DRUG UTILIZATION REVIEW
Pharmaceutical Care Across the Continuum

THOMSON
AMERICAN HEALTH CONSULTANTS

IN THIS ISSUE

SEPTEMBER 2003
VOL. 19, NO. 9 • (pages 65-72)

ASHP moves into the next phase of its 2015 Initiative

Process becomes more complex as member comments are incorporated

The future of pharmacy practice has become a focus for one pharmacy group, and the reaction from members has been favorable and enthusiastic.

The American Society of Health-System Pharmacists (ASHP) in Bethesda, MD, launched its 2015 Initiative earlier this year. The initiative is composed of goals and objectives for pharmacy practice in health systems that are to be achieved by 2015.

The beginning of the project dates back to June 2001, when the ASHP House of Delegates approved a Vision Statement for Pharmacy Practice in Hospitals and Health Systems.

"The important thing about that vision statement is that is was about what practice ought to be like," says **Charles E. Myers**, MS, MBA, group vice president for professional development and member services.

Then attention was drawn to a project of the Department of Health and Human Services' Office of Disease Prevention and Health Promotion (ODPHP). "Healthy People 2010" is a statement of national health objectives designed to identify the most significant preventable threats to health and to establish national goals to reduce these threats. In the development of these objectives, ODPHP decided:

- There are overarching goals.
- There are specific objectives related to those goals.
- There are measurable targets for each objective.

At first, ASHP hadn't thought about creating something such as a 2010 Healthy People (HP) initiative, Myers says. Then as an afterthought, the society decided to give it a try. "We believed we could identify some key goals and objectives that if achieved, would make a substantial difference in terms of patient care in this country."

In a statement about the 2015 Initiative, ASHP says it believes that some well-chosen goals and objectives and demonstrable progress in achieving them over time would speak powerfully about health system pharmacy practitioners' commitment to high-quality patient care and

their collective, national resolve to improve medication use throughout health systems.

The first stage of the initiative involved developing draft goals and objectives. Using the HP process as a model, the ASHP board of directors, with input from state society leaders, drafted possible goals and objectives. During this process, the board of directors and members tried to ensure that:

- Each objective has a plausibly high relationship to practice advancement and achieving the ASHP vision for practice.
- Each objective can be evaluated using quantifiable data.
- There is confidence that progress related to each objective can be measured.
- The number of goals and objectives are manageable.
- Members should feel that, if they work to achieve the goals and objectives, the level of health system pharmacy practice would be advanced.

Drug Utilization Review™ (ISSN# 0884-8521), including **Drug Criteria & Outcomes**™, is published monthly by Thomson American Health Consultants, 3525 Piedmont Road, Building Six, Suite 400, Atlanta, GA 30305. Telephone: (404) 262-7436. Periodical postage paid at Atlanta, GA 30304. POSTMASTER: Send address changes to **Drug Utilization Review**™, P.O. Box 740059, Atlanta, GA 30374.

Subscriber Information

Customer Service: (800) 688-2421 or fax (800) 284-3291, (customerservice@ahcpub.com) **Hours of operation:** 8:30 a.m.-6 p.m. Monday-Thursday; 8:30 a.m.-4:30 p.m. Friday.

Subscription rates: One year (12 issues), $479. Outside U.S., add $30 per year, total prepaid in U.S. funds. Two to nine additional copies, $383 per year; 10 to 20 additional copies, $287 per year. For more than 20 copies, contact customer service at (800) 688-2421. Missing issues will be fulfilled by customer service free of charge when contacted within one month of the missing issue date. **Back issues**, when available, are $80 each. (GST registration number R128870672.)

Editorial Questions

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

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

The goals and objectives dealt with the four main themes in the vision statement: making medication use effective, making it safe, making it scientific, and contributing meaningfully to public health. The draft was published May 2, and members were asked to submit comments and suggestions on it by July 15. **(To see a list of the goals in the draft, see p. 67.)**

ASHP received numerous responses to the draft goals and objectives, Myers says. Everyone seems pleased about the initiative, he adds, and many members have submitted suggestions about the language or the order of the objectives.

Specifically, some members have appreciated goals and objectives that include attention to nonhospital practice. For example, Goal 2 refers to the aid that pharmacists can give nonhospitalized patients to help them achieve the best use of medicines.

ASHP also had suggestions that Goal 3, which aims to increase the extent to which health system pharmacists actively apply evidence-based methods to the improvement of drug therapy, and some of its objectives should be expanded.

Some members said they didn't know how to react to a goal or objective because they didn't know how a term was being defined. ASHP had considered this, Myers says, but thought that the initial draft would be too long if the terms were defined.

Defining the terms will come about in the surveying stage, in which ASHP will construct survey language for ongoing monitoring of the eventual goals and objectives. At this stage, ASHP will have to be meticulous about its definitions, Myers says. Every objective may require multiple questions to get to the heart of what needs to be assessed.

ASHP also says that some of the monitoring will be incorporated into ongoing ASHP surveys. In addition, baseline numbers for most of the objectives will have to be developed.

Member comments have reinforced the idea that people will want the project to be much more specific. "We recognize there are many details," Myers says. We'll have to be way more complex than the simple goals and objectives themselves."

ASHP expects much of the detail to be found in progress reports about the initiative. This has been the case in the HP 2010 project, he says. "If you look at the progress reports, it comes down to not just a simple comment of yes or no. It has a lot of details."

Myers now is in the process of factoring the

Goals of the 2015 Initiative

The American Society of Health-System Pharmacists (ASHP) in Bethesda, MD, released in May a draft of the goals and objectives for pharmacy practice in health systems to be achieved by 2015. For a complete list of the six initial goals and their 25 objectives, visit the ASHP web site, www.ashp.org, and look under the "2015 Initiative" section under the "Highlights" heading in the Member Center.

- **Goal 1.** Increase the extent to which pharmacists help individual hospital inpatients achieve the best use of medicines.
- **Goal 2.** Increase the extent to which health system pharmacists help individual nonhospitalized patients achieve the best use of medicines.
- **Goal 3.** Increase the extent to which health system pharmacists actively apply evidence-based methods to the improvement of drug therapy.
- **Goal 4.** Increase the extent to which pharmacy departments in health systems have a significant role in improving the safety of medication use.
- **Goal 5.** Increase the extent to which health systems apply technology effectively to improve the safety of medication use.
- **Goal 6.** Increase the extent to which pharmacy departments in health systems engage in public health initiatives on behalf of their communities. ■

member comments into the next draft. He expects it will be completed sometime this fall. The new draft will be posted on AHSP's web site. ■

Clinical judgment, standard of care is key

Minimize risk in off-label prescribing

Off-label use of a drug is common in health care, but pharmacists agree that they must minimize the risk by relying on their clinical judgment and the standard of care.

