in patients outside of Australia. There may also be differences in the action of various medications.

ACE inhibitors are discussed in this month's new Pharmacovigilance Forum column on page 170.

Sources: *JAMA* 2013;309:453-460; *MedPage Today*, February 5, 2013

Erlotinib Plus Celecoxib Might Prevent Head and Neck Cancer In High-Risk Patients

A new drug combination shows promise for reducing the risk of squamous cell carcinoma of the head and neck (SCCHN) in patients with advanced oral precancerous lesions.

Based on earlier studies suggesting a role for epidermal growth factor receptor (EGFR) and cyclooxygenase-2 (COX-2) in promoting this cancer, researchers from Emory University suggested that combining an EGFR inhibitor and a COX-2 inhibitor might provide an effective chemopreventive approach. They found that the combination of the EGFR inhibitor erlotinib (Tarceva, OSI, Genentech) and the COX-2 inhibitor celecoxib (Celebrex, Pfizer) was more effective for inhibiting the growth of human SCCHN cell lines compared with either drug alone. In addition, treating mice with the combination before transplanting them with human SCCHN cells suppressed cancer cell growth more effectively than pretreating the mice with either drug alone.

Based on these preclinical analyses, the researchers began a phase 1 chemoprevention trial. Eleven patients

with advanced oral precancerous lesions were assigned to treatment with erlotinib and celecoxib. Biopsies were available for seven patients at baseline and in the follow-up period.

Three of the seven patients had a complete pathological response with no evidence of the precancerous lesions in the follow-up biopsy sample. Two other patients had a partial pathological response, and two had progressive disease.

The drug combination caused some advanced premalignant lesions to disappear completely (advanced premalignant lesions rarely regress).

Several patients withdrew from the trial because of severe adverse effects. The authors say that prevention cannot be achieved through short-term treatment and that more study of the combination's safety and toxicity is necessary before they can plan a large-scale trial.

Source: *Clin Cancer Res*, February 19, 2013 (online)

Lowering Blood Pressure Quickly Is Safe in Patients With Brain Hemorrhage

Rapid lowering of blood pressure (BP) in patients with an intracerebral hemorrhage has been found to be safe and does not compromise cerebral blood flow. The findings were reported from the Intracerebral Hemorrhage Acutely Decreasing Arterial Pressure Trial (ICH ADAPT) and were also presented at the International Stroke Conference in Honolulu.

The intravenous (IV) antihypertensive treatment protocol included labetalol (e.g., Normodyne, Key; Trandate, Prometheus), hydralazine (Apresoline, Novartis) and enalapril (Vasotec, Merck/Biovail/Valeant).

In the study, reported from the University of Alberta, mean systolic BP was significantly lower within 30 minutes in patients receiving the aggressive treatment. Two hours later, mean systolic BP was 140 mm Hg and 162 mm Hg in the

aggressively treated and conservatively treated groups, respectively.

Computed tomography perfusion imaging scans taken 2 hours after randomization showed that blood flow around the hematoma, the primary endpoint, did not differ significantly in 39 patients receiving the aggressive IV treatment targeting a systolic BP of less than 150 mm Hg, compared with 36 patients treated to a target of less than 180 mm Hg.

The authors suggested that a more aggressive absolute target of less than 150 mm Hg did not reduce cerebral blood flow, compared with conservative management, even when treatment was initiated earlier and in those with larger hematoma volumes. They also found no consistent relationship between the magnitude of the BP decrease and perihematoma cerebral blood flow.

There had been concerns that rapidly lowering BP would cause ischemia around the hemorrhage because increased local pressure might impair the ability to perfuse that region. The study suggested that this is not the case.

Although the current trial was underpowered to assess clinical outcomes, the findings should be reassuring to physicians.

Sources: *Stroke*, February 7, 2013 (online); *MedPage Today*, February 9, 2013

Lowering Blood Pressure May Reduce Risk of More Strokes

In a randomized trial reported from the University of British Columbia, treating patients with lacunar strokes to a systolic blood pressure (BP) target of below 130 mm Hg was feasible and safe and may have prevented recurrent strokes. Lacunar strokes are common and are believed to be major contributors to cognitive impairment.

