DRUG UTILIZATION REVIEW™
Pharmaceutical Care Across the Continuum

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IN THIS ISSUE

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Letrozole cuts breast cancer recurrence risk

Questions unanswered after trial is stopped early

Breast cancer patients who have undergone five years of tamoxifen treatment can further limit their risk of recurrence by taking the aromatase inhibitor letrozole (Femara), according to the results of an international clinical trial.

The results were so positive that an independent data and safety monitoring committee recommended early termination of the trial and that all participants be notified of the results. By stopping it early, however, researchers left many important questions unanswered, critics say.

Results show 43% reduced risk

The international, double-blind, placebo-controlled trial was designed to test the effectiveness of five years of letrozole therapy in more than 5,000 postmenopausal women with breast cancer who had completed five years of tamoxifen therapy. The primary endpoint was disease-free survival.

At the first interim analysis, there were 207 local or metastatic recurrences of breast cancer or new primary cancers in the contralateral breast, 75 in the letrozole group and 132 in the placebo group — a reduction of risk of 43%. The estimated four-year disease-free survival rates were 93% and 87%, respectively. Seventeen women in the placebo group and nine women in the letrozole group died of breast cancer. Low-grade hot flashes, arthritis, arthralgia, and myalgia were more frequent in the letrozole group, but vaginal bleeding was less frequent. There also were new diagnoses of osteoporosis in 5.8% of the women in the letrozole group and 4.5% of the women in the placebo group; the rates of fracture were similar. After the first interim analysis, the independent data and safety monitoring committee made its recommendation to stop the trial.

Based on the findings, the researchers say that postmenopausal women with hormone-receptor-positive tumors who have completed

about five years of adjuvant tamoxifen therapy should be considered for letrozole treatment. Physicians have previously lacked a treatment to follow the tamoxifen therapy.

The results of the study were published in the Nov. 6 issue of the *New England Journal of Medicine (NEJM)*. Because of their importance, however, the journal published the results early on its web site.

Stopping trial early creates problems

Proponents of stopping the trial early — median follow-up of the women was 2.4 years — say it would have been unethical to withhold the positive early evidence of letrozole's benefit from women currently not taking the treatment.

Even the researchers, however, say that the discontinuing the study leaves the optimal duration of treatment undefined and the question of long-term toxicity unanswered. Since letrozole blocks estrogen production, there is concern about its long-term effects in terms of osteoporosis or cognition.

One pharmacist who specializes in oncology services was disappointed that the trial was canceled before the question of overall survival was determined. "There was a difference in disease-free survival, so they stopped the trial. But they have no proof that that is going to carry on to be overall survival benefit," says **Dominic A. Solimando Jr**., MA, BCOP, president of Oncology Pharmacy Services in Arlington, VA.

He expects physicians to use the drug, but they won't be sure of any long-term benefit. "They will not have any confidence or any real way of knowing if that translates to longer, overall survival. That's the big reservation of the trial," he says.

An editorial accompanying the study in the *NEJM* echoes that sentiment. "Although the current report does show a relative reduction of 24% in the hazard of death from any cause in the letrozole group as compared with the placebo group, this reduction was not statistically significant, and it is possible that a survival advantage will never be documented, since ongoing follow-up will be confounded by crossover," say **John Bryant**, PhD, and **Norman Wolmark**, MD. They are involved in the National Surgical Adjuvant Breast and Bowel Project, which is evaluating the aromatase inhibitor exemestane. Bryant is an associate professor at the department of biostatistics, Graduate School of Public Health at the University of Pittsburgh, and Wolmark is chairman of the department of human oncology at Allegheny General Hospital in Pittsburgh.

"Nor can the findings be used to support a recommendation of five years of letrozole treatment, since none of the participants have been followed that long," they continue. "Indeed, only about one quarter of the patients have been followed for the analysis of efficacy for 30 months or more, and follow-up for adverse events has been even shorter. Thus, although the results demonstrate a meaningful biologic effect of letrozole therapy after tamoxifen therapy, they do not demonstrate a significant survival benefit, nor do they convey information about the optimal duration of treatment beyond two to three years. It is not even possible to quantify the magnitude of a potential benefit with respect to disease-free survival, not only because of the small number of events that have been reported to date, but also because of uncertainty about the interval for which the treatment benefit may persist."

Solimando equates the letrozole trial to past trials

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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**.

evaluating tamoxifen. The trials showed that there was a survival benefit if women received five years of tamoxifen. If the trials had continued to show a benefit for the next year and a half, researchers could have stopped them and advised that patients be given tamoxifen for 10-15 years. However, the trials continued for several more years and showed a decrease in survival for women taking the drug for 10 years.

Stopping that trial earlier than 10 years would have done many patients a disservice, he says. "It would probably have taken a number of years and a number of unnecessary patients being placed at risk."

That's why he thinks patients should only take letrozole for about 2½ years, for which the benefit is known. "We don't know that at three or four years the benefit holds up. It would have been preferable to continue the trial until its end and actually answer the questions." ■

Patient worldview may influence drug counseling

Direct questions can be best to understand barriers

During their education, pharmacists learn about possible barriers to counseling patients on their medications. IV poles may get in the way; background noise can distract all participants. The patient may have a physical difficulty or speak another language.

Little is said, however, about personal barriers between the pharmacist and patient. These barriers arise from how each interprets the world — and each other. "The effects [of these barriers] are more insidious, but they are powerful, partly because they are not largely recognized," says **Lynnette Ridley**, RPh, a critical care pharmacist at Windsor (Ontario) Regional Hospital.

Unrecognized barriers can result in a pharmacist leaving a counseling session feeling satisfied that the correct information about a drug regimen has been delivered to a patient, without realizing that the patient has reservations about taking the drug that have prevented the patient from receiving the information.

Ridley has spent several years researching the psychology and neurology of how personal expectations can affect communication between individuals. "We are usually not aware on a cognitive level that we have these expectations, but they are still operating in background and affecting how we perceive the world and interact with people. In psychology, this set of expectations is called a 'model of the world,'" Ridley says.

The expectations begin forming at birth as every experience and bit of knowledge forms a new pathway between nerve cells in the brain. This continues at an explosive rate until about age 2. At that point and throughout life, the brain begins to prune away the pathways that aren't used. "The pathways that we use all the time get reinforced on a cellular level," she says. "The ones that we don't use fall away."

Individuals' inherent mindsets are strengthened through experience. "[The mindsets] exert a powerful but largely unconscious influence on our interactions with others," she adds. "What we are taught and what we experience structure our belief system, and then the belief system channels our behavior and limits the number of possibilities our brain will consider. It's a self-perpetuating cycle."