"Off-label use" means ordering or prescribing a drug to treat a condition for which it has not received review and approval by the U.S. Food and Drug Administration (FDA). It also applies to drugs prescribed, or ordered, for a different population group, such as children instead of adults, or at a different dose or duration than what was reviewed and approved by the FDA, and subsequently, a different (than what was deemed by the FDA to have a favorable risk-benefit ratio) population or subgroup, according to FDA regulations.

Since the FDA considers the off-label prescribing of drugs a practice of medicine, pharmacists must protect patients and themselves in the review of such use. To do this, pharmacists usually rely on their clinical judgment and the standard of care, says **Brian Hemstreet**, PharmD, BCPS, assistant professor at the Department of Clinical Pharmacy at the University of Colorado Health Sciences Center in Denver.

Sometimes the assumption is made that for a certain indication approved by the FDA for one drug, every drug in that class will be effective for that indication. That is not always the case, though, Hemstreet says. "Sometimes, there are significant enough differences within the class of drugs that you may not get exactly the same effect as you would with the one with the indication."

To make that determination, therefore, he recommends first looking at the literature. If the literature about the off-label use is sparse, Hemstreet then compares the pharmacology of the drug. "If it looks fairly similar, you can be pretty sure that it is going to have the same effect."

The pharmacokinetic properties, however, may be different. The dosage may need to vary from the approved indication, too. The patient also may have enhanced effects for the off-label use.

"Once you go off-label, you have to use your clinical judgment as to whether the patient population you are treating for that indication is going to put the patient at any more risk for an adverse event based on the experience in the labeled indications," Hemstreet says.

The risk decreases as most physicians use the drug for the off-label indication, even if the drug manufacturer has never gotten the drug approved for that use.

"Sometimes things start getting to be standard of care, and there is not really an incentive for the pharmaceutical company to do the research and the controlled clinical trials that would be required to get something approved," says **Marissa Schlaifer**, RPh, director of pharmacy affairs for the Academy of Managed Care Pharmacy (AMCP) in Alexandria, VA.

The off-label use of medications is more prominent in certain patient populations, such as pediatrics. "Many drugs are used in pediatrics without an FDA indication. Insurance carriers and the medical community recognize that," says **Tim Stacy**, RPh, MBA, system director of pharmacy at

Children's Healthcare of Atlanta.

In pediatrics, you rely on history, and the standards of care in the pediatric community, Stacy says. Lexi-Comp's *Pediatric Dosage Handbook* is a primary resource. "On order entry, the pharmacist has to check all doses. Our new computer system will have those built in so we will have the dosage system linked eventually to our standards."

MCOs follow structured program

Managed care organizations (MCOs) differ from some health organizations in that they follow a structured program when reviewing a drug for off-label use. As AMCP says in its position statement about off-label drug use, "each pharmaceutical agent on the market should be used only in accordance with generally accepted medical practices."

The review process depends upon the situation, says Schlaifer. An older, inexpensive drug that has a common off-label use, for instance, may be covered without a review. An example of this would be the use of the propranolol, a hypertensive drug often used off-label to treat migraines.

A newer drug prescribed for a use that hasn't gone through a full review process, however, would be flagged with an edit in the system before the prescription could be filled. Generally, if this is a one-time occurrence, prior authorization pharmacists will handle the review, Schlaifer says. "They are basically looking for whether the off-label use is considered standard of care. If they can look in the literature and find out this is a common, well-accepted use of the medication, they are going to approve it."

If literature is not available to support the off-label use or more commonly, if the literature says the off-label use has shown no benefit to the patient, the MCO might not cover the drug for that use.

A lack of literature supporting an off-label use, however, does not guarantee that the drug won't be covered. Physicians, for example, may begin telling an MCO that a drug is being used more often in a certain off-label use — with benefit to the patient. For this review, the MCO can present the information to the pharmacy and therapeutics (P&T) committee. If the drug is in a specialized area, such as in cancer or AIDS treatment, a panel of physicians in that specialty may first review the information and make a recommendation to the P&T committee. "If there is any disagreement or any gray area where maybe current practice has gotten ahead of the literature, then the review would generally go to a committee," Schlaifer says.

AMCP says that it supports MCOs in its consideration of these criteria before deciding whether to provide coverage of FDA-approved drugs for certain off-label uses:

- Whether the drug has been proven effective and accepted for the treatment of the specific medical condition for which it has been prescribed according to the current edition of the *United States Pharmacopeia Dispensing Information, Volume I*, or the American Hospital Formulary Service *Drug Information* compendium.
- Whether the drug is recommended for the particular condition involved, and has been proven to be safe and effective for that condition according to formal clinical studies, the results of which have been published in peer-reviewed professional medical journals.

A medication's cost may logically seem to be a deciding factor in whether a drug is reviewed, but Schlaifer says that is not always the case. Oncology physicians, for example, often request — and receive approval for — the off-label use of high-dollar drugs to treat patients with different cancers, she says.

"You use objective criteria and cost is not the deciding factor," Schlaifer says. "It's whether the medication is appropriate and generally accepted and there is literature to support it. Once you have stopped to review it, no matter the cost, you want to know if the literature supports the use." ■

FDA turns up heat on drug counterfeiters

Better education for pharmacists part of plan

The U.S. Food and Drug Administration (FDA) has announced a new initiative to fight drug counterfeiters. As part of the initiative, an internal task force will look into technology and other measures — including better education of pharmacists — to try to stop counterfeit drugs from being distributed with or deliberately substituted for safe and effective drugs.

Although drug counterfeiting is relatively rare in the United States, the amount of such activities has recently increased. The FDA also has reported that counterfeiters now possess a more sophisticated ability to introduce finished dosage counterfeits

into the otherwise legitimate drug distribution channels. The FDA's counterfeit drug investigations have increased to more than 20 per year since 2000, after averaging only about five per year through the late 1990s.

The FDA attributes this increase to a number of factors, including:

• better counterfeiting technology, including improved technology to make labeling, packaging, and products that appear real but are not;

• more organized, more effective criminal groups attracted by financial opportunities; the online sale of prescription drugs by unlicensed pharmacies and/or foreign web sites;

• opportunities for introducing foreign-made counterfeit and unapproved drugs into large and rapidly growing import flows;

• weak spots in the domestic wholesale drug distribution chain, including some wholesalers who acquire most of their inventory from secondary sources, do not maintain effective due diligence efforts on these sources, and ignore warning signs indicative of illegal or unethical behavior.

