**NEW APPROVAL**

**Fighting Chemotherapy Infections**

Up to 40% of cancer patients receiving certain types of chemotherapy develop infections caused by neutropenia, a severe drop in infection-fighting white blood cells. Most physicians manage neutropenia only after patients get sick. Now, however, the FDA has approved pegfilgrastim, a once-per-cycle white blood cell booster (Neulasta, Amgen).

Pegfilgrastim is indicated for decreasing the incidence of infection, as manifested by febrile neutropenia (fever associated with a severe drop in infection-fighting white blood cells) in patients with non-myeloid malignancies (e.g., breast and lung cancer, non-Hodgkin’s lymphoma, and Hodgkin’s disease) who are receiving certain types of chemotherapies.

**Tumor Drug Approved**

The FDA recently approved zoledronic acid for injection (4 mg) (Zometa, Novartis) for the treatment of patients with multiple myeloma and patients with bone complications (metastases) from solid tumors in conjunction with standard antineoplastic therapy. These solid tumors include prostate cancer, lung cancer, and other tumor types for which there is no intravenous bisphosphonate therapy currently approved for treatment, as well as breast cancer and the osteolytic lesions associated with multiple myeloma.

The approval for zoledronic acid is based on data from three large international clinical trials evaluating more than 3,000 patients with myeloma, breast cancer, prostate cancer, lung cancer, and other solid tumors. This is the largest set of clinical trials ever conducted to evaluate the efficacy and tolerability of a bisphosphonate in treating cancerous bone lesions.

Over the 15-month evaluation period of the prostate cancer trial, zoledronic acid demonstrated efficacy when compared to placebo in the treatment of bone metastases. A lower proportion of patients receiving zoledronic acid experienced a skeletal-related event (SRE), such as radiation to the bone, pathological fractures, and spinal cord compression compared to those receiving placebo. Patients on zoledronic acid also had a delay in the onset of the first SRE compared to those on placebo.

In the trial in lung cancer and other solid tumors (excluding breast and prostate cancer), zoledronic acid had a positive impact on median time to the first SRE when compared to placebo. The results of the prostate cancer trial and the lung cancer and other solid tumors trials mark the first time any bisphosphonate has demonstrated efficacy in treating SREs; and the FDA approval of zoledronic acid for these indications marks the first time a bisphosphonate is available to this patient population.

In the breast cancer and multiple myeloma trial, zoledronic acid was as effective and well-tolerated as pamidronate disodium for injection (Aredia, Novartis), the current standard of treatment, but with only a 15-minute infusion time, compared to two to four hours for pamidronate disodium.

Novartis previously received marketing clearance for zoledronic acid in the treatment of hypercalcemia of malignancy (HCM).

In clinical trials involving patients with bone metastases, zoledronic acid was generally well-tolerated, with a safety profile similar to that of other bisphosphonates. Most commonly reported adverse events included flu-like syndrome (fever, arthralgias, myalgias, skeletal pain), fatigue, gastrointestinal reactions, anemia, weakness, cough, dyspnea, and edema. Occasionally, patients experienced electrolyte and mineral disturbances, such as low serum phosphate, calcium, magnesium, and potassium.

Bisphosphonates, including zoledronic acid, have been associated with reports of renal function deterioration. Patients who receive zoledronic acid should have periodic evaluations of standard laboratory and clinical parameters of renal function.

During pregnancy, zoledronic acid should only be used if the potential benefit justifies the risk to the fetus. It is contraindicated in patients with known clinically significant hypersensitivity to zoledronic acid or other bisphosphonates, or any of the excipients in the formulation of zoledronic acid.

**NEW INDICATION**

**Orphan Drug for GISTs**

The FDA approved the drug imatinib mesylate (Gleevec, Novartis) for the treatment of patients with Kit (CD 117) positive unresectable (inoperable) and/or metastatic malignant gastrointestinal stromal tumors (GISTs). GISTs are the most common malignant form of sarcoma that arise in the gastrointestinal tract, affecting an estimated 2,000 to 5,000 patients in the U.S. The limited occurrence of GISTs has resulted in the FDA designating imatinib mesylate as an orphan drug for this indication. The effectiveness of imatinib mesylate in GISTs is designated as an orphan drug for this indication. The effectiveness of imatinib mesylate in GISTs is based on the objective response rate. There are no controlled trials demonstrating a clinical benefit, such as improvement in disease-related symptoms or increased survival.

