NEW DRUG APPROVALS
Hetlioz for Non-24-Hour Sleep-Wake Disorder

The FDA has approved tasimelteon (Hetlioz, Vanda Pharmaceuticals) 20-mg capsules for the treatment of non-24-hour sleep-wake disorder.

Tasimelteon is the first FDA-approved medication for this chronic, circadian rhythm disorder, which results from a misalignment of the endogenous master body clock to the 24-hour day that disrupts the sleep-wake cycle. The disorder affects an estimated 80,000 Americans, including most totally blind individuals.

Tasimelteon’s approval was based on two key efficacy studies and its safety has been evaluated in more than 1,300 individuals. The most common adverse reactions in clinical trials were headache, increased alanine aminotransferase, nightmares or unusual dreams, and upper respiratory or urinary tract infection. After taking tasimelteon, patients should limit their activity to preparing for bed: The drug can impair performance of activities that require complete mental alertness.

Vanda expects to make the drug commercially available in the second quarter of 2014.

Source: Vanda Pharmaceuticals, January 31, 2014

NEW INDICATIONS
Inbruvica for Chronic Lymphocytic Leukemia

The FDA has expanded the approved use of ibrutinib (Imbruvica, Pharmacyclics) to include patients with chronic lymphocytic leukemia (CLL) who have at least one prior therapy.

Ibrutinib works by blocking the enzyme that allows cancer cells to grow and divide. In November 2013, the FDA granted ibrutinib accelerated approval to treat patients with mantle cell lymphoma, a rare and aggressive type of blood cancer, if those patients had received at least one prior therapy. The FDA completed its review of the new indication under the agency’s accelerated approval process. Under that process, the FDA may approve a drug based on surrogate or intermediate endpoint that is reasonably likely to predict clinical benefit.

The FDA’s approval of ibrutinib for CLL is based on a clinical study of 48 previously treated participants. All participants received a 420-mg orally administered dose of ibrutinib until the treatment reached unacceptable toxicity or the disease progressed.

Results showed nearly 58 percent of participants had their cancer shrink after treatment (the overall response rate). At the time of the study, the duration of response ranged from 5.6 to 24.2 months. An improvement in survival or disease-related symptoms has not been established.

Ibrutinib for CLL also received priority review and orphan-product designation because the drug demonstrated the potential to be a significant improvement in safety or effectiveness in the treatment of a serious condition and is intended to treat a rare disease.

The most common side effects observed in the clinical study include thrombocytopenia, diarrhea, bruising, neutropenia, anemia, upper respiratory tract infection, fatigue, musculoskeletal pain, rash, pyrexia, constipation, peripheral edema, arthralgia, nausea, stomatitis, sinusitis, and dizziness.

Source: FDA, February 12, 2014

NEW FORMULATIONS
Copaxone for MS Three Times a Week

The FDA has approved 40 mg/mL glatiramer acetate injection (Copaxone, Teva) to be used three times a week by patients with relapsing forms of multiple sclerosis (MS). Daily glatiramer acetate injection 20 mg/mL will continue to be available. The daily subcutaneous injection was approved in 1996.

The FDA’s approval was based on data from the phase 3 Glatiramer Acetate Low-Frequency Administration (GALA) trial involving more than 1,400 patients. In this study, a 40-mg/mL dose administered subcutaneously three times a week significantly reduced relapse rates at 12 months and demonstrated a favorable safety and tolerability profile in patients with relapsing-remitting MS.

The most common side effects of glatiramer acetate include redness, pain, swelling, itching, or a lump at the injection site, as well as flushing, rash, shortness of breath, and chest pain.

Source: Teva, January 28, 2014

Pennsaid 2% for Knee OA Pain

The FDA has approved a new drug application (NDA) for diclofenac sodium topical solution 2% w/w (Pennsaid 2%, Nuvo Research).

Pennsaid 2% is a follow-on product to the original diclofenac sodium topical solution 1.5% w/w (Pennsaid 1.5%), which has been marketed by Mallinckrodt in the U.S. since 2010.

Pennsaid 2% will be the first twice-daily topical nonsteroidal anti-inflammatory drug (NSAID) available in the U.S. for treatment of the pain of osteoarthritis of the knee.

Source: Nuvo Research, January 17, 2014

DRUG NEWS
Cozaar and Hyzaar Add Boxed Warnings

The FDA has directed Merck to add a boxed warning about fetal toxicity to losartan potassium (Cozaar) and losartan potassium hydrochlorothiazide (Hyzaar). Women taking either of the two hypertension medications should discontinue use immediately when pregnancy is detected.
the boxed warning says. Drugs such as these that act directly on the renin-angio-
tensin system can cause injury and death to the developing fetus, the warning adds.

