FDA Approves First IV Osteoporosis Therapy

BY ELIZABETH MECHCATIE
Senior Writer

Last month, the Food and Drug Administration approved an injectable formulation of ibandronate, the first intravenous treatment for osteoporosis to become available and the first bisphosphonate administered once every 3 months.

The approved dose is 3 mg, administered intravenously over 15-30 seconds, by a health care professional, once every 3 months. Ibandronate is the third such formulation approved by the FDA; the first, a daily 2.5-mg formulation approved in 2003, was never marketed because of the availability of more convenient weekly bisphosphonate formulations that were already available at that time. A monthly oral formulation of ibandronate (150 mg) was approved and marketed almost a year ago. Like the monthly formulation, the IV formulation will be marketed under the trade name Boniva, by Hoffmann-La Roche. It will be available "early this year," according to a press release announcing the approval. At press time, the company had not provided information on its cost.

Bypassing the esophagus and stomach—eliminating the need to sit upright without drinking or eating for 30-60 minutes after taking an oral bisphosphonate that is required to reduce the risk of esophagitis and gastritis—is perhaps the most obvious advantage of the IV formulation, said Dr. Robert Recker, director of the Creighton University Osteoporosis Research Center, Omaha, Neb.

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Injectable ibandronate can also be used for patients who cannot swallow well, and having the patient come to the office once every 3 months for an injection assures compliance and may be more convenient for patients, added Dr. Recker, who is also professor of medicine and chief of the division of endocrinology at the University. He is a consultant to Roche, and to manufacturers of other osteoporosis therapies, and has conducted clinical trials funded by all these companies.

Dr. Recker was among the investigators in the DIVA (the Dosing Intravenous Administration) study, a randomized, double-blind multinational "noninferiority" study of 1,358 women with postmenopausal osteoporosis. The study compared 2.5 mg of ibandronate daily with the injectable formulation once every 3 months; at 1 year, bone mineral density (BMD) of the lumbar spine had increased by a mean of 4.5% among those on the IV treatment vs. a mean of 3.5% among those on daily therapy, a highly statistically significant difference. Increases in the total hip, femoral neck and trochanter BMD were also greater among those on IV ibandronate.

Because the 2.5-mg daily formulation has already been shown to reduce the risk of new vertebral fractures over 3 years in studies that were the basis of that formulation's approval, antifracture efficacy data on IV ibandronate were not required for approval.

Overall safety and tolerability of IV ibandronate was similar to that associated with the daily oral dose in the DIVA study, with arthralgia, abdominal pain, and back pain among the most commonly reported side effects. Some patients experience a mild flu-like syndrome with the first injection, which, if necessary, is easily suppressed with aspirin, acetaminophen, or an NSAID, although some people do not need to take anything, Dr. Recker said.

Because IV bisphosphonates have been associated with renal toxicity, serum creatinine should be checked before each dose, and patients with severe renal impairment should not receive the drug, according to the product's label (package insert), approved by the FDA. No cases of acute renal failure were reported in controlled trials where IV Boniva was administered over 15-30 seconds. Like other bisphosphonates, ibandronate inhibits osteoclast-mediated bone resorption, reducing the elevated rate of bone turnover. The other two bisphosphonates approved for treating postmenopausal osteoporosis are alendronate (Fosamax) and risedronate (Actonel), which are administered weekly, and are also approved for prevention of osteoporosis.

To get the most benefits from bisphosphonates, Dr. Recker stressed taking a daily absorbable calcium supplement of more than 1,200 mg of calcium a day taken in divided doses with meals, and a vitamin D supplement. He recommends 1,000 mg of vitamin D_3 every day, not vitamin D_2, which is in most supplements. ■

Bisphosphonate Compliance No Better Weekly Than Daily

BY KERRI WACHTER
Senior Writer

Nashville, Tenn. — Women with postmenopausal osteoporosis are no more likely to adhere to bisphosphonate therapy with weekly dosing than with daily dosing, according to data presented in a poster at the annual meeting of the American Society for Bone and Mineral Research.

In a retrospective study of 12,538 women with postmenopausal osteoporosis, risk of adherence failure did not differ between patients receiving weekly versus daily bisphosphonate therapy, according to Derek Weycker, Ph.D., of Policy Analysis Inc. in Brookline, Mass., and his colleagues.

