DRUG UTILIZATION REVIEW
Pharmaceutical Care Across the Continuum

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Congress pushes toward $400 billion Medicare reform package

Bills address pharmacy interests in several areas

Congress focused on Medicare reform in June, with both the House and Senate passing their own versions of a Medicare prescription drug program.

The Senate approved its bill by a 76-to-21 margin, but the House bill passed by just one vote, 216 to 215. Both bills would spend $400 billion, take effect in 2006, and give Medicare enrollees more choices among private health plans. However, Medicare participants would have to pay a monthly premium and annual deductible before the government would help pay for the prescription drugs.

The bills might be similar in some respects, but their differences will be challenging to overcome, says **Kristina Lunner**, director of federal government affairs for the American Pharmacists Association (APhA) in Washington, DC. "There are some dramatic differences between the two bills."

House conservatives, for example, are against anything that they think will weaken free-market reform of Medicare. Senate Democrats, on the other hand, think that the House reforms will gut the traditional Medicare program. Congressional sources say that an accord may not be reached until early this month or maybe in the fall.

Provisions address pharmacy concerns

Even with the negotiations that lie ahead, pharmacy groups are pleased to see several provisions added to the bills that address pharmacy concerns. "We are very encouraged that both chambers have listened to our concerns and have attempted to address them. Whether they have gone far enough is yet to be seen," Lunner says.

Here are details (most from APhA) about some of the pharmacy-related provisions included in one or both of the bills:

• The Senate adopted an amendment that would close unintended loopholes in the Hatch-Waxman Act. Those loopholes have delayed the

approval of generic pharmaceuticals for reasons other than safety and efficacy. The bill, introduced by Sen. Judd Gregg (R-NH), chairman of the Senate Health, Education, Labor, and Pensions Committee, and Sen. Charles Schumer (D-NY), would establish the following:

— **One 30-month stay**. The stay would be triggered if a name-brand company sues to block a generic application for infringing on a patent if the application is filed before a generic application is submitted to the U.S. Food and Drug Administration (FDA). Once a generic application is filed, the name-brand company has 45 days to challenge the generic application in court. If the name brand does not challenge the generic company's application within 45 days, the generic can seek a declaratory judgment indicating that it does not violate the name-brand drug's patents.

— **New enforcement mechanism.** To ensure that the name-brand companies do not use frivolous patents to keep generic drugs off the market, the proposal would allow generic companies to file counterclaims if a name-brand company sues them for violating a patent.

— **180-day exclusivity**. Under the bill, a generic drug company would forfeit its rights to this exclusivity if it were found to have made an anticompetitive deal with a brand company or otherwise fails to come to market in a timely manner. If one of the forfeiture provisions outlined in the bill occurs, the exclusivity would be forfeited and the marketplace would open up to any generic company ready to come to market.

— **Authority for establishing bioequivalence**. The bill would clarify that the FDA does have the authority to establish separate tests for determining the bioequivalence of drugs that are not absorbed into the bloodstream — as long as those tests are scientifically valid and meet rigorous standards.

• A Senate amendment would require plan sponsors to disclose discounts, rebates, and other financial incentives and would require plans to authorize pharmacies to dispense 90-day supplies to beneficiaries — although beneficiaries would be responsible for any price differences between providers.

Provider status legislation introduced in the Senate

Legislation to give pharmacists provider status was introduced in the Senate in June by Sen. Tim Johnson (D-SD) and Sen. Thad Cochran (R-MI).

The Medication Therapy Management Act, S. 1270, would amend the Social Security Act to cover medication therapy management service provided by pharmacists to high-risk Medicare patients. Patients who would have access include those receiving medications for asthma, diabetes, or chronic cardiovascular disease, as well as those on anticoagulation or lipid-reducing medications. The services provided by a number of other health care professionals, including registered dietitians, nurse practitioners, physician assistants, certified nurse midwives, and clinical social workers, also are recognized for payment under Medicare.

Pharmacy groups are strongly voicing their support of this bill. "The involvement of pharmacists is imperative so that Medicare patients with complex medical needs can successfully control their disease and avoid multiple doctor and hospital visits to deal with complications," says **Phylliss Moret**, acting executive director of the American Society of Consultant Pharmacists, in a statement. ■

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Editorial Questions

Questions or comments? Call **Lee Landenberger** at (404) 262-5483.

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Editor: **Sue P. Coons**, (spcoons@aol.com).
Vice President/Group Publisher: **Brenda Mooney**, (404) 262-5403, (brenda.mooney@ahcpub.com).
Editorial Group Head: **Lee Landenberger**, (404) 262-5483, (lee.landenberger@ahcpub.com).
Managing Editor: **Paula Cousins**, (816) 960-3730, (paula.cousins@ahcpub.com).
Production Editor: **Nancy McCreary**.

• A Senate amendment allows pharmacists, wholesalers, and individuals to import prescription medications from Canada. The amendment was modified to include several safety provisions, including requiring certification by the Secretary of Health and Human Services that the drugs are safe and that importation would result in "significant" savings before the law can be implemented. The House bill includes a similar provision.

• A Senate amendment instructing the Department of Health and Human Services to develop a Committee on Drug Compounding "to ensure that patients are receiving necessary, safe, and accurate dosages of compounded drugs."

