NEW APPROVALS/
NEW INDICATIONS

DVT Drug
The FDA has approved fondaparinux sodium (Arixtra, Organon and Sanofi-Synthelabo) for the prophylaxis of deep vein thrombosis (DVT). DVT can lead to pulmonary embolism in patients undergoing hip replacement surgery, hip fracture surgery, and knee replacement surgery. Fondaparinux sodium is a synthetic compound, and it is the first in a new class of agents to selectively inhibit factor Xa. The drug launch is expected to occur in the first quarter of 2002.

INTRAVENOUS ANTIBiotic
An intravenous (IV) formulation of moxifloxacin hydrochloride in sodium chloride for injection (Avelox, Bayer) has been approved by the FDA. The drug was first approved in tablet form in 1999. It is used to treat adults with community-acquired pneumonia (CAP), acute bacterial sinusitis (ABS), acute bacterial exacerbations of chronic bronchitis (ABECB), and uncomplicated skin and skin structure infections (uSSSI). This provides hospitals with another option for treating patients with bacterial infections.

The recommended dose for the IV formulation is 400 mg once daily for seven to 14 days for CAP, five days for ABECB, ten days for ABS, and seven days for uSSSI. The IV formulation is available as a ready-to-use dose in a latex-free pre-mixed flexibag; switching to oral administration requires no adjustment. Approval was based on two large, randomized, controlled trials for the treatment of CAP, as well as numerous past studies demonstrating the safety and efficacy of the tablets on CAP, ABS, ABECB, and uSSSI.

A NUCLEOTIDE DRUG AGAINST HIV
Tenofovir disoproxil fumarate (Viread, Gilead Sciences) is the first nucleotide analog approved for HIV-1 treatment. Nucleotides block HIV replication just like nucleosides.

In a 24-week placebo-controlled study and a 48-week controlled-dose study involving over 700 patients who had previously been treated with antiretroviral agents, but who showed signs of continued HIV replication, tenofovir significantly reduced HIV RNA. However, the risk–benefit ratio has not been established for untreated patients. There are also no study results to show that tenofovir inhibits HIV progression over the long term.

The most frequently reported adverse effects were mild to moderate gastrointestinal problems. Patients treated with nucleoside analogues alone or in combination with antiretrovirals have also developed lactic acidosis and hepatomegaly with steatosis, both severe and possibly fatal conditions (FDA Talk Paper T01-50).

NEW DRUGS

Drug Combination for Advanced Breast Cancer
For patients with metastatic breast cancer who were not helped by anthracycline-containing therapy, the FDA has recently approved combination therapy with capecitabine (Xeloda, Hoffman LaRoche) and docetaxel (Taxotere, Aventis). The new treatment was approved following clinical trials in 75 centers worldwide, with 511 patients. The trials showed that the combination significantly slowed disease progression, improved overall survival, and improved response rates.

In the combination therapy arm of the randomized, worldwide trial, 225 patients received capecitabine 1,250 mg/m² twice daily for 14 days, followed by one week without treatment and docetaxel 75 mg/m² as a one-hour intravenous infusion, given in three-week cycles. In the monotherapy arm, 256 patients received docetaxel 100 mg/m² as a one-hour IV infusion, administered in three-week cycles. The mean duration of treatment was 129 days in the combination arm and 98 days in the monotherapy arm.

HER2 Breast Cancer Study
Vinorelbine tartrate injection (Navelbine, GlaxoSmithKline) is indicated as a single agent or in combination with cisplatin for treating ambulatory patients with inoperable, advanced non-small cell lung cancer (NSCLC). However, a phase II study, presented at the 24th Annual San Antonio Breast Cancer Symposium, shows that it can also work to fight breast cancer. Results of the study showed that vinorelbine tartrate injection, along with trastuzumab (Herceptin, Genentech), reported a response rate in 78% of the women with HER2 positive metastatic breast cancer. This study examined the safety and efficacy of vinorelbine tartrate injection and trastuzumab as first-line therapies. HER2 is a growth-promoting chemically closely associated with poor prognosis in breast cancer; nearly a quarter of the women with breast cancer have tumors that overexpress HER2. In the 37 patients evaluated for a response in this study, there were four complete responses and 25 partial responses to the drug combination. After 313 cycles, grade 4 neutropenia was observed in 30% of the patients in 14% of the cycles, and grade 3 neutropenia was observed in 50% of the patients in 20% of the cycles. One patient was hospitalized with neutropenic fever. The vinorelbine tartrate injection did not appear to increase the side-effect profile of trastuzumab.

New Triptans For Migraine
Seven very similar oral triptans will soon be clinically available to treat migraine. Researchers from Innovative Medical Research in Stamford, Connecticut, have conducted a meta-analysis of 53 triptan clinical trials (including 12 unpublished studies) that included 24,089 patients.