The brain also categorizes people based on the belief system. "If I walk into the room of a frail, slow-moving, white-haired person with wrinkled skin, my mind is already putting her in categories," she explains. "I may speak loudly and use simple words because my mind has categorized her as having limited comprehension or dementia. It's perfectly possible that she's a retired physicist with perfect hearing and intact faculties. But my brain has categorized her, and I am now operating from that category."

The brain even fills in gaps based on the person's previous experience and knowledge. "We register information about other people, such as appearance, quality of voice, and mannerisms. We'll put that person in a category. If information is missing, our brain fills it in, whether it is true in this individual or not."

The same mechanism works in the patient, as well. For example, a patient who is in pain may have had a significant male figure in childhood model that taking painkillers is a sign of weakness.

"Any information that I give him on side effects or drug interactions would be completely useless if he has already decided not to take this drug," Ridley says. "These built-in expectations can affect how we approach the client and how they perceive us, including what they expect about the services and products we provide."

Being aware of expectations on both sides is an

important first step in relating to patients, Ridley says.

The next step is more challenging but also more productive. "If we are able to temporarily step outside our belief system, then we can experience what patients are experiencing, thus identifying and circumventing any barriers to compliance."

This is an active, not passive, process. The pharmacist must have a deliberate intent to foster empathy for the patient, she explains. For example, the pharmacist can decide to act as if he or she doesn't have any data about patients, and resist the categorization process until more information is gathered.

"Often our intellect gets in the way. We think we know the answer to a question so we don't ask it in the first place," Ridley says. "If we do ask that question, we might get unexpected information."

Asking questions is key to determining the patient's model of the world, she says. She usually begins by evaluating patients' nonverbal cues. Can they look her in the eye? Do they seem like they just want to get the counseling over with? Are they engaged in the process? Are they asking questions? Do they seem irritated, restless, or frustrated?

If the patient is indicating a resistance toward some aspect of the counseling interaction, Ridley then turns to the direct question, which she has found to be the most effective with patients. She forms her questions so they are pointed, without being aggressive or intrusive.

"I might just come out and say, 'Does the thought of taking this drug disturb you?' Often this kind of open-ended direct statement will get me more information that I can use to get closer to what their issue is."

She was initially concerned that patients would be uncomfortable with such directness and even become offended and withdraw. Instead, the opposite has happened. "When I focus on that aspect of the [problem], which has been underground to that point, they are relieved that they can now voice their concerns or voice their hesitancy."

Identifying and navigating within the patient's model of the world is probably the most challenging aspect of difficult patient counseling sessions, Ridley says. "Since we are the drug specialists, it's our responsibility to promote adherence to drug regimens in all patients, not just the readily compliant ones. It's incumbent on us to practice and master those skills that help us communicate with the challenging patients."

The goal is either to shift patients' belief systems into one that accommodates adherence to the drug regimen or to find a way to work within their belief systems to promote effective drug therapy. Ridley continues. "Not only is such an interaction rewarding for the professional and the client, it also results in fewer drug-related hospitalizations, whether from drug mishaps or noncompliance. And that means improved patient health and reduced health care costs." ■

Genetic tool gives insight into patient drug reactions

Test eventually could give information at birth

Genetic testing to identify possible drug interactions is becoming more commonplace across the country. The emerging technology is here, and such tests eventually may be given at birth, says **John Lima**, PharmD, director of the Nemours Center for Clinical Pediatric Pharmacology in Jacksonville, FL.

Companies are already testing drug-metabolizing enzymes that have been shown to affect how the body handles a drug. "I think the drug-metabolizing enzymes are the first ones that have been discovered. There are labs that are doing this in the country right now. There is one such test that I believe might even be paid by a third party," he says.

But other proteins in the body that are encoded by highly polymorphic genes can influence response to drugs, Lima says. "I believe that certainly within 10 years, we will be doing that not only for drug-metabolizing enzymes but other proteins."

One company that offers genetic testing to see how a particular patient's genetic makeup affects drug metabolism is Seryx in Montreal. The technology, called Signature Genetics, is used primarily at physician offices across the country, although some health systems such as Baylor in Texas have recently signed on. Seryx CEO **Fred Mannausau** notes that more health systems will soon follow.

The offices sign a contract with the testing company, and the technology is made available to the physicians' patients. A patient can then visit the physician's office and have his or her blood drawn and a cheek swab analysis. The samples are sent to Montreal, where DNA material is

extracted. The DNA material then is sent for analysis to a lab in Germany. About a month later, a report that covers how 150 of the most common medicine types are metabolized based on the patient's genetic makeup is sent to the physician.

The test can be costly, about $2,000. However, it particularly benefits two types of patients, Mannausau says. One is the patient who has a history of side effects with drugs. "There is a higher possibility that it could be caused by a genetic component."

The other one is a patient who takes several drugs and doesn't seem to be getting any benefit. "That could mean that they are metabolizing the drug so rapidly that they need a much higher dosage to get to the right level in their blood," he says.

Codeine is one example of a drug that a patient may have trouble metabolizing, Lima says. "By itself, it doesn't have any activity and has to be converted in the liver to morphine, which is the active ingredient."

Patients who don't have the enzyme that converts codeine to morphine will have no response to codeine. "You would want to know that beforehand," he says. "A lot of people believe codeine is safer and is more heavily prescribed. But the patients who can't convert it would have to have morphine or some other drug. If you knew that before, you could save the patient a lot of pain, discomfort, and cost."

Patients using the Signature Genetics technology can continue to be in the system for an annual membership fee of about $250. If new drugs are approved, the service will inform the patient. Also, if a patient changes a drug and is taking other drugs, the patient will get an updated report on the new drug interactions, as well. The updates are automatic and are sent one or two times a year.

Pharmacy has a huge role to play in this business, Lima says. "Particularly early on, clinical pharmacists may have more knowledge about these polymorphisms and their influence so that physicians may want to seek out their advice."

The tests will be cost-effective the more they are done on a broad basis, he reports. "We will be seeing more of them." ■

Report: Off-label prescriptions can compromise safety

A three-part investigative series by Knight Ridder Newspapers claims that patients nationwide are being injured as doctors routinely prescribe drugs off-label.

