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Prescription drug labels will soon require bar codes, FDA announces

ASHP sees action as good first step

The American Society of Health-System Pharmacists (ASHP) in Bethesda, MD, has been pushing for a federal mandate requiring scannable bar codes on prescription drug labels for some time. Now the society has gotten its wish.

At the society's Midyear Clinical Meeting in New Orleans on Dec. 3, 2001, **Bobby Jindal**, assistant secretary for planning and evaluation with the U.S. Department of Health and Human Services (HHS), announced the Food and Drug Administration's (FDA) commitment to require bar coding on all prescription drug labels in an effort to help reduce medication errors. The government's intention of developing a proposed rule was published in the Dec. 3, 2001, *Federal Register*.

ASHP had written a "strongly worded" letter to HHS Secretary Tommy Thompson in July, saying that the time for the bar coding initiative to come to fruition had arrived, says **Gary C. Stein**, PhD, director of federal regulatory affairs in ASHP's government affairs division.

ASHP says there are three primary goals of using bar-coding systems in the inpatient setting:

• Use of such coding would help eliminate medication errors and other preventable adverse drug events by ensuring accurate drug product and patient identification at the point of administration.

• Coding would improve monitoring of drug-use trends within a population of patients so that staff resources can be allocated for optimal patient care.

• Coding would improve overall efficiencies in the medication-use process, including the purchasing, storage, and distribution of drug products.

Even with the push, the announcement came as sort of a surprise, although ASHP knew that FDA had been working on bar coding for a while, Stein says. "The way that it was announced seemed to indicate that it was an actual proposed rule, but it actually was just the unified regulatory agenda."

According to Stein, ASHP thinks the commitment is a good first step. The *Federal Register* announcement says the proposed rule, which will be

open for public comment, will be published around April. FDA sources have since indicated that the publication may be pushed back to summer, Stein says. The society will be ready whenever the proposed rule is released. "We're certainly going to comment as an organization and then have some of our members comment, as well."

Bar code information undecided

According to the *Federal Register*, the bar code would contain certain information about the product, such as its National Drug Code number. The agency is considering whether to require other information, such as the drug's expiration date and lot number, to make it easier to identify expired drugs and recalled drugs that may not be safe and effective for use.

"We're going to suggest that as much information as possible be put into the bar code so that we can assure that the right patient gets the right dose at the right time," Stein says.

The risks of the proposal

Bar coding will decrease the incidence of medical errors, but implementation will be expensive. FDA's preliminary estimate puts the cost of the rule between $500 million and $1.4 billion over a 10-year period, although annual costs associated with errors in administering prescription drugs are much higher. The wide range in the cost estimate reflects the agency's uncertainty as to the costs associated with various pieces of information that might go into a bar code, whether all or some human drug products and biological products will be bar coded, and possible changes in labeling operations.

The changes will be especially costly for drug manufacturers. **Jeff Trewhitt**, a spokesman for the Pharmaceutical Researchers and Manufacturers of America (PhRMA) in Washington, DC, was guarded in his reaction to the FDA's statement.

"This could potentially help cut down on errors but the devil is in the details and we need to see the details," he told the *Associated Press*. "This is going to be technically challenging, potentially time-consuming, and potentially very expensive."

In its statement, FDA admits there is a possible risk that some manufacturers and repackagers, if required to bar code individual unit dose packages, would eliminate that type of packaging and only supply their products in bulk containers to reduce production costs. The individual unit dose packages, however, are more convenient for hospitals.

ASHP says it would be a mistake for drug manufacturers to switch to bulk containers. "It wouldn't really address the problem of getting the right drug to the right patient," Stein says.

Like PhRMA, ASHP will be closely watching the new bar coding developments. "We think it is a major effort on the part of the FDA to reduce medication errors," Stein says. "If it is done right, it will significantly affect patient care in the right way." ■

The debate over placebo controls continues

Should they be used if proven therapy exists?

In the Sept. 20, 2001, issue of the *New England Journal of Medicine (NEJM)*, two editorials addressed a hot topic among clinical researchers — the ethics of using placebo-controlled studies.

"The debate over placebo-controlled trials is implicitly and inextricably linked to concern about withholding treatment — specifically, withholding proven or standard treatment — in the course of investigating new therapies," wrote **Patricia Huston**, MD, MPH, and **Robert Peterson**, MD, PhD, of Health Canada in Ottawa.

When designing clinical trials, researchers can use at least two different standards when deciding the ethical concerns of using placebo controls. One is the Declaration of Helsinki, a statement of ethical principles developed by the World Medical Association (WMA) in France to provide guidance to physicians and other participants in medical research involving human subjects. The

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WMA was founded in 1947; the first Declaration was issued in 1964 and descends in large part from the Nuremberg Code.

In its October 2000 edit, principle 29 of the Declaration caught the attention of many researchers. "The benefits, risks, burdens, and effectiveness of a new method should be tested against those of the best current prophylactic, diagnostic, and therapeutic methods," it says. "This does not exclude the use of placebo, or no treatment, in studies where no proven prophylactic, diagnostic, or therapeutic method exists."

The "diverse interpretations and possible confusion" of principle 29, however, led WMA to issue a note of clarification in October 2001. The association said it reaffirms its position that "extreme care must be taken in making use of a placebo-controlled trial and that in general this methodology should only be used in the absence of existing proven therapy." However, a placebo-controlled trial may be ethically acceptable, even if a proven therapy is available, under the following circumstances:

- Where for compelling and scientifically sound methodological reasons its use is necessary to determine the efficacy or safety of a prophylactic, diagnostic, or therapeutic method.
- Where a prophylactic, diagnostic, or therapeutic method is being investigated for a minor condition and the patients who receive placebo will not be subject to any additional risk of serious or irreversible harm.

The FDA's position

The Food and Drug Administration (FDA), however, is not as strict in the use of placebo controls when a proven therapy exists. Instead, FDA says it is generally inappropriate to use a placebo in cases where an available treatment is known to prevent serious harm, such as death or irreversible morbidity in the study population.

