NEW DRUGS

Mecasermin for Short Stature

The Food and Drug Administration (FDA) has approved mecasermin injection of recombinant DNA origin (Increlex™, Tercica) for the long-term treatment of growth failure in children with severe primary insulin-like growth factor-1 (IGF-1) deficiency or with growth hormone (GH) gene deletion who have developed neutralizing antibodies to GH.

IGF-1 must be present in order for children’s bones, cartilage, and organs to grow normally. Severe primary IGF deficiency is characterized by abnormally low blood IGF-1 levels in the presence of normal or elevated GH. Approximately 6,000 children in the U.S. are affected.

The active ingredient of mecasermin is identical to the natural hormone, IGF-1, which the body produces in response to stimulation by GH.

In both children and adults, this deficiency can lead to lipid abnormalities, decreased bone density, obesity, and insulin resistance.

Mecasermin has also been designated as an orphan drug. Tercica acquired exclusive rights to manufacture this product from Genentech.

(Source: Tercica, Inc., August 31, 2005.)

Combination Vaccine: Measles, Mumps, Rubella, Varicella

A combination vaccine (Proquad®, Oka/Merck) has been approved to protect children 12 months to 12 years of age against measles, mumps, rubella (German measles), and varicella (chickenpox).

This is the first U.S.-approved vaccine approved to offer protection against these four diseases in a single injection.

Proquad® combines two Merck vaccines: M-M-R®II (Measles, Mumps and Rubella Virus Vaccine Live) and Varivax® (Varicella Virus Vaccine Live).

(Source: Merck, September 6, 2005.)

Influenza Vaccine For Coming Flu Season

The FDA has approved Fluarix™ (GlaxoSmithKline), an influenza vaccine for adults 18 years of age and older against influenza virus types A and B.

The first vaccine to be approved via the FDA’s accelerated approval process, Fluarix™ contains inactivated virus. The FDA evaluated the vaccine’s safety and effectiveness after four clinical studies involving approximately 1,200 adults.

(Source: FDA, August 31, 2005.)

Final Approval for Anastrozole In Early Breast Cancer

Anastrozole (Arimidex®, AstraZeneca) has received full approval for the adjuvant treatment of hormone receptor–positive early breast cancer in postmenopausal women. This aromatase inhibitor has proved superior disease-free survival over the company’s tamoxifen (Nolvadex®).

Anastrozole and tamoxifen are the only hormonal FDA-approved therapies as primary adjuvant therapy (following surgery, with or without radiation). The two medications should not be given together, and anastrozole should not be administered with estrogen-containing therapies, which may diminish its pharmacological action.

(Source: AstraZeneca, September 19, 2005.)

Generic Glucophage® Approved

Mylan Pharmaceuticals, Inc., has received final approval from the FDA for its Abbreviated New Drug Applications (ANDAs) for metformin HCl extended-release tablets, 500 and 750 mg. These tablets are the generic version of Bristol-Myers Squibb’s Glucophage® XR Tablets. Metformin, a biguanide, is indicated for improvement of glucose control in patients with type-2 diabetes.

(Source: Mylan, September 14, 2005.)

Generic Avara® for Arthritis

Barr Laboratories, Inc., has received the FDA’s approval for its ANDA to manufacture leflunomide tablets, 10 and 20 mg, the generic equivalent of Arava® Tablets (Aventis). Leflunomide is indicated for adults with active rheumatoid arthritis.

(Source: Barr Pharmaceuticals, September 14, 2005.)

Generic Oral Zidovudine For HIV/AIDS in Children

The FDA has approved several generic versions of drugs that treat human immunodeficiency virus (HIV), which causes acquired immunodeficiency syndrome (AIDS).

The following products have received full authorization for marketing in the U.S.: (1) zidovudine tablets (Ranbaxy, India); (2) zidovudine tablets and oral solution manufactured (Aurobindo, India), and (3) zidovudine tablets (Roxane, Ohio). These are the first generic versions of GlaxoSmithKline’s Retrovir® to be approved for sale in the U.S.

