**NEW DRUGS**

**Low-Dose Estradiol Gel**

BioSante Pharmaceuticals has received approval from the Food and Drug Administration (FDA) to market an estradiol transdermal gel (Elestrin, formerly Bio-E-Gel) for menopausal women with moderate-to-severe hot flashes. Elestrin is a gel formulation of bio-identical estradiol, the same estrogen produced naturally in women.

A metered dose applicator delivers 0.87 g of gel per actuation, allowing for precise titration for each dose. This is the lowest effective dose of estradiol available.

Elestrin is absorbed through the skin after it is applied on the upper arm. Estradiol is delivered to the bloodstream evenly over time in a non-irritating manner. The gel dries in one to two minutes. The gel will be marketed in the U.S. by the Kenwood Therapeutics Division of Bradley Pharmaceuticals. It is scheduled to be launched this summer.

(Source: BioSante, December 18, 2006.)

**Generic Zofran (Ondansetron)**

The FDA has approved the first generic versions of Zofran (ondansetron) tablets, orally disintegrating tablets, and oral solution. These products are indicated to prevent nausea and vomiting associated with surgery, radiotherapy, and cancer chemotherapy.

Ondansetron tablets (Dr. Reddy Laboratories) and the disintegrating tablets (Kali Laboratories) are available in strengths of 4 mg, 8 mg, 16 mg, and 24 mg. Roxane Labs manufactures the oral solution, 4 mg (base)/5 ml.

(Source: FDA, January 2, 2007.)

**Once-Daily Mesalamine For Ulcerative Colitis**

Shire has announced the approval of mesalamine with MMX technology (Lialda), indicated for the induction of remission in patients with active, mild-to-moderate ulcerative colitis. This product is the first once-daily oral formulation of mesalamine.

Mesalamines are a part of a drug class called aminosalicylates.

Because the once-daily product contains the highest mesalamine dose per tablet (1.2 g), patients can take as few as two tablets once daily. Other mesalamines must be taken three to four times per day for a total of six to 16 tablets per day.

The FDA's approval was based on the results of two phase 3 clinical studies. At doses of 2.4 g/day and 4.8 g/day, Lialda was effective in bringing about remission, compared with placebo, after eight weeks of treatment. The safety and effectiveness of Lialda beyond eight weeks have not been established.

(Source: Shire, January 16, 2007; www.lialda.com.)

**NEW FORMULATION**

**Refrigerated Flu Vaccine For Next Season**

Refrigerated FluMist live intranasal influenza virus vaccine (MedImmune) has been approved. The vaccine is used to prevent influenza in healthy children and adolescents 5 to 17 years of age and in healthy adults 18 to 49 years of age.

The new formulation, called CAIV-T (cold-adapted influenza vaccine–trivalent), can be stored in a refrigerator rather than in a freezer, as previously required.

FluMist has been marketed in a frozen formulation since its original FDA approval in 2003. The new formulation will be available for the 2007–2008 influenza season. Both the frozen and refrigerated forms are free of preservatives, including thimerosal.

FluMist should never be injected.

(Source: MedImmune, January 8, 2006; www.flumist.com.)

**DRUG NEWS**

**Medicare Part B Drug Prices Posted**


**Pergolide and Cabergoline Linked to Heart Problems**

Two studies have raised concern about two drugs used to treat Parkinson’s disease (PD) and other disorders, because they might be causing damage to the heart valves. The drugs are the ergot-derived dopamine agonists pergolide (Permax, Valeant) and cabergoline (Dostinex, Pfizer). Permax is approved in the U.S. and overseas for PD. Dostinex is used for PD in other countries but is approved in the U.S. only for hyperprolactinemia, a hormonal disorder.

Permax already carries a boxed warning (added in 2003) about an increased...
risk of heart-valve problems. A milder warning about valve problems was added to Dostinex labeling in December 2006. The two reports involve only PD. The results should not be applied to patients taking Dostinex for the hormone disorder because they take far smaller doses of the drug than do patients with PD.


