**NEW DRUGS**

**H1N1 Influenza Virus Vaccines**

The FDA has approved four vaccines to protect the population against the 2009 pandemic H1N1 influenza virus. About 45 million doses should be available at 90,000 sites in October. The government has ordered 195 million doses. CSL Ltd., MedImmune LLC, Sanofi-Pasteur, and Novartis Vaccines/Diagnostics Ltd. are using the same processes to make the H1N1 vaccines. Based on preliminary data, the 2009 H1N1 vaccines induce a robust immune response in most healthy adults eight to 10 days after a single dose. Clinical studies are under way to determine the optimal dose for children.

As with seasonal influenza vaccines, some of the H1N1 vaccines contain thimerosal, a mercury-containing preservative. People with severe or life-threatening allergies to chicken eggs, or to any other substance in the vaccine, should not be vaccinated.

In ongoing studies, the vaccines have been well tolerated thus far. For the injected vaccine, side effects may include soreness at the injection site, mild fever, body aches, and fatigue for a few days. For the nasal spray, adverse effects may include runny nose or nasal congestion in people of all ages, sore throats in adults, and fever in children two to six years of age.

Vaccines against three seasonal virus strains are already available, but they do not protect against the 2009 H1N1 virus.

Sources: FDA, September 15, 2009; Associated Press, September 16, 2009

**Intuniv For ADHD**

Shire’s Intuniv (guanfacine), a selective alpha2A receptor agonist, has been approved for the treatment of attention-deficit/hyperactivity disorder (ADHD). The product is indicated for children and adolescents 6 to 17 years of age and is expected to be available in November.

A once-daily, extended release formulation, Intuniv is not a controlled substance and has no known potential for abuse or dependence. The drug’s efficacy was evident after two studies of eight and nine weeks in duration.

Sources: Thomson Reuters, September 3, 2009; Medical News Today, August 1, 2009

**Valturna for Hypertension**

Valturna (Novartis), a tablet combining aliskiren and valsartan, is the first medication to target two key points within the renin–angiotensin–aldosterone system. This drug is indicated for the treatment of hypertension that has not been adequately controlled with aliskiren or monotherapy with an angiotensin-receptor blocker and as an initial therapy for patients who may need multiple drugs to achieve their blood pressure (BP) goals.

Valsartan is the active ingredient in Diovan, and aliskiren is the active ingredient in Tekturna, a direct renin inhibitor. Valturna appears to offer greater reductions in BP than either drug alone.

The approval was based primarily on a pivotal eight-week randomized, double-blind clinical trial involving approximately 1,800 patients.

Valturna, Tekturna, and Diovan are not indicated for treating or preventing stroke, heart attack, heart failure, kidney failure or eye problems resulting from hypertension.

The tablets contain aliskiren and valsartan in two strengths: 150 mg/160 mg and 300 mg/320 mg.

Sources: www.pharma.us.novartis.com; Medical News Today, September 17, 2009

**IV Ibuprofen (Caldolor) For Pain and Fever**

An intravenous (IV) formulation of ibuprofen (Caldolor), designed primarily for use in hospitals, is now available. Caldolor is the first injectable product available in the U.S. for the treatment of pain and fever.

The introduction of IV ibuprofen should help achieve improved pain control with less need for opioid analgesics and fewer opioid-related side effects. Until now, the only injectable drugs available to relieve pain were opioids, which can cause sedation, nausea, vomiting, cognitive impairment, and respiratory depression.

IV ibuprofen is indicated for alleviating mild-to-moderate pain, as an adjunct to opioid analgesics for alleviating moderate-to-severe pain, and for reducing fever in adults. It is contraindicated during the perioperative period for patients undergoing coronary artery bypass graft (CABG) surgery, and it should be used with caution in patients with a history of ulcer disease, gastrointestinal bleeding, fluid retention, renal impairment, heart failure, or liver impairment. Caution is also recommended for the elderly and for patients taking diuretics or angiotensin-converting enzyme (ACE) inhibitors.

Blood pressure should be monitored during IV ibuprofen treatment.