On the other hand, the scale of worldwide counterfeiting of drugs is much larger. The World Health Organization has estimated that perhaps 7% or 8% of drugs worldwide are counterfeit, and reports from some countries suggest that as much as one-half of their drugs are counterfeit.

The FDA initiative is designed to better identify the risks and threats from counterfeit drugs, to coordinate public and private efforts to fight drug counterfeiting and distribution, and to develop new tools to aid in identifying, deterring, and combating counterfeiting.

The internal FDA task force will be asked to:

• **Develop** a strategic action plan to decrease the risk of counterfeit drugs entering the U.S. marketplace.

• **Continue** to strengthen the FDA's collaborative relationships with other federal agencies, including the Bureau of Immigration and Customs Enforcement, the Bureau of Customs and Border Protection, the U.S. Secret Service in the Department of Homeland Security, and entities within the Department of Justice, as well as with health professionals, industry, consumer, and other stakeholders. These relationships will help the FDA gather information regarding the best practices for dealing with drug counterfeiting.

• **Identify** ways to strengthen the nation's protections against counterfeiting. These could include model practice acts for adoption by the states, best practices for those who sell and distribute prescription drugs, and better education for patients, pharmacists, and others about how to identify counterfeit drugs and alert others to their existence.

• **Assess** the extent to which new technologies, such as counterfeit-resistant packaging, product identifiers, and implanted radio frequency chips in packaging, can help assure the authenticity of drugs.

The task force is scheduled to submit its initial findings and recommendations in September and will issue a final report in four months, after the task force has the opportunity to hear from the public. In addition, the FDA plans to coordinate more closely with other federal agencies and state and local governments that share the responsibilities with the FDA for ensuring the safety of the U.S. drug supply and distribution system, as well as with members of Congress who have worked closely with the FDA in the past on these important public health issues.

After the FDA made its announcement in July, pharmacy groups such as the American Society of Health-System Pharmacists in Bethesda, MD, issued statements saying they supported the initiative and looked forward to providing the agency with helpful information. ■

Pharmacist shortage continues despite lower vacancies

The pharmacist shortage is continuing, although the vacancy rate has decreased from last year, says the results of an annual survey conducted by the American Society of Health-System Pharmacists (ASHP). In addition, more than half of the respondents report an adverse effect of the shortage on pharmacy programs and services. Here are some key findings of the 2003 ASHP Pharmacy Staffing Survey:

• The reported pharmacist vacancy rate was less in 2003 (5.6%) as compared to 2002 (6.9%).

• Technician vacancy rates were lower than pharmacists and down slightly in 2003 (4.3%) as compared to 2002 (4.6%).

• Pharmacist staff are relatively stable in their positions, with turnover at 7.5% in 2003, down

from 8.5% in 2002.

• Small hospitals, especially those with fewer than 100 beds, have bigger staffing challenges with significantly higher pharmacist vacancy and turnover rates as compared to larger hospitals. Institutions of this size comprise 44.1% of all U.S. hospitals.

• Although respondents perceive all pharmacist positions to be in relatively short supply, the percent reporting severe or moderate shortages declined for several positions. Most notably, those perceiving a shortage of entry-level frontline pharmacists declined from 84% to 75% and clinical specialists from 71% to 67%. The percent reporting a shortage of entry-level pharmacy technicians went from 31% to 22%.

• More than half of pharmacy directors reported that pharmacist vacancies have delayed expansion of pharmacy programs and services into new areas and have resulted in reduction of services so that existing staff could be deployed or assigned to cover other areas.

• More than half of pharmacy directors have changed the practice environment in their settings to be more professionally rewarding and have improved scheduling to make their workplace more appealing and improve pharmacist retention.

• A notable number of pharmacy directors perceive that there have been more errors in the pharmacy (38%) and less pharmacist vigilance toward medication safety in the hospital (45%) as a result of pharmacist vacancies.

• More pharmacy directors are expanding the roles and responsibilities of pharmacy technicians as a response to pharmacist vacancies (44%) than the increased use of automation in the pharmacy (31%).

• Forty-two percent are providing signing bonuses to lure staff, with an average amount of $4,789. The average salary increase for pharmacist staff last year was 6.6% (including cost of living, market adjustments, and merit increases).

• The percentage of pharmacy technicians who are Pharmacy Technician Certification Board-certified continues to grow, up to 47% in 2003 as compared to 37% in 2002.

In May, a random sample of ASHP members identified as pharmacy directors were invited by e-mail to take the on-line survey. A total of 578 questionnaires (19% response rate) were completed. ASHP included only nonfederal practice setting questionnaires in this analysis (564 questionnaires). ▼

Scholarship campaign launched to recruit pharmacy teachers

The nation's oldest pharmacy foundation is taking action to attract additional qualified people into careers teaching the next generation of pharmacists.

The American Foundation for Pharmaceutical Education (AFPE) in Rockville, MD, was joined by Sen. Jack Reed (D-RI) and leaders of the pharmacy community as it launched Investing in the Future of Pharmacy Education.

The campaign, which will be financed by a wide variety of corporations, foundations, and individual donors, is expected to raise $12 million to fund scholarships that support students preparing for pharmacy faculty positions and that support new pharmacy faculty pursuing groundbreaking pharmaceutical research.

AFPE's program will award up to 155 annual scholarships to students pursuing pharmacy degrees that qualify them for careers teaching at schools or colleges of pharmacy. AFPE already has raised $3.5 million in contributions toward this scholarship program.

Specifically, the $12 million scholarship program will help AFPE fund up to:

• Thirty $5,000, one-year research project scholarships for pharmacy students who have demonstrated an aptitude for a career in academic pharmacy and research.

• Ninety-five $25,000, three-year, pre-doctoral fellowships for outstanding students at colleges and schools of pharmacy who seek a career in academic pharmacy and who are in their final stages of their PhD coursework and research.

• Thirty $10,000, one-year pharmacy faculty/new investigator grants to help new pharmacy faculty establish their research programs and secure the government or private-sector research grants helpful in securing a tenured faculty position. ▼

Warnings added to topiramate and somatropin

New safety information recently has been added to prescribing information for both topiramate/topiramate capsules (Topamax) and somatropin (rDNA origin) for injection (Genotropin).

The prescribing information for topiramate/

topiramate capsules has been revised to provide updated information about oligohidrosis and hyperthermia, which have been reported in topiramate-treated patients. This updated information is based on clinical trial and post-marketing experience in more than 2 million patients worldwide.

The reports primarily involved children. Most cases have occurred in association with exposure to elevated environmental temperatures and / or vigorous activity, and children should be observed closely under these conditions. In the majority of patients, topiramate therapy has been continued. Proper hydration before and during activities such as exercise or exposure to warm temperatures is recommended.