• A Senate amendment for a one-year assessment of payment models for pharmacist-provided medication therapy management services. This is different from the stand-alone legislation that gives pharmacists provider status. **(See article on p. 58.)**

• Provisions for medication therapy management programs. These would be for beneficiaries with chronic conditions and/or on multiple medications. The House bill specifically says "pharmacy providers" would provide the services; the Senate bill doesn't make that specification. ■

Senate generic bill more rigorous than FDA regs

In addition to the Senate bill, the U.S. Food and Drug Administration (FDA) announced regulations in mid-June that would streamline the process for making generic drugs available to consumers. The FDA regulations are similar to the Senate bill in some ways, although the Senate bill proponents claim their legislation is more rigorous in closing the loopholes in the Hatch-Waxman Act.

Like the Senate bill, the FDA regulations would limit a drug company to only one 30-month delay of a generic drug's entry into the market while a patent challenge is being resolved.

The regulations also clarify the types of patents innovators must submit for listing in the "Orange Book," the FDA's official register of approved pharmaceutical products. The changes are consistent with concerns raised last year by a Federal Trade Commission report on generic drugs.

The FDA also has begun internal reforms to improve the efficiency of its review process for generic drugs, such as implementing a new system of early communications with generic drug manufacturers that submit applications. In addition, the FDA will provide additional guidance for generic manufacturers preparing and submitting applications. The new resources and other reforms are expected to reduce the total time to approval for most new generic drugs by three months or more over the next three to five years.

The FDA also plans to expand its consumer educational programs and partnerships involving generic drugs, as well as to undertake more scientific studies of generic drug bioequivalence.

The FDA estimates the changes in the regulations will save consumers $35 billion over 10 years. ■

PBM finds generic drug use increasing

Slows overall prescription drug spending

Growth in prescription drug spending for the first quarter of 2003 slowed in part to increased usage of generic drugs, says pharmacy benefit manager Express Scripts of St. Louis.

Express Scripts, which serves more than 50 million consumers, says that greater use of generic drugs reduced the dollar outlay for prescription drugs by 3.2% during the first quarter and, for all of 2002, by 2.1%. During the first quarter 2003, 47% of all prescription claims processed by Express Scripts were for generic drugs, up from 43% a year earlier.

"Several factors led to higher generic usage: Several heavily used brand products lost patent protection, opening the door for generic competition, and more plan sponsors implemented mandatory or restricted generic programs and/or step therapy programs," says **Fred Teitelbaum**, PhD, Express Scripts' vice president of research and planning.

The "cost-reducing effect of expanding generic drug use will continue to help make prescription drugs much more affordable for years to come," says Express Scripts CEO **Barrett Toan**.

The cost-saving potential of generics is critical because some drugs are expected to sustain increased utilization, Toan says. For example, the utilization of medications for blood pressure (10.6%), high cholesterol (14.1%), and diabetes (14.5%) increased at double-digit rates.

"The upward trend for these classes was in line with previous increases, reflecting the aging population and increasing diagnosis and treatment of these conditions," Teitelbaum says.

Express Scripts also conducted a study of physician response to safety warnings. Researchers followed up with physicians, from two regional health plans serving about 1.5 million members, who had received 12,000 letters alerting them to a potential safety hazard between April 1 and Aug. 31, 2002. The majority of warnings were for probable drug-drug interactions.

The study found that 38% of the physicians said they changed or modified their patient's therapy as a result of the information. "We were pleased to learn that when safety information is provided directly to physicians, such a high percentage responded by saying they had changed or modified therapy," Teitelbaum says.

Sending warning letters to physicians after a prescription has been filled supplements Express Scripts' concurrent drug utilization review program, which is the real-time delivery of warnings to pharmacists at the time a prescription is filled.

Last year, the company sent an estimated 33 million safety warnings to pharmacists — about 10% of the 355 million retail prescription claims processed by the company. For nearly 600,000 of the warnings, the pharmacist changed or withdrew the prescription claim. Most warnings were for therapeutic duplication, drug-age warning, drug-drug interaction, high-dose warning, pregnancy warning, ingredient duplication, gender contraindication, and drug-disease interaction. Teitelbaum says Express Scripts is studying the pharmacist response further. ■

Senate panel supports pharmacy education aid act

In other legislation favorable to pharmacists, the Senate Committee on Health, Education, Labor, and Pensions recently passed a bipartisan bill that would provide two student loan repayment programs for certain pharmacists. The bill now moves on to the Senate floor for consideration.

Senate Bill 648, the "Pharmacy Education Aid Act of 2003," would:

• Amend the Public Health Service Act to permit payments of up to $35,000 on behalf of an individual for the repayment of pharmacy education loans for each year the recipient serves in a health care facility with a critical shortage of pharmacists. The individual must have received a baccalaureate degree in pharmacy or a doctor of pharmacy degree from an accredited program, and must agree to serve as a full-time pharmacist in the facility for at least two years.

The recipient would have to repay the government if they fail to maintain acceptable levels of academic standing, are dismissed for disciplinary reasons, voluntarily terminate their programs, or fail to provide health services in accordance with their commitments after their academic program is completed.