A nucleoside reverse transcriptase inhibitor (NRTI), zidovudine is intended for use with other antiretroviral agents.

(Source: FDA, September 19, 2005.)

Generic Version of Neurontin®

The FDA has approved the manufacture and marketing of gabapentin tablets 600 and 800 mg (Ranbaxy). The tablets are the generic version of Pfizer’s Neurontin® tablets.

Gabapentin is indicated for the management of postherpetic neuralgia in adults and as adjunctive therapy for partial seizures in patients with epilepsy.

(Source: Ranbaxy Pharmaceuticals, September 16, 2005.)

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Progestin/Estradiol Combo For Menopausal Symptoms

A combined hormonal therapy of dospirenone and estradiol (Angeliq®, Berlex, a Schering affiliate) has been approved to treat vasomotor symptoms, such as hot flashes and night sweats, in menopausal women. This is the only hormonal therapy containing the unique progestin dospirenone.

(Source: Berlex, Inc., September 29, 2005.)

NEW INDICATION

Infliximab for Ulcerative Colitis

Johnson & Johnson’s biopharmaceutical unit, Centocor, Inc., has announced the FDA’s approval of infliximab (Remicade®) for patients with ulcerative colitis, a chronic inflammatory bowel disease. This agent is also indicated for the treatment of rheumatoid arthritis, ankylosing spondylitis, psoriatic arthritis, and Crohn’s disease.

This is an unprecedented milestone in the treatment of moderate-to-severe ulcerative colitis. Until now, no therapy has been indicated for mucosal healing and eliminating the use of corticosteroids.

(Source: FDA; www.renicade.com.)

DRUG NEWS

FDA Head Leaves

Lester Crawford, 67, has suddenly resigned as head of the FDA, saying that he was stepping aside because of his age. The new acting commissioner is Andrew von Eschenbach, a urological surgeon previously with the University of Texas MD Anderson Cancer Center and the National Cancer Institute.

His three-year tenure at FDA was marked by increasing criticism and a troubled past year. The painkiller Vioxx was pulled off the market for safety problems, and he indefinitely postponed non-prescription sales of emergency contraception over the objections of staff scientists who had declared the pill safe. The FDA’s women’s health chief resigned in protest.

Dr. Crawford had been elevated by President Bush from acting commissioner partly because his experience was deemed important as the FDA tried to better safeguard the food supply against bioterrorism.

(Source: Associated Press, September 24, 2005.)

Glyburide and Glipizide Safe for Breast-Feeding

The use of earlier-generation sulfonylureas during breast-feeding was discouraged after studies with tolbutamide (e.g., Orinase®, Pharmacia/Upjohn) and chlorpropamide (Diabinese®, Pfizer) showed significant transfer of these substances into breast milk. Two small studies now indicate that the second-generation sulfonylureas—including glyburide (DiaBeta®, Aventis) and glipizide (Glucotrol®, Pfizer)—don’t pose the same problem.

Researchers from the University of Toronto, Mount Sinai Hospital, and The Hospital for Sick Children, all in Toronto; Miller Children’s Hospital, in Long Beach, California; and the University of California in San Francisco, gave the women a single oral dose of glyburide 5 or 10 mg. Drug concentrations were measured in maternal blood and milk for eight hours after the dose was given.

In a separate study, five women received glyburide or glipizide 5 mg/day starting on the first postpartum day. For five to 16 days after delivery, drug concentrations in the mothers’ blood and milk were measured, as were the infants’ blood glucose levels.

In the single-dose study, neither drug was detected in breast milk, even though plasma levels were invariably detected. In the daily-dose study, only one woman had a detectable serum level of glipizide.

Three wholly breast-fed infants had normal blood glucose levels (one infant’s mother received glyburide, and two infants’ mothers received glipizide).

Another infant in the glyburide group had normal blood glucose levels, but the mother had supplemented breast-feeding with formula. Glucose levels were not measured in the remaining infant, whose mother also used formula.

(Source: Diabetes Care 2005;28: 1851–1855.)