Pfizer also is advising health care professionals of seven post-marketing reports of fatalities involving the use of somatropin (rDNA origin) for injection in pediatric patients with Prader-Willi syndrome. These patients had one or more of the following risk factors: severe obesity, history of respiratory impairment or sleep apnea, or unidentified respiratory infection. In response, Pfizer is saying that growth hormone is contraindicated in patients with Prader-Willi syndrome who are severely obese or have severe respiratory problems. ▼

ASHP speaks out against market access bill

The American Society of Health-System Pharmacists (ASHP) in Bethesda, MD, "adamantly opposes" legislation passed by the House of Representatives that would allow medications to move freely across U.S. borders without authorization or control by the U.S. Food and Drug Administration (FDA).

The Pharmaceutical Market Access Act of 2003, H.R. 2427, would allow individuals, pharmacists, and wholesalers to import pharmaceuticals with no limits as to the types of drugs allowed or frequency of their importation. Under this legislation, records would not have to be maintained by individuals who import medications, and the drug products would not have to be tested for authenticity or potency.

"Allowing imported drugs to enter the country with the bare minimum in terms of safeguards will create significant safety hazards for patients who cannot know if the medications they are receiving are expired, contaminated, counterfeit, subpotent, or superpotent," says **Henri R. Manasse Jr.**, PhD, ScD, ASHP executive vice president and CEO.

ASHP is strongly urging its members to oppose this legislation. ■

New FDA Approvals

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

• ***New indication for etanercept (Enbrel), which is manufactured by Immunex Corp. and marketed by Amgen and Wyeth Pharmaceuticals.*** The FDA has approved etanercept (Enbrel) — 25 mg twice weekly — for a new indication for treatment of patients with active ankylosing spondylitis (AS).

The FDA's decision follows an expedited review. Etanercept also is licensed for treatment of patients with rheumatoid arthritis, juvenile rheumatoid arthritis, and psoriatic arthritis.

The approved labeling warns physicians about post-marketing reports of serious infections. The labeling says that Enbrel should not be given to patients with any active infection, including chronic or localized infections. It also recommends that patients who develop a new infection while being treated with etanercept should be monitored closely.

Amgen will continue to follow patients in the trial to evaluate the long-term safety of etanercept in patients with AS.

• ***New indication for Somatropin, rDNA origin, for injection (Humatrope) by Eli Lilly Co.*** The FDA has approved somatropin, rDNA origin, for injection (Humatrope), a brand of growth hormone, for the long-term treatment of children

COMING IN FUTURE MONTHS

- Technology tailors drug therapy to patient's genetic makeup
- Rosuvastatin (Crestor) drug evaluation
- Will Congress pass a prescription drug program?
- Drug treatment of post-traumatic stress disorder
- Multitasking in pharmacy practice

with idiopathic (of unknown origin) short stature, also called nongrowth hormone-deficient short stature.

The American Association of Clinical Endocrinologists and the Growth Hormone Research Society have defined "short stature" as height more than two standard deviations (SD) below the mean for age and sex. This corresponds to the shortest 2.3% of children. This new indication restricts therapy to children who are even shorter, specifically more than 2.25 SD below the mean for age and sex, or the shortest 1.2% of children. For example, for 10-year-old boys and girls, this would correspond to heights of less than 4' 1". This would further correspond to heights of less than 5' 3" and 4' 11" in adult men and women, respectively. The new indication for idiopathic short stature is the first indication for growth hormone in children that specifies a height restriction.

The manufacturer says it will limit the marketing for this new indication to pediatric endocrinologists to better ensure the proper use of this product in the indicated pediatric population. In addition, the manufacturer intends to control tightly the distribution of Humatrope.

• ***Porfimer sodium (Photofrin) by Axcan Pharma.*** The FDA has approved porfimer sodium (Photofrin photodynamic therapy) injection for in the ablation of High-Grade Dysplasia in Barrett's Esophagus patients who do not undergo esophagectomy. The drug also was granted orphan drug designation for this indication, which guarantees a seven-year marketing exclusivity.

Side effects of the drug treatment include photosensitivity reactions and esophageal strictures. The labeling includes information on precautions that should be taken to avoid exposure of skin and eyes to bright light.

• ***Antihemophilic Factor (Recombinant), Plasma/Albumin-Free Method (rAHF-PFM) [Advate] by Baxter Healthcare Corp.*** The FDA has licensed a new recombinant DNA-derived clotting factor to treat people with hemophilia A. This new antihemophilic human factor VIII product is the first one produced without using additives derived from human or animal blood in the manufacturing process. The FDA says this advancement provides added reassurance against any theoretical infectious risks that may arise from the use of blood-derived additives in the manufacturing of factor VIII.

rAHF-PFM is approved to prevent and control bleeding episodes or to prepare persons with hemophilia for surgery. It is produced by genetically engineered Chinese hamster ovary cells that have been altered to produce factor VIII.

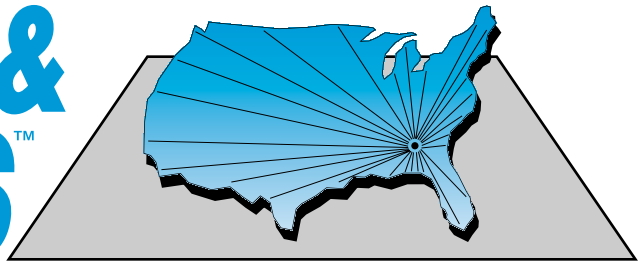
• ***New low dose of conjugated estrogens [CE]/ medroxyprogesterone acetate [MPA] tablet (Prempro) by Wyeth Pharmaceuticals.*** The FDA has approved a new low-dose strength of conjugated estrogens [CE]/ medroxyprogesterone acetate [MPA] tablets (Prempro), containing 0.3 mg CE and 1.5 mg MPA. Prempro 0.3 mg/1.5 mg is approved for the treatment of moderate-to-severe symptoms associated with menopause, such as hot flashes, night sweats, and vaginal dryness; and for the prevention of postmenopausal osteoporosis.

Wyeth also announced that the FDA has expanded the approved uses for Prempro 0.45 mg/1.5 mg to include the prevention of postmenopausal osteoporosis.

• ***Ciprodex Otic, a topical treatment of ciprofloxacin and dexamethasone, by Alcon.*** The FDA has approved Ciprodex Otic, a topical treatment of ciprofloxacin and dexamethasone, for a middle ear infection known as acute otitis media with tympanostomy tubes in children ages 6 months and older.