• Establish student loan programs to increase the number of faculty at schools of pharmacy. The bill directs each school in which such a program is established to pay at least one-ninth of the federal capital contributions, up to $35,000 annually per student. Upon completion of the employment requirements as a faculty member, an amount up to 85% of the loans (plus interest) from such a program is canceled, with the government reimbursing the school for its proportionate share of the canceled amount. ■

Finasteride reduces prostate cancer incidence

Benefits may not be worth the risk, physician says

A recent study shows that finasteride (Proscar) prevents or delays the appearance of prostate cancer. The drug, however, also shows sexual side effects and an increased risk of high-grade prostate cancer.

In the Prostate Cancer Prevention Trial (PCPT), prostate cancer was detected in 18.4% men treated with finasteride as compared to 24.4% of the men in the placebo group, a 24.8% reduction. The study was scheduled to be completed in 2004, but was stopped early because the study objective had been met. The current analysis is based on the 86.3% of men who completed the

seven years of the study.

Finasteride, a synthetic 4-azasteroid compound, is a specific inhibitor of steroid Type II 5*a*-reductase, an intracellular enzyme that converts the androgen testosterone into 5*a*-dihydrotestosterone. It is indicated for the treatment of symptomatic benign prostatic hyperplasia (BPH) in men with an enlarged prostate to improve symptoms, reduce the risk of acute urinary retention, and reduce the risk of the need for surgery, including transurethral resection of the prostate and prostatectomy. (A lower-dose version of finasteride is marketed as Propecia and is indicated for the treatment of male pattern hair loss.) In the PCPT, researchers wanted to see if finasteride might prevent prostate cancer by reducing androgenic stimulation.

To test their hypothesis, researchers randomly assigned 18,882 men 55 years of age or older to a normal digital rectal examination and a prostate-specific antigen (PSA) level of 3.0 ng/mL or lower to treatment with finasteride (5 mg/day) or placebo for seven years. Prostate biopsy was recommended if the annual PSA level, adjusted for the effect of finasteride, exceeded 4.0 ng/mL or if the digital rectal examination was abnormal. Researchers expected that 60% of participants would have prostate cancer diagnosed during the study or would undergo biopsy at the end of the study. The primary endpoint was the prevalence of prostate cancer during the seven years of the study.

Although the incidence of prostate cancer was reduced in the finasteride group of participants, this group did have an increase in the rate of high-grade cancers — 6.4% as compared to 5.1% in the placebo group. In addition, sexual side effects were more common in finasteride-treated men, whereas urinary symptoms were more common in men receiving placebo.

These study results were published on the web site of the *New England Journal of Medicine* to coincide with the National Cancer Institute's announcement of the early termination of this trial. They also appeared in the July 17 issue of the journal.

In an accompanying editorial, a physician argues that finasteride does not seem to be an attractive agent for the chemoprevention of prostate cancer. The reduction of prostate cancer was relative to the incidence in a control group in which biopsy was recommended for all men, regardless of risk factors, says **Peter T. Scardino**, MD, chairman of the Department of Urology at Memorial Sloan-Kettering Cancer Center in New York City.

In addition, the study results suggest that finasteride may accelerate the growth of high-grade cancers, which may pose a threat to life and health if they are not treated successfully, he continues. The effects of finasteride on sexual function also lessen the attractiveness of the drug as a preventive agent.

In the editorial, Scardino suggests that future studies explore whether finasteride would be more effective if it were given earlier in the course of prostate cancer. ■

Omeprazole (Prilosec) approved for OTC heartburn treatment

The U.S. Food and Drug Administration (FDA) has approved the proton pump inhibitor omeprazole (Prilosec) for sale over-the-counter (OTC) to treat frequent heartburn.

Unlike the two classes of currently marketed over-the-counter heartburn treatments, antacids and acid reducers, omeprazole OTC is indicated for the treatment of heartburn that occurs two or more days per week (frequent heartburn).

Prilosec OTC is a delayed-release 20 mg tablet that must be taken before eating once a day, every day for 14 days. Prilosec OTC may take one to four days to achieve full effect, although some consumers may get complete relief of symptoms within 24 hours.

Prilosec OTC is being brought to the over-the-counter market through an alliance between The Procter & Gamble Co. and AstraZeneca.

AstraZeneca will continue to make prescription omeprazole and its other acid inhibitor, esomeprazole magnesium (Nexium). Prescription omeprazole, first approved by the FDA in 1989, still will be available as a prescription treatment for diseases that require diagnosis and supervision by a doctor, such as gastroesophageal reflux disease, inflammation of the esophagus (esophagitis), and ulcers.

Because of the safety studies performed by the manufacturer of Prilosec OTC, this product will have three years of OTC exclusivity. Generic versions of the prescription product will not be able to market an OTC version until the marketing exclusivity has expired. ▼

Recall includes all repacked atorvastatin products

The FDA has announced that its continuing investigation of counterfeit atorvastatin calcium (Lipitor) has resulted in Albers Medical Distributors, of Kansas City, MO, expanding its recall to include all Lipitor products repacked by Med-Pro, of Lexington, NE. In addition, H.D. Smith Wholesale Drug Co., of Springfield, IL, has recalled all Lipitor products repacked by Med-Pro.

