NEW DRUGS

Carbinoxamine Maleate: A “Classic” Antihistamine

The launch of a new prescription antihistamine represents the first Abbreviated New Drug Application (ANDA) approval for carbinoxamine maleate (Palgic®, Pan American Laboratories, LLC), making it the only antihistamine of its type approved by the U.S. Food and Drug Administration (FDA) on the market today.

The medication is indicated for the treatment of seasonal allergic rhinitis, perennial allergic rhinitis, urticaria, angioedema, dermatographism, and allergic conjunctivitis caused by inhalant irritants and foods. It is also used as an adjunctive therapy with epinephrine for anaphylactic reactions.

Although the FDA approved the original NDA for carbinoxamine maleate more than 30 years ago, the antihistamine was not aggressively promoted. It has been available for sale since September 15, 2003.

In a placebo-controlled study of 296 patients, 4 mg of the drug was found to be effective as a single-agent antihistamine with a low side-effect profile. The most common adverse effect was “mild sedation” reported by 11% of patients, although the somnolence effect disappeared after two to three days of continuous use. The 4-mg dose was reported to be optimal in relieving allergy symptoms in 87% of the patients.

Palgic® is available in 4-mg tablets or as an oral solution of 4 mg/5 ml. The dose for children aged one to six years is 2 mg. The cost is expected to be less than $1 per day.

(Source: www.palgic.com; www.pamlab.com)

Brimonidine for Glaucoma

The FDA has approved brimonidine tartrate ophthalmic solution 0.2% (Falcon Pharmaceuticals, an affiliate of Alcon Labs). Brimonidine is indicated for lowering intraocular pressure in patients with open-angle glaucoma or ocular hypertension.

The drug dispenser (Drop-tainer®) is available in three sizes: 5, 10, and 15 ml. The product is expected to have a 24-month shelf life.

(Source: Alcon Laboratories, Inc., September 16, 2003.)

Fewer Menstrual Periods with New Oral Contraceptive

The FDA has approved a new oral contraceptive (Seasonale®, Barr Laboratories) for women. Seasonale® contains a progestin (levonorgestrel) and an estrogen (ethinyl estradiol), which are active ingredients in traditional oral contraceptives.

Seasonale® offers a 91-day regimen. Tablets containing the active hormones are taken for 12 weeks (84 days), followed by one week (seven days) of placebo (inactive) tablets. Conventional oral contraceptive use is based on a 28-day regimen (21 days of active tablets, followed by seven days of placebo tablets).

Under the new dosing regimen, the number of expected menstrual periods usually experienced by women is reduced from once a month to about once every three months. As with the conventional 28-day regimen, women have a menstrual period while taking the placebo tablets.

Although Seasonale® users have fewer scheduled menstrual cycles, many women, especially in the first few cycles of use, had more unplanned bleeding and spotting between the expected menstrual periods than women taking a conventional 28-day cycle oral contraceptive.

Some physicians have raised concerns about the consequences of long-term suppression of menstruation, suggesting that data are insufficient to prove that suppression is safe. They also noted that the women in the studies were already taking oral contraceptives and thus would “automatically” be able to tolerate the medication; they were not compared with a control group of women who were not taking oral contraceptives. The supporters of menstrual suppression argue that ovulation itself can inflame the lining of the ovary and might be linked to ovarian cancer. The debate, no doubt, will rage on.

Because Seasonale® users can expect to have fewer periods, the label also advises women to consider the possibility that they might be pregnant if they miss any scheduled periods.

(Source: FDA, www.fda.gov; Barr Laboratories, September 8, 2003; www.barrlabs.com; www.seasonale.com; Pittsburgh Post-Gazette, June 24, 2003.)

IV Product for Compromised Immune System

Bayer HealthCare LLC, Biological Products Division (Bayer BP), has received approval from the FDA for human immune globulin intravenous (IGIV), 10% caprylate/chromatography purified (Gamunex®), a potentially life-saving therapy for patients with compromised immune systems.