Approved in June 2009, the product is available in 400-mg and 800-mg vials.

Source: Cumberland, September 9, 2009, www.caldolor.com

**NEW INDICATION**

**Zevalin for Follicular Non-Hodgkin’s Lymphoma**

Ibritumomab tiuxetan (Zevalin, Spectrum) has been approved for patients with previously untreated follicular non-Hodgkin’s lymphoma (NHL) who have achieved a partial or complete response to first-line chemotherapy. This recent indication supplements the drug’s 2002 approval as a therapy for patients with relapsed or refractory low-grade or fol-
Valstar Available For Refractory Bladder Cancer

Endo Pharmaceuticals has reintroduced valrubicin (Valstar) for patients with a form of bladder cancer. This is the only FDA-approved intravesical therapy for patients with carcinoma in situ (CIS) of the urinary bladder that is refractory to bacille Calmette-Guérin (BCG) vaccine for whom immediate removal of the bladder would be too risky. Valrubicin may be an option for patients who might have otherwise exhausted all other approved treatment alternatives, including BCG vaccine.

CIS bladder cancer is associated with a 50% to 90% probability of recurrence in five years. Standard treatment involves transurethral resection of the bladder tumor, followed by one or two courses of BCG. Although the initial response rate to BCG is high, recurrence occurs in up to 34% of patients.

Valrubicin is administered once a week for six weeks. If the patient does not have a complete response at three months after beginning therapy or if CIS recurs, it might be necessary to remove the bladder.

The drug had been approved for this indication in 1998 and was then marketed by Anthra. In 2002, Anthra voluntarily withdrew the drug from the U.S. market because of a formulation problem. Since its removal from the market, the drug has been on the FDA’s drug shortages list. In February 2009, Indevus Pharmaceuticals, the previous owner of Valstar, received approval to reintroduce valrubicin after modifying the formulation. In March 2009, Endo acquired Indevus and began preparing to reintroduce valrubicin.

Source: Endo, September 3, 2009; www.ValstarSolution.com

Alpha Blockade And Urinary Stones

Studies have suggested that alpha blockers, such as tamsulosin (Flomax, Boehringer Ingelheim), can be helpful in treating ureterolithiasis by making it easier for stones to pass. However, there are no formal guidelines for using alpha blockade in the emergency department (ED).

Researchers from Advocate Christ Medical Center in Oak Lawn, Illinois, surveyed 103 emergency physicians in five states to find out how often they used tamsulosin. Sixty percent of respondents used it in fewer than 25% of patients with ureteral stones, and many had not heard of using tamsulosin for passage of urinary stones.

The most frequently reported factors associated with infrequent tamsulosin use included the respondent’s uncertainty about formal recommendations for its use in urology, unfamiliarity with the drug’s use for this indication, questioning of the data supporting its use, not remembering to give the medication, and being unsure of contraindications.

Some physicians responded that proximal stones were unlikely to improve and that the cost outweighed the benefit; they also weren’t sure whether tamsulosin could be given to women.

Recent guidelines from the American Urological Association support the use of medical expulsive therapy, with alpha blockers being the currently preferred agents.


Home Therapy for DVT Is Safe

Long-term home treatment with once-daily subcutaneous (SQ) tinzaparin sodium (Innohep, Pharmion) appears to be effective for patients with deep-vein thrombosis (DVT), compared with “usual care”—tinzaparin followed by long-term therapy with warfarin sodium (Coumadin, Bristol-Myers Squibb).

A study known as Home-LITE, conducted at University of Calgary, University of British Columbia, McGill University, and the University of Oklahoma, is one of three trials in the Long-Term Innovations in TreAtmEnt program, designed to evaluate chronic treatment of proximal DVT. This appears to be the...
first study to compare such treatment and a low-molecular-weight heparin with usual care in patients at home from the outset.