**Pregnancy Category Change for Insulin Analogue**

The FDA has approved a Pregnancy Category B rating for insulin aspart (rDNA origin) injection (NovoLog, Novo Nordisk). This rating indicates that adequate studies of pregnant women with type-1 diabetes have shown that NovoLog does not pose an increased risk to the unborn baby. Previously, the product had a Category C rating, which indicated that adverse effects on the fetus had occurred in animal studies and that adequate and well-controlled studies in pregnant women had not been conducted to demonstrate the product’s safety.

(Source: Novo Nordisk, January 30, 2007.)

**Atorvastatin May Benefit Older Diabetic Patients**

Few trials have assessed the efficacy of statins for the primary or secondary prevention of cardiovascular disease in type-2 diabetic patients, let alone older patients, according to researchers from the Collaborative Atorvastatin Diabetes Study (CARDS). Some trials have found a statistically significant benefit, but others have not, perhaps because the numbers of enrolled patients were too small.

In view of these findings, a post hoc analysis of data from CARDS was conducted to compare statin therapy in 1,129 patients 65 to 75 years of age and in 1,709 younger patients. Treatment with atorvastatin 10 mg/day reduced the relative risk of a first major cardiovascular event by 38% in older patients and by 37% in younger patients. The risk of a stroke was nearly halved. Two of 572 (0.3%) older patients who were taking atorvastatin had fatal heart attacks, compared with 12 of 557 (2.2%) receiving placebo.

One patient in the over-65 age group taking atorvastatin had a fatal stroke, and 12 patients had nonfatal strokes, compared with four patients who died and 17 placebo patients with nonfatal strokes. Treatment was well tolerated in both groups, even with the high use of concomitant drugs in the older patients.

(Source: JAMA 2006;295:2378–2384.)

**Imatinib for Leukemia: Still Effective Five Years Later**

Here is some good news for patients with chronic myeloid leukemia (CML): five years after starting imatinib mesylate (Gleevec, Novartis) therapy, nearly all patients in the International Randomized Study of Interferon and ST1571 (IRIS) were still responding to treatment.

IRIS was designed to compare standard therapy (interferon alfa plus cytarabine) with imatinib in 1,106 patients with CML. However, the results were so dramatic that the trial evolved into a long-term study focusing on the 553 patients taking imatinib. After a median follow-up period of 60 months, 93% of the patients had not progressed to accelerated-phase CML (blast crisis). The five-year estimated overall survival of patients receiving imatinib as initial therapy was 89%.

The risk of treatment failure was highest in the second year. Imatinib inhibits bcr-abl tyrosine kinase. Notably, the researchers say, the rate of disease progression is starting to decrease, although the trend has not reached statistical significance. If it persists, such a trend would be consistent with the findings that mutations in the bcr-abl gene are the major cause of relapse in patients treated with imatinib.


**Substituting Sirolimus for Steroids in Transplant Patients**

Switching transplant recipients from prednisone to sirolimus (Rapamune, Wyeth) and cyclosporine is apparently a safe transition that may improve quality of life over the long term.

In a study from The University of Texas Medical School at Houston, 27 of 30 renal transplant patients were converted fairly seamlessly to sirolimus. Prednisone therapy had failed because of chronic allograft nephropathy in one recipient, disease recurrence in a second, and chronic rejection in a third. The main difference after the switch was seen in quality-of-life reports.

After two years, 99% of the switched patients reported greater energy levels, compared with 19% of patients receiving steroids. They also reported “excellent health” (24% vs. 5% receiving steroids), and satisfaction with appearance (67% vs. 41%). The switched patients were also more likely to report amelioration of cyclosporine-related effects such as hypertrichosis, weight gain, and gingival hypertrophy. However, fewer of these patients felt calm (14% vs. 23%), and more patients said that they experienced pain all the time (19% vs. 5%).

The researchers attributed the successful conversions to previous experience with the “marked pharmacokinetic interactions between sirolimus and cyclo-
sporine, which demand tight concentration control."

(Source: Transpl Proc 2006;38:2842–2846.)

Oxytrex: A Less Addicting Version of Oxycodone

Pain relief can come at a price—physical dependence—when opioid therapy is prolonged. Researchers from Lifetree Clinical Research in Salt Lake City, Utah, and Pain Therapeutics in San Francisco, California, suggest adding a little naltrexone.