This guidance is located in the "E10 Choice of Control Group and Related Issues in Clinical Trials," developed within the Expert Working Group (Efficacy) of the International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use. In situations where there is no serious harm, the guidance says, it generally is considered ethical to ask patients to participate in a placebo-controlled trial, even if they may experience discomfort as a result. The setting must be noncoercive and patients must be fully informed about available therapies and the consequences of delaying treatment.

Control groups have different problems, says **Robert Temple**, MD, director for medical policy, Center for Drug Evaluation and Research, Food and Drug Administration. "The placebo control is always informative, but there are some circumstances in which you can't ethically use it. An active control equivalence trial or noninferiority trial [in which an investigational drug is compared with a known active drug] usually is not an ethical problem, but there are a lot of circumstances in which it is simply not interpretable."

Failure to show a difference between treatments may not tell you that the new one works and may mean you don't have any evidence of effectiveness, he says. "You have to have effectiveness to be approved. That is a requirement of law."

Are placebo controls necessary?

Placebo controls are needed to test certain types of drugs, adds **George J. Wright**, PhD, an independent consultant in West Chester, OH. Wright has a number of years' experience in clinical research. He offers the example of antidepressants. "There are quite a number of drugs that have an influence on the progression of the depressive state," he says. "On the other hand, depression is a cyclical disease. An individual often will effectively become cured for a short time with no treatment at all. You then have to sort out whether the drug was responsible for the regression of the disease or the individual was just in one of those cyclical states." Side effect profiles with antidepressants can be difficult to determine in the absence of placebo controls, as well, he adds.

"People like the fact that drugs only have the intended action. And drugs don't," Wright says. "Any drug that is truly effective under certain circumstances will cause other things that you don't want it to do. Some of these side effects are serious."

If the disease is life-threatening and an effective drug (one that will at least prolong life) exists, however, researchers are obligated to use the drug that they know will have some effect. "Then you try to add to that effectiveness with the new drug," Wright says. "Maybe the next time you don't want to use that other drug. But you never leave [patients] untreated."

In a situation where no drug is truly effective, then researchers almost have to have an untreated group to discern that the new drug will or will not have an effect, he says. "The fact that

the disease is untreated already tells you that no one has been terribly effective at finding a drug that does work."

Does a middle ground exist?

The second editorial in the *NEJM* that addressed placebo controls suggests that a middle ground exists between the positions of the Declaration of Helsinki and the FDA. "We propose a middle ground in which placebo-controlled trials are permitted but only when the methodologic reasons for their use are compelling, a strict ethical evaluation has made it clear that patients who receive placebo will not be subject to serious harm, and provisions have been made to minimize the risks associated with the receipt of placebo," write **Ezekiel J. Emanuel**, MD, PhD, and **Franklin G. Miller**, PhD, of the National Institutes of Health in Bethesda, MD.

Temple says the people writing the *NEJM* try very hard to say, "There are extremists on either side and we are in the middle."

"That is distorted," he continues. "The only disagreement they have with FDA is that they think there may be degrees of discomfort so extreme that you wouldn't want to put people into a trial. I don't disagree with that. That may be true. I don't think it's an ethical question. I think people just wouldn't be in the trial."

The writers say they are proposing a middle ground, but they really are in near total agreement with the FDA and the contents of the guidance, Temple continues. "They make a big deal about the fact that we define the degree of discomfort or harm in several different ways. Then they use the term 'serious harm' and say serious harm is a matter of judgment. They are just as vague about it as anyone."

A crucial component in the argument is that people are volunteering, he says. "You are not forcing someone to be in a study. If someone says, 'I am willing to endure pain for an hour or two to see if this new drug or placebo is better,' then they ought to be considered intelligent enough to make that decision."

People sometimes act as if there is no decision to make when you are using an active control trial, Temple says. "That's silly. You are either getting a standard drug that everyone knows works or you are getting a new drug that might have risks that aren't known."

Every time someone enters a trial, there is a decision to be made, he adds. "The whole idea of carrying out trials is dependent on the idea that people can make intelligent decisions if you tell them the truth about what you know. We don't see much difference in these symptomatic conditions between an active control trial and a placebo-controlled trial." ■

Automated dispensing addresses shortage, safety

Should machines replace double-checking of drugs?

A new automated prescription drug dispenser in Minneapolis aims to address two problems at once: medication errors and pharmacist shortages. A user simply inserts the prescription and a credit card into the machine and out pops the medicine. However, some pharmacists say that cutting out the double-checking of prescriptions by trained professionals could be a mistake.

Minnesota's pharmacy regulators have approved the InstyMeds system for use anywhere in the state. The developer of the system, a former emergency room physician, hopes to place the dispensers in doctor's offices and emergency rooms around the country.

After a physician writes the "e-prescriptions," patients or their family members get a prescription printout with a security code to type into InstyMeds. The computer verifies the prescription and checks insurance records. The machine then asks for a credit card to make the co-payment. After the payment is made, the medication is dispensed.

Automated dispensing: Friend or foe?

Automated dispensing is another facet of the trend toward computerizing prescriptions. Some automation can help meet some of the needs in the pharmacy, says **Susan C. Winckler**, RPh, Esq, group director of policy and advocacy for the American Pharmaceutical Association in Washington, DC. "The automated systems are better counters than people are."

However, automated systems that are not overseen by a pharmacist or are used outside of the pharmacy assume that the pharmacy's main role is to count out the product and package the products, she says. "That is the wrong assumption. [When automated systems bypass the pharmacy],

you miss the double-check of assessing whether there are interactions, whether the drug is appropriate for the patient. You miss the second health care professional providing that input.

"There is a role to be filled by automation," she continues, "but I don't believe it is as broad as some of the proponents of automation would suggest."

Automated dispensing programs don't have to bypass the pharmacy. For example, the government recently announced approval of projects at two groups of community health centers intended to make prescription drugs more readily available to safety-net patients and to make them less costly. The first project involves automated dispensing — pharmacists at a central health center site in Spokane, WA, will network with other health centers and use computer equipment to dispense prescription drugs through vending machines to patients at remote health clinics.