The FDA also approved Ciprodex Otic for the topical treatment of acute otitis externa (AOE). The AOE indication is for pediatric, adult, and elderly patients. ■

DRUG CRITERIA & OUTCOMES™



Zoledronic acid (Zometa) drug evaluation

By Anna Morton, PharmD Candidate
Harrison School of Pharmacy
Auburn (AL) University
Clinical rotation at Huntsville (AL) Hospital

Intravenous bisphosphonates

Zoledronic acid (Zometa) — Novartis
Pamidronate disodium (Aredia) — Novartis

Mechanism of action

Zoledronic acid inhibits osteoclast activity while inducing osteoclast apoptosis. By binding to the bone, osteoclastic resorption of mineralized bone and cartilage also is blocked. In addition, zoledronic acid inhibits the skeletal calcium release and osteoclast activity induced by tumors. Zoledronic acid is 100-850 times more potent than pamidronate at inhibiting bone resorption.

Indications

- Zoledronic acid:
  — Hypercalcemia of malignancy
  — Multiple myeloma and bone metastases of solid tumors
- Pamidronate:
  — Hypercalcemia of malignancy
  — Osteolytic bone metastases of breast cancer and myeloma
  — Paget's disease

Pharmacokinetics

The pharmacokinetic parameters of zoledronic acid and pamidronate are similar **(see Table 1, below)**. The pharmacokinetics have not been extensively studied in patients with hepatic or severe renal dysfunction.

Dosing

For hypercalcemia of malignancy, zoledronic acid is dosed 4 mg intravenously over no less than 15 minutes **(see Table 2, p. 2,** for comparative dosing information). Doses are not recommended to exceed 4 mg. In clinical trials, patients receiving infusions shorter than 15 minutes were more likely to experience renal toxicity. When treating multiple myeloma and metastatic bone lesions, treatment should be administered every three to four weeks. Pamidro-nate has a dosage range from 30 mg to 90 mg depending on the

Table 1: Pharmacokinetics

	Zoledronic acid	Pamidronate disodium
Peak effect	5-7 days	5-7 days
Plasma $t_{½}$	167 hours	28 hours
Bone $t_{½}$	Months to years	300 days
Metabolism	Not metabolized	Not metabolized
Excretion	50% unchanged in urine within 24 hours	50% unchanged in urine within 24 hours
Protein binding	22% Independent of drug concentration	N/A

indication. Pamidronate infusions times beyond two hours may reduce the risk of renal toxicity in hypercalcemic patients. The infusion rate is significantly longer than zoledronic acid with times ranging from two to 24 hours. At least seven days should be allowed to show a full response before retreatment with either agent is considered.

Table 2: Administration

Patients should be adequately rehydrated with saline hydration prior to every administration of either agent. An attempt should be made to restore urine output to approximately 2 L/day throughout the treatment period.

Caution should be taken to not overhydrate, particularly in cardiac failure patients. Diuretic therapy should be avoided until hypovolemia is corrected. **Table 3, below,** outlines administration guidelines for both agents.

Table 3: Contraindications

Zoledronic acid and pamidronate are contraindicated in patients with clinically significant hypersensitivity to the agent, other bisphosphonates, or any excipients used in the formulation.

Warnings/precautions

Pharmacokinetic and safety data are limited in renally impaired patients. Zoledronic acid trials excluded patients with serum creatinine (SrCr) levels greater than 3 mg/dL, and pamidronate trials excluded patients with SrCr greater than 5 mg/dL. Zoledronic acid is not recommended for the treatment of bone metastases in renally impaired patients, and the risks and benefits must be evaluated before treating a hypercalcemic, renally impaired patient. Patients with renal impairment should be carefully monitored when treated with pamidronate. Neither drug should be used in pregnancy or in nursing women. Limited data are available regarding the use of zoledronic acid in patients with hepatic insufficiency. Although not observed in clinical trials, other bisphosphonates have been associated with bronchoconstriction in patients with aspirin-sensitive asthma. **Table 4, below,** provides a checklist of warnings and precautions.

Table 4: Drug interactions

Few drug interactions have been identified with either agent **(see Tables 5 and 6, p. 3)**. Zoledronic acid appears to have more additive

Table 2: Dosing

Agent	Hypercalcemia of malignancy	Multiple myeloma and metastatic bone of lesions from solid tumors	Paget's disease
Zoledronic Acid	4 mg IV (intravenously) over 15 minutes Retreatment may be considered after seven days.	4 mg IV over 15 minutes every three or four weeks	N/A
Pamidronate	Moderate*: 60-90 mg IV over two to 24 hours Moderate or severe**: 90 mg IV over two to 24 hours Retreatment may be considered after seven days.	Osteolytic bone lesions: 90 mg over four hours once monthly Osteolytic bone metastases of breast cancer: 90 mg over two hours given every three to four weeks	30 mg daily over four hours on three consecutive days

* Moderate hypercalcemia: 12.0-13.5 mg/dL ** Severe hypercalcemia: >13.5 mg/dL

Table 3: Administration

Zoledronic acid	Pamidronate
• Store between 15-30° C (59-86° F)	• Store between 15-30° C (59-86° F).
• Initially reconstituted in 5 mL sterile water.	• Initially reconstituted in 10 mL sterile water.
• Administered intravenously in 100 mL normal saline or 5% dextrose.	• Administered intravenously in 1,000 mL of normal saline or 5% dextrose.
• Administer in a separate line from all other medications.	• Administer in a separate line from all other medications.
• The diluted infusion must be administered within 24 hours and stored at 2-8° C (36-46° F).	• The diluted infusion is stable for 24 hours at 2-8° C (36-46° F).

Table 4: Warnings/precautions

Warnings/precautions	Zoledronic acid	Pamidronate
Renal impairment/nephropathy	✓	✓
Pregnancy	✓ Category D	✓ Category C
Hepatic insufficiency	✓	
Aspirin-sensitive asthma	✓	
Nursing mothers	✓	✓

drug interactions when combined with aminoglycosides, loop diuretics, and thalidomide. Neither agent should be combined with calcium-containing IV fluids.

Table 6: Adverse effects

The adverse effect profiles of both agents are comparable **(see Table 7, p. 4)**. Renal toxicity is the most serious adverse event reported with both agents.

Table 7: Monitoring parameters

Patients treated with either zoledronic acid or pamidronate should be monitored prior to each treatment for renal function, serum calcium, serum phosphate, serum magnesium, serum electrolytes, complete blood count with differential, and hemoglobin and hematocrit.

Clinical Trials

Trial 1: Body JJ, Lortholary A, Romieu G, et al. A dose-finding study of zoledronate in hypercalcemic cancer patients. *J Bone Miner Res* 1999; 14: 1557-1561.

Objective: To determine the most effective dose of zoledronic acid that was nontoxic and could induce normocalcemia in at least 80% of patients with hypercalcemia of malignancy following rehydration.