In this study, 240 patients were randomly assigned to either group. Rates of recurrent venous thromboembolism (VTE) and death were similar at 12 weeks and one year, and bleeding rates were similar during the 12-week study period. Patients who received tinzaparin for 12 weeks, however, reported greater satisfaction with treatment, particularly freedom from the inconvenience of blood monitoring; a lower risk of post-thrombotic syndrome; fewer leg ulcers after 12 weeks; and less interruption of work. Home-LITE had fewer exclusion criteria compared with previous trials and thus enrolled a population closer to the mix of patients likely to be seen in routine clinical practice, such as patients with renal impairment.


**Sustiva: Smaller Steps, Fewer Adverse Events**

Easing into treatment can help prevent neuropsychiatric adverse events (AEs) for patients taking efavirenz (Sustiva, Bristol-Myers Squibb), say researchers from the Andalusian Society of Infectious Diseases in Spain. In their study of 114 patients with HIV infection at seven clinics, a stepwise dose escalation over two weeks reduced the incidence and intensity of efavirenz-related AEs while maintaining efficacy. Although efavirenz is usually given in a fixed dose of 600 mg/day, more than 50% of patients starting treatment experience drug-related AEs such as dizziness, a feeling of drunkenness or hangover, nightmares, and sleep disorders. Impaired concentration, mood changes, and even severe symptoms of depression and paranoia have also been reported. The AEs are usually mild to moderate and diminish within the first weeks of treatment, but some patients need to interrupt treatment because of the intensity or duration of the symptoms.

In this randomized study, patients received efavirenz 200 mg/day on days 1 through 6, 400 mg/day on days 7 through 13, and 600 mg/day thereafter, or 600 mg/day from day 1. After 24 weeks, HIV RNA levels and CD4+ cell counts were similar in both groups.

Compared with the stepped-dose group, the full-dose group had at least double the incidence and severity of symptoms such as dizziness (66% vs. 33%), hangover (46% vs. 21%), impaired concentration (23% vs. 9%), and hallucinations (6% vs. 0%) during the first week. After that, the incidence of neuropsychiatric AEs was similar in both groups, although the severity was greater with the full doses.

The study revealed a two-fold greater incidence of severe efavirenz-related neuropsychiatric AEs in the full-dose group, but the difference was not significant. Hallucinations, one of the more severe effects, occurred in only four patients receiving the full dose. The low numbers in the groups meant that small differences in effectiveness could not be detected.


**Nycomed Improves Diabetic Neuropathy**

Actovegin (Nycomed), a deproteinized derivative of calf blood, may improve neuropathic symptoms, sensory nerve function, and mental health in patients with neuropathy related to type-2 diabetes. According to findings from a randomized, double-blind study of 567 patients, the main difference for the changes on the symptoms scale was 0.86—a clinically meaningful effect, the researchers say. They assigned 281 patients to receive 20 IV infusions of actovegin, followed by three tablets per day for 140 days; 286 patients received placebo. Improvement in pain, paresthesia, numbness, and sensory deficits was observed.

The mechanism by which actovegin achieves these effects is not clear, but the drug enhances glucose uptake and metabolism and increases oxygen absorption and utilization.

Source: Diabetes Care 2009;32:1479–1484

**Plavix: Using a High Dose Sooner Rather Than Later**

Both the timing and dosage of clopidogrel (Plavix, Bristol-Myers Squibb/Sanofi-Aventis) loading are important, according to a study of pretreatment in patients with ST-segment elevation myocardial infarction (STEMI). The results suggest pretreating patients with high-dose clopidogrel as early as possible.

In this study from Canada and Israel, 217 patients received a clopidogrel loading dose before primary percutaneous coronary intervention (PCI), and 166 patients received it afterward. A similar number of patients received low doses (300 mg) and high doses (600 mg) before and after primary PCI. Clopidogrel loading before primary PCI was associated with a lower incidence of recurrent acute coronary syndrome (ACS), stent thrombosis, congestive heart failure, or death at 30 days (21.7% vs. 33.7%). When the patients were further stratified into four groups according to the timing and dosage of clopidogrel loading, the incidence of the primary outcome was 16% for those who received 600 mg before primary PCI and 27% for those receiving 300 mg before primary PCI, compared with rates of 28% with 600 mg and 39% with 300 mg after primary PCI.