Based on data from the U.S. Food and Drug Administration (FDA), the report estimates that at least 8,000 people became seriously ill last year after taking some of the nation's most popular drugs for off-label purposes. Among the report's findings on prevalence of off-label prescribing:

- 21% of the prescriptions examined were for off-label uses.
- 115 million off-label prescriptions for the drugs analyzed by Knight Ridder were written in the United States last year, nearly double the number of five years ago.
- As many as 90% of the prescriptions for some drugs were off-label uses.
- Three-quarters of antiseizure medications are prescribed off-label, as are nearly two-thirds of antipsychotics and about one-quarter of antidepressants.

To calculate how often drugs are prescribed off-label, Knight Ridder analyzed the three top-selling drugs in 15 classes of medications, comparing what doctors said they prescribed them for with the FDA's approval for each. The analysis looked at 900 million prescriptions written in 1998 and 2003 for more than 1,000 different ailments. Its estimate of the prevalence of off-label prescribing excluded cancer treatments or pediatric off-label uses. The investigative reporters also interviewed patients, doctors, researchers, and drug companies, and reviewed thousands of records from lawsuits, government hearings, regulatory actions, medical records, and scientific studies. ▼

FDA: Difference in infections among leading RA treatments

Data from the U.S. Food and Drug Administration's (FDA) adverse events reporting system (AERS) suggest the number of granulomatous infections, such as tuberculosis and pneumonia, in patients treated with etanercept for rheumatoid

arthritis (RA) may be substantially lower than patients treated with infliximab, according to data presented at the American College of Rheumatology 67th Annual Scientific meeting.

These data suggest there may be biologically and medically important differences in the safety profiles of different marketed tumor necrosis factor (TNF)-inhibitors with respect to rate of infection.

Of the total (755) granulomatous infections reported, substantial differences between the etanercept group and infliximab group were reported (155 vs. 547, respectively) through June 2002. Additionally, the number of *Pneumocystis carinii* pneumonia cases reported was also lower for etanercept group vs. the infliximab group (four vs. 44, respectively). At an FDA advisory meeting in March 2003, it was reported that approximately 400,000 patients had been treated with infliximab and 150,000 patients with etanercept through December 2002.

Researchers say that further studies are needed to determine the exact differences in mechanism of action between etanercept and infliximab that may be leading to these clinically important differences in infection rates. ▼

Be aware of common dispensing errors

Health care professionals are being warned of two dispensing errors that could have serious adverse effects on patients.

First, UCB Pharma is warning of dispensing errors between levetiracetam (Keppra) tablets and oral solution and lopinavir/ritonavir (Kaletra) capsules and oral solution.

Keppra, an antiepileptic, is available as tablets and oral solution. Keppra tablets, 250 mg are blue, 500 mg are yellow, and 750 mg are orange, oblong-shaped, scored, film-coated tablets debossed with "ucb" and "strength" on one side. They are supplied in containers of 120 tablets. Keppra oral solution is a clear, colorless, grape-flavored liquid supplied in 16 fl oz white HDPE bottles containing 500 mg levetiracetam per 5 mL.

Kaletra, an antiretroviral, is available as capsules or oral solution. Kaletra 133.3 mg lopinavir/33.3 mg ritonavir capsules are orange soft gelatin capsules imprinted with the Abbott corporate logo and "PK." It is available in bottles of 180 capsules. Kaletra oral solution is a light-yellow to orange liquid supplied in amber-colored 160 mL glass bottles containing 400 mg lopinavir/100 mg ritonavir per 5 mL.

In addition, Elan Biopharmaceuticals is warning that serious adverse events and deaths have resulted from accidental overdose of high concentration morphine sulfate oral solutions. In most of these cases, morphine oral solutions ordered in milligrams were mistakenly interchanged for milliliters of the product, resulting in twentyfold overdoses. For example, a prescribed dose of 5 mg was mistakenly administered as 5 mL (100 mg) of the morphine sulfate concentrated solution.

Elan currently distributes three concentrated morphine sulfate oral solutions:

- Roxanol CII (morphine sulfate) Concentrated Oral Solution (20 mg/mL), available in 30 mL and 120 mL bottles with calibrated dropper.
- Roxanol-T CII (morphine sulfate) Concentrated Oral Solution (20 mg/mL) — tinted, flavored; available in 30 mL and 120 mL bottles with calibrated dropper.
- Roxanol 100 CII (morphine sulfate) Concentrated Oral Solution (20 mg/mL), available in a 240 mL bottle with calibrated patient spoon.

Prescribers and dispensers should be aware that these and other concentrations of morphine sulfate are available from various manufacturers with the concentration expressed in mg/tablespoon (5 mL). ▼

Researchers report bone loss from oral diabetes drug

Scientists at the University of Arkansas for Medical Sciences (UAMS) in Little Rock report that a widely used oral drug for Type 2 diabetes may pose a significant risk of bone loss.

The researchers say in a laboratory study, the antidiabetic compound rosiglitazone (Avandia) caused a significant decrease in total body bone mineral density, suggesting that the therapy may pose a significant risk of adverse skeletal effects in humans.

The UAMS scientists used microcomputed tomography to analyze the bones of healthy mice that received doses of rosiglitazone over seven weeks. The doses that mice received were the same doses mice received in earlier studies that demonstrated the compound's effectiveness for Type 2 diabetes. The researchers next plan to test the effects of the drug on mice and rats with diabetes.

The results of the study were published in the Sept. 18 issue of the journal *Endocrinology*. ■

New FDA Approvals

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

• ***New delivery system of peginterferon alfa-2b (Peg-Intron Redipen) by Schering-Plough Corp***. The FDA has approved peginterferon alfa-2b (Peg-Intron Redipen), a pre-filled pen for administering peginterferon alfa-2b powder for injection, the most-prescribed interferon treatment for patients with chronic hepatitis C.

The pen is a disposable, single-dose delivery system that allows patients to administer the drug in three steps: mix, dial, and deliver. Mixing occurs by pushing down on the pen to combine the peginterferon alfa-2b powder with sterile water, both of which are stored in the pen. Dialing allows patients to select their predetermined individualized dose, and delivery allows patients to inject their individualized dose of the medication. The pen will be available in four different strengths: 50, 80, 120, and 150 mcg, each indicated by a color-coded label and dosing button. An instructional videotape and brochure for use by patients and health care professionals will also be available. The pen is expected to be available in the United States in early 2004.

• ***Fosamprenavir calcium (Lexiva) by GlaxoSmithKline***. The FDA has approved fosamprenavir calcium (Lexiva), a protease inhibitor (PI), for the treatment of HIV infection in adults in combination with other antiretroviral medications. Fosamprenavir calcium, which can be taken once or twice daily without food or water restrictions, has been evaluated in clinical trials with both PI-experienced and antiretroviral therapy (ART)-naive HIV patients.