Study design: An open-label, dose-finding, Phase I study consisting of 33 hypercalcemic cancer patients.

Intervention: Patients received doses of 0.002, 0.005, 0.01, 0.02, or 0.04 mg/kg zoledronate in a single dose infused over a median time of 30 minutes.

Patient population:

• Inclusion criteria:

— Persistence of tumor-induced hypercalcemia (TIH) after 24 hours of intravenous rehydration with 2-3 L of saline. TIH was defined as $Ca^{++} \geq 11$ mg/dL.

• Exclusion criteria:

— Serum creatinine greater than 1.5 times the upper limit of normal after rehydration.

— Treatment with bisphosphonates within the previous six months.

— Treatment with any agent capable of influencing Ca^{++} levels within previous one month.

— Hypercalcemia as a "flare" reaction within two weeks of initiating endocrine therapy.

— Chemotherapy within previous seven days.

Outcomes measured: The primary efficacy variable was the response to each dosage level.

Results: The two most effective doses were 0.02 mg/kg and 0.04 mg/kg.

Table 5: Zoledronic acid

Agent	Effect	Mechanism	Management
Aminoglycosides	Hypocalcemia	Additive	Use with caution during concurrent therapy
Loop diuretics			
Calcium-containing IV fluids	Incompatible	Incompatible	Administer separately
Thalidomide	Increased risk of renal dysfunction	Additive	Use with caution

Table 6: Pamidronate disodium

Agent	Effect	Mechanism	Management
Calcium-containing IV fluids	Incompatible	Incompatible	Administer separately

Table 7: Adverse effects

Adverse effect	Zoledronic acid	Pamidronate disodium
Abdominal pain	16.3%	12.6%
Anemia	22.1%	17.5%
Anorexia	9.3%	13.6%
Bone pain	11.6%	9.7%
Constipation	26.7%	12.6%
Dehydration	12.0%	9.0%
Diarrhea	17.4%	16.5%
Dyspnea	22.1%	19.4%
Fatigue	36.0%	37.2%
Fever	44.2%	33%
Hypocalcemia	1.2%	3.3%
Hypomagnesemia	10.5%	4.9%
Hypophosphatemia	12.8%	1.9%
Myalgia	21%	26.0%
Nausea	29.1%	27.2%
Redness/swelling at infusion site	N/A	N/A
Renal toxicity	8.0%	N/A
Vomiting	14%	16.5%
Hypotension	10.5%	1.9%
Progression of cancer	16.3%	20.4%

• With a dose of 0.02 mg/kg, 100% (5/5) of patients became normocalcemic.
• With a dose of 0.04 mg/kg, 93% (14/15) of patients became normocalcemic.
• At the lower doses, only 30% (3/10) of patients became normocalcemic.

Strengths: Inclusion and exclusion criteria were appropriate and clearly defined.

Limitations:
• Open-label trial design allows for potential biases.
• No placebo control group.
• Small patient population.
• Financial support from Novartis.

Authors' conclusions: Small doses of zoledronate (0.02 mg/kg and 0.04 mg/kg) administered over a short infusion were effective in treating patients with TIH. Zoledronate was well tolerated.

Trial 2: Major P, Lortholary A, Hon J, et al. Zoledronic acid is superior to pamidronate in the treatment of hypercalcemia of malignancy: A pooled analysis of two randomized, controlled clinical trials. *J Clin Oncol* 2001; 19:558-567.

Objective: To compare the safety and efficacy of pamidronate and zoledronic acid in treating hypercalcemia of malignancy.

Study design: Two concurrent, identical, parallel, randomized, double-blind, double-dummy, multicenter trials consisting of 185 patients.

Intervention: Subjects were randomized to receive either a single IV dose of zoledronic acid (4 mg or 8 mg) by five-minute infusion, or pamidronate disodium (90 mg) by two-hour infusion. The bisphosphonate was administered concomitantly with IV hydration. Refractory patients and patients that relapsed 56 days after initial treatment with either agent were retreated with a single 8 mg dose of zoledronic acid over five minutes and were followed for 28 days.

Patient population:
• Inclusion criteria:
— 18 years of age or older.
— Histologic or cytologic confirmation of cancer and severe hypercalcemia of malignancy (HCM) (corrected serum calcium [CSC]) ≥ 3.00 mmol/L; 12.0 mg/dL.
— Written informed consent.
• Exclusion criteria:
— History of allergic reaction or sensitivity to a bisphosphonate.
— Treated with a bisphosphonate for hypercalcemia within 90 days.
— Treated with a bisphosphonate for other complication within 30 days.
— Serum creatinine greater than 4.5 mg/dL.
— Treated with calcitonin within 72 hours.
— Treated with mithramycin, antineoplastic cytotoxic chemotherapy, or hormone therapy within seven days.
— Treated with gallium nitrate within 14 days.
— Treated with any investigational drug within 30 days.

Table 8: CR rates of Major P, Lotholary A, Hon J, et al study

Outcome	Zoledronic acid 4 mg	Zoledronic acid 8 mg	Pamidronate
4	45%*	55.6% (P = 0.021)	33%
7	83% (P = 0.005)	83% (P = 0.010)	64%
10	88.4% (P = 0.002)	86.7% (P = 0.015)	69.7%

* P value not reported

— Severely dehydrated.
— Could not tolerate IV hydration.
— Hyperparathyroidism.
— Adrenal insufficiency.
— Vitamin D intoxication.
— Milk alkali syndrome.
— Sarcoidosis.
— Granulomatous disease.
— Multiple endocrine neoplasia syndrome.

Outcomes measured:
• Primary:
— Patients were evaluated for complete response (CR) of normalization of CSC to ≤ 10.8 mg/dL by day 10.
• Secondary:
— Time, in days, to relapse (CSC > 10.8 mg/dL) of HCM.
— Duration of CR (time from a CR to last CSC ≤ 10.8 mg/dL).
— Duration of response (time from CR to last CSC < 2.9 mg/dL).
— Efficacy of zoledronic acid 8 mg used as re-treatment for relapse and refractory patients.
— Effects on the biochemical markers of bone resorption.

Results:
• Normalization of CSC occurred by day four in half of the zoledronic acid group and one-third of the pamidronate group.
• Mean CSC levels at days four, seven, and 10 were lower (P ≤ 0.05) in patients treated with either dose of zoledronic acid when compared to pamidronate.
• Serum Calcium Normalization (CR rates, **see Table 8, above)**.