Each vial of IGIV contains antibodies that have been purified from the donated blood plasma of thousands of people. These antibodies are essential for immunocompromised patients.

In a study of primary immunodeficiencies, results have demonstrated excellent efficacy, safety, and tolerability of Gamunex®, with patients experiencing a significant reduction in annual validated infection rates.

The company’s innovative process includes breakthrough purification steps using caprylate/chromatography, which improves product purity and supply reliability. Caprylate is a naturally occurring fatty acid that effectively, safely, and rapidly inactivates enveloped viruses.

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This approach also helps to preserve the biological activity of the product by replacing the solvent-detergent method that was used in previous generations of IGIV products.

Gamunex® is also indicated for the acute and chronic treatment of idiopathic thrombocytopenia purpura (ITP), an autoimmune condition characterized by a low platelet count, leading to occasional life-threatening bleeding episodes.

The most common side effects noted during clinical trials included headache, vomiting, fever, nausea, rash, and back pain.

The product will be available in the U.S. later this fall.

(Source: www.gamunex.com.)

**Generic Drug for Low Blood Pressure**

Mylan Laboratories, Inc., has announced that the FDA has granted final approval for its Abbreviated New Drug Application for midodrine HCl tablets in 2.5-, 5-, and 10-mg strengths. Midodrine HCl is the generic version of ProAmatine® (Shire).

The drug is used to treat hypotension by stimulating nerve endings in blood vessels. Mylan plans to launch the tablets immediately.

(Source: Business Wire, September 11, 2003.)

**Daptomycin for Skin Infections**

Daptomycin for injection (Cubicin®, Cubist Pharmaceuticals, Inc.) has been approved by the FDA to treat complicated infections of the skin and its structures.

Cubicin® was previously known as Cidecin®, Cubist acquired worldwide development and commercialization rights to the product from Eli Lilly & Co. in 1997.

Usually occurring in hospitalized patients, these cutaneous problems can include major abscesses, postsurgical skin wound infections, and infected ulcers. The infections are usually caused by susceptible strains of gram-positive microorganisms, such as *Staphylococcus aureus* (including methicillin-resistant strains), *Streptococcus pyogenes*, *Streptococcus agalactiae*, *Streptococcus dysgalactiae* subspecies *equisimilis*, and *Enterococcus faecalis* (vancomycin-susceptible strains only). Cubicin is not indicated for the treatment of pneumonia.

Cubicin® is the first approved product in a new class of antibiotics called cyclic lipopeptide antibacterial agents and treats infections in a way that is distinct from any other antibiotic.

The FDA based its approval on a review of clinical studies involving more than 1,400 adults. The studies demonstrated that Cubicin® was equivalent to other standard treatments.

Most reported adverse events were mild to moderate in intensity, such as gastrointestinal disorders, injection-site reactions, fever, headache, insomnia, dizziness, and rash.

Blood tests showing muscle injury were rarely found in patients in clinical trials. Most of these patients had no symptoms, and values returned to normal after therapy.

Patients receiving Cubicin® should be monitored for the development of muscle pain or weakness, and creatine phosphokinase levels should be assessed weekly.

The manufacturer expects the medication to be available by early November 2003.


**Propoxyphene Napsylate plus Acetaminophen Combination for Pain**

The FDA has approved propoxyphene napsylate and acetaminophen (Darvocet A500™, AAIPharma) for the treatment of mild to moderate pain. Darvocet A500™ is the only approved propoxyphene napsylate/acetaminophen combination product that contains a lower dose (500 mg) of acetaminophen combined with 100 mg of propoxyphene napsylate. (Darvocet-N® 100 contains 100 mg of propoxyphene and 650 mg of acetaminophen.)

The new product is expected to provide a unique formulation with the safety benefits of less acetaminophen and the full strength of propoxyphene. The FDA has established a 4,000-mg maximum daily dose of acetaminophen for adults, and physicians are concerned about patients who self-medicate using over-the-counter products.

(Source: Applied Analytical Industries, September 11, 2003; www.aaipharma.com.)