Both medications are classified as preg-
nancy category D. The FDA says female
patients of childbearing age should be
told about the consequences of exposure
to either drug during pregnancy. Health
care providers should discuss treatment
options with women planning to become
pregnant and should ask patients to
report pregnancies to their physicians as
soon as possible.

An additional precaution has been add-
ted to both labels for neonates exposed to
the medication in the womb. If oliguria or
hypotension occur, health care providers
should direct attention toward support
of blood pressure and renal perfusion.
“Exchange transfusions or dialysis may
be required as a means of reversing
hypotension and/or substituting for dis-
ordered renal function,” the new FDA-
approved labels note.

The warnings apply to 25-mg, 50-mg, and
100-mg Cozaar tablets and to 50/12.5-mg,
100/12.5-mg, and 100/25-mg Hyzaar tab-
lets. Both drugs are angiotensin II recep-
tor antagonists.

Source: FDA, February 11, 2014

Panel Rejects Change
To Naproxen Warnings
An FDA advisory panel has voted
against recommending changes to the
cardiovascular warnings attached to
products that contain naproxen along
with other nonaspirin, nonsteroidal anti-
flammatory drugs (NSAIDs).

In a two-day joint meeting, the Arthri-
tis Advisory Committee and the Drug
Safety Committee and Risk Management
Advisory Committee reviewed data and
analyses published since the last NSAID
panel review in 2005. The panel did not
find the accumulated data supported a
significant difference in cardiovascular
(CV) risk for naproxen, as compared to
other nonaspirin NSAIDs.

The panel voted 16 to 9 to make no
changes at this time, but some panelists
agreed that recent data are supportive of
naproxen’s low risk. Bayer HealthCare
(the maker of Aleve, a naproxen brand)
said after the vote that a large body of
evidence consistently demonstrates that
naproxen has a low CV thrombotic risk
compared to other nonaspirin NSAIDs.

All nonaspirin over-the-counter
NSAIDs in the U.S. include FDA-mand-
dated CV warnings related to concerns
if the product is used longer or at higher
doses than directed on the label.

Sources: Bayer HealthCare, Reuters,
February 11, 2014

FDA Reviews Onglyza
Heart Failure Risk
The FDA has requested clinical trial
data from Bristol-Myers Squibb, the
manufacturer of saxagliptin (Onglyza),
to investigate a possible association
between the use of the type-2 diabetes
drug and heart failure.

The agency’s request resulted from a
study published in the New England Jour-
nal of Medicine (NEJM), which reported
an increased rate of hospitalization for
heart failure with the use of saxagliptin
compared with an inactive treatment.

The study did not find increased rates
of death or other major cardiovascular
risks, including heart attack or stroke, in
patients who received saxagliptin.

Bristol-Myers Squibb is expected to
submit the trial data to the FDA by early
March.

At this time, the FDA considers infor-
mation from the NEJM study to be pre-
liminary. Its analysis of the saxagliptin
clinical trial data is part of a broader eval-
uation of all type-2 diabetes drug therapies
and cardiovascular risk.

According to the FDA, patients should
not stop taking saxagliptin, and health
care professionals should continue to fol-
low the prescribing recommendations in
the drug labels.

Source: FDA, February 11, 2014

FDA Panel Votes
Against Cangrelor
The FDA’s Cardiovascular and Renal
Drugs Advisory Committee voted 7 to 2
to recommend against approving the
intravenous antiplatelet agent cangrelor
(Medicines Company) for use in patients
undergoing percutaneous coronary inter-
vention. The panel also voted 9 to 0 against
recommending cangrelor’s approval for
patients who require bridging from oral
antiplatelet therapy to surgery.

The cangrelor new drug application
(NDA) and presentations before the com-
mittee focused on four randomized,
double-blind clinical trials (CHAMPION
PHOENIX, CHAMPION PLATFORM,
CHAMPION PCI, and BRIDGE) involv-
ing more than 25,000 patients with coro-
ary artery disease.

In an opinion posted before the meet-
ing, medical team leader Thomas A. Mar-
ciniak, MD, argued that clinical data do
not support the superiority of cangrelor
over a rival treatment, clopidogrel (Plavix,
GlaxoSmithKline).

Like clopidogrel, cangrelor is a plate-
let P2Y12 receptor inhibitor. Unlike
orally administered clopidogrel, however,
intravenous cangrelor is a reversible
rather than an irreversible inhibitor.

