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To reduce and prevent medication errors, the FDA turns to bar codes

Efforts may be turning point in patient safety

The U.S. Food and Drug Administration (FDA) has finally delivered on its promise to propose a mandatory bar code program for medications. Although pleased with the effort, the American Society of Health-System Pharmacists (ASHP) in Bethesda, MD, wishes the FDA had gone a bit further.

The FDA proposed two rules in the March 14 issue of the *Federal Register*. These rules are designed to reduce medication errors and more quickly identify potential errors that may occur, the agency says.

The first proposal calls for bar-coding of all prescription drug products, including biological products and vaccines (except for physician samples) and over-the-counter (OTC) drugs that are commonly used in hospitals and dispensed in a hospital pursuant to an order. Standardized bar codes also would be required on prescription drug products used in other settings such as retail pharmacies.

The required bar code would contain the National Drug Code number in a linear bar code as part of the drug label. The label would include the drug name, dosage form, and strength. The proposed design would allow manufacturers to include additional information, and more information could be added to the bar code standards as information technology progresses.

ASHP, however, says including the medication's lot number and expiration date in the bar code is important, too. "[Including that information] is a critical element to protect patients from medications that may have been recalled or are past their expiration date," says **Henri R. Manasse**, Jr., PhD, ScD, ASHP executive vice president and chief executive officer. In the proposal, the FDA said it had "neither found nor received data to show that the benefits of bar coding lot number and expiration date information would exceed the costs of putting that information in the bar code."

Complying with the proposal would be expensive for both drug manufacturers and hospitals. Under the proposal, most manufacturers,

repackers, relabelers, and private-label distributors of human prescription drug products and OTC drug products regulated under the Federal Food, Drug, and Cosmetic Act or the Public Health Service Act would be subject to the bar-code requirement. The FDA estimates it would cost pharmaceutical companies $50 million to meet the requirement and that hospitals would spend more than $7 billion on scanners and computers.

Some say the proposal is worth the cost. **Mark B. McClellan**, MD, PhD, FDA commissioner, estimates that the bar code requirement would prevent 400,000 adverse drug reactions over the next 20 years.

The proposed rule has a 90-day comment period. After that, the FDA will evaluate the comments and intends to finish work on a final rule in 2003. The bar code requirement would become effective three years after the FDA publishes a final rule.

The FDA also announced a proposal to revamp its safety reporting requirements. The proposed rule would:

- improve the quality and usefulness of safety reports submitted to the agency as well as facilitating the consistency of safety reporting around the world;
- require the submission of all suspected serious reactions for blood and blood products on the market; and
- require reports on important potential medication errors.

To expedite the agency's review of and response to medication errors, the proposed amendments would require companies to submit to the FDA, within 15 calendar days, all reports they receive of actual and potential medication errors occurring in

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Abbott puts bar codes on injectables, IV solutions

Company utilizes Reduced Space Symbology

By the time the government has mandated the bar-coding of medications, at least one drug company already will have finished its own bar-coding program.

Abbott Laboratories has announced that it has completed its initiative to attach unit-of-use bar codes to 100% of its more than 1,000 hospital injectable pharmaceuticals and IV solutions. Abbott says its program is consistent with the preliminary guidance issued in the FDA's March 13 proposed rule to require bar-code labeling on all prescription and some over-the-counter drugs and vaccines. **(For more on the FDA guidance, see p. 33.)**

About one-quarter of Abbott's hospital injectables and IV solutions use the Reduced Space Symbology technology, which allows a miniaturized bar code to be applied to single-unit containers as small as a pen cap. Abbott also has launched a new patient-controlled analgesia device, the LifeCare PCA3 Infusion System, that incorporates a built-in bar code reader to identify and verify drug and dose concentrations automatically.

For more information about Abbott's bar-coding program, visit the company's web site at www.abbott.com. ■

the United States. The proposal also would require the use of universally recognized medical terminology and other safety reporting standards.

Under this proposal, blood establishments would be required to submit to the FDA reports of all suspected serious reactions, not just fatalities, as is required now.

Each of these proposals is expected to have an enormous impact on patient safety, say officers of the Institute for Safe Medication Practices (ISMP) in Huntingdon Valley, PA. Along with recent bills passed by the U.S. House of Representatives **(see story, below)**, these efforts may prove to be "a turning point in health care," say **Michael Cohen**, RPh, MS, DSc, ISMP president, and **Judy Smetzer**, RN, BSN, ISMP vice president.

Both proposed rules can be found on the FDA's web site at www.fda.gov/oc/initiatives/barcode-sadr/. The FDA invites written comments from the public on these proposed rules to the Dockets Management Branch (HFA-305), Food and Drug Administration, 5630 Fishers Lane, Room 1061, Rockville, MD 20852. ■

Legislation targets patient safety, too

National Patient Safety Database to be created

The bar code proposal of the U.S. Food and Drug Administration isn't the only measure being lauded by the Institute for Safe Medication Practices (ISMP) in Huntingdon Valley, PA. The safety organization also praises two bills recently passed by the U.S. House of Representatives.

One bill addresses tort reform and places a cap on non-economic damages in lawsuits involving health care services. The other, the Patient Safety and Quality Improvement Act of 2003 (HR 663), aims to improve reporting of patient safety information by assuring confidentiality and legal protection of information collected and shared with Patient Safety Organizations (PSOs). The secretary of Health and Human Services would certify a number of PSOs, including ISMP, to collect patient safety information and voluntarily submit non-identified information to a national Patient Safety Database for research.

The bill also calls for the adoption of standards that promote communication among clinical information technology (IT) systems and provides $25 million in grants in 2004 and 2005 for the application of electronic prescribing systems and other clinical IT systems.

In addition, the bill prohibits "patient safety work product" from: 1) being subject to a civil or administrative subpoena or order; 2) being required to be admitted as evidence in any state or federal civil or administrative proceeding; or 3) being used by a national accreditation organization in an accreditation action against the provider that reported the information, if the patient safety work product is identifiable information and is received by the accreditation organization its capacity as a patient safety organization.