Warning Signs: Oral Contraceptives and Diabetic Nephropathy

Oral contraceptive (OC) use may be a risk factor for diabetic nephropathy, say researchers from Brigham and Women’s Hospital in Boston; the Steno Diabetes Center in Gentofte, Denmark; the University of Aarhus in Denmark; and Joslin Diabetes Center in Boston. In their study, women with diabetes who used OCs had almost nine times the rate of macroalbuminuria than that of non-users.

Both women with and without diabetes who were using OCs showed an increased renal plasma flow response, compared with those who were not using OCs. In fact, OC use in the absence of diabetes increased angiotensin-dependent control of the renal circulation to levels observed in women with diabetes who did not use OCs.

After the investigators controlled for other risk factors, OC use remained a significant predictor for macroalbuminuria, which reflects more serious glomerulopathy.

The findings could have widespread importance, considering that at least 20% of diabetic women use OCs. The researchers point out that no contraceptive methods are contraindicated in diabetic women; in fact, contraception is particularly advised for these women because of the possibility of serious com-
Flu Riskier for Cancer Patients

It is well known that at-risk patients are urged to get flu shots, but protection from influenza may be crucial for patients with cancer. Hospitalized patients with flu-related infections are 10 times more likely to die than the general population, say researchers from the MD Anderson Cancer Center in Houston, Texas. The very young and the very old are at the highest risk, and the impact is particularly notable among those patients who are 65 years of age and older.

More than 9% of cancer patients with flu complications died in the hospital, and 32% needed further skilled care. The average length of stay was six days. Patients with blood cancer or lung cancer tended to stay longer, need ventilation more often, and died at a higher rate than patients with other types of cancers.

The risk of hospitalization in children with cancer, from age zero to four years, was as much as eight times higher than that for children in the general population. Children aged five to 14 years had up to six times the risk of high-risk patients in general.

(Source: Cancer 2005;104:618–628.)

Testosterone Patch for Women: Better Sexual Functioning

The testosterone patch was found to safely improve sexual function in women whose ovaries had been removed. In a trial involving 447 women at 39 sites in the U.S., 119 women were randomly assigned to receive placebo. The remaining women received the patch in one of three dosages—at 150 mcg/day, 300 mcg/day, or 450 mcg/day—twice a week for 24 weeks.

Despite a large response to placebo, the women using the 300-mcg/day patch experienced increased sexual desire from baseline (67% with the patch vs. 48% with placebo) and in the frequency of satisfying sexual activity (79% vs. 43%). This dose was the most effective; the dose of 150 mcg/day showed no evidence of an effect, and the highest dose was not statistically different from the 300-mcg/day dose.

(Source: Arch Intern Med 2005;163: 1582–1589.)

Cognitive Therapy/Drug Combo Improves Irritable Bowel Syndrome

Researchers from King’s College in London who tested cognitive therapy along with drug treatment in 149 patients with irritable bowel syndrome (IBS) had expected the combination to help ease the symptoms—for a while. They gave the modality about six months to produce benefits, but they anticipated that the effects would begin to wane by one year after treatment, as is commonly observed with other psychological and physical treatments for IBS.

It turns out that they were right on target. While the effects lasted, however, patients did report improvement. Moreover, disability was still reduced at 12 months after treatment. Over one year, the combination therapy reduced total symptom severity scores by 37 points and global impact scores by 14 points. The effects did indeed decline over 12 months, but so did those of the drug alone.

General primary care nurses delivered the cognitive behavior therapy in six 50-minute sessions at weekly intervals, with face-to-face contact. Therapy included education about the nature of IBS, techniques aimed at improving bowel habits, and cognitive techniques designed to help patients focus less on symptoms and to manage stress.

Although the study suggests a clinically useful effect, the investigators note that more research is “clearly required to determine whether patients might benefit from ‘booster’ therapy sessions.”

(Source: BMJ 2005;331:435.)
Non-approvable Letter For Osteoporosis Drug

The FDA has rejected Pfizer’s New Drug Application (NDA) for lasofoxifene (Opora), a selective estrogen receptor modulator (SERM), indicated for the prevention of osteoporosis. An “approvable” decision might have given Pfizer the hope that Opora might be approved and marketed at some point. “Not approvable” means that approval might not be granted in the future, certainly not without the submission of significant additional data.

