

Six-Year Zoledronic Acid Regimen Safe, Effective

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FROM THE ANNUAL MEETING OF THE AMERICAN SOCIETY FOR BONE AND MINERAL RESEARCH

TORONTO – Patients who continued annual treatment with zoledronic acid for 6 years had significantly better bone mineral density and fewer morphometric vertebral fractures than did patients who received 3 years of treatment and

then stopped, in a controlled study with more than 1,200 patients.

Six continuous years of annual zoledronic acid treatment also proved safe, making continued treatment with this bisphosphonate formulation an option for patients who might benefit, Dennis M. Black, Ph.D., said at the meeting.

“After 3 years, it might be beneficial for some women, particularly those at high vertebral fracture risk, to continue zole-

dronic acid for an additional 3 years,” said Dr. Black, professor of epidemiology and biostatistics at the University of California, San Francisco. “These new findings show that continued treatment with zoledronic acid for 6 years continues to maintain bone mass and reduced vertebral fracture risk with no change to its favorable safety profile compared with discontinuation of treatment after 3 years,” he said in a written statement.

On the other hand, the decision to continue bisphosphonate treatment long term must be individualized, he said. It may be possible to identify women who would benefit from a drug holiday.

With the new finding, zoledronic acid joins other bisphosphonates, such as alendronate, shown to prevent loss of bone density when the drug is continued after several years of treatment. In a prior report, continuing treatment with alendronate for 5 years following an initial 5 years of treatment led to less bone density loss than in patients who switched from alendronate to placebo (JAMA 2006;296:2927-38). The same alendronate study failed to show that continued bisphosphonate treatment led to a reduced

Hypertriglyceridemia: Patients with fasting serum TG levels above 500 mg/dL were excluded from the diabetes clinical trials. In the phase 3 diabetes trials, 637 (63%) patients had baseline fasting serum TG levels less than 200 mg/dL, 261 (25%) had baseline fasting serum TG levels between 200 and 300 mg/dL, 111 (11%) had baseline fasting serum TG levels between 300 and 500 mg/dL, and 9 (1%) had fasting serum TG levels greater than or equal to 500 mg/dL. The median baseline fasting TG concentration for the study population was 172 mg/dL; the median post-treatment fasting TG was 195 mg/dL in the WELCHOL group and 177 mg/dL in the placebo group. WELCHOL therapy resulted in a median placebo-corrected increase in serum TG of 5% (p=0.22), 22% (p<0.001), and 18% (p<0.001) when added to metformin, insulin and sulfonylureas, respectively [See Warnings and Precautions (5.2) and Clinical Studies (14.2) in the full prescribing information]. In comparison, WELCHOL resulted in a median increase in serum TG of 5% compared to placebo (p=0.42) in a 24-week monotherapy lipid-lowering trial [See Clinical Studies (14.1) in the full prescribing information].

Treatment-emergent fasting TG concentrations \geq 500 mg/dL occurred in 4.1% of WELCHOL-treated patients compared to 2.0% of placebo-treated patients. Among these patients, the TG concentrations with WELCHOL (median 604 mg/dL; interquartile range 538-712 mg/dL) were similar to that observed with placebo (median 644 mg/dL; interquartile range 574-724 mg/dL). Two (0.4%) patients on WELCHOL and 2 (0.4%) patients on placebo developed TG elevations \geq 1000 mg/dL. In all WELCHOL clinical trials, including studies in patients with type 2 diabetes and patients with primary hyperlipidemia, there were no reported cases of acute pancreatitis associated with hypertriglyceridemia. It is unknown whether patients with more uncontrolled, baseline hypertriglyceridemia would have greater increases in serum TG levels with WELCHOL [See Contraindications (4) and Warnings and Precautions (5.2)].

Cardiovascular adverse events: During the diabetes clinical trials, the incidence of patients with treatment-emergent serious adverse events involving the cardiovascular system was 3% (17/566) in the WELCHOL group and 2% (10/562) in the placebo group. These overall rates included disparate events (e.g., myocardial infarction, aortic stenosis, and bradycardia); therefore, the significance of this imbalance is unknown.

Hypoglycemia: Adverse events of hypoglycemia were reported based on the clinical judgment of the blinded investigators and did not require confirmation with fingerstick glucose testing. The overall reported incidence of hypoglycemia was 3.0% in patients treated with WELCHOL and 2.3% in patients treated with placebo. No WELCHOL treated patients developed severe hypoglycemia.

6.2 Post-marketing Experience

The following additional adverse reactions have been identified during post-approval use of WELCHOL. Because these reactions are reported voluntarily from a population of uncertain size, it is generally not possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

Drug Interactions with concomitant WELCHOL administration include:

- Increased seizure activity or decreased phenytoin levels in patients receiving phenytoin. Phenytoin should be administered 4 hours prior to WELCHOL.
- Reduced International Normalized Ratio (INR) in patients receiving warfarin therapy. In warfarin-treated patients, INR should be monitored frequently during WELCHOL initiation then periodically thereafter.
- Elevated thyroid-stimulating hormone (TSH) in patients receiving thyroid hormone replacement therapy. Thyroid hormone replacement should be administered 4 hours prior to WELCHOL [See Drug Interactions (7)].