The annual rate of a stroke after a mean follow-up of 3.7 years was 2.3% among patients treated to that target and 2.8% among those treated to a target of 130 to



149 mm Hg. The 20% difference, however, fell shy of statistical significance. The results were reported at the International Stroke Conference (ISC) in Honolulu.

There was no significant difference in the annual rate of ischemic stroke (2% for the lower-target patients vs. 2.4%), but there was a significant reduction in intracerebral hemorrhage with the lower target. Taken together with evidence from earlier trials of BP-lowering in patients with stroke and transient ischemic attack, the authors concluded that targeting a systolic BP of less than 130 mm Hg was likely to reduce the occurrence of stroke by about 20%.

The Secondary Prevention of Small Subcortical Strokes (SPS3) study enrolled 3,020 patients (median age, 63 years). The study included antiplatelet therapy and BP targets. The antiplatelet intervention was stopped early because of the risk of bleeding with the combination of aspirin and clopidogrel (Plavix, Bristol-Myers Squibb/Sanofi).

The current trial was conducted at 81 sites in eight countries. Patients had experienced a lacunar stroke occurring within 180 days before enrolling in the trial. The patients did not have cortical stroke, cardioembolic disease, or carotid stenosis. In the BP intervention, the drugs used to achieve the higher or lower target were not specified in the study protocol.

At baseline, the average number of antihypertensive agents used was 1.8 in the higher-target group and 1.7 in the lower-target group. The average BP was about 145/80 mm Hg in both groups. At 1 year, the average number of hypertensive agents remained at 1.8 in the higher-target group but increased to 2.4 in the lower-target group. The proportions of patients taking various classes of medications differed between the two groups, with more medications taken by the lower-target group.

By 1 year, the average systolic BP was 11 mm Hg lower in the lower-target group

(127 vs. 138 mm Hg). This difference was maintained for the duration of the study.

The researchers also examined rates of major vascular events and death. No differences based on BP target were observed.

Treatment to a systolic BP of below 130 mm Hg was considered safe. There were no significant differences in serious complications of hypotension. Orthostatic syncope was more frequent with the lower target, but the difference was not significant. Only one patient in the lower-target group had a serious complication (bradycardia) related to the BP medications.

These data and conclusions are considered preliminary.

Sources: ISC, Abstract LB8; *MedPage Today*, February 9, 2013

Teens Lose Weight With Exenatide

In a small, placebo-controlled randomized trial, exenatide (Bydureon, Byetta, Amylin/Eli Lilly), a drug for type-2 diabetes, was associated with lower body weight and body mass index (BMI) in severely overweight adolescents.

As a glucagon-like peptide-1 (GLP-1) receptor agonist, exenatide suppresses appetite and increases feelings of satiety. It slows gastric motility and activates GLP-1 receptors in the hypothalamus in people with and without diabetes. The modest reductions suggest that the drug, which is approved for adults with type-2 diabetes, might be useful in adolescents with a BMI of 25 kg/m² or higher.

The authors cautioned that the study was short in duration, only 3 months in the randomized phase, followed by another 3 months of open-label treatment. Fewer than two dozen teenagers, 12 to 19 years of age, were enrolled. Larger, longer-term studies would be needed to assess the durability of the weight loss over time.

Although the results of the trial were

statistically significant, their clinical importance remained unclear. The patients were very obese, with an average BMI of 42.5 kg/m²; therefore, the reductions observed in the study would typically reduce body fat from 50% to 48.5% at most. It was not clear whether this change was clinically meaningful.

In a previous nonrandomized study, exenatide reduced BMI by about 5%.

Sources: *Arch Pediatr Adolesc Med* 2013;167:1-3; *MedPage Today*, February 5, 2013

Short Course of Androgen Deprivation Benefits Survival In Prostate Cancer

Men with node-negative high-risk prostate cancer lived just as long with a 50% shorter duration of androgen-deprivation therapy (ADT) compared with the standard length of therapy, according to a randomized clinical trial.