The benefits of pretreatment were
greater in patients with infarction of the anterior wall when the interval from symptom onset to admission was three hours or less and the "door-to-balloon" time was more than 90 minutes. Patients taking chronic aspirin therapy and those receiving glycoprotein (GPIIb/IIIa) antagonists did not benefit less from clopidogrel pretreatment.

The researchers say that their findings might have an even greater effect as a new generation of more potent thienopyridines with more rapid onset of action becomes available.

Source: *Am J Cardiol* 2009;104:514–518

**Insulin Syringes Recalled**

Qualitest Pharmaceuticals, Inc., has issued a voluntary nationwide recall of two Accusure insulin syringes:

- 1/2 cc, 31 G, Short Needle, Lot No. 6JCB1; expiration date, October 2011; NDC 0603-7001-21, distributed between January 2007 and June 2007
- 1 cc, 31 G, Short Needle, Lot No. 7CPT1; expiration date, March 2012; NDC 0603-7002-21, distributed between May 2007 and June 2008

These syringes had needles that could have detached from the syringe. If a needle becomes detached from the syringe during use, it can become stuck in the insulin vial, push back into the syringe, or remain in the skin after an injection.

Consumers should stop using these syringes and should contact Qualitest (1-800-444-4011) for instructions on obtaining a replacement. This recall is being made with the knowledge of the FDA. Adverse reactions or quality problems experienced with the use of these syringes may be reported to the FDA’s MedWatch Adverse Event Reporting program by e-mail, regular mail, or fax.

Source: FDA, August 21, 2009

**Tysabri: New Brain Infections Result in a Safety Update**

The FDA has confirmed three new cases of a rare but potentially lethal brain inflammation linked to natalizumab (Tysabri, Biogen Idec/Elan), a medication that is used for multiple sclerosis (MS) and Crohn’s disease.

There have been 13 reported cases of progressive multifocal leukoencephalopathy (PML) since mid-2006. All of the PML cases are linked to the drug’s use for MS. Natalizumab was approved in November 2004 but was withdrawn from the market in 2005 for 18 months because of PML reports. It was reintroduced in July 2006.

The FDA has updated the safety information for natalizumab and warns that the risk of developing PML appears to increase with the number of infusions received and that the average number of infusions received before the diagnosis of PML was 25. The agent is delivered through an IV infusion about once a month. The duration of therapy may also play a role in the risk of PML. The current rate of PML in patients who have received at least 24 infusions ranges from 0.4 to 1.3 per 1,000 patients. Biogen claims that there is no definite link to duration of therapy, and the company opposes interrupting treatment because MS symptoms can return.

As of June 30, about 43,300 patients were receiving natalizumab.

The FDA is not requiring changes to the prescribing information or to the risk-management plan. The drug is effective, and patients are informed about the risk of PML before they receive it.


**Metformin Kills Breast Cancer Stem Cells in Mice**

A common diabetes drug might be able to reduce tumors faster and prolong remission in mice longer than chemotherapy alone by targeting cancer stem cells, according to Harvard researchers.

These findings suggest that metformin (Glucophage, Bristol-Myers Squibb) might be able to improve breast cancer outcomes in humans. In this study, the drug seemed to work independently of its ability to improve insulin sensitivity and lower blood glucose and insulin levels, all of which are also associated with better breast cancer outcomes.

The results fit within the idea that small subsets of cancer cells have a special power to initiate tumors, fuel tumor growth, and promote the recurrence of 

continued on page 541
cancer. Cancer stem cells appear to resist conventional chemotherapies, which kill the bulk of the tumor. The cancer stem cell hypothesis is that cancer cannot be cured unless the stems cells are also eliminated.

In experiments, metformin plus the cancer drug doxorubicin (Adriamycin) killed human cancer stem cells and non-stem cancer cells in culture. Four genetically distinct breast cancer cell lines were used.