GlaxoSmithKline says the following points should be considered when initiating therapy with fosamprenavir calcium/ritonavir in PI-experienced patients: The PI-experienced patient study was not large enough to reach a definitive conclusion that fosamprenavir calcium/ritonavir and lopinavir/ritonavir are clinically equivalent. Once-daily administration of fosamprenavir calcium plus ritonavir is not recommended for PI-experienced patients.

Fosamprenavir calcium may be dosed three different ways: 1) two 700 mg tablets twice daily (bid); 2) two 700 mg tablets once daily (QD) in combination with two 100 mg capsules of ritonavir QD; or 3) one 700 mg tablet bid in combination with one 100 mg capsule of ritonavir bid. For PI-experienced patients, the recommended dose is one 700 mg tablet bid in combination with one 100 mg capsule of ritonavir bid.

Fosamprenavir calcium was well-tolerated in clinical trials. The most common adverse events were diarrhea, nausea, vomiting, headache, and rash. Fosamprenavir calcium is contraindicated in patients with previously demonstrated clinically significant hypersensitivity to any of the components of this product or to amprenavir. The drug is also contraindicated with ergot derivatives, cisapride, pimozide, midazolam, and triazolam. If fosamprenavir calcium is coadministered with ritonavir, flecainide and propafenone also are contraindicated.

• ***New indication for nateglinide (Starlix) by Novartis Pharmaceuticals Corp***. The FDA has approved nateglinide (Starlix) for use in combination with a thiazolidinedione (TZD) in patients with Type 2 diabetes who are not adequately controlled after a therapeutic response to a TZD. Nateglinide was approved in the United States in 2001 as monotherapy for drug-naive patients with Type 2 diabetes and in combination with metformin.

The most common adverse events associated with nateglinide vs. placebo in clinical trials were upper respiratory infection, back pain, flu symptoms, dizziness, arthropathy, and hypoglycemia. Based on the safety and tolerability in clinical trials, no liver function testing or special monitoring is required when nateglinide is used in monotherapy. In patients whose hyperglycemia is inadequately controlled with metformin or after a therapeutic response to a TZD, nateglinide may be added to, but not substituted for, those drugs.

• ***New dosing for levofloxacin (Levaquin) by***

COMING IN FUTURE MONTHS

- Imatinib mesylate (Gleevec) shows promise in Alzheimer's treatment
- Rosuvastatin (Crestor) drug evaluation
- Drug treatment of post-traumatic stress disorder
- Multitasking in pharmacy practice
- Omalizumab (Xolair) drug evaluation

Ortho-McNeil Pharmaceutical. The FDA has approved levofloxacin (Levaquin) tablets/injection and levofloxacin in 5% dextrose injection 750 mg once-daily regimen to treat mild-to-severe community acquired pneumonia (CAP). With this approval, the drug becomes the only short-course fluoroquinolone indicated to treat CAP in a five-day regimen.

Levofloxacin is dosed once daily and indicated for a wide variety of infections including CAP, nosocomial pneumonia, mild-to-moderate cases of complicated urinary tract infections, acute pyelonephritis, uncomplicated urinary tract infections, acute maxillary sinusitis, acute bacterial exacerbation of chronic bronchitis, and chronic bacterial prostatitis. Levofloxacin is contraindicated in persons with a history of hypersensitivity to levofloxacin, quinolone antimicrobial agents, or any other components of this product. ■

IN THE PIPELINE

• Cypress Bioscience is initiating its Phase III program evaluating the use of milnacipran as a potential treatment for **fibromyalgia syndrome**.

• GenVec has entered into a formal collaboration with the National Cancer Institute (NCI) by signing a Cooperative Research and Development Agreement. Steven K. Libutti, MD, of the NCI Surgery Branch will conduct a Phase II clinical study to determine the activity of TNFerade, GenVec's lead oncology product candidate, in **rectal cancer**.

• ARYx Therapeutics has initiated a Phase I study to evaluate the safety and pharmacokinetic profile of ATI-2042, an amiodarone analog intended to treat **atrial fibrillation**.

• Bayer Pharmaceuticals Corp. and Onyx Pharmaceuticals have begun an international, multicenter Phase III trial to further evaluate the safety and efficacy of the investigational drug BAY 43-9006, a novel signal transduction inhibitor, in the treatment of advanced **renal cell carcinoma** (kidney cancer).

• CV Therapeutics has initiated a pivotal Phase III clinical trial of CVT-3146, a selective A2A-adenosine receptor agonist being jointly developed with Fujisawa Healthcare, for potential use as a pharmacologic stress agent in **cardiac perfusion imaging studies**.

• Repligen Corp. has initiated a clinical trial in healthy volunteers to assess the safety, tolerability, and pharmacokinetic profile of RG1068 (synthetic human secretin) when administered via subcutaneous injection.

• Chiron Corp. is initiating plans for a Phase III trial for tifacogin in patients with **severe community-acquired pneumonia**. Tifacogin is a recombinant form of tissue factor pathway inhibitor.

• YM BioSciences has received written confirmation from the U.S. Food and Drug Administration that it may initiate a Phase III, or registrational trial, for its lead small-molecule anticancer therapeutic, tesmilifene, in the treatment of **metastatic breast cancer**.

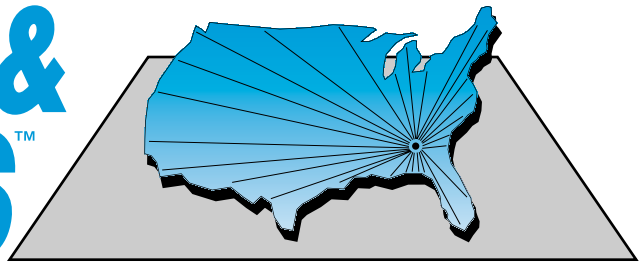
• ICN Pharmaceuticals is initiating Phase III studies of its antiviral compound, Viramidine, a nucleoside (guanosine) analog that the company intends to develop in oral form for the treatment of **hepatitis C**.

• GTx has initiated a Phase III clinical trial of toremifene citrate (Acapodene) tablets to reduce the incidence of skeletal fractures and other serious complications of androgen deprivation therapy in men who have **advanced prostate cancer**.

• Pharmaceuticals Corp. has announced that the FDA has granted orphan drug designation to its drug candidate AEOL 10150 for the treatment of **amyotrophic lateral sclerosis**.