**Gallium Nitrate Injection for Cancer-Related Hypercalcemia**

Genta Inc. has received approval from the FDA to market gallium nitrate injection (Ganite™) for the treatment of cancer-related hypercalcemia that is resistant to hydration. Cancer-related hypercalcemia is a life-threatening elevation of blood calcium that can occur in up to 50% of patients with advanced cancer. The disorder is usually caused by the release of tumor cell factors, which markedly accelerate the loss of calcium from bone. Hypercalcemia is particularly common in patients with cancers of the lung, breast, head and neck, and kidney, and multiple myeloma. In several trials, Ganite™ was effective against hypercalcemia in a variety of cancers.
Cointing with the launch of the medication, Genta also announced the initiation of an assistance program to facilitate patient access to Ganite™ treatment, known as GentaCARES™ (Creating Access to Reimbursement Expertise Solutions).

Ganite™ was originally developed by the National Cancer Institute (NCI) as a cancer chemotherapy drug. In a series of independent studies, the drug was found to markedly reduced the loss of calcium from bone. This observation led to the suggestion that the drug might be useful in hypercalcemia and other conditions associated with the loss of bone mass.

Ganite™ has proved safe and effective in normalizing high levels of blood calcium by inhibiting calcium resorption from bone. In a double-blind clinical trial that compared calcitonin (a commonly used anti-hypercalcemia drug), 50 patients were randomly selected to receive either Ganite™ 200 mg/m² per day for five days or calcitonin at a dosage of 8 IU/kg four times per day for five days. Of the patients who received Ganite™, 75% achieved normalization of calcium levels; of the patients receiving calcitonin, 27% experienced return of calcium levels to normal ranges (P = .0016). Ganite™ was useful in treating hypercalcemia associated with various types of cancer, irrespective of the initial severity of the disorder.

Ganite™ is contraindicated in patients with severe renal impairment (serum creatinine levels above 2.5 mg/dl). Although it was generally well tolerated in clinical trials, its concurrent use with other potentially nephrotoxic drugs (e.g., aminoglycosides and amphotericin B) may increase the risk for severe renal insufficiency in patients with cancer-released hypercalcemia.

If a potentially nephrotoxic drug is indicated during Ganite™ therapy, Ganite™ should be discontinued and hydration should be instituted for several days.

Genta is currently conducting a multicenter clinical trial to evaluate the efficacy of Ganite™ as a treatment for patients with relapsed or refractory low-grade or intermediate-grade non-Hodgkin’s lymphoma.

(Source: Genta, Inc., September 18, 2003; www.genta.com; www.ganite.com.)

**NEW INDICATION**

Valacyclovir for Reducing Spread of Genital Herpes

Valacyclovir HCl (Valtrex® Caplets, GlaxoSmithKline) has been approved to reduce the risk of heterosexual transmission of genital herpes to susceptible partners with healthy immune systems when used as suppressive therapy in combination with safer sex practices. The drug was first approved for the treatment of genital herpes in 1995.

Many individuals have no or only minimal signs or symptoms and may transmit the virus during sexual contact when they show no signs of active infection, such as genital lesions.

The FDA revised the labeling for Valtrex® on the basis of an international, double-blind, placebo-controlled eight-month clinical trial involving approximately 1,500 monogamous, heterosexual couples. At the beginning of the study, only one member in each couple had evidence of genital herpes. The results showed a 48% reduction in herpes simplex virus acquisition, although individual results may have varied on the basis of safer sex practices.

The medication has caused kidney and nervous system problems (e.g., aggressive behavior, unsteady or shaky movements, confusion, speech problems, hallucinations, seizures, and coma) in some patients with pre-existing renal disease and in elderly patients with impaired renal function. Patients should inform their health care providers if they have had kidney problems or other medical conditions before taking Valtrex®.

(Source: FDA Talk Paper, September 2, 2003; www.fda.gov.)