Marciniak concluded that clinical
trial data do not demonstrate either the
superiority or noninferiority of a cangre-
lor regimen compared with a clopidogrel
regimen or standard of care. He offered
several arguments:

• Clopidogrel administration was
delayed in pivotal clinical trials. The
studies provided evidence that ear-
lier administration of clopidogrel
was more effective than cangrelor.
Flibanserin, a nonhormonal treatment, is believed to work on key neurotransmitters in the brain that affect sexual desire. Flibanserin is thought to correct an imbalance of levels of these neurotransmitters by increasing dopamine and norepinephrine (both responsible for sexual excitement) and by decreasing serotonin (responsible for sexual inhibition).

Sources: Sprout Pharmaceuticals and Reuters, February 11, 2014

Ledipasvir/Sofosbuvir Hepatitis C Combo Sought

A new drug application (NDA) has been submitted to the FDA for a once-daily fixed-dose combination of the NSSA inhibitor ledipasvir (LDV) 90 mg and the nucleotide analog polymerase inhibitor sofosbuvir (SOF) 400 mg for the treatment of chronic genotype-1 hepatitis C virus (HCV) infection in adults.

According to the drug’s developer (Gilead Sciences), the data submitted in the NDA support the use of LDV/SOF in this patient population, with a treatment duration of eight or 12 weeks depending on patients’ prior treatment history and whether they have cirrhosis.

Approximately 75% of people infected with HCV in the U.S. have the genotype 1 strain of the virus.

The FDA rejected flibanserin last year, saying its effects were “modest” and did not outweigh adverse effects such as dizziness, nausea, and fatigue. Sprout filed for Formal Dispute Resolution. Women’s groups have been pressing the FDA to approve the product, claiming gender bias in the drug-approval process.

Flibanserin, a nonhormonal treatment, is believed to work on key neurotransmitters in the brain that affect sexual desire. Flibanserin is thought to correct an imbalance of levels of these neurotransmitters by increasing dopamine and norepinephrine (both responsible for sexual excitement) and by decreasing serotonin (responsible for sexual inhibition).

Sources: Sprout Pharmaceuticals and Reuters, February 11, 2014

Validive on Fast Track For Oral Mucositis

Clonidine Lauriad (Validive, BioAlliance Pharma) has received a “fast track” designation from the FDA for the prevention and treatment of oral mucositis induced in cancer patients by radiotherapy, chemotherapy, or both. The “fast track” procedure is designed to optimize the development and review period for drugs investigated as treat-

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FDA to Review Budesonide Foam for Ulcerative Colitis
The FDA has accepted for filing a new drug application (NDA) for budesonide 2 mg rectal foam for the induction of remission in patients with active mild-to-moderate distal ulcerative colitis extending up to 40 cm from the anal verge.

The agency has issued an action date of September 15, 2014, under the Prescription Drug User Fee Act (PDUFA).

Budesonide, a high-potency corticosteroid, was developed to minimize the systemic adverse consequences of classic corticosteroids, such as hydrocortisone, which have higher levels of systemic absorption.

Budesonide 2 mg rectal foam was effective in treating distal ulcerative colitis in several large studies. According to the product’s developer (Salix Pharmaceuticals), clinical data suggest that the budesonide foam formulation offers improved reach (or spread) and rapid distribution of budesonide to the sigmoid colon and the rectum, without the difficulties and inconvenience associated with the retention of enema formulations.

These trials also suggest that the foam provides more immediate and targeted therapy for distal ulcerative colitis than is available with oral therapies. The foam formulation for rectal administration was designed to improve both the patient's ability to retain the drug in the rectum following administration and the distribution of the active drug to the rectum and sigmoid colon.

Source: Salix Pharmaceuticals, January 30, 2014

Aspirin Use May Cut Ovarian Cancer Risk
Women who take aspirin daily may reduce their risk of ovarian cancer by 20%, according to a study by scientists at the National Cancer Institute (NCI). However, further research is needed before clinical recommendations can be made.

The study was published February 6 in the Journal of the National Cancer Institute.

Previous studies have suggested that the anti-inflammatory properties of aspirin and nonaspirin NSAIDs (nonsteroidal anti-inflammatory drugs) may reduce cancer risk overall. However, studies examining whether the use of these agents may influence ovarian cancer risk have been largely inconclusive.

The investigators analyzed data pooled from 12 large epidemiologic studies to determine whether women who used aspirin, nonaspirin NSAIDs, or acetaminophen have a lower risk of ovarian cancer. The scientists evaluated the benefit of these drugs in nearly 8,000 women with ovarian cancer and in close to 12,000 women who did not have the disease.

Among study participants who reported whether or not they used aspirin regularly, 18% used aspirin, 24% used nonaspirin NSAIDs, and 16% used acetaminophen. The researchers determined that participants who reported daily aspirin use had a 20% lower risk of ovarian cancer than those who used aspirin less than once a week.