After a median follow-up of 6.5 years, 76.2% of patients who received pelvic radiotherapy and androgen blockade remained alive after 18 months of ADT compared with 77% of the men who had hormonal treatment for twice as long. The findings were reported from Sherbrooke University Hospital in Quebec.

The treatment groups did not differ in 5- and 10-year overall or disease-specific survival. The results suggested that in men with localized high-risk prostate cancer who received radiation and androgen blockade, the duration of androgen blockade could safely be reduced from 36 to 18 months.

The addition of ADT to radiation therapy has been shown to improve survival in men with high-risk prostate cancer, but the optimal duration of ADT has not been determined. The current standard of 24 to 36 months showed superiority of ADT over a period of 6 months.

The longer a man's exposure to ADT, the more likely the occurrence of adverse effects, such as bone pain, nausea



and vomiting, acute renal insufficiency, back pain, mental confusion, bronchopulmonary complications, sweating, fever, cardiac arrhythmias, and blood glucose fluctuations. Symptoms of “castration syndrome” include a loss of libido, erectile dysfunction, and impotence, as well as fatigue, cognitive dysfunction, mood swings, decreased muscle mass, increased abdominal fat, and osteoporosis.

Sources: Genitourinary Cancer Symposium, Abstract 3, Orlando; *MedPage Today*, February 12, 2013

New Drug Non-inferior to Linezolid for Skin Infections

In a phase 3 randomized trial, acute bacterial skin infections responded equally well to treatment with linezolid (Zyvox, Pfizer) and a short course of an investigational agent, tedizolid phosphate (Trius Therapeutics).

About 80% of patients had early responses to both drugs, which proved to be durable in about 70% of patients. Post-treatment follow-up showed success rates of 85% to 86%, regardless of the therapy used. A high percentage of methicillin-resistant *Staphylococcus aureus* (MRSA) infections responded to either drug.

Treatment with 200 mg of tedizolid phosphate once daily for 6 days was statistically non-inferior in efficacy to 600 mg of linezolid twice daily for 10 days at both early and late time points and was generally well tolerated in a trial of patients with acute bacterial skin and skin structure infections. The researchers noted that tedizolid phosphate might become a reasonable alternative to linezolid for treating these skin infections.

In most cases, acute bacterial skin infections respond to available antibiotic therapies, but the emergence of antimicrobial resistance and adverse effects has limited their use. Linezolid is the only antibiotic approved for these infections when complicated by MRSA, but safety concerns have arisen since the agent be-

came available more than a decade ago.

Tedizolid phosphate is a novel oxazolidinone prodrug that is converted rapidly *in vivo* into tedizolid. The drug has shown activity against all clinically relevant gram-positive pathogens, including linezolid-resistant *S. aureus*. Tedizolid and linezolid are orally available, but the lowest effective dose of tedizolid is 200 mg/day for 5 to 7 days. The dosage for linezolid is 600 mg twice daily for 14 days.

Clinical response rates at initial follow-up were 79.5% in the tedizolid group and 79.4% in the linezolid group. Sustained clinical responses at the end of randomized treatment were 69.3% with tedizolid and 71.9% with linezolid. The tedizolid patients had a clinical success rate of 85.5% at the last follow-up visit, compared with 86% in the linezolid patients.

The tedizolid arm’s rate of adverse events was 40.8% versus 43.3% in the linezolid arm. Thrombocytopenia rates were 2.3% with tedizolid and 4.9% with linezolid.

If tedizolid is approved by the FDA, it would be the first oral drug in the Infectious Diseases Society of America’s initiative to bring 10 new antibiotics to market by 2020.