The FDA also announced that its Forensic Chemistry Center in Cincinnati has determined that the counterfeit tablets that have been tested as of this date contain atorvastatin. The Forensic Chemistry Center's analysis to date has not identified any known harmful substances in the counterfeit tablets, although analytical testing continues.

Despite these results, FDA cannot assure that the counterfeit products are safe and effective. Individual tablets of this counterfeit medicine may vary significantly, even within individual lots, because the source of the atorvastatin is unknown and because there is no evidence that the tablets have been produced according to good manufacturing practices that are meant to ensure consistency from batch to batch.

Consequently, FDA's advice to health care providers and consumers remains the same as when the agency issued its original alert on counterfeit Lipitor on May 23, 2003. Patients who have any of the product labeled as "Repackaged by: MED-PRO Inc.; Lexington, NE 68850" should not take it, and they should return the product to their pharmacy. Patients who are not sure whether they have the recalled product should check with their pharmacist. ▼

Paroxetine (Paxil) should not be used in children

The FDA is reviewing reports of a possible increased risk of suicidal thinking and suicide attempts in children and adolescents younger than age 18 treated with the drug paroxetine (Paxil) for major depressive disorder (MDD). Although the FDA has not completed its evaluation of the new safety data, FDA is recommending that paroxetine not be used in children and adolescents for the treatment of MDD. There currently is no evidence that paroxetine is effective in children or adolescents with MDD, and paroxetine is not currently approved for use in children and adolescents. Other approved treatment options are available for depression in children.

Three well-controlled trials in pediatric patients with MDD failed to show that the drug was more effective than placebo. The new safety information that currently is under review was derived from trials of paroxetine in pediatric patients.

The FDA advises that caretakers of pediatric patients already receiving treatment with paroxetine for MDD to talk to their doctor before stopping use of the drug. Patients should not discontinue use of paroxetine without first consulting their physicians, and it is important that paroxetine not be discontinued abruptly. ▼

FDA announces pilot program to post warning letter responses

The FDA has announced that it will begin a pilot program to post recipients' responses to FDA warning letters on the agency's web site.

In compliance with the Electronic Freedom of Information Act Amendments, the FDA posts on its web site warning letters that are or are likely to be frequently requested documents under the Freedom of Information Act (FOIA). However, the FDA does not post recipients' written responses to warning letters. Under the pilot program, which will begin in the fall and continue for six months, warning letter recipients who wish to have their responses made public will be able to request that the agency do so.

Responses submitted to the FDA with a request that they be posted and in a word processing format will be considered for the pilot program. After six months, the FDA will evaluate the pilot and determine whether the program should become permanent.

If during the pilot program the agency determines that the public is being misled, experiences undue burden in dealing with the process, or finds that the process is too resource-intensive, the FDA may discontinue the program.

The pilot program is a partial response to a 1999 citizen's petition, which asked the agency to draft regulatory procedures that would require the agency to promptly post, to the extent permitted under FOIA, agency records related to any previously posted warning letters. ■

New FDA Approvals

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

• *Tositumomab and Iodine I 131 Tositumomab (Bexxar) by Corixa and GlaxoSmithKline*. The FDA has approved tositumomab and iodine I 131 tositumomab (Bexxar) for the treatment of patients with CD20-positive, follicular, non-Hodgkin's lymphoma (NHL), with and without transformation, and whose disease is refractory to rituximab and has relapsed following chemotherapy.

Tositumomab and iodine I 131 tositumomab is a dual-action therapy that pairs the tumor-targeting ability of a cytotoxic monoclonal antibody (tositumomab) and the therapeutic potential of radiation (Iodine-131) with patient-specific dosing.

Combined, these agents form a radiolabeled monoclonal antibody (Iodine I 131 Tositumomab) that is able to bind to the target antigen CD20 found on NHL cells, thereby initiating an immune response against the cancer and delivering a dose of radiation directly to tumor cells.

The efficacy of the therapeutic regimen was examined in a multicenter, single-arm study of 40 patients with follicular NHL whose disease had relapsed following or had not responded to treatment with rituximab. (The therapeutic regimen consists of four components administered in two steps over seven to 14 days, usually on an outpatient basis.)

In patients with rituximab-refractory disease, 63% of patients had a response to tositumomab and iodine I 131 tositumomab, with a median duration of response of 25 months. Twenty-nine percent of patients had a complete response (no clinical signs of disease) to the therapy. The median duration of complete responses has not been reached after a median follow-up of 26 months.

The results of this study were supported by demonstration of durable objective responses in four other single-arm studies enrolling 190 patients with rituximab-naive, follicular NHL, with or without transformation, who had relapsed following or were refractory to chemotherapy. In these studies, the overall response rates ranged from 47% to 64% and the median durations of response ranged from 12 to 18 months.

The most common adverse reactions occurring in the clinical trials included neutropenia, thrombocytopenia, and anemia that can be both prolonged and severe. The most common nonhematologic side effects included asthenia (weakness), fever, nausea, infection, and cough.

• *Omalizumab (Xolair) by Genentech*. The FDA has approved the first biotechnology product to treat patients with a type of asthma that is related to allergies.