For nonaspirin NSAIDs, the picture was less clear. The scientists observed a 10% lower ovarian cancer risk among women who used NSAIDs at least once a week compared with those who used NSAIDs less frequently. However, this finding was not statistically significant.

In contrast to the findings for aspirin and NSAIDs, the use of acetaminophen, which is not an anti-inflammatory agent, was not associated with a reduced risk for ovarian cancer.

Source: NIH, February 6, 2014

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Orphan Status for Vatiquinone
The FDA has granted orphan status to vatiquinone (EPI-743, Edison Pharmaceuticals), which is in phase 2 development for the treatment of Friedreich’s ataxia.

A phase 2B randomized, double-blind, placebo-controlled trial in adults is fully enrolled, and a study in patients with the rare point mutation genotype is actively enrolling subjects.

The FDA has previously granted orphan status to EPI-743 for the treatment of inherited respiratory chain diseases.

Friedreich’s ataxia is an autosomal recessive nuclear DNA inherited mitochondrial disease, affecting an estimated one in 30,000 individuals in the United States and Europe. Patients present with “energy failure” symptoms, including ataxia, muscle weakness, heart failure, diabetes, and visual, speech, and hearing deficiencies. There are no FDA-approved drugs for Friedreich’s ataxia.

Source: Edison Pharmaceuticals, February 4, 2014

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Vitamin D in Diabetes

Vitamin D may help patients with type-2 diabetes reduce cardiovascular damage. Researchers from Wolfson Medical Center and Tel Aviv University, both in Israel, say one year of high-dose vitamin D significantly reduced the central aortic augmentation index (AI)—that is, arterial stiffness.

In the study, 47 adults with type-2 diabetes were randomly assigned to receive 1,000 units per day of oral vitamin D, supplements or placebo. Nineteen patients from the vitamin D group and 13 from the placebo group completed the 12-month study.

While glucose homeostasis parameters, such as fasting glucose, did not change in the vitamin D patients, AI declined significantly (from 32.9 to 25.9), as did aortic augmentation pressure. The placebo group showed no significant changes in hemodynamic, arterial stiffness, and metabolic parameters.

Circulating adiponectin levels rose in the patients given high-dose vitamin D. Adiponectin plays an important role in insulin sensitivity, inflammation, and ath-erogenesis.

Previous clinical and experimental data show that vitamin D affects the renin-angiotensin-aldosterone system, vascular smooth muscle cell proliferation, calcification, and inflammation, the researchers note. Low levels of vitamin D have been linked with high blood pressure, impaired glucose homeostasis, and a higher risk of myocardial infarction and cardiovascular mortality.

Studies on the beneficial effects of vitamin D in humans have produced varied results. The researchers’ find-ings suggest that the recommended daily allowance of vitamin D may need to be changed, since people with diabetes tend to have levels that are too low.

Source: Clin Nutr 2013;32:970–975

Taking Less Tacrolimus

Simplifying the medication regimen is usually a good way to help patients stick with their treatment. Could it work for renal transplant patients taking tacrolimus?

Until recently, tacrolimus had to be taken twice daily, but a once-daily form became available in Europe in 2007. Researchers from Radboud University Medical Centre in the Netherlands conducted a prospective cohort study to find out whether the once-daily version could aid adherence. They switched 75 patients from tacrolimus twice daily to once daily (and when possible switched other drugs to once daily).

The number of times drugs were ingested daily dropped 33% (from 2.4 to 1.6) and the mean daily number of tablets dropped from 12.4 to 9.1. Because patients were taking fewer pills less often, 64% reported higher scores on satisfaction with convenience (up from a mean of 66 to 78.5). The changes made it easier for patients to follow their treatment plan. Self-reported adherence to the medication regimen rose from 79.7% to 94.6%.

Most renal-transplant patients who are being treated with tacrolimus also take other drugs, such as immunosuppres-sives and antihypertensives. Switching to once-daily tacrolimus simplifies the schedule and makes it more flexible, the researchers say. Patients can take their medicines at more convenient times, which enhances adherence.

Improved adherence is particularly important for renal-transplant patients who are on immunosuppressive therapy. About 25% of those patients are nonadher-ent, which can contribute to dangerous complications, including acute rejection episodes and graft losses.

According to the manufacturer, the researchers say, tacrolimus twice daily can be converted to once daily in stable renal transplant recipients on a 1:1-mg total daily dose basis. The manufacturer recommends measuring trough level after conversion. In this study, preconversion and postconversion trough levels did not differ significantly, but 15% of patients needed a dose adjustment on conversion. Studies have linked once-daily tacrolimus with lower tacrolimus exposure than was initially assumed. The researchers note that the conversion policy and dose adjustment did not cause short-term rejections in the first six months of the simplified regimen.