Sources: *JAMA* 2013;309:559–569; *MedPage Today*, February 12, 2013

OTC Oxytrol Patch For Overactive Bladder In Women

A patch containing oxybutynin (Oxytrol for Women, Merck) may now be sold as an over-the-counter (OTC) medication for female patients 18 years of age and older with symptoms of overactive bladder. Men will continue to need a prescription for the drug.

Oxybutynin is an anticholinergic agent that helps to relax the bladder muscle. This is the first available OTC agent in this drug class. The 3.9-mg patch is applied to the skin every 4 days.

The FDA’s advisory panel voted against the reclassification in November

because of concerns about the potentially inappropriate use of the drug without a physician’s oversight or without a confirmed diagnosis of overactive bladder.

Approval of the OTC formulation was supported by nine studies in more than 5,000 patients. Consumers generally understood the information on the label and used the drug appropriately.

In the studies, men were unsure as to whether oxybutynin was the appropriate treatment for their urination problems. There is concern that incorrect self-diagnosis in men could delay the detection of prostate cancer. Consequently, Merck did not seek OTC status for the product in men.

Sources: FDA and *MedPage Today*, January 25, 2013

Anti-Copper Agent Helps To Prevent Triple-Negative Metastatic Breast Cancer

An anti-copper drug compound that blocks the ability of bone marrow cells to receive migrating cancer tumor cells has shown a benefit in a very difficult-to-treat form of cancer—high-risk triple-negative breast cancer. The drug used was etra-thiomolybdate (TM).

Copper depletion appears to inhibit the production, release, and mobilization of endothelial progenitor cells (EPCs) from the bone marrow, thereby leading to tumor dormancy. The findings were reported from Weill Cornell Medical College.

The median survival for metastatic triple-negative breast cancer patients is about 9 months, but a new phase 2 trial showed if patients at high risk of relapse with no current visible breast cancer are depleted of copper, a prolonged period of time with no cancer recurrence resulted. Only two of 11 study participants with a history of advanced triple-negative breast cancer experienced relapse within 10 months after using TM.

Four of the study participants with a history of metastatic triple-negative

continued on page 147



continued from page 140

breast cancer have remained disease-free for 3 to 5.5 years.

The compound may work by affecting the tumor microenvironment, specifically the bone marrow–derived cells that are critical for metastasis.

Study participants with either stage 3 or stage 4 breast cancers who had no evidence of disease after treatment also fared well to date. The progression-free survival rate among these 29 patients in the study has been 85%.

The authors concluded that TM still needs to be compared with other therapies. Dr. Linda Vahdat of Weill Cornell expects to launch a phase 3 randomized clinical trial in the near future.

This research is a report of the first 40 patients. The clinical trial began in 2007 and was expanded many times. Currently, 60 patients are enrolled, and more than half of these women have triple-negative breast cancer.

Investigators at the college, including some of the current study's coauthors, previously found that a collection of bone marrow–derived cells, which include vascular endothelial growth factor receptor (VEGFR1) and hematopoietic progenitor cells (HPCs), prepare a site in distant organs to accept cancer cells. HPCs also recruit EPCs, among others, to activate a switch for angiogenesis that establishes blood vessels at the site to feed newly migrated cancer cells.

Breast cancer studies conducted at Weill Cornell also found that immediately before a relapse, levels of EPCs and HPCs rise significantly further, suggesting that the EPC target of the copper depletion approach is one that makes sense.

The EPCs and HPCs leave a trail for cancer cells to follow and provide the building blocks for blood vessels to greet them as they arrive, according to Dr. Vahdat.

Copper is critical to mobilizing these cells and is essential to the metastatic process. It is a key component of enzymes

that help turn on angiogenesis in the tumor microenvironment, and it appears to direct cancer cell migration and invasion.

TM is a copper chelation compound used to treat Wilson's disease, a hereditary copper metabolism disorder, and has been studied in phase 1 and phase 2 clinical trials for several disorders. In animal studies, depleting copper decreased the proliferation of EPCs and blocked blood vessel formation and tumor growth.

Dr. Vahdat's study is the first human clinical trial to use a copper-depletion strategy to modulate EPCs in breast cancer patients with a very high risk of relapse from occult residual disease.