The product, omalizumab (Xolair), is a monoclonal antibody that has been shown to be safe and effective to treat people 12 years of age and older with moderate-to-severe allergy-related asthma inadequately controlled with inhaled steroid treatments. (The product's labeling states that this type of asthma should be established by skin or blood test before treatment.)

In these patients, omalizumab has been shown to decrease the number of asthma exacerbations or episodes of airway narrowing that result in wheezing, breathlessness, and cough. The product is given as an injection under the skin.

During the clinical trials, more patients treated with omalizumab developed a new or recurrent cancer (0.5%) compared to control patients (0.2%). The sponsor is planning long-term studies in an attempt to determine whether there is a relationship between omalizumab treatment and cancer. The other major safety concern with omalizumab identified in the clinical trials was severe allergic reactions or anaphylaxis. Anaphylaxis occurred in three patients; all responded to and recovered following medical treatment.

• *Atazanavir sulfate (Reyataz) by Bristol-Myers Squibb Co.* The FDA has approved atazanavir sulfate (Reyataz), a protease inhibitor to be used in combination with other antiretroviral agents for

COMING IN FUTURE MONTHS

- Fight over prescription drug program continues
- Zoledronic acid (Zometa) drug evaluation
- A look at off-label drug use
- ASHP strives to improve pharmacy practice
- Drug treatment of post-traumatic stress disorder

the treatment of patients with HIV infection. Approval of this drug will now allow patients access to a protease inhibitor that only needs to be taken once daily with food and has a low "pill burden" (two pills each day).

A significant safety concern commonly observed with the use of protease inhibitors is hyperlipidemia (high cholesterol). Atazanavir sulfate appears to have minimal impact on lipid parameters such as triglycerides and cholesterol.

The most common laboratory abnormality observed with the use of atazanavir sulfate is hyperbilirubinemia. This laboratory abnormality resulted in the clinical adverse event of jaundice (yellowing of the skin) or scleral icterus (yellowing of the eyes) in 15%-24% of subjects taking atazanavir sulfate.

This abnormality was shown to be reversible upon discontinuation of the drug. Hyperbilirubinemia with atazanavir sulfate did not appear to be associated with an increased risk of liver injury.

The most frequently reported adverse events among patients in the clinical trials were nausea, infection, headache, vomiting, diarrhea, abdominal pain, somnolence (drowsiness), insomnia, and fever.

• *Influenza Virus Vaccine Live, Intranasal (FluMist) by MedImmune Vaccines.* The FDA has approved the first nasally administered influenza vaccine to be marketed in the United States. It also is the first live virus influenza vaccine approved in the country.

FluMist is approved to prevent influenza illness due to influenza A and B viruses in healthy children and adolescents, ages 5 to 17 years, and healthy adults, ages 18-49. Children 5 to 8 years old need two doses at least six weeks apart in their first year of influenza vaccination with FluMist, and individuals 9 to 49 years old need one dose.

Each dose of FluMist is formulated to contain each of the three influenza virus strains recommended by the U.S. Public Health Service for the 2003-2004 influenza season: two strains of influenza A, which causes the most severe and widespread outbreaks, and one strain of B, which usually causes a more mild illness.

In a large safety study, children younger than age 5 were found to have an increased rate of asthma and wheezing within 42 days of vaccination compared to placebo recipients. For people age 50 years and older, the safe and effective use of FluMist also has not been established.

The most common adverse events associated with the vaccine were nasal congestion, runny nose, sore throat, and cough.

• *Copackaged pravastatin sodium and buffered aspirin tablets (Pravigard PAC) by Bristol-Myers Squibb Co.* The FDA has approved copackaged pravastatin sodium and buffered aspirin tablets (Pravigard PAC) for use when treatment with both pravastatin (Pravachol) and buffered aspirin is appropriate. This copackaged product may be more convenient for some patients.

Pravastatin and buffered aspirin are both indicated to reduce the occurrence of cardiovascular events, including death, myocardial infarction, or stroke, in patients who have clinical evidence of cardiovascular and / or cerebrovascular disease. Patients receiving treatment with the copackage also should be placed on a standard cholesterol-lowering diet.

The usual dose of Pravigard PAC is one aspirin tablet with one Pravachol tablet once a day. Pravigard PAC is available in cartons containing 30 buffered aspirin (either 81 mg or 325 mg) tablets packed with 30 Pravachol (either 20 mg, 40 mg, or 80 mg) tablets. ■

DRUG CRITERIA & OUTCOMES™

Almotriptan Formulary Evaluation

By **Melissa Headrick**, PharmD
Written while on clinical rotation at Huntsville (AL) Hospital,
Harrison School of Pharmacy at Auburn (AL) University

Triptans

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

Description

Almotriptan malate (Axert) a selective 5-hydroxytryptamine$_{1B/1D}$ (5-HT$_{1B/1D}$) receptor agonist, otherwise known as a "triptan," was approved by the U.S. Food and Drug Administration (FDA) in May 2001. Almotriptan is indicated for the acute treatment of migraine with or without aura in adults 18 years of age or older.

Mechanism of action

Almotriptan, like the other triptans, binds with high affinity to 5-HT$_{1B/1D}$ receptors on the extracerebral, intracrancial blood vessels that become dilated during a migraine attack. Activation of these receptors results in cranial vessel constriction, inhibition of neuropeptide release, and reduced

transmission in trigeminal pain pathways.