For more information about HR 663, visit www.house.gov. ■

Judge stays Medicaid discount drug program

Michigan now joining with other states

In a move that will encourage such programs across the nation, a federal judge has ruled in favor of a Medicaid program that uses preferred drug lists and prior authorization.

The Pharmaceutical Research and Manufacturers Association (PhRMA) in Washington, DC, and patient advocacy organizations such as the National Alliance for the Mentally Ill of Michigan, filed the lawsuit in the U.S. District Court for the District of Columbia. The case asked the federal court to issue a preliminary injunction invalidating a program approved by the secretary of Health and Human Services and implemented by the state of Michigan.

The program restricts Medicaid beneficiaries' access to prescription drugs unless the manufacturer pays the state additional rebates beyond those required by the Medicaid program. If doctors want to use a drug that is not on the list, they must first get state permission. The lawsuit also asked the court to prohibit the Secretary from approving other states' programs that share some or all of the characteristics of the Michigan program.

U.S. District Judge **John Bates** dismissed the lawsuit in late March, saying the states had "broad room" to establish prior-authorization

prescription drug programs. The judge also said the drug manufacturers failed to show that the state acted illegally when it asked the companies for lower rates to get on the list.

Michigan currently spends more than $1 billion a year on pharmaceutical costs for its 1.4 million Medicaid and other low-income program participants. The state says its Pharmaceutical Best Practices Initiative, which has been in place since February 2002, saves Michigan approximately $850,000 a week.

PhRMA says it plans to appeal, contending that programs such as Michigan's could harm patients by limiting or denying access to medicine for the state's most vulnerable patients, the group says.

In the meantime, Michigan plans to extend its program. Michigan Gov. **Jennifer Granholm** recently announced that the state would collaborate with Vermont and South Carolina to implement the nation's first multi-state purchasing arrangement for pharmaceuticals purchased under their respective Medicaid programs. The joint venture would use the same structure as the Michigan program. ■

Study: HRT has little effect on quality of life

New treatments needed, physician says

Research has indicated that women have risked their health by long-term use of hormone replacement therapy. Now new research says the therapy seems to have little benefit in aiding quality-of-life measures either.

Both sets of findings are taken from a study that was part of the federally funded Women's Health Initiative (WHI). The study involved 16,608 postmenopausal women ages 50-79 years with an intact uterus. The women either received the combination hormone replacement therapy, 0.625 mg conjugated equine estrogens plus 2.5 mg medroxyprogesterone acetate, or placebo.

Researchers conducted the first study to assess whether long-term use of the combination hormone therapy would reduce the risk of coronary heart disease in postmenopausal women. This study was stopped more than three years early (after an average follow-up of 5.2 years) because of an increased risk of invasive breast cancer.

The trial also found that increases in coronary heart disease, stroke, and pulmonary embolism in study participants (compared to women taking placebo) exceeded the benefits of the drug. The benefits included fewer cases of hip fractures and colon cancer.

The most recent study was conducted to determine the effect of hormone therapy on health-related quality of life. To do this, quality-of-life measures were collected at baseline and at one year in all women and at three years in a subgroup of 1,511 women.

No quality-of-life benefits at three years

The results showed that randomization to estrogen plus progestin resulted in no significant effects on general health, vitality, mental health, depressive symptoms, or sexual satisfaction. The use of estrogen plus progestin was associated with a statistically significant but small and not clinically meaningful benefit in terms of sleep disturbance, physical functioning, and bodily pain after one year. At three years, there were no significant benefits in terms of any quality-of-life outcomes.

Among women ages 50-54 years with moderate-to-severe vasomotor symptoms at baseline, estrogen and progestin improved vasomotor symptoms and resulted in a small benefit in terms of sleep disturbance but no benefit in terms of the other quality-of-life outcomes.

A physician not related to the research states the results bluntly in an editorial accompanying the study findings. "Postmenopausal therapy with estrogen and progestin results in increased risks of disease, does not make asymptomatic women feel better, does not improve cognition. There is no role for hormone therapy in the treatment of women without menopausal symptoms," says **Deborah Grady**, MD, MPH. Grady is professor of epidemiology and biostatistics, professor of medicine, and vice chair of the department of epidemiology and biostatistics at the University of California San Francisco (UCSF). Grady also is director of the UCSF Women's Health Clinical Research Center and the UCSF Women's Health Faculty Development Program.

"Women with vasomotor symptoms must weigh the risks associated with treatment against the benefit of symptom relief," she continues. "Vasomotor symptoms occur in about two-thirds of women and are very distressing in 10% to 20%.

We clearly need to identify new treatments that are highly effective and safe."

The results of the study will be published in the May 8 issue of the *New England Journal of Medicine*. Because of the study's importance, however, the journal made the research available on-line March 17. ■

Screen smallpox vaccinees for cardiac factors

Reports of cardiac adverse events in smallpox vaccinees have resulted in recommendations that people with certain cardiac risk factors be excluded from the nation's voluntary smallpox immunization program.

The Centers for Disease Control and Prevention's (CDC's) Advisory Committee on Immunization Practices made the recommendations after holding an emergency meeting by conference call on March 28. The committee convened to discuss the cardiac adverse events reported after some smallpox vaccinations.

At the time of the meeting, 10 cases of myopericarditis had been reported among several hundred thousand members of the military, and two such cases (one of myocarditis and one of pericarditis) had been reported among civilian vaccinees. In addition, CDC had received reports of five patients with cardiac ischemic events following smallpox vaccination, including three patients with myocardial infarctions and two patients with angina. Two of the people who suffered heart attacks died.

The committee recommended that CDC exclude persons with known underlying heart disease and persons with three or more major cardiac risk factors. Therefore, CDC announced that potential vaccinees should not get the smallpox vaccine if they have been diagnosed by a doctor as having a heart condition with or without symptoms. The conditions include:

- known coronary disease, including previous myocardial infarction and angina;
- congestive heart failure;
- cardiomyopathy;
- stroke or transient ischemic attack;
- chest pain or shortness of breath with activity; and
- other heart conditions under the care of a doctor.