Triple-negative breast cancer patients have a poor prognosis even when the cancer is diagnosed in early stages. Dr. Vahdat says that these women represent a substantial proportion of metastatic breast cancer patients.

In the study, 75% of patients achieved the copper-depletion target using TM after 1 month of therapy. Copper depletion was most efficient (91%) in patients with triple-negative tumors compared to other tumor types (41%). In the copper-depleted patients only, there was a significant reduction in EPCs, and the 10-month relapse-free survival was 85%.

Sources: *Ann Oncol*, February 13, 2013 (online); Weill Cornell Medical College

Obesity Raises MS Risk in Girls

In a study from Kaiser Permanente, increasing levels of obesity in adolescent girls were linked to a heightened risk of multiple sclerosis (MS) or with a precursor condition, clinically isolated syndrome (CIS). The presenting symptom was more likely to be transverse myelitis in the obese children than in the overweight or normal-weight children.

Obesity is associated with low-level systemic inflammation, but whether the obesity epidemic among adolescents is related to the increased recognition of MS in young patients is unknown.

Researchers analyzed data from a cohort of 75 children with demyelinating diseases and 913,097 unaffected controls from a large children's health study in Southern California. The diagnosis of MS required two or more episodes of demyelination in the central nervous system, whereas CIS was a single demyelinating event without encephalopathy.

A total of 72% of children diagnosed with MS/CIS were at least 11 years old, 52% were Hispanic, and more case patients than controls were female (54.7%). Slightly more than half of the patients in the MS/CIS group were either overweight or obese. Among the children who developed MS/CIS between ages 2 and 11, there was a nonsignificant trend for increasing risk with higher BMI among girls. There was no association for boys with increasing weight.

Optic neuritis was found in 36.8%, 50%, and 11.1% of the overweight, moderately obese, and extremely obese patients, respectively. The diagnosis of MS was made in 47.3% of the overweight children and in 50% and 66.7% of those who were moderately or extremely obese.

It was unclear why weight did not influence the risk among boys. Possible factors included the earlier onset of obesity in boys and the influence of puberty, as well as the effects of inflammation on hormones. Previous research has suggested that low-level inflammation can increase the levels of estrogens in both sexes and can lower androgen levels.

The rapid rise and high estrogenic exposure of obese, peripubescent girls, combined with the inflammatory mediators released by adipose tissue may accelerate CIS/MS onset into adolescence. In boys, it may take longer for this excess exposure to estrogen to occur, delaying the development of disease into later adulthood. Pediatric MS/CIS is rare and does not warrant screening of obese adolescents for transverse myelitis.



Sources: *Neurology* 2013;80:548–552; *MedPage Today*, January 30, 2013

Endocarditis and Cancer Link

Endocarditis is a strong clinical marker for occult cancer, say researchers from Denmark and the Danish Cancer Society. Unfortunately, intensive antibiotic therapy does not reduce the long-term risk of cancer.

Data from 8,445 patients with a first hospital diagnosis of endocarditis from 1978 to 2008 were analyzed. The median follow-up time was 3.5 years, for a maximum of 31 years. During that time, 997 cancers were observed in patients with endocarditis (620 cancers had been expected). The risk was slightly higher for patients with prior heart-valve disease, recent surgery, or recent infection.

The most dangerous time for patients with endocarditis was in the first 3 months after admission. Risks were higher for gastrointestinal (GI) and hematological cancers and lower for lung, prostate, and breast cancer.

The risk of most cancers fell markedly after the first 3 months, but the overall risk stayed at 1.5-fold for the next 5 years of follow-up. After that, the risk was still increased but less so, at 1.21-fold. The continued slightly increased risk attributed to endocarditis might also have been related to shared risk factors, including lifestyle (e.g., smoking, alcohol use) and immunosuppression. Notably, the risk of liver, colon, rectal, and small-intestine cancers remained high—double to triple—throughout the first 2 years.