Pharmacokinetics

Almotriptan has the highest oral bioavailability of all the current triptans. This drug undergoes metabolism in the liver to inactive metabolites. The remaining pharmacokinetic parameters of almotriptan and the triptans currently on the Huntsville Hospital formulary are shown in **Table 1, p. 1.**

Clinical studies

Efficacy

Efficacy of almotriptan was based on three multicenter, randomized, double-blind, placebo-controlled trials conducted in Europe. Patients enrolled in study one were mostly female (85.3%) with a mean age of 40.5 years.

Study one

Patients were asked to treat a moderate-to-severe migraine headache with placebo, almotriptan 6.25 mg, or almotriptan 12.5 mg.

The percentage of patients achieving a response two hours after treatment was significantly greater in patients who received almotriptan 6.25 mg or 12.5 mg, compared to those patients who received placebo. A higher percentage of patients reported pain relief after taking the 12.5 mg dose than with the 6.25 mg dose, but statistical significance was not assessed (no P value reported).

Another endpoint was pain relief at measured time intervals. Almotriptan 6.25 mg was significantly superior in providing pain relief at hour 1, 1.5, and 2 as compared to placebo. This dose also showed significant pain freedom as compared to placebo at two hours after treatment initiation. Almotriptan 12.5 mg was significantly superior to placebo on all four measured time intervals. Patients who received this dose also had significantly better pain freedom compared to placebo at hour 1, 1.5, and 2 after treatment initiation. Patients in the almotriptan 6.25 mg group had significantly less migraine-associated symptoms (nausea, vomiting, photophobia, and phonophobia) at two hours compared to placebo.

Almotriptan 12.5 mg showed significantly less photophobia and phonophobia only. The results for study one are shown in **Table 2, above**.

Study two

Patients enrolled in study two were mostly female (86.5%) with a mean age of 42.1 years. Patients were asked to take almotriptan 12.5 mg or sumatriptan 100 mg for moderate or severe migraine pain. Patients who received almotriptan and sumatriptan showed a significantly better response two hours after treatment as compared to placebo. Patients in the almotriptan group had significantly more pain relief and pain freedom at two hours as compared to placebo (see Table 3). Sumatriptan and almotriptan response rates were not statistically compared. Almotriptan-treated patients showed significantly less migraine-associated symptoms two hours after treatment initiation. Sumatriptan significantly decreased nausea, photophobia, and phonophobia only. Equipotent doses of almotriptan and sumatriptan were not used in this study.

Study three

The population for study three was similar to the previous two studies (85.6% female with mean age

of 40.6 years). Patients were asked to take almotriptan 6.25 mg or 12.5 mg for moderate or severe migraine pain. This study showed similar results as the two previous studies.

Both almotriptan 6.25 mg and 12.5 mg showed significantly better response rates two hours after treatment as compared to placebo, with the 12.5 mg dose showing higher response rates than the 6.25 mg dose. Both study groups also showed significantly better pain relief and pain freedom at hours 1.5 and 2 as compared to placebo. Patients in both active treatment groups had significantly less nausea, photophobia, and phonophobia two hours after treatment initiation. Results from this study are summarized in **Table 4, below.**

All almotriptan groups demonstrated significantly higher response rates than placebo in the three studies. Also, a higher percentage of patients reported pain relief after treatment with the 12.5 mg dose than with the 6.25 mg dose. The results from these trials with almotriptan doses higher than 12.5 mg are reported not to be significantly superior to this dose, but specific data are not available. Overall, the incidence of migraine-associated photophobia, phonophobia, nausea, and vomiting decreased in the almotriptan groups compared with the placebo group.

Meta-analysis

A meta-analysis of four double-blind, placebo-controlled clinical trials was reported in an abstract. A total of 2,294 patients were included. Patients taking almotriptan showed greater pain relief and pain freedom compared to placebo. The results of the meta-analysis are shown in **Table 5, p. 4.**

The pooling of results for this meta-analysis could lead to bias because nonsignificant findings may not have been included. Specific patient data are not available to evaluate, which is another weakness.

Comparative efficacy

A single pre-release study that was performed to assess the efficacy of almotriptan also compared

almotriptan to sumatriptan. The results are shown in the previous tables. As illustrated in Table 3, 57.1% of patients on almotriptan 12.5 mg tablets had pain relief after taking the drug, as compared to 63.2% of patients who took sumatriptan 100 mg. This difference was not statistically significant.

The only post-release published trial that compares almotriptan to another member of the triptan class is a randomized, double-blind, parallel-group, optimum-dose comparison of almotriptan versus sumatriptan conducted by Spierings, et al. This study included 1,173 patients with a history of migraine headaches with or without aura. The results of the two study medications' ability to produce headache relief (defined as a decrease in pain intensity from moderate or severe at baseline to mild or no pain at the time of post-baseline assessment) and headache freedom (defined as a decrease in pain intensity from moderate or severe at baseline to no pain at the time of post-baseline assessment) are summarized in **Table 6, below.**

The difference between the two study medications' ability to reduce migraine-associated symptoms (nausea, vomiting, photophobia, and phonophobia) was not statistically significant. Of the responders in the almotriptan-treated group, 27.4% had recurrence of moderate or severe migraine headache within 24 hours, as compared with 24.0% of patients in the sumatriptan-treated group. This difference was not statistically significant. A slightly greater percentage of patients in the almotriptan group required escape medication a well.