Using the 100-mg dose of sumatriptan as their benchmark, the researchers
found a mean of 59% of patients responded within two hours. Exactly 29% were pain-free at two hours and one-fifth had a sustained response with no recurrence in 24 hours. In at least two of three attacks, 67% responded consistently to sumatriptan. Thirteen percent of patients had at least one adverse event.

By comparison, the 10-mg dose of rizatriptan was more effective and consistent, and similarly tolerated. The 80-mg dose of eletriptan was more effective but not as well tolerated. The 12.5-mg dose of almotriptan was similarly effective at two hours but more consistent and better tolerated. The 2.5- and 5-mg doses of zolmitriptan, the 40-mg dose of eletriptan, and the 5-mg dose of rizatriptan had similar results. The 2.5-mg dose of naratriptan was better tolerated but less effective. Researchers say the data for frovatriptan indicates a lower efficacy than that for sumatriptan.

The results of the analysis show that clinicians now have an even greater opportunity to match the correct drug to fit the patient’s needs, according to the researchers [Lancet. 2001. Nov 17, 358(9294):1668-1675].

**Weight Loss for Patients with Type 2 Diabetes**

Weight loss and dietary modification can help patients with type 2 diabetes to improve their insulin levels, glycemic control, and lipid-profile findings, thus reducing long-term complications of the disease. In animal studies, sibutramine has been shown to reduce weight gain, lower the levels of nonesterified fatty acids, reduce hyperinsulinemia, and reduce insulin resistance. Moreover, in trials involving non-dieting obese women, sibutramine reduced insulin resistance and body mass index.

Based on these findings, researchers at Baskent University Endocrinology and Metabolism Clinic in Adana, Turkey, assigned 60 women with type 2 diabetes, poorly controlled glucose levels, and HbA1c greater than 8% to one of two groups. Both groups received their prescribed hypoglycemic agents (maximum doses of sulfonylureas and metformin) but one group was also given sibutramine 10 mg BID for six months while the other was given placebo.

Women taking sibutramine lost significantly more weight (mean, 9.61±1.37 kg). In fact, the women taking placebo tended to gain weight (0.91±0.53 kg). BMI was also significantly reduced in the sibutramine group (3.92±0.54 kg/m²), compared with a gain in the placebo group (0.36±0.21 kg/m²). Fasting and postprandial blood glucose fell significantly below baseline in the sibutramine-treated patients (124.8±8.58 and 102.2±51.99 mg/dL, respectively). Insulin resistance, HbA1c, diastolic blood pressure, waist measurement, uric acid, pulse rate, and all lipids except HDL cholesterol and apolipoprotein A1 also fell significantly.

The weight loss, while marked, was still less than that seen in nondiabetic women. Although previous studies had noted small rises in BP and heart rate in patients treated with sibutramine, the patients in this study actually had lower diastolic BP and heart rate. The researchers call it “noteworthy” that only one patient dropped out because of hypertension. Eleven patients reported dry mouth and 16 reported constipation, but apart from those effects, the drug was well-tolerated [Diabetes Care. 24(11):1957-1960].

**Morning-after Hypoglycemia**

Researchers from Royal Bournemouth Hospital, UK and Yale University School of Medicine, Connecticut, studied how the nighttime consumption of alcohol can trigger a hypoglycemic episode the next morning. Of six men in their study, five required treatment for hypoglycemia the morning after they had consumed some after-dinner wine.

The men received regular insulin injections before standardized meals, at 6 p.m. and 8 a.m., and a basal insulin infusion from 11 p.m. They drank either dry white wine (0.75 g ethanol/kg body weight) or mineral water at 9 p.m. over 90 minutes.

The next morning, although blood ethanol was undetectable, fasting and postprandial blood glucose levels were significantly lower. The researchers called the average reduction of 5 to 6 mmol/L “striking.” After breakfast (8 a.m.), five men had hypoglycemia. One had transient biochemical hypoglycemia after drinking the mineral water.

The researchers also found that after the men drank the wine, their growth hormone secretion dropped significantly between midnight and 4 a.m. (although the drop might have been caused by a poor night’s sleep or reasonable glucose control, the researchers note). They suggest that if the subsequent postprandial hypoglycemia were attributable to lower nocturnal secretion of growth hormone, it might be mediated by a relative increase in peripheral insulin sensitivity.

To the researchers’ knowledge, a blunted dawn glucose increase (lowering of blood glucose the next morning) with a reduction in the nocturnal secretion of growth hormone has not been previously demonstrated. The amount of alcohol the men drank was chosen to represent an average evening’s drinking and an amount that would generate a peak blood level just above the legal limit for driving in the U.K. (17.4 mmol/L). The researchers suggest clinicians let patients know of the risk of late-morning hypoglycemia and advise them to have rapid-acting carbohydrates available if they plan to consume alcohol in the evening [Diabetes Care. 24(11):1888-1893].