Oxytrex (Pain Therapeutics), an investigational drug combining oxycodone (OxyContin, Purdue Pharma) and ultralow-dose naltrexone, provided strong analgesia while minimizing physical dependence.

In a phase 3 clinical trial, 719 patients were randomly assigned to placebo, oxycodone four times daily, or Oxytrex four times daily or twice daily. Each Oxytrex tablet contained naltrexone 1 mcg. The twice-daily and four-times-daily Oxytrex treatments provided naltrexone 2 mcg/day and 4 mcg/day.

Opioid-related adverse events did not differ significantly among the three treatment groups; however, the Oxytrex patients needed a significantly lower amount of medication to achieve comparable analgesia. Patients taking Oxytrex twice a day reported 55% less physical dependence than did patients receiving oxycodone 24 hours after stopping treatment; they also reported less moderate-to-severe constipation (44%), less somnolence (33%), and less pruritus (51%).

Oxytrex twice daily also provided a better safety profile, compared with four-times-daily oxycodone, by significantly reducing the number of moderate-to-severe events. A subgroup analysis showed a slightly stronger effect in reducing dependence on the medication in patients older than 50 years of age.

Although the researchers acknowledged that lowering the oxycodone dose might have contributed to the reduction in dependence, they suggest that it is unlikely that the difference of 4.3 mg would have caused such a profound decrease.

One major limitation of the study was the large number of patients who dropped out—more than 50%—in all treatment groups. The percentage of dropouts attributable to adverse events during titration was somewhat higher in those receiving twice-daily Oxytrex (14% versus 22%). The difference was most likely a result of the higher individual doses of oxycodone in twice-daily versus four-times-daily administration, the researchers say. They advised titrating the twice-daily Oxytrex dose more slowly and starting with a lower dose.

(Source: J Pain 2006;12:937–946.)

Heal Anemia, Help the Heart

Giving erythropoietin (EPO) and oral iron to patients with congestive heart failure (CHF) instead of oral iron alone may have several benefits.

In a study by researchers from Italy and Israel, EPO improved New York Heart Association status, exercise endurance, renal function, and plasma B-type natriuretic peptide (BNP) levels. The patients also needed less oxygen during exercise and were less likely to be hospitalized.

Forty patients with moderate-to-severe CHF and anemia received EPO subcutaneously twice weekly for three months along with daily iron, or placebo with daily iron. Although the EPO patients improved in all measures, the iron-only group did not. Over the course of the study and during a subsequent nine-month open-label study, four of 20 EPO patients were hospitalized, compared with eight of 18 in the iron-only group.

The results were not entirely unexpected, but this was the first study that was both placebo-controlled and double-blind, the researchers say. To their knowledge, it was the first study of CHF patients showing that treating anemia with EPO plus iron might help reduce BNP levels. BNP, they note, is accepted as a good marker of the presence and severity of CHF.

In other studies, BNP was inversely related to hemoglobin, but it was not clear whether the anemia was an actual cause of the rising BNP levels. In this study, it was certainly at least partially responsible. The decline in BNP could be related to the improvements in many aspects, the researchers suggest, including a better oxygen supply to the heart.

(Source: Am Heart J 2006;152:1096.e9–1096.e15.)

Heartburn Drugs And Hip Fractures

According to a British study, people older than 50 years of age who took proton pump inhibitors (PPIs) for a year or more had a significant increase in the risk of breaking a hip.

The study looked at medical records of more than 145,000 patients whose average age was 77. Patients who used PPIs for more than a year had a 44% higher risk of hip fracture than non-users.

Also known as “heartburn” or reflux agents (e.g., Nexium, Prevacid, Prilosec), PPIs may interfere with calcium absorption. Long-term PPI therapy, particularly at high doses, was associated with an increased risk of hip fracture. The researchers speculated that when the drugs reduce hydrochloric acid in the stomach, they might make it more difficult for the body to absorb bone-building calcium.

A similar but smaller risk of hip fractures for H₂ blockers (e.g., Tagamet, Pepcid) was also noted.

Even though the study suggested only a potential association, patients should
take the proper dosage, report how long they have been taking the drugs, undergo bone density testing, and follow a calcium-rich diet.