In addition, potential vaccinees should not get the smallpox vaccine if they have three or more of the following risk factors:

- A doctor has told them they have high blood pressure.
- A doctor has told them they have high blood cholesterol.
- A doctor has told them they have diabetes or high blood sugar.
- They have a first-degree relative who had a heart condition before the age of 50.
- They smoke cigarettes now.

If someone receives the smallpox vaccine and develops chest pain, shortness of breath, or other symptoms of cardiac disease after vaccination, he or she should see a health care provider right away. ▼

Unannounced surveys will be Joint Commission's norm

The Board of Commissioners of the Joint Commission on Accreditation of Healthcare Organizations in Oakbrook Terrace, IL, has announced its intention to begin conducting all regular accreditation surveys on an unannounced basis beginning in January 2006. Unannounced surveys will be pilot-tested in volunteer organizations during 2004 and 2005.

The Joint Commission says its plans to introduce a substantially new accreditation process beginning in January 2004 have been widely discussed with accredited health care organizations during the past year. The proposal to transition to unannounced surveys — approved by the Board of Commissioners at its March 28-29 meeting — resulted from those discussions.

During 2004, the Joint Commission expects to initiate pilot-testing of the unannounced triennial survey process in up to 100 hospitals that have

volunteered to be among the first participants. In 2005, the Joint Commission will continue to conduct voluntary unannounced surveys on a limited basis, opening up the option to all types of accredited organizations, and then will transition to a completely unannounced survey program in 2006. During this period, the Joint Commission plans to work closely with its various advisory groups, accredited organizations, and other stakeholder groups to gain their input and progressively refine the new accreditation process and smooth the transition to unannounced surveys.

The Joint Commission plans to continue to conduct random, unannounced, one-day surveys in an annual 5% sample of the health care organizations it accredits through the end of 2005. After that time, random unannounced surveys will be discontinued.

Details about the plan to introduce unannounced triennial surveys will be shared with accredited organizations in the coming months through educational programs, newsletters, and other outreach activities. ▼

FDA warns of cancer drug misrepresentations

The U.S. Food and Drug Administration (FDA) is warning consumers and health care practitioners about misrepresentations in a SuperGen press release dated Nov. 15, 2002, regarding the company's recently approved cancer drug, mitomycin for injection (Mitozytrex).

According to the FDA, the press release, titled "FDA approves SuperGen's New Drug Application to Market Mitozytrex (MitoExtra)" and disseminated by SuperGen, exaggerates the efficacy of mitomycin for injection and fails to include the significant risks associated with the use of the drug. The FDA says the press release does not mention acute adverse reactions that can result from administration of mitomycin for injection, which include fever, anorexia, nausea, and vomiting. The press release also fails to disclose that mitomycin for injection is associated with more serious adverse events, such as myelosuppression and hemolytic uremic syndrome.

The agency lists several statements in the press release that it says are misrepresentations by SuperGen. In response, the Dublin, CA, company says it is carefully reviewing the FDA's concerns and will address them. "SuperGen will take all appropriate steps to ensure that future news announcements are in compliance with all FDA regulations," the company states. SuperGen notes that the anticancer drug currently is not marketed or distributed and that at no time were any consumers or health care providers at risk. ▼

FDA revises warnings, recalls drug

The Food and Drug Administration (FDA) recently announced that it and Biogen have revised the Warnings, Precautions, Adverse Reactions, Patient Information, and Clinical Studies sections of the prescribing information for Interferon beta-1a (Avonex). The updated safety information includes a cautionary note regarding use in patients with depression and other severe psychiatric symptoms.

Post-marketing reports of depression, suicidal ideation, and/or development of new or worsening of pre-existing psychiatric disorders, including psychosis, as well as reports of anaphylaxis, pancytopenia, thrombocytopenia, autoimmune disorders of multiple target organs, and hepatic injury manifesting as elevated serum enzyme levels and hepatitis were added to the labeling. An FDA-approved Patient Medication Guide, providing patient safety information and comprehensive instructions for patient self-administration of the drug, was added.

In addition, the FDA has announced that Tai Chien has recalled all 100-tablet bottles of Ancom Anti-Hypertensive Compound Tablets, an unapproved new drug labeled to contain several prescription drug ingredients, including reserpine, diazepam, promethiazine, and hydrochlorothiazide. The sale of a product with this combination of ingredients poses possible serious health risks including sedation, depression, and potentially life-threatening abnormalities of the blood.

This recall includes all lot codes of the product remaining on the market. Ancom Tablets were sold without prescriptions to consumers at Tai Chien's retail establishment in New York City. Product also was sold to a distributor in Puerto Rico. At least one illness consequent to use of the drug has been reported to date. ■

New FDA Approvals

These drugs recently received final approval from the U.S. Food and Drug Administration (FDA):

• *Enfuvirtide (Fuzeon) by Roche Pharmaceuticals.* The FDA has announced the accelerated approval of enfuvirtide (Fuzeon) for use in combination with other anti-HIV medications to treat advanced **HIV-1 infection** in adults and children ages 6 years and older.

The announcement makes enfuvirtide the first product in a new class of medications called fusion inhibitors to receive marketing approval anywhere in the world. Drugs in this class interfere with the entry of HIV-1 into cells by inhibiting the fusion of viral and cellular membranes. This inhibition blocks the virus' ability to infect certain components of the immune system.

Enfuvirtide can be used as part of a medication regimen in patients for whom there are limited options. Enfuvirtide should only be used in patients who have previously used other anti-HIV medications and have ongoing evidence of viral replication. The drug is administered as a twice-daily subcutaneous injection.

The approved labeling for enfuvirtide warns physicians to monitor patients carefully for signs and symptoms of pneumonia. Although bacterial pneumonia was uncommon in clinical study participants, more patients treated with the drug developed bacterial pneumonia than did patients who did not receive it. In addition, enfuvirtide can cause both serious systemic allergic reactions and local skin reactions at the site of injection.