The Community Health Association of Spokane (CHAS) will rely on a four-step process to send drugs through vending machines to patients at remote clinics:

1. Health care providers at the clinics fax prescription orders to the central CHAS pharmacy.
2. A pharmacist at the central facility receives the prescription and fills it via computer link to a locked vending machine in a secure area of the network clinics, where it is dispensed in a bottle.
3. A pharmacy technician picks up the bottle, attaches a label and delivers it to the waiting patient.
4. The process may end at this point, or the patient may use videoconferencing equipment — another element of the demo — to receive counseling on proper drug usage from the pharmacist at the central CHAS facility.

CHAS will manage its four clinics in partnership with Native Health of Spokane, an urban Native American program, and Northeast Washington Health Programs, a community health center in Chewelah, WA. The network will provide medications to approximately 13,500 low-income or rural patients who otherwise would have difficulty obtaining their prescription drugs.

The demonstration project is part of a initiative announced June 18, 2001, to help organizations that participate in the 340B drug discount program find ways to reduce administrative costs and improve access to prescription drugs for patients.

In general, if the right tools and the opportunities for interaction with pharmacists are in place, then automated dispensing is just one more way that technology might be used, says **David Witmer**, PharmD, director of the professional practice and scientific affairs division and director of the section of clinical specialists at the American Society of Health-System Pharmacists in Bethesda, MD. "There is still a need for that professional interaction and overview of the medication use process." ■

The GAO takes a look at the pharmacist shortage

Hiring and retention still a multifaceted problem

Although automation is becoming more commonplace, vacant pharmacy positions are not filling any faster, according to an October report issued by the U.S. General Accounting Office (GAO) in Washington, DC.

The report, "Supply of Selected Health Workers" (GAO-02-137R), looks at the current and projected supply and demand for pharmacists and laboratory and radiology workers and trends in their employment and earnings. The report gave the following statistics on pharmacy vacancy rates:

- A 2001 American Hospital Association survey of hospitals reported an average pharmacist vacancy rate of 21% in 2001, and half of all hospitals reported more difficulty in hiring pharmacists than in the previous year.
- An American Society of Health-System Pharmacists survey of its pharmacy-director members reported that the average pharmacist vacancy rate was 11% in 2000.
- The Department of Veterans Affairs recently reported that many of its facilities have filled fewer than half of their authorized pharmacist positions.

Unfilled pharmacy positions on the rise

When discussing the pharmacist shortage problem, the GAO often quoted a comprehensive report issued in December 2000 by the U.S. Department of Health and Human Services' Health Resources and Services Administration (HRSA).

The study, "The Pharmacist Workforce: A Study of the Supply and Demand for Pharmacists," was mandated by Congress and concluded that the number of unfilled full- and part-time drug store pharmacist positions nationally rose sharply from

about 2,700 vacancies in February 1998 to nearly 7,000 vacancies by February 2000. The report is available on the web at www. bhpr.hrsa.gov / healthworkforce / pharmacist.html.

Although the demand for pharmacists is increasing, the study says, the active pharmacy workforce is expected to increase only by 28,500 pharmacists over this decade — 800 fewer than last decade. There also is a decline in pharmacy school applications, with the number of 1999 applicants 33% lower than 1994, the high point of the past decade.

There are multiple reasons for the current shortage of pharmacists, says **David Witmer**, PharmD, director of the professional practice and scientific affairs division and director of the section of clinical specialists, American Society of Health-System Pharmacists (ASHP) in Bethesda, MD. HRSA's study identified a number of causes for the growing demand for pharmacists, including:

- increased use of a wide range of prescription medications;
- increased access to health care and more health care providers authorized to prescribe medications;
- expanded health insurance coverage resulting in increased prescriptions and time-consuming third-party payment tasks, which take an estimated 10-20% of a pharmacist's time;
- the growing emphasis in pharmacy education on a Doctor of Pharmacy degree, which lengthens the education program and increases the amount of training in clinical practice;
- strong competition for pharmacists trained at the residency or fellowship level, with schools of pharmacy, managed care organizations, pharmaceutical corporations, and hospitals all competing for these highly trained pharmacists — resulting in sector shortages, especially for schools and hospitals less able to compete economically.

But is there a shortage of pharmacists or a hyperdemand, asks **Susan C. Winckler**, RPh, Esq, group director of policy and advocacy for the American Pharmaceutical Association in Washington, DC. "You have opportunities for pharmacists that didn't exist when my parents finished pharmacy school in the mid-1950s. There was not the breadth of activity available today. It's another side effect of the growth of prescription drug use."

Pharmacists' skills have been more widely recognized across the entire realm of health care, Witmer says. "As a result, there has been a much greater demand for pharmacists in a variety of practice settings and in different job functions. That is likely to continue to grow, particularly as we have a workforce that is more highly educated with PharmD degrees and with more people graduating from residencies."

He predicts that the profession is going to continue to see people moving into key positions in the pharmaceutical industry, both in medical science liaison positions as well as research positions. "You are going to see managed health care and other business entities recognizing the skills of pharmacists, in terms of pharmaceutical economics and managing populations of care."

According to the study, the shortage results in less time for pharmacists to counsel patients; job stress and poor working conditions with reduced professional satisfaction; longer working hours and less scheduling flexibility with greater potential for fatigue-related errors; and fewer pharmacy school faculty because of their recruitment into the workforce.

Has anything changed?

More than a year since the report, ASHP continues to see difficulties in hiring pharmacists and keeping those positions filled. "[Our surveys] have shown that there are increasing difficulties in recruiting pharmacists in all facets of our membership, whether that be home care,

acute care, or chronic care settings," Witmer says.

He suggests addressing the shortage by:

• Increasing the efficiency of the drug distribution process through automation and the increased use of technicians so that pharmacists can spend more of their time on the important patient care aspects.