Treatment-emergent adverse events occurred in 15.2% of patients in the almotriptan group and 19.4% of patients in the sumatriptan group. This difference was not statistically significant. The authors of this trial concluded that almotriptan is similarly effective as compared to sumatriptan in the abortive treatment of moderate or severe migraines.

The study also concluded that almotriptan showed similar tolerability and safety. Patient randomization was not fully explained in the article, which is a possible weakness.

Percent of patients who experienced headache relief and freedom

Indications and dosing

The only FDA-approved indication for almotriptan is the acute treatment of migraine with or without aura in adults. This is the same indication that the other triptans have, except subcutaneous sumatriptan also is indicated for the treatment of cluster headache episodes.

The choice to administer the 6.25 mg dose or the 12.5 mg dose to adults with acute migraine should be made on an individual basis; however, in clinical studies, the 12.5 mg dose showed a greater increase in response rates. If the headache returns, the dose may be repeated after two hours, but should not exceed two doses (25 mg) in 24 hours.

Hepatic impairment: Pharmacokinetics have not

been studied in this population. The decrease expected in the clearance of almotriptan in this population is 60%. Therefore, the starting dose of 6.25 mg should be used, and the maximum daily dose should not exceed 12.5 mg over a 24-hour period.

Renal impairment: The starting dose for this population is 6.25 mg. The maximum daily dose should not exceed 12.5 mg over a 24-hour period.

Adverse events

Incidence of adverse events in controlled clinical trials (reported in at least 1% of patients treated with almotriptan and at an incidence greater than placebo) is listed in **Table 7, above.** The numbers are the percentage of people reporting the event (as reported in the package insert).

Adverse events

Table 8, below, compares the adverse effects of the current triptans in the Huntsville Hospital formulary interchange program, including almotriptan. Reported adverse effects are similar among the five drugs. A complete list of adverse events can be found in the package insert.

Adverse effects of five triptans in the Huntsville Hospital formulary interchange program

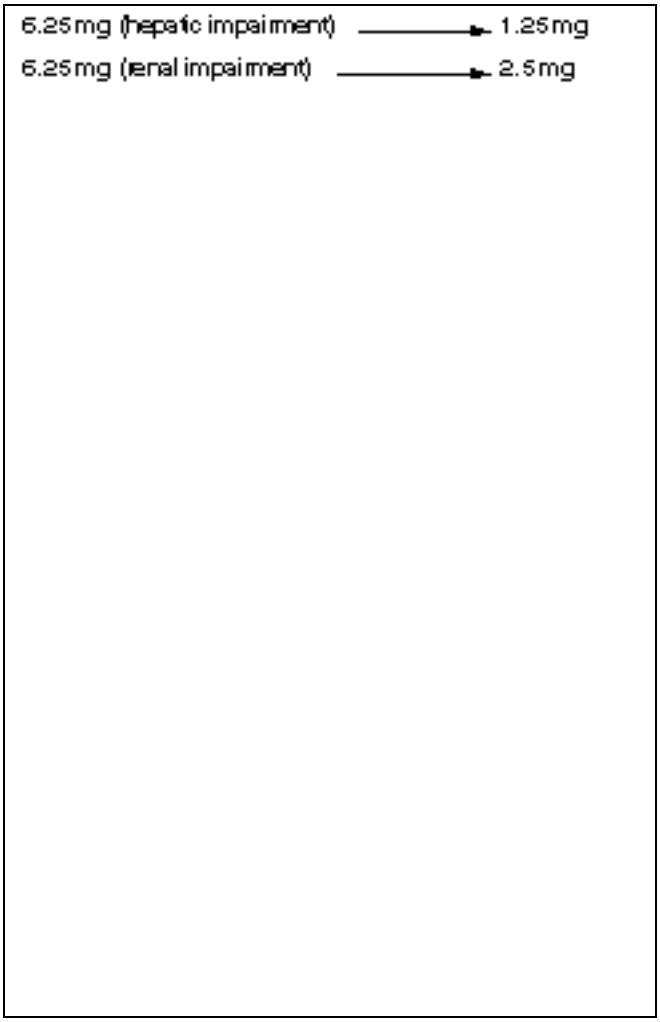
The manufacturer of almotriptan has focused on the decreased incidence of chest pain associated with almotriptan as compared to sumatriptan. In the previously mentioned study by Spierings et al., with patients randomized to either almotriptan 12.5 mg or sumatriptan 50 mg, treatment-emergent adverse events that involve the cardiovascular system were evaluated. The occurrence of these adverse events was low in both treatment groups.

No P values were reported for this information. Symptoms of chest pain also were specifically reported in this study in both treatment groups. The difference between the two groups for chest pain was significantly less for the almotriptan group (almotriptan 12.5 mg: 0.3% vs. sumatriptan 50 mg: 2.2%, P = 0.004); however, almotriptan is

contraindicated in patients with any type of ischemic heart disease, as are the other triptans.