• XenoPort has initiated Phase I clinical studies of its lead investigational drug, XP13512. XenoPort has designed XP13512 to overcome limitations in the pharmacokinetic properties of gabapentin. ■

DRUG CRITERIA & OUTCOMES™



Teriparatide (rDNA) origin (Forteo) formulary evaluation

By **Brian Lee**, PharmD candidate
Harrison School of Pharmacy
Auburn (AL) University
Richard Cramer, PharmD
Drug Information Coordinator
Huntsville (AL) Hospital

Osteoporosis treatment medication

Teriparatide (rDNA) origin (Forteo) — Eli Lilly & Co.

Alendronate sodium (Fosamax) — Merck & Co. [To be used as standard therapy for comparative purposes in this evaluation.]

Mechanism of action

Teriparatide is the first synthetic, recombinant human parathyroid hormone (1-34) [rhPTH(1-34)] to stimulate new bone growth and increase bone mineral density (BMD) of the hip and lumbar spine by accelerating osteoblastic activity and restore bone integrity and architecture. The rhPTH has the same biological properties as the endogenous PTH synthesized by the parathyroid gland. The PTH is an endogenous 84-amino acid peptide that is secreted due to a low plasma Ca (calcium) concentration in the extracellular fluid. The released PTH rapidly binds to the specific high-affinity PTH-1 receptors and initiates a cascade of events: adenylyl cyclase activation, increased cAMP production, and phospholipase C activity induction.

PTH regulates Ca and phosphate metabolism at these three target sites: bone, kidney, and gastrointestinal (GI) tract. PTH increases ionic Ca and phosphate resorption at the bone and increases bone formation. The kidney responds to PTH by 1) increasing the reabsorption of both Ca and Mg (magnesium) at the distal convoluted tubule and the ascending Loop of Henle; 2) accelerating the transport of phosphate, amino acids, Na (sodium), Cl (chlorine), SO_4^{2-} (sulfate ion), and HCO_3^- (bicarbonate ions) into the urine; and 3) increasing the production of the active form 1α,25-dihydroxy-vitamin D (Calcitriol). PTH stimulates intestinal Ca and phosphate absorption across the small intestine. A negative feedback system inhibits hormone release when ionic Ca levels in the plasma achieve homeostasis.

Indications

- Teriparatide (rDNA) origin
  - Postmenopausal osteoporotic women at high risk for fracture.
    - — History of osteoporotic fracture.
    - — Multiple risk factors for fracture.
    - — Intolerant of bisphosphonates, selective estrogen-receptor modulators, or hormone replacement therapy/estrogen replacement therapy.
  - Primary or hypogonadal osteoporosis in men at high risk for fracture
    - — History of osteoporotic fracture.
    - — Multiple risk factors for fracture.
    - — Intolerant of bisphosphonates, selective estrogen-receptor modulator, or hormone replacement therapy/estrogen replacement therapy.

- Alendronate is used to prevent and treat postmenopausal osteoporosis, glucocorticoid-induced osteoporosis, and Paget's disease, and to increase bone mass in men with osteoporosis.

Table 1: Pharmacokinetics of teriparatide

Variables	Teriparatide
Volume of distribution	0.1 L/kg
Peak effect	30 minutes
Bioavailability	95% (SQ)
$T_{½}$	1 hour
Metabolism/Excretion	No data available

One of the most significant clinical differences between teriparatide and other treatments for osteoporosis is the subcutaneous route of administration. **Table 1** summarizes the pharmacokinetic parameters associated with teriparatide. The pharmacokinetic data for teriparatide in pediatric patients are not currently available. There are no age-related pharmacokinetic differences among patients between 31 and 85 years of age. There are also no pharmacokinetic differences in patients with mild or moderate renal insufficiency, but limited data demonstrate patients with severe renal insufficiency may have a 73% increase in area under the curve (AUC) and a 77% increase in $T_{½}$. There are no specifically recommended dosage reductions in these patients at this time. No pharmacokinetic data are available for patients with chronic renal failure undergoing dialysis, heart failure, hepatic impairment, and pediatrics.

The pharmacokinetics of alendronate differ significantly from teriparatide. Alendronate may remain in the bone tissue for many years and is not hepatically metabolized. Alendronate is not recommended in patients with a creatinine clearance of less than 30 mL/min.

Dosing

The Forteo pen is supplied in a glass cartridge, disposable pen injector (750 mcg/3.3 mL). The device contains 3.3 mL of drug (a 28-day supply). The recommended dosage is 20 mcg/day for currently approved indications.

For treatment and prevention of osteoporosis, 70 mg/week and 35 mg/week are recommended, respectively. Patients diagnosed with Paget's disease should take 40 mg daily for six months or 5 mg daily for glucocorticoid-induced osteoporosis.

Administration

Teriparatide is given as a subcutaneous injection in the thigh or abdominal wall. When administering an initial injection, the patient should be in an area where they can quickly sit or lie down should they experience orthostatic hypotension. RhPTh should be refrigerated (36-46° F) and not frozen. The safety and efficacy of this drug has not been evaluated beyond two years; a trial funded by Eli Lilly currently is testing the efficacy of Forteo for a 10-year period.

Alendronate should be taken one-half hour before food with plain water. Patients should not lie down for 30 minutes and until after their first meal of the day.

Contraindications

Forteo should not be administered to patients with hypersensitivity to teriparatide or any excipients used in the formulation.

Warning/precautions

The only significant black box warning for teriparatide is the increased potential risk of developing osteosarcoma. This incidence was observed in laboratory rats exposed to three to 60 times the recommended dosage of 20 mcg. **Table 2** lists the warnings/precautions of teriparatide.

Because no clinical trials have been conducted on the safety in patients with active urolithiasis or hypercalcemia using teriparatide, it should be used with caution. Usage of teriparatide in these patients may exacerbate their condition; therefore,

Table 2: Warning/precautions for teriparatide and alendronate

Warning/precautions	Teriparatide	Alendronate
Osteosarcoma	X X	
Paget's disease	X	
History of radiation therapy	X	
Metabolic bone disease	X	
Hypercalcemia	X	
Urolithiasis	X	
Orthostatic hypotension	X	
Hepatic insufficiency	X	
Renal insufficiency	X	X
Cardiac insufficiency	X	
Nursing mothers	X	X
Pregnancy	X Category C	X Category C
Pediatrics	X	X
Dysphagia		X
Esophagitis		X
Gastric ulcer		X

XX — Black box warning

close monitoring of urine calcium is highly recommended. A transient orthostatic hypotension may occur after the first several doses of teriparatide. However, the adverse reaction should resolve within a few minutes to hours. Placing a patient in a reclining position in a chair relieves the dizziness, lightheadedness, or palpitations associated with the hypotension.