• Increasing the number of pharmacists by providing more funding for pharmaceutical education and larger class sizes.

Winckler expects to see some streamlining of pharmacists' activities through the improved use of automation and better use of certified pharmacy technicians. She also hopes to see improvement in the administrative requirements. "That situation is really untenable and adds costs to the health care system that haven't really been tracked accurately. That simply has to change.

"I'm not sure we will have a surplus of pharmacists anytime soon," she adds, "but we can manage the shortage by improving the environment so that more pharmacists will want to stay or perhaps even return to practice." ■

NEWS BRIEFS

Drugs wrongly prescribed to millions of elderly

A study from the U.S. Agency for Healthcare Research and Quality in Rockville, MD, highlights the problem of inappropriate prescribing in elderly patients in the United States. The study also underscores the importance of the safe use of prescription medications as a critical component of quality of care and demonstrates the

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Editorial Questions

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challenges involved in assessing safe use.

According to the findings published in the Dec. 12, 2001, *Journal of the American Medical Association*, about one-fifth of the approximately 32 million elderly Americans not living in nursing homes in 1996 used one or more of 33 prescription medicines considered potentially inappropriate. Nearly one million elderly used at least one of 11 medications that a panel of geriatric medicine and pharmacy experts advising the researchers agreed should always be avoided in the elderly. These 11 medications include long-acting benzodiazapines, sedative or hypnotic agents, long-acting oral hypoglycemics, analgesics, anti-emetics, and gastrointestinal antispasmodics.

The study also suggests that elderly women and older people who are in poor health and who use more prescriptions are more likely than others to receive inappropriate drugs.

According to lead author, **Chunliu Zhan**, MD, PhD, the actual extent of inappropriate medication prescribing may be much higher than the estimates because of the conservative criteria the researchers used and because of the rate of introduction of new pharmaceutical agents into the market. ▼

FDA creates new drug safety subcommittee

On Dec. 18, 2001, the Food and Drug Administration (FDA) announced the creation of a new Drug Safety and Risk Management Subcommittee to the Advisory Committee for Pharmaceutical Science.

The new subcommittee is composed of nationally recognized experts in the areas of risk perception, risk management, pharmacoepidemiology, clinical pharmacology, clinical research, and medication errors who will advise FDA on general and product-specific safety issues. The subcommittee was created because of the need for expert advice on complex drug-specific safety issues as well as methods of risk assessment, management, and communication, the FDA says. These issues play a role in FDA's overall evaluation of the risk/benefit ratio of drugs, and are common topics of discussion at advisory committee meetings.

The roster for the subcommittee can be found on the FDA web site at www.fda.gov/ohrms/dockets/ac/cderrosters/committees.htm. The subcommittee is expected to have its first public meeting in the spring of 2002. ▼

Merck recalling VAQTA hepatitis A vaccine

Merck & Co., Inc. is voluntarily recalling specified lots of VAQTA (hepatitis A vaccine, inactivated) in prefilled syringes. Re-tests of VAQTA have revealed a decreased antigen content in some syringes below the established minimum specification. As a result, a possibility exists that persons vaccinated with VAQTA in prefilled syringes from the indicated lots may be insufficiently protected against hepatitis A.

Patients who may have received doses from the indicated lots would have been vaccinated after May 29, 2001, with the adult formulation (50 U/1 mL), and after Aug. 9, 1999, with the pediatric/adolescent formulation (25 U/0.5 mL). Guidelines for antibody testing and revaccination of these patients are available. See the "Dear Healthcare Professional" letter for more details located on the web: www.fda.gov/medwatch/SAFETY/2001/safety01.htm#vaqta. ■

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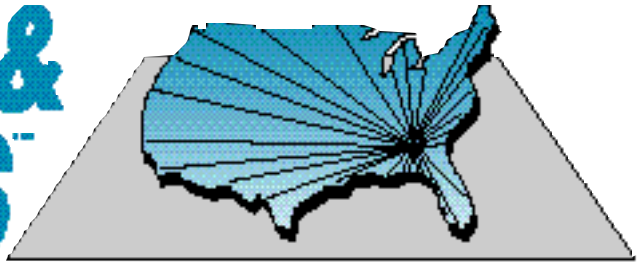

Actonel and Fosamax Formulary Evaluation

By **Travis Ball**, PharmD
Written as a PharmD candidate at Auburn University School of Pharmacy, Auburn, AL

Description

Alendronate (Fosamax) and risedronate (Actonel) are bisphosphonates used to increase bone mineral density (BMD) in patients with osteoporosis and glucocorticoid-induced osteoporosis. In addition, both drugs are used to treat Paget's disease.[1,2]

Mechanism of action[1,2]

Bisphosphonates are synthetic analogs of pyrophosphate that bind to bone hydroxyapatite and become a permanent part of the bone structure. Once bound, they act as a specific inhibitor of osteoclast-mediated bone resorption. When osteoclasts bind to the bisphosphonate-contained bone surface, their structure and function are altered, preventing adherence and resorption.

Alendronate differs from other bisphosphonate compounds by its side chain amino group. This side chain imparts greater potency and specificity by preferentially localizing resorption sites of active bone turnover. Normal doses have been shown to inhibit bone resorption, but have minimal or no effect on bone mineralization.

Risedronate is a pyridinyl bisphosphonate that is more potent and specific than other bisphosphonates, including alendronate. Risedronate has been shown to decrease bone resorption without impairing mineralization or interfering with bone formation.

Pharmacokinetics[1,2]

The timing of bisphosphonate administration in relation to food intake influences both the extent and rate of absorption. Alendronate's bioavailability is almost negligible if administered within two hours following a meal. Administration with coffee or orange juice can decrease the amount of drug absorbed by 60%. Approximately 20-50% of the bisphosphonate in blood binds to bone surfaces, and the remainder of the drug is excreted unchanged in the urine. The circulating serum half-life is relatively short, but the terminal half-life, bound to bone surface, involves extended time periods. See Table 1, below left, for more pharmacokinetic information.