The long-term effects of enfuvirtide are not known at this time but are being evaluated by the ongoing clinical studies. The drug is expected to cost about $20,000 a year.

• *Lower-dose single tablet of a combination estrogen and progestin drug (Prempro) by Wyeth Pharmaceuticals.* The FDA has approved a lower-dose single tablet of Prempro, containing 0.45 estrogen and 1.5 progestin (medroxyprogesterone), to treat specific **symptoms of menopause**. The lower dose provides favorable tolerability and an efficacy profile comparable to the most frequently prescribed strength of Prempro, with 28% less estrogen and 40% less progestin.

The drug is effective for treating moderate-to-severe symptoms of hot flashes and night sweats and is indicated for the treatment of moderate-to-severe symptoms of vulvar and vaginal atrophy. However, topical vaginal products should be considered when being prescribed solely for the treatment of symptoms of vulvar and vaginal atrophy.

The new lower dose will provide an additional option for postmenopausal women. The FDA continues to advise women to talk to their doctors and, if they decide that estrogen and progestin combination products are appropriate, they should use the lowest dose for the shortest duration to reach treatment goals.

The FDA reminds women that estrogens and progestins should not be used to prevent heart disease, heart attacks, or strokes.

• *Aprepitant (Emend) by Merck & Co.* The FDA has approved aprepitant (Emend) to be used in combination with other anti-nausea and anti-vomiting drugs for prevention of **acute and delayed nausea and vomiting** associated with initial and repeat courses of chemotherapy known to cause these problems, including high-dose cisplatin.

Aprepitant is the first FDA-approved treatment that prevents the delayed nausea and vomiting symptoms that many patients experience more than 24 hours after receiving chemotherapy. Aprepitant is part of a three-drug therapy that works with other drugs to treat nausea and vomiting. It reduces nausea and vomiting in a new way by blocking receptors in the brain called NK1 receptors.

Aprepitant may interact with some drugs, including some chemotherapies, birth control

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pills, blood thinners, and other drugs. Aprepitant also may reduce the effectiveness of oral contraceptives.

Patients being treated with blood thinners such as warfarin will need to have their blood tested after the completion of a three-day regimen that includes aprepitant with each chemotherapy cycle to determine whether the dose of the blood-thinning medicine needs to be changed.

• *Propranolol hydrochloride (InnoPran XL) by Reliant Pharmaceuticals, LLC.* The FDA has approved propranolol hydrochloride (InnoPran XL), a bedtime-dosed, extended-release formulation of propranolol hydrochloride, for the treatment of **hypertension**.

Propranolol hydrochloride provides 24-hour blood pressure control in a once-daily formulation and a dosing range from 80 mg to 120 mg. It is the only product in its class approved for administration in the evening. Propranolol hydrochloride can be used alone or in combination with other anti-hypertensive agents. With evening administration, clinical trials have shown reduction in blood pressure in the early morning hours and sustained control throughout the day.

The most commonly reported side effects were fatigue, dizziness, and constipation. Propranolol hydrochloride is contraindicated in cardiogenic shock, sinus bradycardia, and greater than first-degree block bronchial asthma, and in patients with known hypersensitivity to propranolol hydrochloride.

Propranolol hydrochloride will be available in 80 mg and 120 mg capsules.

• *Pegvisomant for injection (Somavert) by Pharmacia Corp.* The FDA has approved pegvisomant (Somavert) for the treatment of **acromegaly**. The drug is approved for patients who have had an inadequate response to existing therapies.

Pegvisomant, the first in a new class of drugs called growth hormone receptor antagonists, normalized concentrations of IGF-I in more than 90% of patients by blocking the effects of growth hormone.

Acromegaly causes headaches, profuse sweating, swelling, joint disorders, changes in facial features, and enlarged hands, feet, and jaw. If untreated, patients with acromegaly often have a shortened life span because of heart and respiratory diseases, diabetes mellitus, and cancer.

In clinical studies, the most commonly reported side effects of pegvisomant use were injection site reactions, sweating, headache, and fatigue. Patients should have tests to monitor their liver function during the first six months of therapy with pegvisomant. The drug also is contraindicated in patients with hypersensitivity to any of its components. The stopper on the vial contains latex.

• *New indication for infliximab (Remicade) by Centocor.* The FDA has granted marketing approval for infliximab (Remicade) for reducing the number of draining enterocutaneous and rectovaginal fistulas and for maintaining fistula closure in patients with **fistulizing Crohn's disease**. The new maintenance indication requires treatment every eight weeks, following an induction regimen in which patients receive doses at weeks 0, 2, and 6. Infliximab, a tumor necrosis factor-alpha therapy, is the only biologic drug indicated for the treatment of both Crohn's disease and rheumatoid arthritis.

In June 2002, the FDA approved infliximab for use in inducing and maintaining clinical remission in patients with moderate-to-severe Crohn's disease using maintenance dosing every eight weeks. ■

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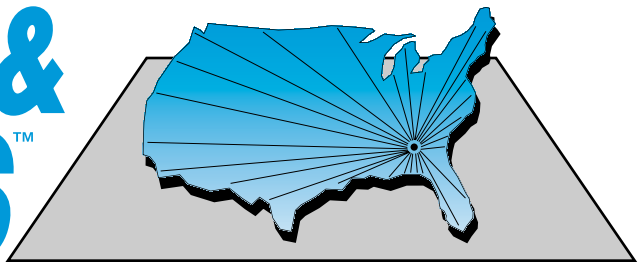

Frovatriptan formulary evaluation

By **Melinda Spray**, PharmD
Written while on clinical clerkship with
Auburn University at Huntsville (AL) Hospital

Triptans

Sumatriptan (Imitrex) — GlaxoSmithKline
Naratriptan (Amerge) — Glaxo-Wellcome
Rizatriptan (Maxalt, Maxalt MLT) — Merck
Zolmitriptan (Zomig) — AstraZeneca
Almotriptan (Axert) — Pharmacia
Frovatriptan (Frova) — Elan Corp.