**No Early Statin Benefit?**

Surprising findings about benefits and drawbacks have some researchers questioning whether early treatment with statins should be routine for heart patients. At the American Heart Association’s...
NEW DRUGS

DRUG NEWS

continued from page 38

Scientific Sessions 2001, researchers from the Duke Clinical Research Institute in North Carolina reported on some new considerations in statin therapy.

The researchers took a retrospective look at early statin therapy in acute coronary syndrome (ACS) patients in two trials involving almost 16,000 patients. They examined the relationship between early treatment (statins given within a median of two days after the ACS event) and death, myocardial infarction, and severe recurrent ischemia. By comparing 3,952 patients with 8,413 who never received a statin, they found an incremental benefit for those with higher cholesterol levels but a possible detrimental effect at normal or lower levels. The lead investigator suggests stratifying statin therapy in prospective studies by patients’ LDL levels. For more information, please visit www.theheart.org.

Add-on Seizure Therapy

Levetiracetam (Keppra, UCB Pharma), an antiepileptic drug, was the topic of 46 abstracts at the 55th American Epilepsy Society meeting in Philadelphia. Two studies are presented below.

The Swiss Epilepsy Centre evaluated levetiracetam as an add-on therapy for elderly patients with refractory epilepsy. Investigators of the study isolated the data on patients over the age of 50 from the data of patients who participated in the drug’s developmental program. Of the 1,422 patients, 211 were between the ages of 50 and 78. The median administered dose of levetiracetam was 3,000 mg per day. The median duration of exposure was 697 days.

During the six months prior to the final evaluation and during the last year, the elderly on levetiracetam had a higher rate of freedom from seizures (19% vs. 12% and 15% vs. 9%, respectively). Adverse events (AEs), which included somnolence, asthenia, and dizziness, were mainly CNS-related and mild. Some other CNS-related AEs—confusion, hostility, emotional lability—affected the elderly more than the total population. However, levetiracetam lacks the drug–drug interaction seen in other antiepileptic agents.

The Yale School of Medicine presented its study on how early improvement in the health-related quality of life for epilepsy patients, whose seizures were resistant to standard treatment, were sustained with levetiracetam. The trial included patients with refractory partial-onset seizures who were randomized to levetiracetam or placebo add-on therapy for 18 weeks. Those who continued on levetiracetam or who crossed from placebo to levetiracetam were followed for four years.

Patients treated with levetiracetam had significant improvements in total score and health-related quality-of-life areas (e.g., anxiety about seizures, overall quality of life, health status) at 18 weeks. These improvements were significant when compared to the placebo group, and they were sustained long-term. The patients who had started on placebo improved to the level of the levetiracetam group after crossing over to levetiracetam.

Therapy for Children with Epilepsy

A study presented at the 55th American Epilepsy Society meeting evaluated data from a 13-month trial with oxcarbazepine (Trileptal, Novartis) as adjunctive therapy in children with partial seizures. Two hundred twenty nine subjects, aged three to 17 years, were involved in the trial, which started with a 16-week double-blind, placebo-controlled study of oxcarbazepine adjunctive therapy. The trial then transitioned to a 40-week open-label extension to evaluate long-term safety and efficacy. Half of the patients experienced a greater than 50% reduction in seizure frequency through the first 56 week, and 7% of the patients had no seizures. Side effects, most commonly headache, vomiting, and dizziness, were mild to moderate and lasted approximately one day. Of the 229 patients, 150 completed at least one year of open-label therapy.

Trial researchers also presented a pharmacokinetic model that recommends an effective dose of oxcarbazepine as monotherapy in children with epilepsy. The results of adults receiving oxcarbazepine adjunctive therapy are similar, in terms of plasma levels, to children receiving oxcarbazepine adjunctive therapy. Data from 20 safety and efficacy studies, which included pediatric patients under 17 years of age, were used to create the model. The model evaluated the dose levels required to produce steady-state plasma concentrations in children that would be equal to effective levels in adults on monotherapy. The model suggested that the most efficacious dose range of oxcarbazepine was 20 to 55 mg/kg/day, which was confirmed by a meta-analysis of seizure data from double-blind monotherapy studies.

HIV Combination Has No Drug Resistance Yet

Study M98-863, a randomized, double-blind phase III study on antiretroviral-naïve HIV patients, was presented at the 41st Interscience Conference on Antimicrobial Agents and Chemotherapy. Six hundred and fifty three patients received either Kaletra (lopinavir/ritonavir, Abbott Laboratories) or nelfinavir (Viracept, Agouron) in combination with stavudine (d4T) and lamivudine (3TC). At 96 weeks, the study identified patients with detectable HIV (HIV> 400 copies). Of those with viral isolates that could be identified, none (0/40) of the patients on the Kaletra-based regimen had a protease inhibitor resistance, compared to 33% (15/48) of the patients on the nelfinavir-based regimen. Resistance to 3TC was detected in 38% (15/40) of the viruses from patients using Kaletra versus 82% (69/84) of the patients taking nelfinavir. Resistance might be observed in a longer study.