Table 1. Pharmacokinetics[1,2]

Variable	Alendronate	Risedronate
Bioavailability	0.5-1%	0.54-0.75%
Protein binding	78%	24%
Clearance	< 200 mL/min	122 mL/min
$T_{½}$	< 6 hours	1.5 hours
Terminal $T_{½}$	~ 10 years	480 hours
Renal excretion	50%	40%
Formulation	Oral	Oral
Dose	5-40 mg/d or 35-70 mg/wk	5-30 mg/d
Pregnancy category	C	C

Indications and dosage

Both alendronate and risedronate are indicated for treatment and prevention of osteoporosis in postmenopausal women, glucocorticoid-induced osteoporosis, and Paget's disease.[1,2] Alendronate, however, is additionally indicated for osteoporosis in men and also can be dosed once weekly for osteoporosis in postmenopausal women. The risedronate dosage regimen specifies only two months of treatment for Paget's disease; the alendronate dosage regimen recommends six months.

Both alendronate and risedronate should be taken with 6-8 ounces of water 30 minutes prior to food. In addition, the patient should remain in an upright position for 30 minutes after taking medication to reduce the chances of experiencing upper GI irritations. Currently, studies are in progress to investigate the safety and efficacy of risedronate, 35 mg once weekly, for treatment of

osteoporosis; Food and Drug Administration approval of this regimen is expected in 2002.

Risedronate

Treatment and prevention of osteoporosis in postmenopausal women: 5 mg once daily. Treatment and prevention of glucocorticoid-induced osteoporosis: 5 mg once daily. Treatment of Paget's disease: 30 mg once daily for two months; retreatment may be necessary.

Table 2. Risedronate (Actonel) for postmenopausal osteoporosis

Study	Regimens	Treatment Duration	N	Endpoints	Results
Reginster et al[4] (treatment)	Risedronate: 2.5 mg/d, 5 mg/d, or placebo	3 years	1,226	Vertebral fractures	5 mg/d group had significantly fewer new vertebral fractures than the control group after three years, 53 vs. 89 ($P < 0.001$). However, there was not a significant difference in the number of osteoporosis-related nonvertebral fractures between the 5 mg/d group and the control group, 36 vs. 51.
Harris et al[3] (treatment)	Risedronate: 2.5 mg/d, 5 mg/d, or placebo	3 years	2,458	Vertebral and nonvertebral fractures	5 mg/d decreased cumulative incidence of new vertebral fractures by 41% ($P < 0.003$) and decreased incidence of nonvertebral fractures by 39% ($P < 0.02$) compared to placebo.

Alendronate

Treatment of osteoporosis in postmenopausal women: 10 mg once daily or 70 mg once weekly.

Prevention of osteoporosis in postmenopausal women: 5 mg once daily or 35 mg once weekly.

Treatment to increase bone mass in men with osteoporosis: 10 mg once daily (70 mg once weekly currently is being studied).

Treatment and prevention of glucocorticoid-induced osteoporosis: 5 mg once daily.

Treatment of Paget's disease: 40 mg once daily for six months; retreatment may be necessary

Contraindications

Alendronate and risedronate have similar contraindications. However, since some studies show that risedronate may not be as irritating to the GI tract, the manufacturer did not include esophageal abnormalities as a contraindication for that drug. In addition, patients who are unable to stand up for 30 minutes after taking their dose are not contraindicated to receive risedronate.[1,2]

Alendronate

- Hypersensitivity to alendronate or any component of the product;
- Hypocalcemia;
- Esophageal abnormalities that delay esophageal emptying;
- Patients unable to stand or sit upright for 30 minutes after dose.

Risedronate

- Hypersensitivity to risedronate or other bisphosphonates;
- Hypocalcemia.

Precautions[1,2]

Caution should be exercised in patients with a CrCl < 35 mL / min or with GI disorders. In addition, vitamin D and mineral deficiencies should be corrected before initiating therapy.

Clinical studies

To date, there are no head-to-head clinical trials comparing the efficacy of alendronate to risedronate. However, there are numerous trials that examine the effects of each drug in different indicated disease states. Tables 2-9 **(see charts, above and p. 3-6)** show the abbreviated results of the major studies with each drug.

All of the clinical trials reviewed were reliable. The sample size in a few trials was small, but overall there were not any apparent major credibility problems. The doses used in each trial and the criteria used to evaluate the results were appropriate for each disease state. According to the results of the studies, both risedronate and alendronate are effective for their indicated disease states. However, because there were no comparative efficacy trials between the two drugs, and endpoints differed in many trials (e.g., BMD vs. fracture risk), it would be difficult to conclude which drug is more effective.

Adverse effects[1,2]

Some studies show that the degree of GI irritation may differ among the bisphosphonates, particularly with risedronate. Risedronate is a pyridinyl bisphosphonate, whereas alendronate is a primary amino bisphosphonate. The primary amino structure of alendronate is thought to be more irritating to the GI tract due to interference

Table 3. Risedronate (Actonel) for glucocorticoid-induced osteoporosis

Study	Regimens	Treatment Duration	N	Endpoints	Results
Reid et al[6] (treatment)	Risedronate: 2.5 mg/d, 5 mg/d, or placebo Patients had to have been on at least 7.5 mg of prednisone (or equivalent) for 1 year	1 year	290	Bone mineral density (BMD) of lumbar spine, femoral neck, and trochanter	5 mg/d dose increased lumbar spine, femoral neck, and trochanter BMD by 1.6% ($P < 0.001$), 1.8% ($P < 0.004$) and 2.4% ($P < 0.010$), respectively. The authors claimed that risedronate decreased incidence of vertebral fractures by 70%; however, this study did not have sufficient power to determine fracture efficacy. The result was given as a relative risk ratio. All patients were required to take Vitamin D 400 IU daily and calcium carbonate 1 gm daily.
Cohen et al[5] (prevention)	Risedronate: 2.5 mg/d, 5 mg/d, or placebo Patients had to have been on at least 7.5 mg of prednisone (or equivalent) for 1 year	1 year	224	Percentage change in lumbar spine BMD, proximal femur BMD, and incidence of vertebral fractures	Lumbar spine BMD did not change significantly in the treatment groups but decreased significantly in the placebo group ($-2.8\% \pm 0.5\%$; $P < 0.05$). There was a 5.1% difference in the femoral neck BMD of the 5 mg/d group compared to placebo ($P < 0.001$). There was no significant difference overall in the incidences of new vertebral fractures in the 5 mg/d group vs. placebo. Some of the female patients were on hormone replacement therapy during the trial. Sponsored by Proctor & Gamble Pharmaceuticals (Actonel)