**DRUG NEWS**

Abciximab Safe in Renal Insufficiency

Abciximab (ReoPro®, Centocor), a glycoprotein IIb/IIIa inhibitor that keeps platelets from sticking together, can safely be given to patients with chronic renal insufficiency who are undergoing a percutaneous coronary intervention (PCI), such as angioplasty, according to a Mayo Clinic study. That’s good news, because these patients face a high risk of failure associated with the procedure, at least a fivefold increase in major adverse drug events (ADEs), and a 10-fold increase in mortality during hospitalization. Even if the PCI succeeds, the mortality rate on long-term follow-up in these patients is nearly four times that for patients with a baseline creatinine level of 1.5 mg/dl or lower.

Although glycoprotein IIb/IIIa antagonists already have a successful record in reducing periprocedural thrombotic events and long-term mortality, they have not been used aggressively in renally impaired patients. Little is known about their safety or efficacy in patients with significant chronic renal insufficiency who are at risk for both platelet and coagulation problems.

(Source: Am Heart J 2003;146:345–350; editorial, 2003;146:213–214.)

**NSAIDs and Parkinson’s Disease Risk**

Nonsteroidal anti-inflammatory drugs (NSAIDs) can reduce the risk of Parkinson’s disease (PD) by 45%, according to researchers from Harvard School of Public Health, Brigham and Women’s Hospital, and Massachusetts General Hospital.
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Using data from 142,902 participants in the Health Professionals Follow-up Study and Nurses' Health Study, they studied the potential association between NSAID use and the risk of PD, which had not been evaluated in population studies.

During the follow-up examination, PD developed in 415 participants. The relative risk of PD was lower with the regular use of NSAIDs and with two or more aspirin tablets a day.

Animal and postmortem studies suggest that inflammation is involved in the pathogenesis of PD. The researchers also cited studies showing ongoing inflammatory reactions in the brain up to 16 years after the onset of PD and in the brains of patients who died with PD. At lower dosages, aspirin has minimal anti-inflammatory effects, the researchers note, which might explain why low-dose aspirin was not associated with lower PD risk.

(Source: Arch Neurol 2003;60:1059–1064.)

Do Antipsychotic Drugs Induce Diabetes?

Some atypical antipsychotic drugs, especially olanzapine (Zyprexa®, Eli Lilly) and clozapine (Clozaril®, Novartis), may induce glucoregulatory dysfunction that can lead to diabetes. Researchers who analyzed data on 5,837 patients in the Veterans Affairs database found that olanzapine therapy was associated with a 37% higher risk of diabetes compared with risperidone treatment.

Of 5,837 patients, 368 (6.3%) had a marker for diabetes, on average within 15 months. Only olanzapine was associated with the increased risk, which was consistent across all analyses, including those that controlled for factors such as other drugs, race, age, and substance abuse.

The researchers note that their numbers might be low, because the markers they used (i.e., the International Classification of Disease ICD-9-CM diagnosis codes and prescriptions for hypoglycemic drugs) tend to underestimate the prevalence of new-onset diabetes.

(Source: Pharmacotherapy 2003;23:1037–1043.)

Risperidone and Osteoporosis Risk

Risperidone (Risperdal®, Janssen) therapy may lead to loss of bone mineral density (BMD) in premenopausal women with schizophrenia, according to a small study. Another atypical antipsychotic agent, olanzapine (Zyprexa®, Eli Lilly), appears to exert no such adverse effects, Israeli physicians report.

Many antipsychotic agents, including risperidone, are associated with hyperprolactinemia, and schizophrenia itself has been linked to osteoporosis.

The researchers compared hormone profiles and BMD in 12 premenopausal schizophrenic women who were taking risperidone and in 14 who were taking olanzapine for about two years. All subjects had previously been taking conventional antipsychotic agents. Serum prolactin levels averaged 25.9 ng/ml in the olanzapine group and 123 ng/ml in the risperidone group. Other hormone levels were comparable.

Age-adjusted ultrasound measurements of bone density were lower after risperidone therapy at the radius and the phalanx but not at the tibia. Z-scores at the phalanx were inversely correlated with urinary excretion of deoxypyridinoline, indicating a high turnover of bone. (The Z-score is the number of standard deviations from the age-matched value of healthy women. A low Z-score, for instance, indicates that BMD is lower than it should be for a patient's age and sex.)