Description

Of the triptans listed above, frovatriptan succinate is the triptan most recently approved by the Food and Drug Administration. The triptans are 5-hydroxytryptamine (5-HT) 1B/1D receptor agonists. The major use for this class of drugs is for the acute treatment of migraines with or without an aura in adults (age ≥ 18 years). The current oral triptan on Huntsville Hospital System's Formulary Interchange Program is zolmitriptan.

Mechanism of action

Frovatriptan binds to and stimulates the 5-HT 1B/1D receptors on extracerebral, intracranial arteries. This inhibits excessive vasodilation of these arteries, which occurs during a migraine.

Pharmacokinetics

The triptans are all very similar in many aspects; however, kinetic profiles differ from drug to drug. Frovatriptan's beneficial pharmacokinetic difference from the other triptans is its long half-life. Frovatriptan's disadvantage is a slower onset of action. The pharmacokinetics of the triptans are shown in **Table 1, below**.

Indications and dosing

All triptans are indicated for the acute treatment of migraines with or without an aura in adults. Subcutaneous sumatriptan injection also is indicated for the acute treatment of cluster headaches. Dosing information is listed in **Table 2, p. 2**.

Table 1: Pharmacokinetics

Drug	Route	Onset	T_{max}(h)	$T_{½}$(h)	Bioavailability	Metabolism
Sumatriptan	SQ Intranasal Oral	10-15 min 15-20 min 30-90 min	0.17 1.5 1.5	2 2 2	97% 17% 15%	Monoamine oxidase (MAO) MAO MAO
Naratriptan	Oral	1-3 h	2	5.5	70%	Renal/Cytochrome P450 isoenzyme (CYP P450)
Rizatriptan	Oral	0.5-2 h	1	2	45%	CYP 450/MAO
Zolmitriptan	Oral	1 h	1.5	2-3 h	40%	CYP 450/MAO
Almotriptan	Oral	1-3 h	2.5	3	70%	CYP 450/MAO
Frovatriptan	Oral	2-4 h	3	26 h	20% Males 30% Females	CYP 450/Renal

Table 2: Dosage

Drug	Dosing
Sumatriptan	Subcutaneous — 6 mg, may repeat in one hour (Max: 12 mg/day) Intranasal — 5-20 mg, may repeat in two hours (Max: 40 mg/day) PO — 25-50 mg, may repeat in two hours (Max: 100 mg/dose, 300 mg/day)
Naratriptan	2.5 mg, may repeat in two hours (Max: 5 mg/day)
Rizatriptan	5 mg, may repeat in two hours (Max: 30 mg/day)
Zolmitriptan	2.5-5 mg, may repeat in two hours (Max: 5 mg/dose, 10 mg/day)
Almotriptan	12.5 mg, may repeat in two hours
Frovatriptan	2.5 mg, may repeat in two hours (Max: 7.5 mg/day)

Adverse events

Adverse events are similar with all drugs included in this class. These reactions are generally mild. Rare adverse events that could occur with the use of any triptan include coronary vasospasm, myocardial infarction, ventricular tachycardia, and ventricular fibrillation. Adverse reactions are listed by drug in **Table 3, below**.

Contraindications

The contraindications for frovatriptan are similar to those of other triptans **(see Table 4, p. 3)**. Frovatriptan is not contraindicated in patients with severe renal or hepatic dysfunction.

Drug interactions

Drug interactions generally are similar among the drugs of the triptan class **(see Table 5, p. 4)**. However, the triptan metabolic pathways differ,

Table 3: Adverse reactions

	Sumatriptan	Naratriptan	Rizatriptan	Zolmitriptan	Almotriptan	Frovatriptan
Central Nervous System	Dizziness Drowsiness Fatigue Head heaviness/ pressure Seizures	Dizziness Fatigue Drowsiness Paresthesias	Dizziness Fatigue Drowsiness Paresthesias	Asthenia Dizziness Paresthesia Somnolence	Paresthesias Somnolence Dizziness	Dizziness Fatigue Headache Paresthesia
Cardiovascular	Palpitations Chest tightness Flushing Vasospasms Hypertension Hypotension Tachycardia Bradycardia Arrhythmias Myocardial infarction	Palpitations Increase blood pressure (BP) Arrhythmias	Chest pain Increase BP Syncope	Chest tightness Increase BP Palpitations Tachycardia Bradycardia	Vasodilation Palpitation Tachycardia Hypertension Syncope	Increase BP Chest pain Flushing
Gastrointestinal	Nausea	Nausea	Nausea Dry mouth Abdominal pain	Nausea Dry mouth Anorexia	Diarrhea Vomiting Dyspepsia Colitis Gastritis Dry mouth	Dry mouth
Miscellaneous	Visual changes		Neck/throat tightness	Neck/throat tightness	Increase glucose Increase cholesterol	

Table 4: Contraindications

	Sumatriptan	Naratriptan	Rizatriptan	Zolmitriptan	Almotriptan	Frovatriptan
Hypersensitivity	Yes	Yes	Yes	Yes	Yes	Yes
Cerebrovascular syndromes (stroke, transient ischemic attack)	Yes	Yes	No	No	No	Yes
Concomitant administration within 24 hours of another 5-HT agonist or ergot-containing compound	Yes	Yes	Yes	Yes	Yes	Yes
Concurrent administration with a monoamine oxidase inhibitor within two weeks	Yes	No	Yes	Yes	No	Yes
Hemiplegic or basilar migraine	Yes	Yes	Yes	Yes	Yes	Yes
Ischemic heart disease	Yes	Yes	Yes	Yes	Yes	Yes
Peripheral vascular disease	Yes	Yes	No	No	Yes	Yes
Uncontrolled hypertension	Yes	Yes	Yes	Yes	Yes	Yes
Severe renal impairment	No	Yes	No	No	No	No
Severe hepatic impairment	No	Yes	No	No	No	No

which could lead to different drug interactions. Some of the reactions are not documented with all the triptans; however, they still could occur. Many of the drug interactions that cause an increase in serum frovatriptan do not require dosage adjustment of the drug. Frovatriptan dosages as high as 40 mg have been observed to be safe.