with the hydrophobic phospholipid barrier of the gastric tissue. This interference may lead to damage of the esophageal and gastric lining. Due to the nitrogen found in the pyridinyl ring structure in risedronate, phospholipid interference may not be as significant as that seen with alendronate.

The data from the head-to-head comparison showed that there was a statistically significant difference in the incidence of gastric ulcers between alendronate and risedronate **(see Table 10, p. 6)**. In addition, patients in the alendronate group had higher average gastric endoscopy scores. However, there was neither a significant difference in the incidence of esophageal or duodenal ulcers, nor in the average esophageal or duodenal endoscopy scores. The results of this trial are not consistent with previous reports of gastric ulcers caused by bisphosphonates. Prior to this trial, reports of gastric ulcers caused by alendronate or risedronate were rare. Because this trial was not placebo-controlled, it is difficult to evaluate the reliability of these results.

Lanza et al conducted both of these studies and had conflicting findings. In the study comparing alendronate to aspirin and placebo **(see Table 11, p. 7)**, the results were similar to other reports of gastric ulcers. In this study, the incidence was shown to be low in a small sample size. However, in the study comparing alendronate to risedronate **(see Table 10, p. 6)**, the reported incidence of gastric ulcers increased greatly (~ 13.2%). Unlike the first study, there was no placebo group to compare the results to in the alendronate vs. risedronate study. Therefore, it is difficult to base a conclusion as to which bisphosphonate is safer. The results of the alendronate vs. risedronate study differ from any other literature currently available, including a study by the

same author. Due to this discrepancy, a conclusion cannot be based on its results.

The following adverse events also have been reported with alendronate: hypocalcemia (13%), acid regurgitation (2%), esophagitis (1.5%), rash (< 1%), and headache (2.6%). Adverse events reported with the use of risedronate include (vs. placebo if available): diarrhea (10.6% vs. 9.6%), arthralgia (23.7% vs. 21.1%), epgasric discomfort (2%), rash (7.7% vs. 7.2%), and headache (2.9%).

Drug interactions

Alendronate[1]

• Products containing antacids and calcium may decrease the bioavailability of alendronate if they are taken at the same time as the dose.

• Drugs that are known to cause GI damage (salicylates and NSAIDs) may potentiate the GI effects of alendronate.

• IV ranitidine has been shown to increase the bioavailability of alendronate; however, the clinical significance of this reaction has yet to be determined.

Risedronate[2]

• Products containing antacids and calcium may decrease the bioavailability of risedronate if they are taken at the same time as the dose.

• Due to a lower incidence of GI irritation, salicylates and NSAIDs are not documented drug interactions with risedronate.

Administration

To reduce the potential for gastrointestinal reactions and to maximize oral absorption, a special administration procedure with bisphosphonates is recommended. They should be taken with 6-8 ounces of plain water at least 30 minutes prior to the first food, drink, or medication of the day. The patient then should avoid lying down for at least 30 minutes and until after the first food of the day. Patients should be instructed not to take either drug at bedtime or before rising for the day. The tablets should also not be sucked or chewed. These administration recommendations are the same for both the once-daily and once-weekly dosages. Within an institution, development of a standard bisphosphonate administration protocol may prove valuable. Cost information is available in Table 12 **(see chart, p. 7)**.

Table 4. Risedronate (Actonel) for Paget's Disease

Study	Regimens	Duration Treatment	N	Endpoints	Results
Miller et al[7]	Risedronate: 30 mg/d Etidronate: 400 mg/d	Risedronate: 2 months Etidronate: 6 months	123	Serum alkaline phosphatase (SAP), serum bone specific alkaline phosphatase, and urinary deoxypyridinoline were monitored for 12-18 months	Serum alkaline phosphatase normalized by month 12 in 73% of risedronate patients and 15% of etidronate patients ($P < 0.001$). Relapse rates were 3% for the risedronate group and 15% in the etidronate group ($P < 0.05$). The sample size was small.
Singer et al[8]	Risedronate: 30 mg/d	8 weeks; followed for additional 16 weeks	13	SAP	Risedronate produced a mean decrease from baseline in SAP of 77% by week 24 (no P-value). However, the sample size was very small.

Table 5. Alendronate (Fosamax) for postmenapausal osteoporosis

Study	Regimens	Treatment Duration	N	Endpoints	Results
McClung et al[9] (prevention of post-menopausal bone loss)	Alendronate: 1 mg/d, 5 mg/d, 10 mg/d, 20 mg/d, or placebo	2 years	447	BMD of lumbar spine, femoral neck, and trochanter	Alendronate 5, 10, and 20 mg/d increased BMD from baseline at the lumbar spine, femoral neck, and trochanter by 1-4%. The 1 mg dose and placebo led to losses of 2-4% at these sites. Small sample size relative to the number of treatment groups (n ~ 90 per group).

Summary

Due of the lack of head-to-head trials comparing the efficacy of alendronate and risedronate, it is difficult to conclude which drug is more effective or safe. One study demonstrated that risedronate might have an advantage over alendronate

with the incidence of gastric erosions and ulcers; however, the results may not be reliable because the study lacked a placebo group and the results differed from all other previous reports of gastric ulcers caused by alendronate.