BMD scores that were determined by dual-photon absorptiometry at the lumbar spine and femoral neck did not differ between groups.

Even though further study is needed, the researchers recommended that women with hyperprolactinemia induced by antipsychotic therapy be monitored for the possible onset of osteoporosis.


Losartan and Atenolol for Hypertension

Losartan (Cozaar®, Merck), an angiotensin II AT1-receptor antagonist, has been found to be more effective than atenolol (Tenormin®, AstraZeneca), a beta blocker, in preventing cardiovascular morbidity and mortality in hypertensive patients without clinically evident cardiovascular disease, according to the Losartan Intervention For Endpoint Reduction in Hypertension (LIFE) study. Of 6,686 patients aged 55 to 80, those receiving losartan had a nearly 20% lower rate of cardiovascular morbidity and mortality.

In this study, losartan reduced the rate of fatal and nonfatal stroke by 34% (stroke was 44% more common than myocardial infarction [MI]). The incidence of MI did not differ between patients taking losartan and those taking atenolol, a finding the researchers call “encouraging,” because the observed reduction in heart rate among patients taking atenolol may have been expected to result in significantly greater cardioprotection.

The lack of difference in the incidence of MI between the groups suggests that losartan’s ability to protect the coronary arteries from the direct toxic effects of angiotensin II might have offset atenolol’s benefits of greater reduction in the myocardial demand for oxygen.

(Source: Ann Intern Med 2003;139:169–177.)

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Quinolones and Tendon Rupture

Since their introduction in the 1980s, quinolones have been associated with tendon disorders. So it isn’t farfetched to speculate that the rising number of case reports of Achilles’ tendon ruptures and other similar problems might be linked to the increased use of quinolones. That’s the basis of a study analyzing 1,367 cases reported in the United Kingdom between 1988 and 1998.

The researchers defined cases as those in which the patient had a first-time recorded Achilles’ tendon rupture and who had at least 18 months of a valid history of rupture before the index date. The control group included a random sample of 50,000 patients.

The risk of tendon rupture was highest among elderly patients (an odds ratio of 20.4 in those aged 80 and older, compared with 6.4 among those aged 60 to 79). The researchers say that approximately 2% to 6% of all Achilles’ tendon ruptures in people older than 60 years of age can be attributed to quinolones. Patients using ofloxacin (Floxacin®, Ortho-McNeil) had the highest risk of rupture, a finding consistent with those of earlier studies.

Although the mechanism of rupture is not well understood, it is thought that quinolones tend to have a weakening effect on connective tissues. Concomitant use of corticosteroids increased the risk substantially. Other risk factors included osteoarthrosis, inflammatory joint diseases, gout, dialysis, and renal transplantation, but adjusting for those risk factors did not change the risk estimate for quinolones considerably, the researchers say.

Although the absolute risk for Achilles’ tendon rupture is low, even in the elderly, the researchers advise against combining quinolones with oral corticosteroids; if possible, alternative antimicrobial agents should be prescribed.

(Source: *Arch Intern Med* 163:1801–1807.)

COX-2 Inhibitors Do Not Raise Cardiovascular Risk

Cyclooxygenase-2 (COX-2) inhibitors now have an established reputation for causing less gastrointestinal toxicity than nonsteroidal anti-inflammatory drugs (NSAIDs). However, some speculation remains about a possible increased cardiovascular thrombotic risk, because COX-2 inhibition—unlike the simultaneous inhibition of COX-1 and COX-2 by NSAIDs—does not stop platelet thromboxane synthesis and, therefore, platelet aggregation. COX-2 inhibition also reduces systemic prostacyclin production, which may impair vasodilation. In addition, recent reports of a higher incidence of myocardial infarction (MI) in patients taking the COX-2 inhibitor rofecoxib (Vioxx®, Merck) have raised still more questions.