In mice, pretreatment with metformin prevented the otherwise dramatic ability of human breast cancer stem cells to form tumors. In other mice, in which tumors took hold for 10 days, the combination therapy also reduced tumor mass more quickly and prevented relapse for a longer time compared with doxorubicin alone. In the two months between the end of treatment and the end of the experiment, tumors regrew in the mice treated with chemotherapy alone but not in those who received both drugs. Metformin was ineffective in treating tumors when used alone.

A large-scale phase 2 trial is planned to study metformin’s impact on recurrence in women treated for early-stage breast cancer. So far, observational studies have suggested a lower risk of cancers, including breast cancer, and better responses to chemotherapy in patients with diabetes who received metformin.

The researchers were encouraged by the low dose of metformin needed for the effect in the laboratory, compared with the amount needed in basic diabetes research.

Sources: Cancer Res, September 14, 2009; The Wall Street Journal, September 15, 2009

**Obesity Hinders Chemotherapy In Children with Leukemia**

Obesity may be contributing to chemotherapy resistance and increasing relapse rates among children with leukemia. Obesity is associated with an increased incidence of many types of cancer. Given the increasing prevalence of obesity worldwide, these findings could have important implications for cancer treatment and may help to explain the increased leukemia relapse rate in obese patients.

Steven D. Mittelman, MD, PhD, from the University of Southern California, says that the fat cells themselves may impair the immune system’s ability to block cancer growth or might predispose cells to become cancerous.

Dr. Mittelman and colleagues developed a mouse model of obesity and leukemia, cultured fat and leukemia cells together, and treated the leukemia cells with traditional chemotherapy drugs used in children—vincristine, nilotinib, daunorubicin, and dexamethasone. Obese mice with leukemia had higher relapse rates than lean mice after treatment with vincristine. Chemotherapy worked less effectively in culture when fat cells were nearby. When relapse occurred, the researchers observed that leukemia was “hiding out” in the fat tissue during chemotherapy.

“These four drugs attack leukemia cells by different routes, so when we saw fat cells blocking them, we realized there could be an important mechanism promoting their ability to live and divide,” Dr. Mittelman said. “We were surprised to find leukemia cells in the fat tissue.”

The study suggested that obesity is associated with a poor prognosis in multiple cancers. In another study, adipose tissue seemed to function as a “safe haven” for leukemia cells during therapy. More research is needed to learn how fat cells are a part of the tumor microenvironment and how they block potentially lifesaving treatments.

Sources: Cancer Res online; Science Codex, September 22, 2009

**NEW DRUGS**

**NEW MEDICAL DEVICES**

**Marvin M. Goldenberg, PhD, RPh, MS**

**Name:** Peak PlasmaBlade TnA for Tonsils and Adenoids

**Manufacturer:** Peak Surgical, Palo Alto, Calif.

**Approval Date:** August 6, 2009

**Use Classification:** The PlasmaBlade is indicated for dissecting and coagulating soft tissue during otolaryngologic surgery, including removal of the tonsils and adenoids.

**Description:** The blade represents a family of disposable, low-temperature surgical devices. The pulsed plasma technology represents an advance in radio-frequency (RF) surgery, which originated with traditional electrosurgery and progressed to plasma-mediated energy devices. The surgery system includes the Pulsar generator.

**Purpose:** Almost 600,000 tonsillectomies are performed in the U.S. each year, and many of these procedures are accompanied by an adenoidectomy. The blade has interchangeable tips designed for tonsillectomy and adenoidectomy.

**Benefit:** The device offers the precision of a traditional scalpel, the bleeding control of traditional electrosurgery, and minimal collateral damage to surrounding tissue.

**Source:** www.peakurgical.com

**Name:** CryoPatch SynerGraft Pulmonary Human Patch Material

**Manufacturer:** CryoLife, Inc., Kennesaw, Ga.

**Approval Date:** August 12, 2009

**Use Classification:** CryoLife’s SynerGraft technology is indicated for repairing or reconstructing the right ventricular outflow tract. This procedure is commonly performed in children with congenital heart defects, such as tetralogy of Fallot, truncus arteriosus, and pulmonary atresia. Three anatomic configurations are available: pulmonary hemi-
artery, pulmonary trunk, and pulmonary branch.