Table 8
• The median time to relapse was 30 days for the zoledronic acid 4 mg group (P = 0.001), 40 days for the 8 mg groups (P = 0.007), and 17 days for the pamidronate group.
• The median CR durations were 32 days for the zoledronic acid 4 mg group, 43 days for the 8 mg groups, and 18 days for the pamidronate group.
• Following retreatment with 8 mg zoledronic acid, the mean CSC decreased from 12.68 mg/dL to 10.84 mg/dL by day 10. The median time of CR was 10.5 days, the median time of response was 15 days, and the median time to relapse was eight days.
• The most common adverse events were fever, anemia, nausea, constipation, and dyspnea. The occurrences were similar between all groups. Renal adverse events occurred in two patients in the zoledronic acid 4 mg group, five patients in the zoledronic acid 8 mg group, and three patients in the pamidronate group.

Strengths:
• Randomized, double-blind, double-dummy, multicenter trials.
• Inclusion and exclusion criteria were appropriate and clearly stated.
• Large patient population.
• Patient demographics similar at baseline.

Limitations:
• Results reported as a combined analysis with no recording of individual trial data.
• A priori sample size analysis was reported, but the zoledronic acid 4 mg did not meet the 90-subject set point.
• Patient population predominantly male and Caucasian.
• Supported by Novartis.

Author's conclusions: Intravenous zoledronic acid is superior and more convenient than pamidronate when treating hypercalcemia of malignancy. The safety profile of both agents is similar.

Trial 3: Berenson J, Rosen L, Howell A, et al. Zoledronic acid reduces skeletal-related events in patients with osteolytic metastases. *Cancer* 2001; 91:1191-1200.
Objective: To compare pamidronate with three different doses of zoledronic acid regarding the need for radiotherapy to bone metastases.
Study design: A randomized, controlled, double-blind trial lasting 10 months and including 280 patients.

Intervention: The trial consisted of three doses of zoledronic acid infused over five minutes. The studied doses were 0.4 mg, 2 mg, and 4 mg. As an internal control for tolerability and efficacy, a two-hour infusion of 90 mg pamidronate was used.

Patient population:

• Inclusion criteria:

— A histological confirmed diagnosis consistent with metastatic breast cancer or multiple myeloma.

— Radiologic evidence of a minimum of one osteolytic lesion.

— Life expectancy of at least 10 months.

— Eastern Cooperative Oncology Group (ECOG) performance status of 0, 1, or 2.

• Exclusion criteria:

— Osteolytic lesions only present in areas of previous radiation.

— Previous bisphosphonate therapy.

— Participation in a previous pamidronate protocol.

— Other investigational drug use within 30 days.

— History of hypercalcemia.

— History of bisphosphonate allergy or sensitivity.

— Scheduled for or recently undergone orthopedic surgery or radiation therapy within two weeks of study entry.

Outcomes measured:

• Primary:

— Frequency of radiation to bone — less than 30% receiving radiation to bone.

• Secondary:

— Other skeletal related events.

— Bone mineral density.

— Safety.

— Bone markers.

The primary and secondary results of this study are summarized in **Table 9, below**.

Strengths:

• A randomized, controlled, double-blind trial.

• Length of trial appropriate to assess outcome.

• Inclusion and exclusion criteria appropriate and clearly stated.

Limitations:

• Population predominantly female.

• Several patients dropped out of the study, but the data were not reported.

• Financial support from Novartis.

Authors' conclusions: Zoledronic acid infusions of 2.0-4.0 mg given over a five-minute infusion are as effective as a two-hour infusion of pamidronate in the treatment of osteolytic bone metastases. Both agents were well tolerated.

Trial 4: Rosen L, Gordon D, Kaminski M, et al. Zoledronic acid versus pamidronate in the treatment of skeletal metastases in patients with breast cancer or osteolytic lesions of multiple myeloma: A Phase III, double-blind, comparative trial. *Cancer J* 2001; 7:377-387.

Objective: To compare zoledronic acid to pamidronate in the treatment of osteolytic or mixed bone metastases/lesions.

Study design: A Phase III, double-blind, randomized, double-dummy, multicenter, international, parallel-group study lasting 12 months. The trial included 1,648 patients.

Intervention: Patients were randomized to receive IV infusions of either zoledronic acid (4 mg or 8 mg) or pamidronate (90 mg). The infusions were given every three to four weeks for 12 months. Initially, the zoledronic acid was given over five minutes and diluted in 50 mL of hydration solution, but was changed to a 15-minute infusion with 100 mL of hydration solution due to concerns of renal safety. The concerns of renal safety at higher doses also prompted the 8 mg treatment group to be

Table 9: Results of the Berenson J, Rosen L, Howell A, et al study

Outcome	Zoledronic acid 0.4 mg n = 68	Zoledronic acid 2 mg n = 72	Zoledronic acid 4 mg n = 67	Pamidronate 90 mg n = 73
Radiation to bone	24% (P > 0.05)	19% (P < 0.05)	21% (P < 0.05)	18%
Skeletal event plus hypercalcemia of malignancy	46% (P < 0.05)	35% (P < 0.05)	33% (P < 0.05)	30%
Skeletal event without hypercalcemia of malignancy	44% (P < 0.05)	32% (P < 0.05)	33% (P < 0.05)	30%
Pathological fractures	28% (P < 0.05)	22% (P < 0.05)	21% (P < 0.05)	21%

Table 10: Primary efficacy of Rosen L, Gordon D, Kaminski M, et al study

	Zoledronic acid 4 mg	Pamidronate 90 mg
Combined groups	44%	46%
Multiple myeloma	47%	49%
Documented bone metastasis from breast cancer	43%	45%

Table 11: Secondary efficacy of Rosen L, Gordon D, Kaminski M, et al study

	Zoledronic acid 4 mg	Pamidronate 90 mg
SRE	45%	47%
SMR for all SREs	1.13 (P = 0.157)	1.47
Time to first SRE	373 days	363 days
Required bone radiation	15% (P = 0.031)	20%
Time to progression of bone metastases	179 days	171 days
Mean SMR for radiation therapy	0.47 events/year (P = 0.018)	0.71 events/year

changed to 4 mg. All patients received a 500 mg calcium supplement daily and a multivitamin with 400-5,000 units of vitamin D.

Patient population:

• Inclusion criteria:

— 18 years of age or older.

— Durie-Salmon stage III multiple myeloma.

— At least one osteolytic bone lesion or breast cancer patients with at least one bone metastasis.

• Exclusion criteria:

— Received treatment with any bisphosphonate during the 12 months prior to screening.

— Hypercalcemia.

— Serum creatinine ≥ 3 mg/dL.

— Bilirubin > 2.5 mg/dL.

— Pregnant or lactating females.

— History of noncompliance with medical regimens.