Source: Clin Ther 2013;35:1821–1829

Gauging Asians’ Health Needs

The U.S. Asian population is growing rapidly, but knowledge about Asians’ cardiovascular health is not keeping pace. Studies have produced mixed results, say researchers from Peking University Third Hospital in Beijing and Duke Clinical Research Institute in Durham, North Carolina.

To learn more, they analyzed data from CRUSADE (Can Rapid risk stratification of Unstable angina patients Suppress ADverse outcomes with Early implementation of the American College of Cardiology/American Heart Association Guidelines). They linked CRUSADE data to Medicare claims data to study short- and long-term outcomes for 307 Asian and 37,395 white patients treated at 444 hospitals between 2003 and 2006.

Asians were younger and more likely to have hypertension and diabetes mellitus but less likely to have peripheral arterial disease, prior myocardial infarction, or prior coronary revascularization. Asians had lower body mass index and creatinine clearance, but admission systolic blood pressure, heart rate, ST depression, and signs of heart failure were similar between groups.

Treatment patterns differed slightly. White patients were more likely to be treated early with clopidogrel and heparin and less likely to be treated with statins at

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discharge. There were no other significant differences in use of evidence-based therapies, such as aspirin, beta-blockers, angiotensin-converting enzyme inhibitors, or angiotensin-receptor blockers. Invasive procedures were used at similar rates.

Overall, older Asian patients and white patients had similar in-hospital clinical outcomes and risk of in-hospital death. Mortality rates at 30 days tracked together—but at one year the curves began to diverge. Asians’ risk of death at one year was 20.9%, compared with 24.5% for whites. After adjusting for baseline clinical differences, Asian ethnicity was associated with a lower adjusted one-year mortality and, conditional on 30-day survival, remained lower.

Asians and whites had similar rates of all-cause readmission at one year, but Asians were less likely to be readmitted for cardiovascular causes (37%, vs. 42% among whites).

Various mechanisms—genetic, environmental, behavioral—have been proposed to explain the ethnic differences in outcomes. These researchers suggest that Asians’ lower risk for long-term mortality and cardiovascular readmission can be explained in several ways. For instance, although Asians more often had risk factors for coronary heart disease, such as hypertension, diabetes, and renal insufficiency, whites were more likely to have atherosclerosis. They hypothesize that the ethnic variability might be due in part to differing mechanisms of plaque progression, rupture, and thrombosis.

Some researchers posit that Asians adhere more to treatment. This study found little difference in discharge prescriptions, although the authors did not assess long-term adherence. They think ethnic differences in the effectiveness of medicine might play a role.

The PROGRESS study found active treatment reduced blood pressure more in Asians with cardiovascular disease (10.3/4.6 mm Hg, vs. 8.1/3.6 mm Hg in Western patients). Major vascular events fell 38% among Asians, compared with 20% among Western patients. Substantially lower doses of antithrombotic medications are effective in Asian patients compared with white patients.

Am Heart J 2013;166:1050–1055

Lurasidone for Bipolar Disorder

Lurasidone HCl (Latuda, Sunovion Pharmaceuticals) has been approved for adult patients with bipolar depression, both as monotherapy and as adjunctive therapy with lithium or valproate. The drug, an atypical antipsychotic, was already indicated for schizophrenia.

Lurasidone’s efficacy was established in a six-week monotherapy trial and a six-week adjunctive therapy study with lithium or valproate.

In the multicenter monotherapy trial, 485 adults with major depressive episodes associated with bipolar I disorder were randomly assigned to one of two flexible-dose ranges of lurasidone (20 to 60 mg daily or 80 to 120 mg daily) or placebo. The mean daily dose was 31.8 mg in the 20-to-60-mg group and 82.0 mg in the higher-dose group. In both groups, nearly all patients were titrated to a higher dose during the study. Eight percent to 19% of patients in the three groups reported as-needed treatment with lorazepam or zolpidem.

Lurasidone was superior to placebo in reducing depressive symptoms and lowering disease-severity scores. There was a statistically significant reduction from baseline to week 6 in core depression symptoms for both dosages; the higher dose range did not provide additional efficacy. The proportion of patients in remission at endpoint was significantly greater in the two drug groups (42% and 40%) compared with placebo (25%). Both dosages significantly improved anxiety symptoms.