Description: The device is designed to remove allogeneic donor cells and cellular remnants from tissue without compromising the integrity of the underlying collagen matrix.

Purpose: Implantation of the device reduces the risk of induction of human leukocyte antibody (HLA) class I and class II alloantibodies. Results are based on the Panel Reactive Antibody (PRA) test, which measures anti-human antibodies in the blood. Data are not yet available to evaluate the effect of reduced alloantibodies on the long-term durability of the device or on the long-term resistance to rejection by the patient.

Benefit: Preventing elevated PRA scores is important, because some patients may ultimately need a heart transplant. The link between immune response and allograft tissue performance is still being debated, but an elevated PRA score may pose a significant risk to future organ recipients. A high score can decrease the number of possible donors for subsequent organ transplants and can increase the time spent on transplant waiting lists because the risk of transplant rejection is increased.

Sources: www.medicalnewstoday.com/articles/160535.php; www.cryolife.com

Name: Accent and Anthem Radiofrequency Pacemakers with Wireless Technology (Cardiac Resynchronization Therapy Pacemakers)

Manufacturer: St. Jude Medical Inc., Little Canada, Minn.

Approval Date: August 10, 2009

Use Classification: RF telemetry enables secure, wireless communication between the implanted device and the programmer when it is used by a clinician or a home monitor. This is the first integrated system of pacing devices with wireless telemetry from implantation through follow-up.

Description: Wireless communication is used during implantation of the pacemaker and during follow-up appointments, which can take place in the clinic or in the patient’s home.

Purpose: Follow-up visits can be scheduled to take place automatically, in a hands-free manner, with no patient interaction required. Information from the device is then captured by the Merlin@home transmitter. The clinician can view the data via the Merlin.net patient care network. In addition to the fast access provided for obtaining the data, physicians can compile a more complete patient record by transferring the data into an electronic health record in a timely fashion.

Benefit: The pacemakers issue an alert when patients have atrial tachycardia or atrial fibrillation, and they include technology that measures the heart’s reaction to pacing beat by beat. An algorithm also enables the heart’s natural rhythm to take over, if appropriate, thus reducing unnecessary ventricular pacing. With these remote monitoring capabilities, physicians can observe patients, and patients can benefit from the convenience of care from home.


Devices in the News

Safety alert. The FDA and the Office of In Vitro Diagnostic Device Evaluation and Safety and other offices have notified health care professionals of the possibility of falsely elevated blood glucose results with the use of glucose dehydrogenase–pyrroloquinolone quinone (GDH–PQQ) test strips in patients who are receiving therapeutic products containing certain non-glucose sugars. These sugars can cause falsely elevated glucose results and may mask hypoglycemia or may prompt excessive insulin administration, leading to serious injury or death.

GDH–PQQ monitoring is used to measure a patient’s blood glucose level, but it does not distinguish between glucose and other sugars. Some non-glucose sugars (e.g., maltose, xylose, and galactose) are present in certain drugs or can result from the metabolism of a drug. The FDA recommends that the strips be avoided in medical facilities or in patients receiving products that can cause an interaction; the agency also encourages the voluntary reporting of any adverse events related to glucose meters or test strips that do not meet the requirements for mandatory reporting.


Recall. Hospira and the FDA have issued a nationwide recall of devices with defective alternating current power cords. The recall resulted from customers’ reports of sparking, charring, and fires on the plug of the power cord. The company determined that the cord’s prongs could crack and fail at or inside the plug. The potential risks from a power cord failure include electrical shock, delay in setup, a delay or interruption of therapy, device failure, and fires that can occur in an oxygen-rich environment. These failures can lead to potentially serious injury or death.

Customers with affected cords that have bent or cracked prongs, burnt plastic, or excessive wear and tear should stop using them immediately. They can contact their Hospira sales representative or Hospira Technical Support Operations at 1-800-241-4002 for instructions on how to receive replacement parts.