Despite these concerns, researchers from the University of Connecticut School of Medicine, Cornell University, and Yale School of Medicine, after analyzing the data on 31,879 patients in all completed clinical arthritis trials comparing celecoxib (Celebrex®, Pharmacia) with NSAIDs and placebo, found no evidence of higher risk of MI, stroke, or cardiovascular death with celecoxib.

Patients taking celecoxib experienced 1.29 primary cardiovascular thrombotic events per 100 patient-years, and patients taking a placebo experienced a rate of 1.51 events.

In trials comparing celecoxib and NSAIDs, the rate was 1.13/100 patient-years with celecoxib and 1.05 patient-years with NSAIDs. The findings applied to all patients and to the 90% of patients who were not receiving aspirin at the same time.

(Source: *Am J Cardiol* 2003;92:411–418.)

Nasal Spray for Allergic Rhinitis

In a study at the University of California in Irvine, azelastine HCl (Astelin®, MedPointe Pharmaceuticals) nasal spray provided effective symptomatic relief in patients with moderate to severe allergic rhinitis who had not responded well to treatment with other medications.

Allergic rhinitis can lead to complications, including sinusitis, eustachian tube dysfunction, sleep disturbances, asthma, and ear infections.

The trial was conducted at 21 sites during the 2002 fall allergy season. The study enrolled 440 male and female patients, 12 years of age and older, all of whom had experienced unsatisfactory results after receiving monotherapy with loratidine (Claritin®, Schering) for seven days prior to the start of the trial.

Divided into four groups, the patients received (1) azelastine nasal spray and an oral placebo, (2) azelastine nasal spray and loratidine, (3) desloratadine (Clarinex®, Schering) and a placebo nasal spray, or (4) a placebo nasal spray and an oral placebo.

The patients taking azelastine nasal spray showed improvement in their overall Total Nasal Symptom Score (TNSS) and experienced statistically significant symptom relief over that shown with placebo.

Astelin® Nasal Spray is the only FDA-approved prescription second-generation antihistamine that is formulated for intranasal administration and indicated to treat symptoms of both seasonal allergic rhinitis in adults and children five years of age and older and nonallergic vasoconstrictor rhinitis in adults and children 12 years of age and older.

The most commonly reported adverse drug events (ADEs) in seasonal allergic rhinitis are headache, flushing, dry mouth, and epistaxis. In addition, there have been cases of worsening of asthma and exacerbations of viral infections. The most common serious adverse events were cardiovascular and gastrointestinal in nature.


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rhinitis and nonallergic vasomotor rhinitis patients 12 years of age and older were bitter taste, headache, somnolence, and nasal burning. The ADE profile in seasonal allergic rhinitis patients five to 11 years of age was similar to that in adults.

(Sources: Ann Allergy Asthma Immunol 2003;91:205–211; www.astelin.com; www.medpointepharma.com.)

**Limiting Access to Antihistamines in Allergic Patients**

In response to the availability of one non sedating antihistamine as an over the counter drug, state Medicaid and several large health insurers are considering whether to end prescription drug coverage for all non sedating antihistamines. These policies, by their design, would diminish access to recognized standards of treatment for millions of patients with allergic diseases. Professional experience suggests that these actions not only would lower the quality of medical care for affected patients but also would have significant health and safety implications for the general public.

Allergic diseases occur in 10% to 25% of the population, and up to 40% of those affected are children.

To varying degrees, antihistamines have the capacity to compete with histamine for type H1 receptors and to reduce receptor-mediated activation, thus blocking histamine’s adverse effects. Although all of the members of this class of medications are referred to as “antihistamines,” they vary in their pharmacology. Therefore, the selection of any one of these agents should be made in consultation with an experienced health care practitioner, especially for the majority of patients with persistent disease.

One of the concerns created by these policies is the danger associated with self medication.

Policies that limit patients’ access to appropriate medications impede a physician’s ability to prescribe the best treatment regimens and should not be mistakenly viewed as being endorsed by trained health care professionals.