The researchers reviewed integrated medical and outpatient pharmacy claims for women aged 45 years and older with postmenopausal osteoporosis from 30 U.S. health plans. Claims from January 1998 to December 2003 were included in the review.

Women were determined to have postmenopausal osteoporosis based on one or more medical claims with a corresponding diagnosis code. The women also had no evidence of secondary causes of osteoporosis. Patients were considered to have initiated therapy if their first corresponding prescription was preceded by a 6-month period of continuous health benefits without evidence of antiosteoporosis drug use.

Adherence was assessed on a daily basis from the date of therapy initiation through the date of a switch to another antiosteoporosis drug or formulation, date they left the plan, or Dec. 31, 2003—whichever came first. An adherence ratio was calculated by dividing the cumulative number of bisphosphonate therapy days by the number of elapsed calendar days (from therapy initiation). To calculate these measures, the researchers identified all outpatient pharmacy claims for weekly and daily bisphosphonate therapy based on corresponding codes from the National Drug Code system, arrayed them temporally based on dispensing dates, and assessed days of therapy supplied for each script based on the quantity of pills dispensed.

Within 6 months of initiating therapy, 57% of the 9,117 women on weekly therapy and 62% of the 3,421 women on daily therapy were considered to have adherence failure—defined as an adherence ratio less than 80%.

At 1 year, 66% of those on weekly therapy and 71% of those on daily therapy had adherence failure. At 2.5 years, the rates were 80% for weekly therapy and 82% for daily therapy.

After adjusting for age, fracture history, drug received, selected comorbid conditions, and selected concomitant medications, the two groups did not differ in risk of adherence failure. Risk of adherence failure was higher among women aged 65 years and older but was lower in those with a history of fracture.

The researchers did not assess adherence for specific drugs.

The research was funded by Amgen Inc., which is currently investigating a fully monoclonal antibody for the treatment of osteoporosis. ■

Tracking FSH Annually Said to Help Predict Bone Loss in Perimenopause

Tracking follicle-stimulating hormone levels every year from premenopause onward can help predict bone loss during the menopausal transition, reported MaryFran R. Sowers, Ph.D., of the University of Michigan, Ann Arbor, and her associates.

The researchers conducted what they described as the first study to longitudinally characterize bone mineral density (BMD) loss at the spine and hip in conjunction with changes in reproductive hormone concentrations. They found that the interaction between the baseline FSH level obtained before menopause and serial FSH levels taken every year thereafter predicted bone loss. However, this interaction "is complex, requires at least two FSH values, and may be challenging to apply in a busy clinical setting," they cautioned.

The study population comprised 2,311 women aged 42-52 at baseline who were assessed at several medical centers across the United States for 5 years. Half of the women were white, 28% were African American, 11% were Japanese, and 11% were Chinese.

The women underwent annual spine, femoral neck, and total hip BMD assessments with densitometers. Blood samples obtained annually during the early follicular phase of the menstrual cycle were analyzed for estradiol, FSH, testosterone, sex hormone–binding globulin (SHBG), and dehydroepiandrosterone sulfate (DHEAS) content.

At baseline, 53% of the women were classified as premenopausal because they reported no decrease in menstrual regularity during the preceding year, and 47% were classified as being in the "early perimenopausal" period because they reported decreased menstrual regularity in the preceding 3 months (J. Clin. Endocrinol. Metab. doi:10.1210/jc.2005-1836, published Jan. 10, 2006).

The interaction between baseline FSH levels and subsequent levels predicted bone loss. "If baseline FSH was lower (<25 mIU/mL), then statistical modeling indicated that more lumbar spine change occurred only when the follow-up FSH concentrations were higher (40-70 mIU/mL), and the greatest amount of spine BMD loss (–0.05 g/cm^2) was projected when the follow-up FSH value was greater than 70 mIU/mL.

"However, if the baseline FSH was higher (35-45 mIU/mL), then modeling indicated that lower levels of follow-up FSH (40-50 mIU/mL)" predicted a decrease in spine BMD, the investigators said. They devised charts to show predicted bone loss for various levels of baseline and subsequent FSH.

Estradiol levels measured throughout this transitional period "were poor predictors of incremental BMD change," Dr. Sowers and her associates noted.

Similarly, there was no correlation between BMD changes and levels of testosterone, DHEAS, or SHBG.

—Mary Ann Moon