Some of the precautions in using alendronate include renal insufficiency, pregnancy, pediatrics, and patients with gastric ulcers. Nursing mothers should take precautions before taking alendronate.

Drug interactions

Serum calcium levels should be assessed 16 hours post-injection of teriparatide. If persistent hypercalcemia occurs, the medication should be discontinued promptly pending further evaluation. **Table 3** lists potential drug interactions with teriparatide.

Table 3: Drug interactions for teriparatide

Drug	Clinical effect
Hydrochlorothiazide	Hypocalciuria
Furosemide	Hypercalcemia, hypercalciuria
Digoxin	Hypercalcemia

Table 4: Adverse effects of teriparatide vs. placebo

Adverse effects	Teriparatide	Placebo
Neck pain	3.0%	2.7%
Asthenia	8.7%	6.8%
Hypertension	7.1%	6.8%
Nausea	8.5%	6.7%
Diarrhea	5.1%	4.6%
GI disorder	2.3%	2.0%
Dyspepsia	5.2%	4.1%
Constipation	5.4%	4.5%
Vomiting	3.0%	2.3%
Arthralgia	10.1%	8.4%
Depression	4.1%	2.7%
Rhinitis	9.6%	8.8%
Dizziness	8.0%	5.4%
Pharyngitis	5.5%	4.8%
Rash	4.9%	4.5%
Headache	7.5%	7.4%
Angina pectoris	2.5%	1.6%
Syncope	2.6%	1.4%
Insomnia	4.3%	3.6%
Vertigo	3.8%	2.7%

Adverse effects

Most adverse effects associated with teriparatide involve the nervous and respiratory systems. **Table 4** summarizes the adverse effects of teriparatide.

The adverse effects of alendronate are mild and include abdominal pain, constipation, and nausea.

Monitoring parameters

No clinical studies have been conducted on overdose with teriparatide. Treatment of overdose should include discontinuing the drug, implementing supportive treatment, and monitoring serum concentrations of phosphate and calcium. Serum uric acid levels should be assessed since a clinical trial has demonstrated increased uric acid concentrations in 2.8% of patients treated with teriparatide, although the hyperuricemia did not cause the development of arthralgia, urolithiasis, or gout in these patients.

Patients on alendronate should have their alkaline phosphatase and serum potassium monitored periodically.

Costs

A month supply of alendronate costs $53.10 — much less than a month supply of teriparatide, approximately $450 per month. Due to Forteo pen injector's availability only as a 28-day drug supply, the hospital would incur significant outpatient therapy costs by supplying Forteo for inpatients.

Clinical trials

Trial one: Neer RM, Arnaud JR, Zanchetta RP, et al. Effect of parathyroid hormone (1-34) on fractures and bone mineral density in postmenopausal women with osteoporosis (*N Engl J Med* 2001;344: 1434-1441).

Objective: To determine the efficacy of teriparatide and a safe dose in the treatment of postmenopausal women diagnosed with osteoporosis who had two or more vertebral fractures.

Study design: A double-blind, randomized, placebo-controlled Phase III study up to 24 months (median of 21 months), including 1,637 postmenopausal women with at least two vertebral fractures.

Intervention: All women received 1,000 mg calcium and 400-1,200 IU of vitamin D for one to six months. All women gave themselves daily injections of a placebo for the first two weeks and then were randomly chosen to receive a placebo (n = 544,

18 months), 20 mcg teriparatide (n = 541, 18 months), or 40 mcg teriparatide (n = 552, 17 months).

Patient population

- Inclusion criteria
  - Postmenopausal women (at least five years) with at least one moderate or two mild vertebral fractures. If the women had fewer than two moderate fractures, they had to have a bone mineral density of the hip or lumbar spine of one or more standard deviations below normal premenopausal women (20-35 years).
- Exclusion criteria
  - Bone or calcium metabolism.
  - Drug abuse.
  - Urolithiasis within five years.
  - Corticosteroid treatment within six months.
  - Renal insufficiency (Scr > 2 mg/deciliter).
  - Abnormal urine calcium levels.
  - Hepatic insufficiency.
  - Abnormal serum calcium levels.
  - Alcohol abuse.

Statistical analysis: Pearson's chi-square test and evaluation by analysis of variance.

Outcomes measured:

- Serum calcium measured before and four to six hours after injection at baseline and at one, three, six, 12, 18, and 24 months.
- Urine calcium and creatinine measured at baseline and at one, six, 12, and 24 months.
- Thoracic and lumbar spine radiograph measured at baseline and 12 months.
- Bone density of spine measured at baseline and at three, six, 12, 18 months, and the last month.
- Bone density of hip, forearm, and total body measured at baseline, 12 months, and the last month.
- Height measured at baseline and 12 months.
- Blood counts and chemical tests measured at baseline and at one, six, 12, and 24 months.
- Urinanalysis measured at baseline and at one, six, 12, and 24 months.
- Tested circulating antibodies to PTH at baseline and at three, 12, and 24 months.

Results

Tables 5-7 summarize the risks of the Neer, et al. study.

Table 5: Risk for vertebral fractures*

Variables	Placebo (n = 448)	rhPTH 20 µg (n = 444)	rhPTH 40 µg (n = 434)
≥ 1 mild fracture	64	22 (65% reduction)	19 (69% reduction)
Multiple fractures	22	5 (77% reduction)	3 (86% reduction)
≥ 1 moderate or severe fractures	42	4 (90% reduction)	9 (78% reduction)

*Only women with adequate radiographs were used to evaluate vertebral fractures.

Table 6: Risk for nonvertebral fractures^

Variables	Placebo (n = 544)	PTH 20 µg (n = 541)	PTH 40 mg (n = 552)
≥ 1 Fracture			
Total	53 Absolute risk (6%) Relative risk (0.47)	34 (P = 0.04) (36% less likely vs. placebo) Absolute risk (3%) Relative risk (0.46)	32 (P = 0.02) (40% less likely vs. placebo) Absolute risk (3%) Relative risk (0.46)
Fragility*	30	14 (P = 0.02) (54% less likely vs. placebo)	14 (P = 0.01) (54% less likely vs. placebo)
Total	16	14	9
Fragility	8	6	3
Total number of nonvertebral fractures	62	36	37
Total number of nonvertebral fragility fractures	33	15	17

^ All women were included (adequate or without adequate radiographs).

* Fragility fractures: if the associated trauma would not have resulted in the fracture of a normal bone; fracture sites are at hip, wrist, ankle, humerus, rib, foot, and pelvis.