Lurasidone has been extensively studied in treating schizophrenia; the monotherapy trial revealed no new safety concerns. Adverse events were mostly mild or moderate. Researchers found a modest, dose-related increase in the frequency of nausea, sedation, vomiting, and extrapyramidal symptoms for the higher dose range. Similar numbers of patients withdrew from each group.

In a second multicenter double-blind study, 279 patients who remained symptomatic after treatment with lithium or valproate were randomly assigned to flexibly dosed lurasidone 20 to 120 mg daily or placebo. Patients in the treatment groups showed significantly greater improvement in depressive symptoms, associated anxiety, quality of life, and functioning.

The researchers say this is, to their knowledge, the first large-scale, randomized, placebo-controlled trial to demonstrate efficacy of any medication adjunctive to mood stabilizers for the acute treatment of bipolar depression.

Lurasidone’s effectiveness beyond six weeks has not been established in controlled studies. The manufacturer advises periodically re-evaluating the long-term usefulness of the drug for the individual patient. As with other antidepressants, there is an increased risk of suicidal thoughts or actions. Lurasidone may cause serious side effects, including increased risk of death in elderly people who are confused or have memory loss.

Lurasidone has a small dose-related effect on prolactin, as well as weight, lipids, and measures of glycemic control. However, it has fewer weight and metabolic effects than other atypical antipsychotic agents. The metabolic profile of lurasidone in the adjunctive-therapy trial, the researchers say, suggests that it may be “associated with low cardiometabolic risk in this vulnerable clinical population.”


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Hepatitis B Screening Recommended

The U.S. Preventive Services Task Force has recommended screening for hepatitis B virus (HBV) infection for people with the following risk factors:

- People who were born in countries and regions with a high prevalence of HBV infection, such as Africa, Southeast Asia, the Middle East, Eastern Europe, and the northern countries in South America.
- Persons born in the U.S. who were not vaccinated as infants and whose parents were born in regions with a high prevalence of HBV infection.
- People who are human immunodeficiency virus–positive, injection drug users, and men who have sex with men.
- Patients who have a weakened immune system or undergo hemodialysis for kidney failure.

The most important way to prevent HBV infection is to get vaccinated, the task force says.

The screening standards are part of a draft recommendation statement and draft evidence report posted by the task force after a review of the evidence.

Source: USPSTF, February 11, 2014

Common Infections May Harm Memory

Exposure to common infections is linked to memory and brain function even if the infections never make people ill, according to research presented at the American Stroke Association’s International Stroke Conference 2014 in San Diego.

Researchers found that antibody levels caused by exposure to Chlamydia pneumoniae, Helicobacter pylori, cytomegalovirus, and herpes simplex viruses 1 and 2 were associated with worse cognitive performance, including memory, speed of mental processing, abstract thinking, planning, and reasoning ability.

Earlier studies have linked certain infections to an increased risk of stroke and Alzheimer’s disease. Researchers investigated whether evidence of past exposure to these infections affected performance on tests of memory, thinking speed, and other brain functions.

In the new study, the researchers conducted brain-function tests and took blood samples from 588 people who participated in the Northern Manhattan Study. Half of the participants took cognitive tests again in five years.

Experts already believe that exposure to these infections may be associated with an increase in stroke risk, as well as with an increase in atherosclerosis and inflammation. The new study doesn’t explain why the infections are related to worsening cognitive function.

Source: American Heart Association, February 13, 2014

FDA Seeks More Posidur Studies

The FDA has issued a complete response letter for Saber-bupivacaine (Posidur, Durect Corporation), an investigational drug for administration into the surgical site to produce postsurgical analgesia.

Based on its review of the product’s new drug application (NDA), the FDA determined that it cannot approve the application in its present form. The FDA said the NDA does not contain sufficient information to demonstrate that the drug is safe when used in the manner described in the proposed label. The agency indicated the need for additional clinical safety studies.

Saber-bupivacaine is a postoperative pain-relief depot that utilizes patented technology to deliver bupivacaine to provide up to three days of pain relief after surgery.

Source: Durect Corporation, February 13, 2014

Victrelis and Pancytopenia

Serious cases of pancytopenia have been reported postmarketing in patients receiving boceprevir (Victrelis, Merck) in combination with peginterferon alfa and ribavirin, the FDA says. A label change states that complete blood counts (with white blood cell differential counts) should be obtained at pretreatment, and at treatment weeks 2, 4, 8, and 12, and should be monitored closely at other times as clinically appropriate.

Source: FDA, February 12, 2014

Tandem Recalls Insulin Cartridges

Tandem Diabetes Care is expanding a voluntary recall of specific lots of insulin cartridges used with its t:slim insulin pump. The cartridges may be at risk for leaking, which could result in delivery of too much or too little insulin.