The FDA approval for the GIST indication is supported by data from an open-label, multinational study, which had 147 patients with unresectable or metastatic malignant GISTs. Patients were randomized to receive either 400 or 600 mg of imatinib mesylate daily for up to 24 months. The overall response rate was 38% (400 mg=33%; 600 mg=43%), based...
on confirmed partial responses at the time of the cut-off for data submission.

A majority of the patients in clinical trials reported an adverse event at least once, but most events were mild to moderate in severity. The drug was discontinued in the GIST trial in six patients (8%) in both of the dose levels studied. The most common adverse events were edema, nausea, diarrhea, abdominal pain, muscle cramps, fatigue, and rash. Seven trial patients (5%) reported gastrointestinal (GI) bleeds and/or intratumoral bleeds. Gastrointestinal tumor sites might have been the source of the GI bleeds. Imatinib mesylate is contraindicated in patients with known hypersensitivity. Women of childbearing age should be advised to avoid becoming pregnant while taking imatinib mesylate.

Prior to the availability of imatinib mesylate, patients with GISTs had no effective treatment options beyond surgery. GISTs have been very difficult to treat because of their high levels of resistance to treatment with traditional chemotherapy and radiation therapy. For patients with metastatic or unresectable disease, GISTs had represented an incurable malignancy with a median survival of approximately 10 to 12 months.

Imatinib mesylate, a signal transduction inhibitor, is one of the first cancer drugs to be developed with a new understanding of how some types of cancer cells work. Imatinib mesylate targets the activity of certain enzymes called tyrosine kinases that play an important role within certain cancer cells. The activity of one of these tyrosine kinases, known as c-kit, is thought to drive the growth and division of most GISTs.

Imatinib mesylate received FDA approval as an orphan drug for the chronic myeloid leukemia (CML) indication on May 10, 2001 for the treatment of patients in the blast crisis, accelerated phase, or chronic phase after failure of interferon-alpha therapy.

**DRUG NEWS**

**Changing Patterns in UTI Prescriptions**

A study of drug treatment for uncomplicated urinary tract infections in women has revealed some interesting prescribing patterns. According to researchers from the University of Chicago (Illinois) and the Stanford (California) Center for Research in Disease Prevention, who looked at data on 1,478 women, prescriptions for trimethoprim–sulfamethoxazole, (the therapy recommended by the Infectious Disease Society of America), declined compared to fluoroquinolones and nitrofurantoin, the second-line choices. The proportion of trimethoprim–sulfamethoxazole prescriptions for UTIs declined from 48% in 1989–1990 to 24% in 1997–1998. By contrast, fluoroquinolone prescriptions rose from 19% to 29% and nitrofurantoin use more than doubled (from 14% to 30%).

Other trends observed by the researchers included: women younger than 45 years of age were more likely to receive trimethoprim or trimethoprim–sulfamethoxazole than older women (41% vs. 28%); new patients were more likely to receive trimethoprim–sulfamethoxazole than established patients (51% vs. 34%); and those who had no history of UTIs were more likely to receive trimethoprim–sulfamethoxazole than those who did (41% vs. 23%).

The study also found than nonwhites, established patients, those who went to obstetricians/gynecologists, those with dysuria, and those with a history of UTIs were more likely to receive trimethoprim–sulfamethoxazole than those who did not (41% vs. 23%).

Researchers from Flinders Medical Centre, Adelaide, and John James Medical Centre in Deakin, Australia, evaluated five patients using skin prick testing after the patients had suffered adverse reactions to echinacea.

Two patients suffered anaphylaxis after earlier uneventful doses; a third had an acute asthma attack within 10 minutes.
of taking echinacea for the first time. The fourth patient had recurrent episodes of mild asthma each time he took echinacea. The fifth developed a maculopapular rash within two days, which occurred when she was rechallenged.

The researchers also reviewed 51 case reports implicating echinacea in adverse reactions. Of these case reports, 41 implicated echinacea as the sole trigger of the reaction. Researchers found 26 cases suggestive of immunoglobulin E-mediated reactions. One of the researchers added echinacea to the routine panel of allergens tested in patients referred for asthma or allergic rhinitis. He found 20% of 100 atop patients had positive skin-prick results from first-time echinacea use.