SERMs are known to increase the risk of venous thromboembolism, an effect that is also associated with the use of hormone replacement therapy (HRT). In January 2003, after the release of the Women’s Health Initiative trial data in 2002, this effect—along with the reported increased breast cancer risk and increased risk of other cardiovascular events—contributed to the addition of black-box warnings on all HRT products prescribed in the US. As a result, the FDA has increased its scrutiny of HRT in postmenopausal women. Although Opora is not a hormone, it exerts a hormonal effect, potentially leaving it open to the same concerns in terms of adverse events and long-term use.

The drug was at least as effective as Eli Lilly’s raloxifene (Evista®); however, the FDA is becoming more stringent on the safety aspect of NDAs, particularly for products that are likely to require long-term use and in areas of less urgent medical need, such as with preventive interventions.

(Sources: Pfizer and Data Monitor, September 16, 2005.)

Stopping HRT: Night Sweats, Hot flashes May Return

Nearly two-thirds of women who use hormone replacement therapy (HRT) to reduce menopausal symptoms have experienced a recurrence or a worsening of symptoms after they stop treatment.

In the months following the unexpected halting of the Women’s Health Initiative (WHI) trial in July 2002, many older women abruptly stopped taking HRT after it was found that HRT might be causing more harm than good.

It is not uncommon for symptoms associated with menopause to last for a decade or more. Some women may have symptoms for the rest of their lives.

Women who took estrogen or estrogen plus a progestin were six times more likely to report moderate-to-severe hot flashes and night sweats after discontinuing HRT, compared with women taking placebo, and were more than twice as likely to report an increase in overall stiffness and pain.

The women took HRT for an average of 5.7 years.

Before the WHI findings were published, postmenopausal women often took estrogen therapy for decades because physicians believed that the treatment helped reduced the risk of age-related illnesses, including heart disease. However, the large government study revealed that HRT did not prevent heart disease in older women; in fact, it seemed to be associated with an increased risk of strokes, blood clots, and breast cancer.

Health experts recommend that HRT be used to treat only hot flashes and vaginal dryness and be given in the lowest effective dosage for the shortest possible time (ideally, no more than five years).

It has become clear that the combination of progestin and estrogen may pose more health risks than estrogen alone. Progestin is recommended for women who have not had hysterectomies.

(Sources: JAMA 2005;294:183–193; Los Angeles Times, July 13, 2005; WebMD Medical News July 12, 2005.)

Memory, Mice, and Genes: A Clue to Alzheimer’s Disease?

Mice with brain damage recovered lost memories after scientists “turned off” a gene known to cause symptoms similar to those found in patients with Alzheimer’s disease (AD). AD destroys the brain’s nerve cells and leads to loss of memory and the ability to learn.

Scientists used this gene, derived from human DNA, to induce brain damage and premature aging in mice. When scientists turned this gene off, 70% of the mice regained memories on how to exit an underwater maze. The study was conducted at the University of Minnesota.

Although the study did not involve AD directly, the gene used caused a type of brain damage similar to damage believed to be a marker for AD. The markers or proteins, called tangles, were present in the rodents’ brains but did not decrease when memory was recovered.

The investigators were surprised at this finding; they were also surprised to learn that the mice recovered memories from parts of the brain that had been damaged before the gene was turned off.

Bill Thies, vice president of medical and science affairs for the Alzheimer’s Disease Association, said that even though human brains might not react the same way, the study should inspire pharmaceutical companies to develop treatments.


NEW MEDICAL DEVICES

Marvin M. Goldenberg, PhD, RPh, MS

Name: Chilli II™ Cooled Ablation Catheter

Manufacturer: Boston Scientific Corporation, Natick, MA

Approval Date: August 31, 2005

Use Classification: This is the first continued on page 560
bidirectional cooled-tip catheter that offers the benefits of cooled ablation technology coupled with the performance characteristics of the company’s Blazer® catheter platform.