Outcomes measured:

• Primary efficacy variable:

— Proportion of patients that experienced at least one skeletal related event (SRE).

• Secondary efficacy variables:

— The proportion of patients that experienced any SRE.

— Time to the first SRE.

— Skeletal morbidity rate (SMR).

— Proportion of patients experiencing individual SREs.

— The time to progression of bone metastasis.

— Objective bone lesion response.

— The time to overall progression of disease.

— ECOG performance status.

— Analgesic and pain scores.

— Bone resorption and formation markers.

— Primary and secondary efficacy results are summarized in **Tables 10 and 11, at left**.

Limitations:

• Majority of patient population were female.

• Financial support from Novartis.

Strengths:

• A phase III, double-blind, randomized, double-dummy, multicenter, international, parallel-group study.

• A priori sample size analysis was reported and criteria were met.

• Patient demographics similar at baseline.

• Intention-to-treat analysis utilized.

Author's conclusions: Zoledronic acid given as a 4 mg, 15-minute infusion was well tolerated and as effective as pamidronate 90 mg in the treatment of osteolytic lesions of multiple myeloma.

Further clinical trials: Zoledronic acid has a promising future in the treatment of osteolytic bone metastases, Paget's disease, and osteoporosis, but further clinical studies are needed to define its place in therapy. There are ongoing trials evaluating zoledronic acid and pamidronate in metastatic bone disease due to breast cancer or multiple myeloma. Several larger studies have been proposed to determine the efficacy and safety of zoledronic acid in the prevention of disease recurrence in patients with node-positive breast cancer and the prevention of bone metastases in breast cancer and prostate cancer.

Two previous trials have shown zoledronic acid efficacy in Paget's disease; however, a trial comparing the agent to pamidronate has yet to be performed. One study has evaluated zoledronic acid as a single annual injection for the treatment of

postmenopausal osteoporosis. The study was a placebo-controlled trial enrolling 351 patients with T scores less than -2. Zoledronic acid was administered at does of 0.25 mg, 0.5 mg, and 1 mg every three months, 4 mg as a single annual dose, and 2 mg every six months. Increases of bone mineral density were shown at the hip and spine with all dosage regimens, but further clinical trials are warranted to define efficacy and place in therapy.

Summary and recommendations: Advantages of zoledronic acid over pamidronate include indications for metastasis of all solid tumors, a shorter and more convenient infusion duration, a longer therapeutic effect, and a higher response rate. However, the significantly higher cost of zoledronic acid compared to generic pamidronate is a disadvantage **(see Table 12, at right)**, which cannot be ignored.

Table 12: Cost comparison:

• Hypercalcemia of malignancy:

— Zoledronic acid is effective and safe for the treatment of moderate-to-severe hypercalcemia of malignancy.

— Clinical trials have shown zoledronic acid to be superior to pamidronate in treating hypercalcemia by lowering serum calcium at a faster rate and by maintaining normalization for longer periods of time.

— Patients with hypercalcemia of malignancy do not receive scheduled infusions of bisphosphonates. Initiation of therapy is based on laboratory results and signs and symptoms of the disease.

— Most patients receive infusions as inpatient therapy so the cost and time savings associated with the shorter infusions may not be as pertinent when compared to outpatient therapy. However, the increased efficacy warrants the use in both settings.

— Patients with a SrCr greater than 1.8 mg/dL should not receive zoledronic acid infusions. Orders for zoledronic acid should be changed to pamidronate 90 mg infused over four hours.

• Multiple myeloma and metastatic bone lesions from solid tumors:

— Zoledronic acid has been proven equivalent to pamidronate for this indication. Superiority has not been shown at this point and therefore pamidronate should remain the formulary agent for this indication.

— Most infusions are scheduled and occur in the outpatient setting.

— Orders for zoledronic acid 4 mg over 15 minutes should be changed to pamidronate 90 mg over two to four hours given once monthly.

Table 12: Cost comparison

Zometa (brand-name product)	4 mg vial = $690.69
Aredia (brand-name product)	30 mg vial = $227.04 90 mg vial = $681.12
Pamidronate disodium (generic product)	30 mg vial = $90.86 90 mg vial = $272.58

• Paget's disease:

— There are ongoing trials studying zoledronic acid for this indication, but it has not received FDA approval at this time.

— Orders written for zoledronic acid 4 mg IV over 15 minutes should be changed to pamidronate 30 mg daily over four hours on three consecutive days.

• Postmenopausal osteoporosis:

— Neither zoledronic acid nor pamidronate have indications in postmenopausal osteoporosis.

— Zoledronic acid has shown efficacy for this indication but has not been approved at this point.

— Zoledronic acid should not be used as inpatient therapy for osteoporosis.

Resources

• Anon. Zoledronate (Zometa). *Med Lett Drugs Ther* 2001; 43:110-111.

• Berenson J, Rosen L, Howell A, et.al. Zoledronic acid reduces skeletal-related events in patients with osteolytic metastases. *Cancer* 2001; 91:1191-1200.

• Bisphosphonates. Drug Facts and Comparisons. St. Louis: *Facts and Comparisons* 2003; 279-286b.

• Body J, Lortholary A, Romieu G, et al. A dose-finding study of zoledronate in hypercalcemic cancer patients. *J Bone Miner Res* 1999; 14:1557-1561.

• Cada D, Levien T, Baker D. Zoledronic Acid for Injection. *Hospital Pharmacy* 2001;36:1-8.

• Major A, Lortholary A, Hon J, et al. Zoledronic acid is superior to pamidronate in the treatment of hypercalcemia of malignancy: A pooled analysis of two randomized, controlled clinical trials. *J Clin Oncol* 2001;19:558-567.

• Novartis Pharmaceutical Corp. Pamidronate disodium (Aredia) package literature. Cambridge, MA; 2002.

• Novartis Pharmaceutical Corp. Zoledronic acid (Zometa) package literature. Cambridge, MA; 2002.

• Pamidronate disodium. In: McEvoy GK, ed. *AHFS 2002: Drug Information.* Bethesda, MD: American Society of Health System Pharmacists; 2002:3697-3700.

• Personal communication. Cindy Hall, Buyer, Pharmacy Department. Huntsville (AL) Hospital System; January 2003.

• Rosen L, Gordon D, Kaminski M, et al. Zoledronic acid vs. pamidronate in the treatment of skeletal metastases in patients with breast cancer or osteolytic lesions of multiple myeloma: A Phase III, double-blind, comparative trial. *Cancer J* 2001; 7:377-387.

• Zoledronic acid. In: McEvoy GK, ed. *AHFS 2002: Drug Information.* Bethesda, MD: American Society of Health System Pharmacists; 2002:3739-3740. ■