(Source: JAMA 2006;296:2947–2953; Associated Press, December 27, 2006.)

**Longer Life For Drug-Coated Stent**

Boston Scientific Corporation has announced that the FDA has approved extending the shelf life of its Taxus Express2 paclitaxel-eluting coronary stent system in the U.S. to 18 months from its current shelf life of 12 months.

The decision was based on data showing that the stent’s performance—its drug content, drug-degradation profile, and system of drug release—was maintained within the FDA’s specifications at 18 months. The new shelf life is longer than that for other drug-eluting stents.

The extended expiration date applies to all available sizes of the stent for sale in the U.S. The shelf life for the Taxus stent outside the U.S. is still 18 months.

(Source: Boston Scientific, January 18, 2007.)

**Does Androgen Lower Risk of Alzheimer’s Disease?**

Experiments in mice seem to indicate that treatment with male sex hormones might slow the progression of Alzheimer’s disease (AD), which affects 4.5 million Americans.

Researchers established a correlation between low testosterone levels and elevated beta-amyloid, a protein that accumulates abnormally in patients with AD. This finding suggests that testosterone depletion in aging men might be a risk factor for AD by promoting accumulation of beta-amyloid in the brain. Because testosterone is rapidly converted to estrogen after entry into neurons, the new data do seem logical.

Using a mouse model of AD in which three genes had been altered, the researchers evaluated how experimental manipulation of sex hormones affected AD progression. They removed the testes of young adult male mice. Over a period of several months, some mice were given a testosterone hormone and others were given a placebo.

After treatment, memory-related behavior and measures of AD-like pathology were measured in the different groups of mice. The castrated mice receiving placebo showed poor working memory and high brain levels of beta-amyloid, but both beta-amyloid accumulation and cognitive decline were avoided in mice receiving hormone therapy.

Although androgen therapy might be able to reduce the risk of AD in at least some men, more studies are needed.

(Source: J Neurosci, December 20, 2006.)

**Fewer Benzodiazepines: Fewer Hip Fractures? Not Necessarily!**

Because of concerns about benzodiazepine misuse and adverse events, including hip fractures among elderly, some state and national policies have tried to regulate access to these drugs. The use of benzodiazepines has been associated with cognitive dysfunction and loss of balance in the elderly.

Medicare Part D excludes benzodiazepines from coverage, and many state government policies limit their use; however, it is not clear whether such policies have decreased the incidence of hip fracture.

An experiment was performed to assess whether a statewide policy that decreased the use of benzodiazepines by more than 50% among elderly people would reduce the incidence of hip fracture. More than 51,000 Medicaid recipients in New York and about 42,000 patients in New Jersey were enrolled; some received a benzodiazepine, and some did not.

It was thought that a decrease in benzodiazepine prescribing in New York would result in a decreased incidence of hip fractures, particularly in those at highest risk—women who use benzodiazepines—whereas rates of hip fracture would not decrease in New Jersey. The New York enrollees were older.

Since January 2006, benzodiazepines have been excluded from coverage through the Medicare Part D drug benefit. On January 1, 1989, the New York State Department of Health’s policy had stated that all physicians in the state had to obtain, pay for, and use special triplicate forms to prescribe benzodiazepines.

The triplicate prescription policy resulted in a 60.3% reduction of benzodiazepine use in women and in a 58.5% reduction in men. Benzodiazepine use in New York decreased abruptly, from about 40% of enrollees each month before the policy change, to about 15% after the change. Benzodiazepine use remained stable in New Jersey.

In contrast to the sudden, large reductions in rates of benzodiazepine use, the rates at which hip fractures accumulated did not change after the policy was implemented. It was concluded that the policies that led to reductions in the use of benzodiazepines in elderly patients did not necessarily lead to a decreased incidence of hip fracture. Therefore, limitations on coverage of benzodiazepines under Medicare Part D might not achieve this assumed benefit.

(Source: Ann Intern Med 2007;146:96–103.)

**Arsenic Improves Survival in Rare Form of Leukemia**

In a trial sponsored by the National Cancer Institute, adults with previously untreated acute promyelocytic leukemia (APL) who had standard chemotherapy...
(Trisenox, Cephalon) to induce remission and who then received arsenic trioxide to maintain remission had better event-free and overall survival times than patients who received only standard chemotherapy.