The authors note that echinacea’s popularity has soared in recent years: an estimated 200 million doses are consumed in Australia each year (the equivalent of 10 doses per person per year) and echinacea’s market share in the U.S. grew 68% between 1995 and 1996 alone. They urge practitioners to caution all patients, especially atop patients, that alternative medicines can interact with conventional medicines and can be intrinsically toxic [Ann Allergy Asthma Immunol. 2002 Jan;88(1):42–51].

New Asthma Drug-Delivery System
In 1987, the Montreal Agreement provided for the phasing out of chlorofluorocarbon (CFC) production because of the damage that CFCs have caused to the ozone layer. Since 1996, CFCs have been banned in developed countries, except for a few essential uses, such as asthma inhalers. GlaxoSmithKline is now releasing Ventolin HFA (albuterol sulfate HFA), a new drug-delivery system for the treatment of asthma.

Ventolin HFA has the same active ingredient—albuterol—as the asthma drug Ventolin, but it uses hydrofluorolekane instead of CFCs to propel the medication out of the canister and into the lungs. Clinical trials have shown that the HFA product has the same efficacy and safety as the one that uses CFC. Albuterol is a short-acting bronchodilator that helps relax constricted airways during asthma attacks.

RESEARCH NEWS
ARPKD Gene Discovered
Researchers at the Mayo Clinic have identified and fully characterized the gene (PKHD1) that causes autosomal recessive polycystic kidney disease (ARPKD). This discovery raises hopes for a treatment and eventual cure for infants born with the disease.

ARPKD is one of a group of polycystic kidney diseases (PKDs) that together make up the world’s most common life-threatening genetic disease, affecting 600,000 children and adults in the U.S. and 12.5 million people worldwide. In the U.S., more people have PKD than cystic fibrosis, muscular dystrophy, Down’s syndrome, hemophilia, sickle cell anemia, and Huntington’s disease combined. The disease affects people irrespective of age, race, gender, ethnicity, geographic location, or socioeconomic status.

ARPKD, often referred to as “infantile PKD,” is a particularly lethal form of PKD. ARPKD results in the development of multiple fluid-filled cysts in the kidney and fibrosis in the liver, and is often associated with poor lung development and infant death. There is currently no treatment or cure; however, the discovery of the ARPKD gene provides researchers with a genetic “road map” for a functional understanding of how PKD progresses, and paves the way for gene testing, more conclusive diagnoses, and treatments to retard development of the disease.

Researchers believe that the identification of PKHD1 will eventually allow expectant parents to learn whether their babies have a genetic predisposition toward the disease. They also believe that knowing what causes the gene defect will provide a better understanding of the disease, which could lead to new therapies. If both parents carry one abnormal ARPKD gene, there is a one-in-four chance that every child they have will be afflicted with ARPKD. The vast majority of those with PKD develop kidney failure, which costs U.S. taxpayers an estimated annual $2 billion for dialysis, kidney transplantation, and related therapies.

The gene discovery resulted from earlier work done on the Human Genome Project and with support from the PKD Foundation, an international not-for-profit organization devoted to programs of PKD research, patient education, public awareness, and advocacy for PKD families. More information about PKD and the PKD Foundation can be found at www.pkdcure.org or by calling 800-PKD-CURE (753-2873). This research will be published in the March 2002 issue of Nature Genetics (Internet Wire News).

Examining the Link Between Air Pollution and Stroke Death
Researchers from four Korean institutions and the Harvard School of Public Health evaluated three years’ worth (1995–1998) of pollution readings from 20 stations in Seoul, Korea, and the 22,000+ stroke deaths that occurred during the same period. They compared the frequency of stroke death to changes in the rates of carbon monoxide, nitrogen dioxide, sulfur dioxide, and small particulate matter (PM10–particulates 10 microns in diameter or smaller), which is easy to inhale. They found that on days with increases in PM10 and ozone levels, there were corresponding increases in deaths. The increased presence of nitrogen dioxide, sulfur dioxide, and carbon monoxide seemed to lead to deaths two days later. Variables such as lifestyle, income level, living conditions, and health care were not factored in, however, because they were not expected to vary daily like air pollutant concentrations did. This study was published in Environmental Health Perspectives. (Internet Wire News)