Cost

The hospital cost of frovatriptan is similar to that of most other triptan drugs at equivalent doses (in the $10-$12 range for a single dose).

Clinical studies

Two large-scale dose-finding studies were used to establish the therapeutic dose of frovatriptan. These studies established frovatriptan 2.5 mg as the dose that balanced efficacy and safety.

There also are trials evaluating pharmacokinetics and drug interactions. One published article compared tolerability and safety of frovatriptan and sumatriptan; however, this article did not compare efficacy or headache recurrence rate. The data demonstrated that up to three doses of frovatriptan 2.5 mg over a 24-hour period were well-tolerated by patients with migraine with short-term and long-term use.

There are five placebo-controlled trials establishing the efficacy of frovatriptan. Two of these studies are unpublished and unavailable from the drug company at this time. The published efficacy studies are VML 251/96/06 (study 1), VML 251/96/07 (study 2), and VML 251/96/09 (study 3). The three published studies were multi-center, randomized, double-blind, placebo-controlled, parallel-group clinical trials. Study 3 also used an active comparator. The demographic characteristics of the trial participants were similar among the treatment and placebo groups of all three studies, as well as among the three study groups. The participants of all three trials were mostly women (85-90%), and the mean age of the trial participants was 40.2-42.3 years. The primary efficacy endpoint of study 1 was two-hour headache response. Study 2 primary efficacy endpoints were two-hour and four-hour headache response and 24-hour headache recurrence. Study 3 primary efficacy endpoints were two-hour headache response and 24-hour headache recurrence.

(Continued on page 5)

Table 5: Drug interactions

Serotonin 5-HT1 Receptor Agonist Drug Interactions		
Precipitant Drug	**Object Drug**	**Description**
Cimetidine	Zolmitriptan	Half-life and area under the curve (AUC) of zolmitriptan were approximately doubled.
Ergot alkaloids	Naratriptan Sumatriptan Zolmitriptan Rizatriptan Almotriptan Frovatriptan	May increase risk of vasospastic reaction. Contraindicated to administer this drug combination within the same 24-hour period.
Ketoconazole (CYP3A4 inhibitor)	Almotriptan	60% increase in the AUC and maximal plasma concentration of almotriptan.
5-HT1 agonist	Naratriptan Sumatriptan Zolmitriptan Rizatriptan Almotriptan Frovatriptan	Increased risk of vasospastic reaction. Contraindicated to administer any two within the same 24-hour period.
MAO inhibitors	Sumatriptan Zolmitriptan Rizatriptan Almotriptan	The use of these triptans with or within two weeks of MAO inhibitor use is contraindicated. Naratriptan and frovatriptan appear to be less likely to interact with MAO inhibitors.
Oral contraceptives	Frovatriptan Naratriptan Zolmitriptan	30% increase in mean C_{max} and AUC of frovatriptan and zolmitriptan. Clearance and Volume of distribution of naratriptan decreased.
Propranolol	Zolmitriptan	1.5-fold increase in C_{max} and AUC of zolmitriptan, but a decrease in the C_{max} and AUC for the N-desmethyl metabolite. No effects on blood pressure or heart rate were observed.
	Rizatriptan	Rizatriptan's mean plasma AUC was observed with concomitant administration.
	Frovatriptan	Increase in AUC and C_{max} of frovatriptan with concomitant administration.
Sibutramine	Naratriptan Sumatriptan Zolmitriptan Rizatriptan	A "serotonin syndrome" could occur. Coadministration is not recommended. Monitor the patient for adverse effects if combination cannot be avoided. Consideration should be given to the potential occurrence of this drug interaction with any triptan drug.
Naratriptan **Sumatriptan** **Zolmitriptan** **Rizatriptan** **Frovatriptan**	SSRIs Fluoxetine Fluvoxamine Paroxetine Sertraline	Rare reports of weakness, hyper-reflexia, and incoordination with combined use of SSRIs. If coadministered, observe the patient carefully. No interaction observed between rizatriptan and paroxetine.

Table 6: Headache recurrence

Incidence and Time of Headache Recurrence for Frovatriptan vs. Placebo						
	Study 1		Study 2		Study 3	
	Frovatriptan	Placebo	Frovatriptan	Placebo	Frovatriptan	Placebo
Number of patients	204	104	733	378	475	242
Number of patients with response at hour 4	88	25	378	115	242	65
Recurrence within 24 hours of first dose	9 (10%)	6 (24%)	89 (24%)	32 (28%)	60 (25%)	20 (31%)
P value	0.082		0.33		0.32	
Time to headache recurrence, mean in hours	12.1	8.4	13.2	9.9	13.7	8.2

Headache response at hour 4 is shown in **Table 6, above**. Two-hour headache response ranged from 37% to 46% with frovatriptan and 21% to 27% with placebo. The two-hour pain-free rates for frovatriptan were 9-14% compared with 1-5% with placebo. Four-hour headache response ranged from 56% to 65% with frovatriptan and 31% to 38% with placebo. Both of these efficacy endpoints established a statistically significant difference between the efficacy of frovatriptan and the efficacy of placebo.

Frovatriptan has a long half-life and therefore is expected to have a lower headache recurrence rate. Studies 2 and 3 investigated headache recurrence as a primary endpoint, and study 1 also investigated incidence of headache recurrence.