The company found that under certain conditions, equipment used in the cartridge test process caused the risk of leakage. The company has taken corrective actions to prevent recurrences.

Customers should discontinue using cartridges labeled with any of the lot numbers, which are available at www.tandemdiabetes.com.

The affected lots shipped to customers or distributors represent approximately 13,000 boxes of cartridges (10 cartridges per box). Customers who received affected cartridges can call Tandem at 1-877-801-6901 to receive replacement cartridges at no charge.

Source: Tandem, January 20, 2014

FDA Rejects Oral Film For Migraines

The FDA has issued a complete response letter (CRL) regarding the new drug application (NDA) for RHB-
103 (RedHill Biopharma/IntelGenx) for the treatment of acute migraines. CRLs inform companies that remaining questions and deficiencies preclude approval of an NDA in its present form.

The FDA’s questions in its CRL regarding RHB-103 primarily relate to third-party chemistry, manufacturing, and controls (CMC) and to the packaging and labeling of the product. No questions or deficiencies were raised regarding the product’s safety; the CRL does not require additional clinical studies.

RHB-103 is an oral thin-film formulation of rizatriptan benzoate, a 5-HT1 receptor agonist and the active drug in Maxalt (Merck). Rizatriptan is considered to be one of the most effective oral triptans, a class of molecules that constrict blood vessels in the brain to relieve swelling and other migraine symptoms.

The film dissolves rapidly in the mouth, leading to absorption of the drug through the gastrointestinal tract and into the bloodstream. The administration method of the RHB-103 oral thin film does not require the patient to swallow a pill or consume water.

Source: RedHill Biopharma, February 4, 2014

**FDA Rejects Expanded Feraheme Labeling**

The FDA has issued a complete response letter (CRL) for the supplemental new drug application (sNDA) for ferumoxytol injection (Feraheme, Amag Pharmaceuticals). Amag is seeking to expand the intravenous drug’s use beyond the current chronic kidney disease (CKD) indication to include all adult iron deficiency anemia (IDA) patients who have failed or cannot tolerate oral iron treatment.

In a CRL, the FDA informs a company that an application cannot be approved in its present form. The FDA stated that Amag did not provide sufficient information to permit the labeling of Feraheme for safe and effective use for the proposed indication. The FDA indicated that its decision was based on cumulative ferumoxytol data, including the global phase 3 IDA program and global post-marketing safety reports.

The FDA suggested that Amag generate additional clinical trial data in the proposed broad IDA patient population with a primary composite safety endpoint of serious hypersensitivity/anaphylaxis, cardiovascular events, and death. In addition, the FDA proposed that the company evaluate alternative dosing and/or administration of the drug.

In the U.S., ferumoxytol injection is indicated for the treatment of IDA in adult patients who have failed oral iron therapy. The drug received marketing approval on June 30, 2009, for the treatment of IDA in adult patients with CKD and was commercially launched in the U.S. shortly thereafter.

Source: Amag Pharmaceuticals, January 22, 2014

**DEVICE NEWS**

**Continuous Glucose Monitoring for Children**

The FDA has approved the G4 Platinum Continuous Monitoring System (Dexcom Inc.) for diabetes patients ages 2 to 17 years. The system, which monitors blood glucose levels, was previously approved for patients ages 18 and older.

A continuous glucose monitor (CGM) includes a small wire-like sensor inserted just beneath the skin that provides a steady stream of information about glucose levels in the interstitial fluid. Used with a blood glucose meter, CGM information can help alert people with diabetes when blood glucose values are becoming dangerously high or low.

The FDA has not approved the use of CGM values alone to determine dosing of diabetes medications. CGMs must be calibrated by blood glucose meters, and treatment decisions, such as insulin dosing, should be based on readings from a blood glucose meter.

Worn externally, the G4 Platinum System continuously displays an estimate of blood glucose levels and the direction and rate of change of these estimates. The device can be worn for up to seven days. It requires a prescription and is meant to complement, not replace, information obtained from standard home glucose monitoring devices.

The previously approved G4 Platinum System called for insertion of the sensor in the abdomen only. The sensor for the new G4 Platinum (Pediatric) System, the first approved CGM system for use in patients 2 to 17, can be inserted in the upper buttock or abdomen. The system components (sensor and transmitter) are unmodified from the previous system.

The FDA reviewed a pivotal clinical study of in-clinic and home-use patients to assess the system’s accuracy and precision. For seven days, 176 patients ages 2 to 17 wore the pediatric system. Its accuracy was evaluated in comparison to a clinical laboratory reference method (for patients ages 6 to 17) and to results obtained from finger stick samples on a blood glucose meter (for patients ages 2 to 17).