Early cancer risk was highest in subjects without other risk factors for endocarditis, supporting a causal role of occult cancer in endocarditis development. The researchers suggested that bacterial pathogens causing endocarditis might have affected cancer development. There is a well-documented link between *Helicobacter pylori* and gastric adenocarcinoma and lymphoma, and acutely

impaired cell-mediated immunity is strongly associated with lymphomas, leukemias, and systemic bacterial infection.

Although it is not clear whether antibiotics affect cancer risk, the fact that longer-term cancer relative risks were elevated for endocarditis patients with predisposing risk factors supports the hypothesis that intensive antibiotic treatment increases general cancer risk, possibly by harming intestinal microflora.

Source: *Am J Med* 2013;126:58–67

DEVICE NEWS

Zecuity Patch for Migraine

Adults with migraine headaches and nausea, with or without aura, may find relief with Zecuity, a battery-powered sumatriptan skin patch, made by NuPathe. The single-use patch is applied to the upper arm or thigh during a migraine and can deliver 6.5 mg of sumatriptan over the course of 4 hours. A pushbutton activates the patch. Sumatriptan (Imitrex, Cerenex/GlaxoSmithKline) was initially approved for the treatment of migraine in 1992.

The system was approved after a phase 3 trial of 800 patients. The FDA had declined to approve the company's application for a different transdermal sumatriptan patch (Zelrix) in August 2011. The agency requested additional data for Zelrix, citing concerns over the product's safety, chemistry, and manufacturing. The approval of Zecuity may obviate the need for more data.

The patch should not be used by patients with a history of heart disease or stroke, peripheral vascular disease, transient ischemic attack, blood circulation problems, uncontrolled blood pressure, basilar migraines, contraindications to sumatriptan, Wolff–Parkinson–White syndrome, or other arrhythmias.

The patch should not be applied within 24 hours of using another migraine drug or within 2 weeks of using a monoamine oxidase A inhibitor. Serotonin syndrome

can be exacerbated when triptans are used with certain antidepressants.

Sources: NuPathe, <http://ir.nupathe.com>, and *MedPage Today*, January 18, 2013

Retinal Photos for the iPhone

A new smartphone-based system enables physicians to take wide-view photos of the retina through an undilated pupil. The photos can then be stored in the patient's medical record or e-mailed to a retinal specialist for interpretation.

The portable Welch Allyn iExaminer has been approved to work with the iPhone 4 and 4S. This advance has the potential to improve the quality of care, especially for remote users who might not have easy access to specialists. Images also can be printed for office use.

Sources: WelchAllyn, www.welchallyn.com; MedCity News.com, January 23, 2013; Medscape.com, January 29, 2013

Better Images, Less Radiation With New CT Scanner

In an analysis of 107 patients undergoing heart scans, a new-generation, FDA-approved computed tomography (CT) scanner substantially reduced potentially harmful radiation while still improving overall image quality. National Institutes of Health (NIH) researchers, along with engineers at Toshiba, developed the scanner. Radiation exposure was reduced by as much as 95% when compared with that of current machines.

Most CT scanners in use have 64 rows of x-ray detectors. The newly approved scanner has 320 detector rows, which allow imaging of a larger area of the body at one time; the x-ray beam generator is also more powerful. A full rotation can be completed in 275 milliseconds (msec), compared with 350 msec for current scanners. These improvements may help clinicians to identify problems in very small blood vessels and measure blood flow in the heart.



The median effective radiation dose was 0.93 millisieverts (mSv), compared with 2.67 mSv for the first-generation scanner. Most patients received less than 4 mSv of radiation. (The average person receives about 2.4 mSv of background radiation each year.) Coronary CT angiography typically involves radiation doses between 5 and 20 mSv, depending on the patient's body type and the quality of the machine.

More studies are needed before the scanner can be adopted for wide clinical use.

Sources: *Radiology*, January 22, 2013 (online); NIH, January 31, 2013

NEW MEDICAL DEVICES

Marvin M. Goldenberg PhD, RPh, MS

Name: Xience Xpedition Drug Eluting Stent System

Manufacturer: Abbott, Abbott Park, Ill.