Table 7: Triptan interchange program

Naratriptan	Zolmitriptan
1 mg	2.5 mg
2.5 mg	2.5 mg
2.5 mg (mild-to-moderate hepatic impairment)	1.25 mg
2.5 mg (mild-to-moderate renal impairment)	2.5 mg
Rizatriptan	Zolmitriptan
5 mg	2.5 mg
10 mg	5.0 mg
Sumatriptan	Zolmitriptan
25 mg	2.5 mg
50 mg	5.0 mg
100 mg	5.0 mg
50 mg (hepatic impairment)	1.25 mg
Almotriptan	Zolmitriptan
6.25 mg	2.5 mg
12.5 mg	5.0 mg
6.25 mg (hepatic impairment)	1.25 mg
6.25 mg (renal impairment)	2.5 mg
Frovatriptan	Zolmitriptan
2.5 mg	2.5 mg

Table 6, above, shows the results for all three studies. These results do not show a statistically significant difference between frovatriptan and placebo with regard to headache recurrence.

Summary and recommendation

The placebo-controlled trials establish that frovatriptan's efficacy is superior to placebo. However, these trials are published together, and all the information about the trials is not published in this article. There currently are no published studies comparing frovatriptan with another triptan. For this reason, it is difficult to evaluate frovatriptan's place in therapy at the Huntsville Hospital System. Frovatriptan's long half-life is a possible strength; however, there was not a statistically significant difference between the headache recurrence rates of frovatriptan and placebo. A weakness of frovatriptan is its slow onset of action when compared to other drugs of the triptan class. For these reasons, it is recommended that frovatriptan not be added to the Huntsville Hospital formulary at this time. Frovatriptan should be interchanged to the equivalent dose of the formulary drug, zolmitriptan, if no substitution is written with the drug order. **(See Table 7, left.)**

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Off-label drug use: Etanercept (Enbrel) for Crohn's disease?

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Inflammatory bowel disease (IBD) has been clinically described for more than a century. Crohn's disease, one major type of IBD, has an incidence rate in the United States of approximately seven per 100,000. Advancing biotechnological knowledge regarding this idiopathic disease has led to the development of therapies aimed at specific targets in the disease pathway.

In Crohn's disease, the inflammatory process is consistent with a T-helper 1 immune response. The T-helper 1 immune response is characterized by an increased expression of interferon γ, interleukin (IL)-2, IL-12, IL-18, and pro-inflammatory mediators IL-1 β, tumor necrosis factor (TNF), and nuclear factor β, as well as a compensatory increase in anti-inflammatory IL-10 and transforming growth factor κB. Of particular interest to clinical researchers is the detection of elevated TNF levels in the serum and stool of Crohn's disease patients. TNF appears to be a pivotal target in the Crohn's disease pathway, which could result in the interruption of the inflammatory cascade when inhibited.

Currently, two genetically engineered TNF antagonists are available and approved by the Food and Drug Administration (FDA). Infliximab (Remicade) is a chimeric IgG1 monoclonal antibody for anti-TNF therapy in patients with moderate-to-severe Crohn's disease. The drug has demonstrated significant improvement of symptoms in patients with severe Crohn's disease refractory to standard treatment, fistulas, and rheumatoid arthritis. It is thought that infliximab binds and neutralizes soluble and membrane-bound TNF. Infliximab demonstrates unique additional effects such as antibody-dependent cellular toxicity, complement-dependent cytotoxicity, and induction of T-lymphocyte apoptosis.

The other FDA-approved TNF antagonist, etanercept (Enbrel), is a dimeric fusion protein with two identical chains of the recombinant human p75 TNF receptor monomer linked to the Fc portion of human IgG1 for the treatment of rheumatoid arthritis. It has demonstrated significant improvement in disease activity and improves quality of life in rheumatoid arthritis patients. The proposed mechanism of action for etanercept is the antagonism of TNF activity by binding to membrane-bound and soluble forms of TNF.

Because etanercept and infliximab are classified as TNF antagonists and are efficacious in rheumatoid arthritis therapy, etanercept use in Crohn's disease was investigated. Two clinical trials that examined the use of etanercept for active Crohn's disease provide conflicting results.

D'Haens et al conducted a single-center pilot trial that enrolled 10 patients with at least six months of active Crohn's disease. Each patient was treated for 12 weeks with the dose of etanercept recommended for rheumatoid arthritis, 25 mg subcutaneously twice weekly, as well as any additional therapy that the patient was taking prior to the study. The patient's response to treatment was evaluated using the Crohn's Disease Activity Index (CDAI). The index was developed in 1976 by Best et al and was used as a monitoring tool in the National Cooperative Crohn's Disease study. The CDAI consists of an eight-question survey evaluating bowel function, emotional status, and systemic involvement. After 12 weeks of treatment, seven patients demonstrated a clinical response measured by a decrease in the CDAI of 70 or more points, and four patients attained remission, with a total CDAI of less than 150. Three out of the four subjects in remission relapsed within four weeks after discontinuing etanercept. D'Haens et al concluded that etanercept at 25 mg subcutaneously twice weekly might be effective in Crohn's disease refractory to standard therapy, yet may be insufficient to induce remission. Limitations of this study include a small sample size and lack of a placebo control, blinding, or randomization.

Subsequently, Sandborn et al conducted an eight-week, randomized, double-blind, placebo-controlled trial evaluating etanercept use in 43 active Crohn's disease patients. The patients were

randomized to receive 25 mg of etanercept or placebo subcutaneously twice weekly. At week four of the study, the placebo-treated patients had a higher clinical response of 45%, measured by a decrease in CDAI of 70 or more points or total score of less than 150 points, compared to 39% clinical response among the etanercept-treated patients. Sandborn et al concluded that etanercept at 25 mg subcutaneously twice weekly is ineffective for the treatment of active Crohn's disease. The authors cite an unpublished placebo-controlled dose-finding study with etanercept that produced a similar negative outcome. One plausible explanation for the results of this study is the possibility that dissimilar binding affinities between etanercept and infliximab resulted in distinct rates of response. However, these differences have not been evident in rheumatoid arthritis patients. It also may be possible that etanercept has poor penetration in the gastrointestinal (GI) tract when administered by injection. Additionally, Sandborn et al postulate that perhaps a higher dose or more frequent dosing may be needed to acquire clinical benefit. Although this study had a small sample size, similar demographics between subject groups, and a randomized, double-blind, placebo-controlled design, it provided more convincing evidence compared to the single-center trial.