The study found that the system’s performance in pediatric subjects was not as accurate as its performance in adults. In addition, the performance of the hypoglycemic detection alert in the pediatric study was poor relative to that seen in adults, particularly at blood glucose concentrations below 70 mg/dL. Still, the study demonstrated that the device is effective for tracking and trending to determine patterns in glucose levels, and for alerting patients when glucose values are approaching potentially hyperglycemic or hypoglycemic levels.

To communicate the reduced accuracy continued on page 185
NEW MEDICAL DEVICES

Marvin M. Goldenberg, PhD, RPh, MS

Name: CrossCHECK Plating System  
Manufacturer: Solana Surgical LLC, Memphis, Tennessee  
Approval Date: December 30, 2013  
Purpose: A new implant system for orthopedic and pediatric surgeons’ use in foot and ankle procedures.

Description: The first phase of commercialization will include plates that will be primarily used for stabilization and fixation (leading to fusion) in the forefoot and midfoot. The plates used in Solana’s system are manufactured with Type II anodization to increase the device’s strength and make it less vulnerable to fatigue. Additionally, ridges designed especially for the device enhance its grip and buttress it during the compression process. Studies have shown that similar ridges can improve host bone health.

Benefit: Unlike other plating systems, the CrossCHECK System offers unique compression and stabilization features based on its Type II anodization manufacturing. Fusion is often the preferred procedure to relieve pain and correct skeletal alignment issues in patients with arthritis, as well as small joint fractures and bunions. The CrossCHECK Plating System offers various sizes and configurations for specific surgical needs.

Source: www.businesswire.com

Name: 3D Mapping System (latest generation)  
Manufacturer: Topera Inc., Palo Alto, California  
Approval Date: January 6, 2014

Purpose: This novel 3D analysis and mapping system assists electrophysiologists in identifying the electrical source of complex cardiac arrhythmias.

Description: The new 3D mapping system processes information in seconds, providing near-instantaneous intraproc- dural mapping and remapping capabilities. In addition, the system incorporates a new color-imaging module to aid identification of “rotors,” an electrophysiologic phenomenon previously shown to sustain atrial fibrillation. These functionalities enable electrophysiologists to diagnose complex arrhythmias more efficiently.

The system consists of the RhythmView Workstation and FIRMap diagnostic catheter that opens up into a wire ball with sensing electrodes along its surface. The workstation processes the signals coming in from the catheter and displays the electrophysiology data in near-real time on the screen.

Benefit: Atrial fibrillation is an extremely challenging arrhythmia to treat; its complexity has defied interpretation and visualization by electrophysiologists’ traditional mapping approaches. Topera’s technology is the first to demonstrate an ability to reflect faithfully the complex mechanisms of this arrhythmia and provide a reliable way to visualize the tissue sources sustaining it.

The Topera 3D Mapping System is designed to improve patient outcomes by enabling electrophysiologists to view a dynamic representation of the electrical activity of the heart, supporting diagnosis and treatment planning for a variety of arrhythmias, including atrial fibrillation, atrial flutter, atrial tachycardia, and ventricular tachycardia.

Sources: www.toperamedical.com, www.medgadget.com

Name: Vent-Os Sinus Dilation System  
Manufacturer: SinuSys, Palo Alto, California  
Approval Date: January 8, 2014

Purpose: The Vent-Os two-step osmotic expansion sinus dilation system is designed to resolve sinusitis symptoms in a simple, two-step interventional procedure. The device enables low-pressure, gradual dilation of the maxillary sinus ostia, which is intended to maximize patient tolerability of the procedure in an office setting under local anesthesia.

Description: The system, which demonstrated 95 percent patency in a multicenter study, is inserted into the maxillary sinus opening with the device entered vertically and the tip superiorly. The device is then rotated posterior to the uncinate with the tip angled slightly inferiorly. Once engaged, the device expands by absorbing the moisture from the lining of the passage. After an hour, it can be removed.

Benefit: Chronic sinusitis affects more than 31 million people in the United States. It is more prevalent than heart disease and asthma and has a greater impact on patients’ quality of life than chronic back pain or congestive heart failure, SinuSys says. The majority of patients with chronic sinusitis are treated with oral antibiotics, nasal steroids, or both, which can increase the risk of antibiotic resistance and cause unwanted side effects such as epistaxis, nasal ulcers, and nasal and oral infections.

According to SinuSys, the Vent-Os’s small, low-pressure, self-expanding insert opens the maxillary ostia more gently and gradually than balloon technology.

Sources: www.sinusys.com; Device Daily Bulletin