Alendronate is available in a once-weekly tablet that may increase patient compliance compared to once-daily dosing. However, since the average stay in the hospital is now five days or less, once-weekly alendronate may not be cost-effective for the hospital since the cost of one 70 mg tablet is equal to the price of seven 10 mg tablets. Therefore, once-weekly alendronate may actually increase drug cost in patients who will be admitted to the hospital for a short period of time. However, for patients who are admitted for more than two weeks (i.e., rehabilitation hospital), once-weekly dosing generally would not appreciably increase drug costs.

Additionally, due to the higher risk of esophageal erosions in acutely ill bedridden patients receiving bisphosphonates, it is reasonable for acute care hospitals to remove these two drugs from the formulary and not administer them to patients for prevention or treatment of osteoporosis. Because of the long terminal half-life of these agents, temporary discontinuation during a hospital stay should have no significant clinical impact on long-term outcomes with osteoporosis. If appropriate, either drug could be continued during hospitalization for the infrequent cases of Paget's disease. At Huntsville (AL) Hospital, a 900-bed acute care hospital, annual drug expenditures could be reduced by approximately $12,000-$15,000 if alendronate and risedronate were recognized as non-formulary drugs and inpatient therapy was deferred.

Currently, daily alendronate is less expensive and offers more dosing options than daily risedronate. Additional studies should be conducted, directly comparing both the safety and efficacy of these two bisphosphonates.

Table 6. Alendronate (Fosamax) for glucocorticoid-induced osteoporosis

Study	Regimens	Treatment Duration	N	Endpoints	Results
Saag et al[10] (prevention and treatment)	Alendronate: 2.5 mg/d, 5 mg/d, 10 mg/d, or placebo Patients had to have been on at least 7.5 mg of prednisone (or equivalent) for 1 year	2 years	560	BMD of lumbar spine, hip, and total body	The 10 mg group had significant increases in lumbar spine, trochanter, and total body BMD. The 5 mg group had significant increases in total body BMD. The 2.5 mg group had small but nonsignificant increases in lumbar spine BMD.

Table 7. Alendronate (Fosamax) for Paget's disease

Study	Regimens	Treatment Duration	N	Endpoints	Results
Reid et al[11]	Alendronate: 40 mg/d or placebo	6 months	55	Serum alkaline phosphatase, N-telopeptide, and radiologic assessment	N-telopeptide and serum alkaline phosphatase decreased by 86% and 73%, respectively ($P < 0.001$). Adverse events in the treatment group were comparable to placebo. The sample size for this study was small.

Table 8. Alendronate (Fosamax) for men

Study	Regimens	Treatment Duration	N	Endpoints	Results
Orwoll et al[12] (treatment)	Alendronate: 10 mg/d or placebo	2 years	241	Percentage change in lumbar spine, hip and total body BMD.	The alendronate group had significant increases in lumbar spine (7.1 ± 0.3%), femoral neck (2.5 ± 0.4%) and total body (2.0 ± 0.2%) BMD ($P < 0.001$). The placebo group only had an increase in lumbar spine BMD (1.8 ± 0.5%) ($P < 0.001$). There were no significant changes in femoral neck or total body BMD in the placebo group.

Table 9. Alendronate (Fosamax) for once-weekly dosing in postmenopausal osteoporosis

Study	Regimens	Treatment Duration	N	Endpoints	Results
Schnitzer et al[13] (treatment)	Alendronate: 10 mg/d, 35 mg 2x/wk, or 70 mg/wk	1 year	1,258	Percentage change of lumbar spine, total hip, femoral neck, and trochanter BMD from baseline; biochemical markers of bone turnover	Mean increases in lumbar spine BMD at 12 months were: 5.1% in the 70 mg/wk group, 5.2% in the 35 mg 2x/wk group, and 5.4% in the 10 mg/d group. There were no significant differences in the number of gastroduodenal adverse effects among the three groups. Merck Pharmaceuticals (Fosamax) funded the study.

Table 10. Incidence of gastric ulcers with risendronate and alendronate

Study	Regimens	Treatment Duration	N	Endpoints	Results
Lanza et al[14]	Risedronate: 5 mg/d Alendronate: 10 mg/d	2 weeks	515	Gastric esophageal and duodenal endoscopy scores. Incidence of gastric, esophageal, and duodenal ulcers.	Gastric ulcers (> 3 mm): risedronate (4.1%), alendronate (13.2%) ($P < 0.001$). Mean gastric endoscopy scores for the risedronate were lower than those for the alendronate group at days 8 and 15 ($P < 0.001$). Mean esophageal and duodenal endoscopy scores were similar in the two groups at days 8 and 15. The study did not evaluate 5 mg alendronate and had a short duration. Proctor & Gamble (Actonel) funded the study.

Recommendation

Alendronate and risedronate could be deleted from most acute-care hospital formularies, based on safety, efficacy, and economic considerations. Alternatively, either drug could represent the other on the formulary.

For example, if alendronate is the formulary agent, patients who are admitted to the hospital on alendronate for the treatment or prevention of osteoporosis or Paget's disease could be continued on alendronate. If a patient is admitted to the hospital on alendronate 70 mg / wk, then the patient could be continued on the once-weekly dose or placed on once-daily dosing, depending on the predicted length of stay, or bisphosphonate therapy could be held during hospitalization. If a patient presents to the hospital on risedronate for the treatment or prevention of osteoporosis or Paget's disease, then the drug could be changed to the equivalent dose of alendronate. If a patient needs to be started on a bisphosphonate for treatment or prevention of postmenopausal osteoporosis, glucocorticoid osteoporosis, or Paget's disease, then alendronate could be started, either in the hospital or at discharge.

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Table 11. Incidence of gastric ulcers with alendronate, aspirin, and placebo

Study	Regimens	Treatment Duration	N	Endpoints	Results
Lanza et al[15]	Alendronate: 5 mg/d 10 mg/d Aspirin: 650 g QID placebo	14 days	95	Esophageal, gastric, and duodenal endoscopic scores. Incidence of gastric erosions at days 8 and 15.	There were no significant differences between the placebo group and the alendronate groups. However, there were significant differences in all endoscopic endpoints at days 8 and 15 for the aspirin group when compared to placebo. There was a combined total of two patients (~ 4.7%) in both alendronate groups with a gastric score greater than 4. In comparison, there were 10 patients (71.4%) in the aspirin group with a score greater than 4. The sample size for this study was small. Merck (Fosamax) funded the study.