Table 7: Change from baseline in BMD and total body bone mineral

	Placebo			PTH 20 µg				PTH 40 µg			
BMD	B	T	(%Δ)	B	T	(%Δ)	P value	B	T	(%Δ)	P value
Lumbar spine	0.82	0.829	1.1	0.82	0.899	9.7	S	0.82	0.932	13.7	S
Femoral neck	0.64	0.635	-0.7	0.64	0.657	2.8	S	0.64	0.672	5.1	S
Trochanter	0.57	0.568	-0.2	0.57	0.589	3.5	S	0.57	0.595	4.4	S
Intertrochanter	0.86	0.848	-1.3	0.85	0.872	2.6	S	0.85	0.884	4.0	S
Total hip	0.71	0.702	-1.0	0.70	0.718	2.6	S	0.70	0.725	3.6	S
Distal radius	0.32	0.314	-1.6	0.31	0.309	-0.1	NS	0.32	0.315	-1.5	NS
Shaft of radius	0.58	0.572	-1.3	0.58	0.567	-2.1	NS	0.59	0.571	-3.2	S
Total body BMD					S				S		
Hologic	1303	1286	-1.3	1250	1250	0.6		1324	1337	1.0	
Lunar	1444	1444	0	1453	1498	3.1		1481	1547	4.5	

B = Baseline, T = Treatment, S = Significant (< 0.001), NS = Nonsignificant

Note: No statistical test directly compares treatment groups. A statistical test compared % changes from baseline to endpoint.

Adverse effects

- **Cancer:** Placebo (4%), PTH 20 µg (2%, P = 0.02), PTH 40 µg (2%, P = 0.07).
- **Nausea:** Placebo (8%, P < 0.001), PTH 40 µg (18%).
- **Headache:** Placebo (8%, P = 0.01), PTH 40 µg (13%).
- **Dizziness:** Placebo (6%, P = 0.05), PTH 20 µg (9%).
- **Leg cramps:** Placebo (1%, P = 0.02), PTH 20 µg (3%).
- **Other adverse effects:** Hypercalcemia (> 10.6 mg/deciliter), hypercalciuria (> 300 mg/day), and uric acid and circulating antibodies cross-react with teriparatide.

Strengths

- Prospective, double-blind, randomized, placebo-controlled study.
- Pearson's chi-square test in the three study groups.
- Methods in study design were appropriate (bone mineral density).
- Participants from 17 countries.

Limitations

- Study subjects predominantly Caucasian women.
- Study period was set for 24 months but was conducted for 12 months.
- No data available from 13-24 months.
- Women with illnesses affecting bone or calcium metabolism, urolithiasis, hepatic insufficiency, renal insufficiency (Scr > 2 mg/deciliter), and drug and alcoholic abusers were not participants of the study
- Some P values were not calculated in the comparison between placebo and PTH-treated associated adverse events.
- Supported by Eli Lilly, and co-author of the study owns Eli Lilly stocks.
- Compliance rate of 79-83%.

Author's conclusions: PTH in doses of 20 µg and 40 µg daily increases bone mineral density of the spine up to 13% compared to placebo and that reduces the risk of vertebral fractures by 69%. PTH-treated (40 µg) postmenopausal women with osteoporosis had a 54% reduction in nonvertebral fractures.

Trial two: Orwoll ES, Scheele WH, Paul S, et al. The effect of teriparatide [human parathyroid hormone (1-34)] therapy on bone mineral density in men with osteoporosis. *J Bone Miner Res* 2003;18:9-18.

Objective: To determine the effect of teriparatide in men with osteoporosis with a bone mineral density at least two standard deviations from the average young men.

Study design: Centralized block randomization, double-blind, placebo-controlled study.

Intervention: 437 men were randomly assigned to receive a placebo (n = 147), 20 µg/day teriparatide (n = 151), or 40 µg/day teriparatide (n = 139). However, only 311 men actually received teriparatide or placebo. All patients received 1,000 mg calcium and between 400 and 1,200 IU vitamin D at

least one month before the study.

Patient populations

- Inclusion criteria
  - Men ages 30-85, not chronically disabled, with osteoporosis. Recruited from 11 countries.
  - Subjects with normal or low levels of testosterone.
  - Hypogonadal patients with a stable dose of androgen or anabolic steroids that would be continued during the study for at least six months of therapy.
- Exclusion criteria
  - Men diagnosed with metabolic bone diseases including excess glucocorticoid.
  - Use of estrogen agonists or antagonists, coumarin and indandione derivatives, anticonvulsants, or calcium- or aluminum-containing antacids.
  - Diagnosed with nephrolithiasis or urolithiasis within two years, sprue, inflammatory bowel disease, malabsorption syndrome, poor intestinal absorption of calcium, low urinary calcium excretion, and elevated endogenous parathyroid hormone levels, hepatic or renal insufficiency, drinks more than six alcoholic beverages a day, or abuses drugs.
  - Paget's disease, renal osteodystrophy, or osteomalacia.
  - Received androgen, anabolic steroids, progestins, calcitonin, fluorides, oral bisphosphonates, vitamin D of more than 50,000 IU/week, or calcitriol within six months.
  - Growth hormone deficiency, previous pituitary surgery, tumor, or radiation.
  - History of carcinoma or suspected carcinoma within five years.
  - Abnormalities of lumbar spine inhibiting the assessment of bone mineral density.

Statistical analysis

- ANOVA to analyze continuous measures including treatment and country.
- Pearson's chi-square test ($P < 0.05$ for significance).

Outcomes measured

- Intact serum PTH (1-84) measured at baseline and 12 months.
- Serum bone alkaline phosphatase measured at baseline and at one, three, six, and 12 months.
- Lumbar spine bone mineral density measured at baseline and at three, six, and 12 months.
- Hip, whole body, and radial bone mineral density measured at baseline and 12 months.
- Serum calcium levels measured at one, six, and 12 months.
- Calcium and creatinine excretion measured at baseline and at one, six, and 12 months.
- An elevation in serum calcium or urinary calcium excretion rates of greater than 350 mg/day, and increased urinary calcium to creatinine ratio in patients treated with teriparatide received a reduced dose of calcium supplement or were discontinued.
- Testosterone levels were measured to establish a baseline value using radioimmunoassay.
- Serum estradiol, complete blood count, urinalysis, and serum chemistry were measured at baseline and at six and 12 months.
- Serum parathyroid hormone (1-84) was assessed at baseline and 12 months.
- Radioimmunoassay was used to measure serum antibodies to teriparatide at baseline and 12 months.
- Smoking and consumption of alcoholic beverages were noted and documented at baseline.