Despite questionable efficacy in the treatment of Crohn's disease, etanercept is considered a safe medication overall. The most common adverse events reported in both of the published trials were local pain at the injection site, headaches, asthenia, mild anemia, and skin reactions. A retrospective study of etanercept use in rheumatoid arthritis patients showed that approximately 20% of the patients receiving subcutaneous etanercept experienced a transient injection site reaction, mostly within the first two months of treatment. Infections are the most frequent systemic adverse effects and are primarily present as upper respiratory tract infections. This possibility exists with TNF antagonists because of the mediation of inflammatory and immune responses. Adverse GI effects occurring with use of etanercept include abdominal pain, dyspepsia, nausea, vomiting, and mouth ulcers. Serious, infrequent adverse effects include cardiovascular complications, cholecystitis, pancreatitis, bursitis, depression, deep vein thrombosis, pulmonary embolism, membranous glomerulonephropathy, polymyositis, or thrombophlebitis. In clinical trials, the incidences of these serious adverse effects with etanercept were similar to placebo.

The manufacturer, Amgen (formerly Immunex), launched the Enbrel enrollment program in November 2000 to assist in controlling a shortage and to ensure a continuous supply to patients already taking etanercept. Patients have to be enrolled in the program prior to obtaining the drug. The shortage of etanercept has now been resolved; however, the Enbrel enrollment program is still in place and is not accepting new patients until a new manufacturing plant is completed.

In conclusion, evidence documenting the efficacy of etanercept for the treatment of Crohn's disease is lacking. Considering the conflicting results demonstrated in the two published studies, etanercept should not be considered as a primary therapeutic option for active Crohn's disease. Presently, Crohn's disease therapy with etanercept might be considered as a last alternative for patients who have demonstrated poor response to all other possible treatments. Because both studies evaluated the use of etanercept in Crohn's disease using the dose recommended for rheumatoid arthritis, researchers suggest further consideration with larger trials to establish efficacy, optimal dosing, dosing frequency, and appropriate candidates for Crohn's disease therapy with etanercept. It is hoped that discovering possible differences among TNF antagonists ultimately will result in a better understanding of the molecular mechanisms in order to produce long-term biotechnological agents that are safe and effective for Crohn's disease therapy.

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New FDA Approvals

These drugs recently received final approval from the U.S. Food and Drug Administration (FDA):

• *New indication for Carvedilol (Coreg) by GlaxoSmithKline.* The FDA has approved carvedilol (Coreg) for patients who have had a myocardial infarction and who have **left ventricular dysfunction**. Carvedilol is the only beta-blocking agent approved to reduce the risk of death in mild, moderate, and severe heart failure. It is now the only beta-blocking agent with an approved indication to reduce the risk of death among patients who have had a recent heart attack and have impaired cardiac function, whether or not they have symptoms of heart failure. Carvedilol also is indicated for essential hypertension.

• *Reactive Skin Decontamination Lotion (RSDL) by O'Dell Engineering Ltd./E-Z-EM Canada.* The FDA has cleared for use by the U.S. military a liquid decontamination lotion intended to remove or neutralize **chemical warfare agents and T-2 fungal toxin** from the skin. The lotion, called Reactive Skin Decontamination Lotion (RSDL), must be applied to exposed skin as soon as possible after exposure to a chemical agent.

The lotion is impregnated in a sponge pad packaged as a single unit in a heat-sealed foil pouch. When exposed to chemical warfare agents, the user wipes the exposed skin with the lotion. The lotion removes the agents or the T-2 toxin and also reacts with the chemical agents, rapidly neutralizing them so they are non-toxic.

• *New indication for valacyclovir HCl (Valtrex) by GlaxoSmithKline.* The FDA has approved a supplemental new drug application for valacyclovir HCl (Valtrex) caplets for the suppression of **recurrent genital herpes in HIV-infected people**.

Valacyclovir HCl is the first and only antiviral approved in the United States for suppression of recurrent genital herpes outbreaks in HIV-infected people. The drug also is indicated for initial and recurrent treatment and for suppression of genital herpes outbreaks in immunocompetent people. ■

IN THE PIPELINE

• Cardiome Pharma Corp. has commenced patient dosing of oxypurinol in a Phase II/III study of patients with **congestive heart failure**.

• SuperGen has announced that patient enrollment has been completed in an open-label, randomized Phase III clinical study of decitabine, an investigational treatment for **advanced myelodysplastic syndrome**.

• Telik has initiated a randomized, controlled Phase III registration trial of TLK286, administered as a single agent in **ovarian cancer** patients whose disease has progressed following platinum-based chemotherapy and one second-line treatment.

• Vion Pharmaceuticals has initiated a Phase I trial of Triapine, an inhibitor of ribonucleotide reductase, in combination with cytarabine (Ara-C) in patients with **advanced leukemia**.

• Barrier Therapeutics has announced that enrollment has begun in Phase III clinical trials for Seboride in both Europe and the United States. Seboride, a combination topical agent containing ketoconazole, an antifungal agent, and desonide, a steroid, is a patented gel formulation. The trials have been designed to show that the agent is effective in **seborrheic dermatitis** with a treatment regimen of once per day for two weeks.

• Schering AG, Berlin has announced that its novel experimental agent PTK787/ZK 222584, which is being developed in collaboration with Novartis AG, has entered Phase III clinical trials for treatment of **metastatic colorectal cancer**.

• Barrier Therapeutics has begun enrolling patients in its final Phase III clinical trial for its lead product, Zimycan, a topical ointment containing 0.25% of the antifungal miconazole, in a zinc oxide and petrolatum base. If approved, Zimycan would be the first and only product approved for use in **Candida-associated diaper dermatitis**.

• Access Pharmaceuticals has begun a Phase I clinical study to evaluate AP5346, a DACH Polymer Platinate. Upon successful completion of the Phase I study, a Phase IIA study will be conducted in **ovarian cancer** patients to determine the initial efficacy of AP5346. ■