Table 12. Cost of risedronate and alendronate

Drug	Dose	Cost/tablet[16]
Risedronate (Actonel)	5 mg	$1.83
	30 mg	$10.00
Alendronate (Fosamax)	5 mg	$1.60
	10 mg	$1.60
	40 mg	$5.30
	70 mg	$12.02

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IN THE PIPELINE

• Amylin Pharmaceuticals has begun a Phase III trial of synthetic exendin-4 (AC2993). This study will evaluate the ability of AC2993 to improve glucose control in people with **Type 2 diabetes** who currently are not achieving target blood glucose levels with metformin alone.

• GPC Biotech AG has announced that the FDA has granted Orphan Drug Designation for its Phase II clinical compound Bryostatin-1 in combination with Taxol for the treatment of **esophageal cancer**.

• Genmab A/S has received permission from the FDA to begin a Phase III study with HuMax(TM)-CD4 to treat patients with **active rheumatoid arthritis** (RA) who have failed to respond to treatment with methotrexate and TNF-alpha blocking agents.

• Elan Corporation, plc has enrolled and dosed the first patients in their multicenter Phase III clinical trials of natalizumab (Antegren) in **multiple sclerosis**.

• Transgene has begun a Phase II clinical trial of its immunotherapeutic MVA-HPV-IL2 vaccine candidate for the treatment of **vulvar intra-epithelial neoplasia** (VIN3). The trial will be conducted in France and will include up to 30 women with VIN3.

• Antex Biologics has begun a Phase I human clinical trial for the second component of its combination ACTIVAX vaccine to prevent **travelers' diseases** caused by the consumption of contaminated food and water. The trial, to be carried out at the Johns Hopkins University Vaccine Testing Unit in Baltimore, is designed to test the safety and immunogenicity of a vaccine against *Shigella sonnei* infection.

• AtheroGenics has begun a Phase IIb clinical trial, the Canadian Antioxidant Restenosis Trial-2 (CART-2), of its proprietary v-protectant drug, AGI-1067, for the treatment of **restenosis and atherosclerosis**.

• Neurocrine Biosciences and Taisho Pharmaceutical Co., Ltd. have initiated the first Phase IIb clinical trial of NBI-6024, a therapeutic vaccine, in approximately 400 adult and adolescent patients with **new onset Type 1 diabetes**. A second Phase IIb trial is planned to begin during 2002.

• BioCryst Pharmaceuticals has announced that patient enrollment has begun in a Phase III trial with once-a-day orally administered peramivir (RWJ-270201), BioCryst's influenza neuraminidase inhibitor. The objective of the trial is to assess the efficacy and safety of peramivir for the treatment of **acute influenza A and influenza B infections** in otherwise healthy adults.

• Emisphere Technologies has announced that enrollment for the PROTECT Trial has been completed. The PROTECT Trial is investigating an oral heparin solution formulation for the prevention of **deep vein thrombosis** (DVT) following total hip replacement surgery.

• Versicor began a Phase III clinical trial with the novel investigational agent, anidulafungin, in an additional indication: the **treatment of invasive aspergillosis**. Alexion Pharmaceuticals has commenced enrollment in the Phase III clinical trial of pexelizumab in patients undergoing coronary artery bypass graft surgery with cardiopulmonary bypass.

• Human Genome Sciences has announced that the FDA has approved its Investigational New Drug application to begin clinical trials of Albuleukin, a novel recombinant human protein, for treatment of certain types of **cancer**.

• Life Medical Sciences has received approval from the FDA to conduct a multi-center, feasibility clinical trial on its REPEL-CV bioresorbable adhesion barrier. REPEL-CV is designed to **reduce the formation of adhesions on the surface of the heart after open heart surgery**.

• InterMune has received Fast Track Designation from the FDA for Interferon gamma-1b (Actimmune) injection for the treatment of **idiopathic pulmonary fibrosis**, a debilitating and usually fatal disease for which there is no effective therapy.

• Millennium Pharmaceuticals has begun multiple Phase I clinical trials of MLN341 (formerly LDP-341, PS-341), in combination with docetaxel (Taxotere) for Injection Concentrate, Aventis Pharmaceuticals' chemotherapy agent used in the treatment of some **breast and lung cancers**.

• AstraZeneca filed a supplemental New Drug Application with the FDA for its oral, once-daily hormonal medication bicalutamide (Casodex) for the treatment of **early-stage non-metastatic prostate cancer.**

New FDA Approvals

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

• *Fondaparinux sodium (Arixtra) by Sanofi-Synthelabo and Organon.* The FDA has approved fondaparinux sodium (Arixtra) injection for reducing the risk of **blood clots after orthopedic surgery for hip fracture, hip replacement, and knee replacement**. Fondaparinux sodium is the first synthetic anticoagulant indicated for use in these types of surgeries.

The major side effect of fondaparinux sodium is serious bleeding. Fondaparinux sodium is not to be used in patients with severely impaired kidney function or in patients who weigh less than 110 pounds. Elderly patients also may be more likely to experience serious bleeding complications.

In addition, the labeling for this product includes a black box warning that fondaparinux sodium is not to be used when spinal anesthesia or spinal puncture is employed. There is a risk of developing a blood clot in the spine, which can result in long-term or permanent paralysis.

• *Trimethobenzamide hydrochloride (Tigan) by King Pharmaceuticals.* The FDA has approved the new drug application (NDA) for Trimethobenzamide hydrochloride (Tigan) 300 mg capsules. Trimetho-benzamide hydrochloride is indicated for the treatment of **post-operative nausea and vomiting and for nausea associated with gastroenteritis**. ■