Results

- Mean serum Ca concentration was higher in the teriparatide-treated groups than placebo throughout the 12 months of study, but only 6.2 % and 16.8% of the patients receiving 20 µg and 40 µg teriparatide, respectively, were hypercalcemic. Four patients in the 20 µg group and 12 patients in the 40 µg group needed to reduce their calcium supplementation due to hypercalcemia, elevated urinary Ca excretion, and symptoms of headache or nausea. Seven patients in the 40 µg group reduced their dose to 20 µg while three patients in the 20 µg group and six patients in the 40 µg group withdrew from the study.
- Mean serum concentrations of 1,25 $(OH)_2$ vitamin D increased in both teriparatide treatment groups.
- A negative test on serum antibody against teriparatide was demonstrated.
- Uric acid levels were above normal in 0.7%, 0%, and 2.3% in the placebo, 20 µg group, and 40 µg group, respectively.
- Serum chloride levels were below normal in 2.1%, 1.4%, and 1.5% in the placebo, 20 µg group, and 40 µg group, respectively.
- Serum magnesium levels were below normal in 2.3% of the 40 µg group.

Table 8: Percent change in bone mineral density within 12 months

BMD (g/cm²)	Placebo	Teriparatide 20 µg	Teriparatide 40 µg
Lumbar spine	0.52%	5.87% (P < 0.001)	9.03% (P < 0.001)
Femoral neck	0.31%	1.53% (P = 0.029)	2.93% (P = 0.023)
Intertrochanter	0.61%	1.18% NS	2.34% (P < 0.001)
Total hip	0.54%	1.17% NS	2.33% (P < 0.001)
Whole body bone mineral content (g)	-0.45%	0.64% (P = 0.021)	0.87% (P = 0.005)

NS = nonsignificant

Note: The percent change in bone mineral density of the trochanter, distal radius, ultradistal radius, and whole body was insignificant.

- Changes in bone mineral density were not significantly affected by free testosterone and estradiol levels (P = 0.398).
- Of the 39 patients withdrawn, 4.8%, 9.3%, and 12.9 % were in the placebo, 20 µg group, and 40 µg group, respectively.
- The teriparatide 40 µg group experienced a statistically significant increased rate (P < 0.001) of nausea compared to placebo.
- The teriparatide 40 µg group experienced a statistically insignificant increased rate (P = 0.053) of headache compared to placebo.

Tables 8 and 9 summarize the the changes in bone mineral density and bone formation reported in the Orwoll et al study.

Strengths

- Centralized block randomization, double-blind, placebo-controlled study.
- Inclusion and exclusion criteria were appropriate.
- Men from 11 countries.
- Intention-to-treat analysis performed.
- Standard deviation reported.
- α value set at 0.05 at the beginning of the study.
- A study conducted in men with osteoporosis although less common than in women.

Limitations

- Compliance rate was 79% and no statistical analysis was performed.
- All data were not presented in this article.
- Initial intact serum PTH (1-84) was not measured.
- Patient population consisted of mainly Caucasians.
- Percentage of patients with headaches in the placebo and teriparatide 20 µg group were not given.
- Eli Lilly supported the study, and the authors were consultants or employees of Eli Lilly.
- The baseline T-scores in the placebo, teriparatide 20 µg group, and 40 µg group were more representative of patients with osteopenia than osteoporosis (National Society of Osteoporosis Guidelines not followed).

Author's conclusions: Teriparatide increases lumbar spinal and femoral neck bone mineral density in men with osteoporosis during a period of 11 months. Teriparatide-treated patients had an increase in serum calcium levels and an increase in 1,23 $(OH)_2$ vitamin D levels.

Other clinical trials: A third randomized double-blind, placebo-controlled trial examined the effects of teriparatide on the skeletal changes and adverse effects in rats over a 24-month period. There was a substantial increase in bone mineral density after the administration of teriparatide. One unique finding from this study was that rats developed osteoblastoma, osteoma, focal osteoblast, and osteosarcoma in a dose-dependent and duration-dependent manner. Although the findings in this study cannot directly be extrapolated to humans, this clinical data should be factored into the drug's profile of benefits vs.

Table 9: Percent bone formation (ALP)/resorption (NTX) changes

Months	Bone ALP markers		Bone NTX markers	
	Placebo	20 µg	40 µg	Placebo	20 µg	40 µg
1	0	10 (P < 0.01)	35 (P < 0.01)	0	0 (P = 0.04)	18 (P < 0.01)
3	0	18 (P < 0.01)	39 (P < 0.01)	0	40 (P < 0.01)	80 (P < 0.01)
6	0	29 (P < 0.01)	70 (P < 0.01)	0	41 (P < 0.01)	160 (P < 0.01)
12	0	29 (P < 0.01)	59 (P < 0.01)	2	60 (P < 0.01)	12 (P < 0.01)

ALP — Serum alkaline phosphatase

NTX — urinary N-telopeptide

risks. This significant finding has prompted the U.S. Food and Drug Administration to require Eli Lilly to place a black box warning in the package insert that teriparatide may cause osteosarcoma.

Interestingly, two clinical trials compared the bisphosphonate alendronate to teriparatide in postmenopausal women with osteoporosis. The study design and outcomes measured were similar to the first two trials described in this evaluation. Teriparatide increased lumbar spine bone mineral density, femoral neck bone mineral density, and total hipbone mineral density significantly more than 10 mg alendronate daily. The Body, et al. study showed that postmenopausal women treated with teriparatide for 12 months had a greater than a 150% change in bone resorption and a 50% change in bone formation; however, alendronate reduced biochemical markers of bone resorption and formation by 50%. There was no explanation given as to why alendronate reduced bone resorption and formation in 12 months and statistical tests were not conducted to determine if bone resorption was significantly different from bone formation in the two treatment groups (teriparatide and alendronate). However, other studies have demonstrated that alendronate inhibits bone resorption and not bone formation, and increases bone mineral density.

Summary and recommendations: Clinical trials of teriparatide provided data that it increases bone mineral density at certain bone sites. No study has been conducted to test the efficacy of teriparatide on humans beyond the two years. Furthermore, the risk of developing osteosarcoma by using teriparatide was found to be dose- and duration-dependent in animals. Formulary recommendations are as follows: 1) do not stock as formulary drug; 2) defer starting drug in hospital for chronic drug therapy, and start in outpatient setting where therapy costs can be correlated with insurance reimbursement; and 3) patients on chronic outpatient therapy should use their home supply for in-hospital use.

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