Approval Date: January 3, 2013

Purpose: Xience coronary stent systems are used to treat symptomatic heart disease caused by *de novo* native coronary artery lesions. These are the only everolimus-eluting stents in the U.S. to be proven safe for direct stenting. With this technique, no preliminary device, such as a balloon dilatation catheter, is required to prepare the lesion.

Description: The Xience Xpedition stent is available in the largest size matrix in the U.S. Diameters range from 2.25 mm to 4.25 mm, including 3.25 mm. Lengths range from 8 mm to 38 mm for more accurate vessel sizing. The new stent can be used in patients with complex or challenging anatomy.

Benefit: The Xience stent is also indicated for patients with diabetes and those undergoing dual antiplatelet therapy for a minimum of 3 months. The data show an excellent safety profile and less thrombosis with this stent compared with a bare-metal stent.

Sources: www.fda.gov; www.cxvascular.com www.cathlabdigest.com

Name: Skyla Intrauterine Device

Manufacturer: Bayer Healthcare, Wayne N.J.

Approval Date: January 10, 2013

Purpose: Skyla is the first new intrauterine device (IUD) to be approved by the FDA in 12 years. This levonorgestrel-releasing system can prevent pregnancy for up to 3 years.

Description: The small, flexible plastic T-shaped device contains 13.5 mg of levonorgestrel, a progestin. The size of the T-body is 28 mm x 30 mm. The outer diameter of the placement tube is 3.8 mm.

Benefit: Women may use Skyla whether or not they have had children. Mirena, also manufactured by Bayer, is a 5-year IUD for women who have had at least one child.

Skyla slowly releases only small amounts of levonorgestrel into the uterus. During the first 3 to 6 months of use, women may experience irregular menstrual periods; an increased number of bleeding days; or spotting, light bleeding, or heavy bleeding. With continued use, the number of bleeding and spotting days tends to lessen. There is a small chance that periods may stop altogether.

The IUD can be inserted during an office visit and may be removed by a health care provider at any time. About 77% of women who desire pregnancy become pregnant sometime in the first year after the IUD is removed. Skyla is 99% effective.

The cost is \$652.32; however, with the product's approval following the passage of the Patient Protection and Affordable Care Act (ACA) and the contraceptive mandate, some women with commercial insurance might be able to obtain Skyla without a copay.

Precautions: Adverse effects may include changes in bleeding patterns, vulvovaginitis, abdominal or pelvic pain,

acne or seborrhea, ovarian cysts, and headache. Serious adverse reactions have included ectopic or intrauterine pregnancy, infections, pelvic inflammatory disease, perforation, and expulsion of the device.

Source: www.drugs.com; www.medpagetoday.com

Name: Deep Transcranial Magnetic Stimulation Device

Manufacturer: Brainsway Ltd., Jerusalem, Israel

Approval Date: January 10, 2013

Purpose: Transcranial magnetic stimulation (TMS) is a noninvasive technique for use in depression, schizophrenia, and other neurological disorders. The device is designed for patients with depression who have not responded to their current antidepressant medication.

Description: Areas that lie deep in the brain can be either excited or inhibited, depending on the frequency of the magnetic field. The pulses are administered by passing high currents through an electromagnetic coil placed adjacent to a patient's scalp.

The pulses induce an electric field in the underlying brain tissue. When the induced field is above a certain threshold and is directed in an appropriate orientation in relation to the brain's neuronal pathways, localized axonal depolarizations are produced, thereby activating the neurons in the relevant brain structure.

Benefit: The Brainsway system was developed by Professor Abraham Zangen while he worked at the U.S. National Institutes of Health. Patients now have an opportunity to receive comfortable treatment without the need for anesthesia, hospitalization, or significant adverse effects that might affect their quality of life.

Sources: www.brainsway.com; www.bioportfolio.com; www.medicaldevices-today.com ■