Contraindications

Almotriptan shares several contraindications with other triptans, such as its use in ischemic heart disease, concurrent ergotamine use, and concurrent serotonin agonist use **(see Table 9, above)**; however, its use is not contraindicated with concomitant MAO inhibitors.



Contraindications of triptans (Almotriptan + Huntsville Hospital Formulary Exchange Drugs

Drug interactions

Drug-drug interactions involving the triptans are summarized in **Table 10, p. 6.**

Cost/usage

Current cost of almotriptan to the hospital is approximately 25% less than the current formulary triptan zolmitriptan. Almotriptan's hospital usage has been low up to this time. (The main usage of this drug class is for employee outpatient prescriptions.)

Summary and recommendations

Almotriptan's pharmacokinetic profile does not differ to a great extent from the other triptans currently in the formulary interchange program. There are no controlled trials that directly compare almotriptan to the current workhorse triptan zolmitriptan. However, there are several trials that compare almotriptan to sumatriptan, to which both drugs showed similar efficacy and safety.

Almotriptan 6.25 mg and 12.5 mg tablets currently are less expensive to purchase than zolmitriptan 2.5 mg and 5 mg. Almotriptan use at Huntsville Hospital has up to now been extremely low. Also, the majority of zolmitriptan that has been dispensed was for outpatient use (from the pharmacy for hospital employees) and does not reflect use in actual hospital inpatients.

Because almotriptan is a newly released drug, and there has been little experience with it at Huntsville Hospital, almotriptan should be added to the current triptan formulary interchange program **(see Table 11, left)**. Until additional outpatient experience with almotriptan is gained, zolmitriptan should remain the triptan workhorse drug.

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IN THE PIPELINE

• Connetics Corp. has completed enrollment in its Phase III clinical trial for Actiza, a formulation of 1% clindamycin delivered in Connetics' proprietary foam delivery system, for the treatment of **acne**.

• Adolor Corp. has completed enrollment in its Phase III clinical trial studying the use of the company's product candidate, alvimopan, for the management of **postoperative ileus**.

• Medarex has initiated a Phase I clinical trial of MDX-010, a fully human anti-CTLA-4 antibody, for patients infected with **HIV**, the causative agent of AIDS.

• SuperGen has announced that a Phase II clinical study of the investigational anticancer agent decitabine (Dacogen) for injection, in combination with imatinib mesylate (Gleevec) capsules, has been initiated in patients with **chronic myelogenous leukemia**.

• Therapeutics has received fast track designation from the U.S. Food and Drug Administration (FDA) for CT-2103 (Xyotax), its polyglutamate paclitaxel, for the treatment of advanced **nonsmall cell lung cancer** in patients with a poor performance status.

• Exelixis has initiated the Phase I first-in-man safety trial for its proprietary small molecule **anticancer** compound XL784.

• Titan Pharmaceuticals has initiated clinical testing of Probuphine, a novel treatment for **opiate addiction**. Probuphine is a proprietary product in development by Titan that delivers buprenorphine, an approved opiate addiction treatment, for an extended period.

• Nuvelo has commenced dosing in a Phase II trial with its lead product candidate, alfimeprase, for the treatment of **acute peripheral arterial occlusion**.

• Myriad Genetics has opened enrollment for patients in its Phase II trial of its drug, R-flurbiprofen (MPC-7869), in the treatment of mild-to-moderate **Alzheimer's disease**.

• Immtech International has initiated patient enrollment of an expanded Phase IIa human clinical trial of its oral drug candidate DB289 to treat **malaria**.

• Millennium has initiated a Phase II clinical trial with bortezomib (Velcade) for injection in patients with **relapsed** or **refractory mantle cell lymphoma**.

• Aton Pharma has begun enrollment in a Phase I clinical trial of SAHA, an inhibitor of histone deacetylase, in patients with **advanced leukemias**.

• Celgene Corp. has initiated a clinical trial of dexmethylphenidate hydrochloride extended-release capsules (Focalin) LA in adults with **attention deficit disorder/attention deficit hyperactivity disorder.**

• Pharmos Corp. has begun U.S. enrollment in its Phase III study of dexanabinol for **traumatic brain injury**.

• Millennium Pharmaceuticals and Xenova Group, plc have initiated a Phase I clinical trial of MLN944 (also known as XR5944), a novel DNA-targeting agent under investigation for the treatment of **advanced cancers**.

• Pain Therapeutics has initiated a Phase III clinical study with Oxytrex, the company's investigational new drug to treat **chronic, severe low-back pain**.

• Pharmaceuticals has initiated a multicenter, randomized, controlled Phase IIb clinical trial with its anticancer drug Pivanex in the treatment of advanced **nonsmall cell lung cancer**. The study will evaluate the safety and efficacy of Pivanex plus docetaxel, vs. docetaxel alone.

• SuperGen and Cancer Research UK have initiated a Phase I/II clinical study of decitabine (Dacogen), in combination with carboplatin, in cancer patients with **advanced solid tumors**.

• Genta has announced that the FDA has designated oblimersen sodium (Genasense) as a fast track product for the treatment of patients with **chronic lymphocytic leukemia**.

• AtheroGenics has begun enrollment of patients in its ARISE Phase III clinical trial of AGI-1067, an oral anti-inflammatory agent targeting **atherosclerosis**. ■