**Somatropin Relieves Wasting from AIDS**

Serono, Inc., has announced the FDA’s final approval of somatropin (recombinant DNA origin) for injection (Serostim®) for the treatment of patients with human immunodeficiency virus (HIV) infection who are experiencing body wasting or cachexia (decreased intake of food and loss of appetite). The drug has helped patients increase their lean body mass and body weight and improve their physical endurance.

Serostim® received accelerated approval in 1996, a special regulatory status for drugs that are used to treat patients with serious or life-threatening illnesses and that provide therapeutic benefits over other existing treatments.

The recommended dose is 0.1 mg/kg daily or 6 mg/day for patients weighing more than 55 kg. The starting dose in patients thought to be at risk of certain adverse effects, such as glucose intolerance, is considered to be 0.1 mg/kg every other day.

Serostim® is generally well tolerated. The most common adverse events are mild to moderate muscle and joint pain and swelling or edema, which are dose-related and often subside with continued treatment or dose reduction.

New-onset impaired glucose intolerance, new-onset type 2 diabetes mellitus, and exacerbation of preexisting diabetes mellitus have been reported; diabetic ketoacidosis and diabetic coma have developed. In some patients, initiation or adjustment of antidiabetic treatment was required. Patients with a history of hyperglycemia or other risk factors for glucose intolerance should be monitored closely during treatment with Serostim®. Transient increases in glucose levels occur early in treatment, and monitoring is required.

Growth hormone is contraindicated in patients in intensive-care units (because of surgical complications, trauma, or acute respiratory failure), patients with active neoplasia, and patients with a known hypersensitivity to the hormone.

Serostim® must be used in conjunction with antiretroviral therapy.

(Sources: FDA Talk Paper, August 23, 2003; www.fda.gov; www.serostim.com.)

**Fewer Antibiotics Being Prescribed for Children**

There appears to have been a significant decline in the number of antibiotics prescribed for American children in recent years, researchers at Harvard Medical School have reported.

The decrease took place between 1996 and 2000, concurrent with a reduced incidence of potential bacterial (e.g., middle-ear) infections.

The reduction in antibiotic prescriptions for children from three months to three years of age varied among health plans and age groups from 6% to as much as 39%. There were also general declines in the older age groups.

One major reason for the decrease among the youngest children was that doctors were finding fewer children with otitis media, the painful middle ear condition that is common in the first few years of life. Recent studies have shown that the condition usually resolves without antibiotics.

Drug Interaction Warning for Repaglinide

Researchers have observed a drug–drug interaction between repaglinide (Prandin®, Novo Nordisk), a short-acting insulin secretagogue, and gemfibrozil (Lopid®, Pfizer), a lipid-lowering agent used to treat dyslipidemia.

Co-administration of gemfibrozil with repaglinide in healthy volunteers resulted in significant elevations of repaglinide levels, and co-administration of itraconazole (Sporanox®, Janssen), an antifungal agent, with gemfibrozil and repaglinide further increased such effects. Changes in the pharmacokinetics of repaglinide were attributed to inhibition of the cytochrome P-450 enzyme system by gemfibrozil and itraconazole. Alterations in blood glucose levels were also affected by these concomitant medications, with enhanced and prolonged pharmacodynamic effects of repaglinide.

Although the study involved healthy volunteers, Novo Nordisk considers these results to be important, because an increased risk of hypoglycemia cannot be ruled out for patients with type-2 (non–insulin-dependent) diabetes. According to what is now known about the metabolism of other lipid-lowering fibrate derivates, a similar interaction between repaglinide and other agents within the class is not expected.

The European Agency for the Evaluation of Medicinal Products (EMEA) has issued a public statement and has pointed out the following information to physicians:

1. Because of the documented interaction and risk of hypoglycemia, the concomitant use of the two agents is contraindicated.

2. For patients already receiving the two drugs, an alternative combination treatment should be considered along with close monitoring of diabetic status.

(Sources: FDA, September 30, 2003; www.fda.gov/medwatch/safety/2003; Diabetologia 2003;46(3)347–351; www.emea.eu.)