**Description:** Cooled cardiac ablation uses radiofrequency (RF) energy in treating ventricular tachycardia (VT), a serious cardiac arrhythmia characterized by a heart rate above 100 beats/minute. The cooling system is designed to reduce complications often encountered in standard ablation procedures.

**Purpose:** To treat VT.

**Benefit:** Consistent, continuous fluid circulation cools the catheter tip, reducing the formation of coagulum and allowing deeper lesions to be created. The closed-loop design eliminates the need to add fluid and to monitor flow rates during the procedure, reducing the potential for fluid overload.

**Source:** www.devicelink.com

**Name:** Xact® Carotid Stent System  
**Manufacturer:** Abbott Vascular Devices, Redwood City, CA  
**Approval Date:** September 6, 2005  
**Use Classification:** This stent system is indicated for patients who have experienced a stroke, who have a very tight blockage (80% or more) in the neck vessels, and who have medical problems that would place them at great risk if they underwent carotid endarterectomy.

**Description:** Two systems are included: (1) the stent, a metal mesh tube on a delivery catheter, and (2) the embolic protection device, a micromesh filter basket on the end of the delivery catheter.

The system is inserted during angioplasty, a less invasive procedure than carotid endarterectomy. The stent is threaded up to the carotid artery via a catheter that is inserted in the groin. The Emboshield® embolic protection system is inserted into the vessel in the groin and advanced up to the blocked neck blood vessel. The Emboshield® filtration element has holes small enough to allow blood to flow through and to catch any particles that might break off from the blockage during the operation.

After the filtration element is deployed, the physician uses the same wire to advance the metal stent to the blocked area. The metal (nitinol) is then allowed to come out of the catheter. The catheter is removed, and another catheter is placed up into the neck vessel to close the filtration element. It is removed along with any pieces of debris that were trapped.

**Purpose:** To open blocked blood vessels in order to prevent future strokes.

**Benefit:** The stent allows blood flow to the brain beyond the first year after the procedure.

**Precautions:** This system is not indicated for patients who cannot take blood thinners, who have bleeding disorders, who are allergic to nitinol, or who have blockages at the start of the neck artery.

**Source:** www.fda.gov/cdrh/mda/docs/p040038.html

**Name:** Matrix VSG™ System  
**Manufacturer:** AccessClosure, Inc., Mountain View, CA  
**Approval Date:** August 17, 2005  
**Use Classification:** This system is indicated for sealing a puncture site in the femoral artery to stop the bleeding after cardiac catheterization.

**Description:** The balloon catheter is inserted through the introducer sheath into the femoral artery at the puncture site. Two polymer powders are mixed together to form a polyethylene glycol gel that is injected at the puncture site. After delivery of the polymer, the balloon catheter is deflated and removed along with the introducer sheath. Manual compression is applied for one to two minutes to ensure that bleeding stops. The gel is absorbed into the body within 30 days.

**Purpose:** To temporarily stop bleeding after cardiac catheterization.

**Benefit:** The device allows patients to get out of bed and walk sooner than is possible with standard compression methods.

**Source:** www.fda.gov/cdrh/mda/docs/p040044.html

**Controversy:**

**Guidant Defibrillator Units**

When should the FDA release newly discovered adverse information from medical device companies to physicians?

This question arose after it was learned that Guidant Corporation informed the FDA about the short-circuiting of some of its Ventak Prizm 2 DR defibrillator units. However, the FDA did not make the data public at the time because it treats the information in a company’s annual report as confidential.

Guidant knew about the model’s flaw for three years but did not tell physicians until May 2005. In June 2005, the FDA issued an alert stating that short-circuiting of the device, although rare, presented a significant risk because it could render the device useless at a critical point in arresting erratic heart rhythms.

The FDA claims that annual reports contain a large amount of data and that it takes a lot of time to sift through the information to find a significant adversity. The agency does not believe that the effort of disclosing the “massive” amount of data would be an effective use of its resources or time. Guidant claims that it made all required disclosures to the FDA.

As a result of this controversy, it appears that the FDA may have to change its review policy of medical devices. Time will tell whether an official change will occur.

**Source:** The New York Times, September 12, 2005.