Acute promyelocytic leukemia, an uncommon subtype of acute myeloid leukemia (AML), accounts for about 10% of AML cases. It occurs most often in young and middle-aged adults.

Standard chemotherapy regimens produce complete remission rates of approximately 70% and show a five-year survival rate without disease recurrence in 35% to 45% of patients.

More recently, arsenic trioxide was shown to be effective for producing a second remission in patients who had a relapse or recurrence of APL after the first treatment. The percentage of adult patients who remained alive and in remission three years after diagnosis was 77% with treatment (which included arsenic trioxide), compared with 59% receiving standard treatment.

The greater effectiveness of the experimental combination also resulted in better overall survival after three years: 86% with arsenic trioxide and 77% with standard therapy.

There was no difference in hematological toxicities between the groups, but the arsenic trioxide patients reported a slightly higher incidence of headache and infection.


**NEW MEDICAL DEVICES**

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

**Name:** Kinetic Anterior Cervical Plating System

**Manufacturer:** Life Spine, Hoffman Estates, IL

**Approval Date:** November 28, 2006

**Use Classification:** This device is used in spinal surgery.

**Description:** The plating system features 2 mm of fully adjustable internal dynamization per level and an ultra-slim prelordosed profile. Dynamization refers to the process of transforming a static data structure into a dynamic one. Prelordosed plates restore the lordotic curvature of the cervical spine.

The dynamic plates range in sizes from 21 to 111 mm and from levels 1 to 5. The design allows for generous screw angulation and provides a large graft window. The bone screws feature a patented locking mechanism that produces an audible and tactile “click” when locked.

**Purpose:** The plating system allows surgeons another option when performing cervical spine procedures and adjusts for individual variations in anatomy.

**Benefit:** The flexibility of design allows surgeons to accommodate the differing needs of each patient’s anatomy. The locking mechanism prevents both screw rotation and backout while still enabling screw angulation.

**Sources:** www.lifespine.com; www.medicalnewstoday.com

**Name:** FilterWire EZ Embolic Protection System

**Manufacturer:** Boston Scientific Corp., Natick, MA

**Approval Date:** December 14, 2006

**Use Classification:** This system is used in carotid artery stenting procedures.

**Description:** The device is designed to prevent embolic debris from reaching the brain during stent procedures. Simplified filter sizing allows for easy preparation, delivery, and retrieval. The system can be placed in vessel diameters between 3.5 and 5.5 mm.

The FDA initially approved the system in August 2004 for use in coronary saphenous vein graft interventions.

**Purpose:** The system is designed to capture plaque and other embolic material that might dislodge during stent implantation and acts to prevent the material from traveling into the microvasculature, where it can pose an increased risk for stroke or heart attack.

**Benefit:** The system can be used in the U.S. for patients with carotid artery disease who are at high risk for surgery.

**Sources:** www.bostonscientific.com; www.medgadget.com

**Name:** Radiesse

**Manufacturer:** BioForm Medical, Inc., San Mateo, CA

**Approval Date:** December 27, 2006

**Use Classification:** This cosmetic dermal filler is used to correct facial wrinkles.

**Description:** Formerly known as Radiance, Radiesse is composed of calcium hydroxyapatite microspheres in a water-based gel carrier. An improved appearance is noted the moment the product is injected. The calcium microsphere technology also enables the body to generate new collagen, providing longer-lasting effects.

**Purpose:** This product is indicated for the long-lasting correction of moderate-to-severe facial wrinkles such as nasolabial folds (smile lines). Radiesse was also approved to correct facial fat loss (lipoatrophy) in patients with human immunodeficiency virus (HIV) infection.

**Benefit:** Radiesse provides volume replacement to wrinkles, folds, and sunken depressions. It stimulates the production of new collagen and restores the fullness and contours of the face with sustained results that last one year or more. It is an alternative for patients who prefer to avoid the potential side effects of bovine and solid implant materials. Patients do not need a skin allergy test; the product is made of the same mineral component found in bones and teeth.

**Sources:** www.pharmacyonesource.com; www.radiesse.com

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