Gastrointestinal Adverse Reactions

Bowel obstruction (in patients with a history of bowel obstruction or resection), dysphagia or esophageal obstruction (occasionally requiring medical intervention), fecal impaction, pancreatitis, abdominal distension, exacerbation of hemorrhoids, and increased transaminases.

Laboratory Abnormalities

Hypertriglyceridemia

7 DRUG INTERACTIONS

Table 4 lists the drugs that have been tested in *in vitro* binding or *in vivo* drug interaction studies with colesevelam and/or drugs with postmarketing reports consistent with potential drug-drug interactions. Orally administered drugs that have not been tested for interaction with colesevelam, especially those with a narrow therapeutic index, should also be administered at least 4 hours prior to WELCHOL. Alternatively, the physician should monitor drug levels of the co-administered drug.

Table 4
Drugs Tested in *In Vitro* Binding or *In Vivo* Drug Interaction Testing or With Post-Marketing Reports

Drugs with a known interaction with colesevelam ^a	cyclosporine ^c , glyburide ^a , levothyroxine ^a , and oral contraceptives containing ethinyl estradiol and norethindrone
Drugs with postmarketing reports consistent with potential drug-drug interactions when coadministered with WELCHOL	phenytoin ^a , warfarin ^b
Drugs that do not interact with colesevelam based on <i>in vitro</i> or <i>in vivo</i> testing	cephalexin, ciprofloxacin, digoxin, warfarin ^b , fenofibrate, lovastatin, metformin, metoprolol, pioglitazone, quinidine, repaglinide, valproic acid, verapamil

^a Should be administered at least 4 hours prior to WELCHOL

^b No significant alteration of warfarin drug levels with warfarin and WELCHOL coadministration in an *in vivo* study which did not evaluate warfarin pharmacodynamics (INR). [See Post-marketing Experience (6.2)]

^c Cyclosporine levels should be monitored and, based on theoretical grounds, cyclosporine should be administered at least 4 hours prior to WELCHOL.

In an *in vivo* drug interaction study, WELCHOL and warfarin coadministration had no effect on warfarin drug levels. This study did not assess the effect of WELCHOL and warfarin coadministration on INR. In postmarketing reports, concomitant use of WELCHOL and warfarin has been associated with reduced INR. Therefore, in patients on warfarin therapy, the INR should be monitored before initiating WELCHOL and frequently enough during early WELCHOL therapy to ensure that no significant alteration in INR occurs. Once the INR is stable, continue to monitor the INR at intervals usually recommended for patients on warfarin. [See Post-marketing Experience (6.2)]

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Pregnancy Category B. There are no adequate and well-controlled studies of colesevelam use in pregnant women. Animal reproduction studies in rats and rabbits revealed no evidence of fetal harm. Requirements for vitamins and other nutrients are increased in pregnancy. However, the effect of colesevelam on the absorption of fat-soluble vitamins has not been studied in pregnant women. This drug should be used during pregnancy only if clearly needed.

In animal reproduction studies, colesevelam revealed no evidence of fetal harm when administered to rats and rabbits at doses 50 and 17 times the maximum human dose, respectively. Because animal reproduction studies are not always predictive of human response, this drug should be used in pregnancy only if clearly needed.

8.3 Nursing Mothers

Colesevelam hydrochloride is not expected to be excreted in human milk because colesevelam hydrochloride is not absorbed systemically from the gastrointestinal tract.

8.4 Pediatric Use

The safety and effectiveness of WELCHOL as monotherapy or in combination with a statin were evaluated in children, 10 to 17 years of age with heFH [See Clinical Studies (14.1) in the full prescribing information]. The adverse reaction profile was similar to that of patients treated with placebo. In this limited controlled study, there were no significant effects on growth, sexual maturation, fat-soluble vitamin levels or clotting factors in the adolescent boys or girls relative to placebo [See Adverse Reactions (6.1)].

Due to tablet size, WELCHOL for Oral Suspension is recommended for use in the pediatric population. Dose adjustments are not required when WELCHOL is administered to children 10 to 17 years of age.

WELCHOL has not been studied in children younger than 10 years of age or in pre-menarchal girls.

8.5 Geriatric Use

Primary Hyperlipidemia: Of the 1350 patients enrolled in the hyperlipidemia clinical studies, 349 (26%) were \geq 65 years old, and 58 (4%) were \geq 75 years old. No overall differences in safety or effectiveness were observed between these subjects and younger subjects, and other reported clinical experience has not identified differences in responses between the elderly and younger patients, but greater sensitivity of some older individuals cannot be ruled out.

Type 2 Diabetes Mellitus: Of the 1128 patients enrolled in the four diabetes studies, 249 (22%) were \geq 65 years old, and 12 (1%) were \geq 75 years old. In these trials, WELCHOL 3.8 g/day or placebo was added onto background anti-diabetic therapy. No overall differences in safety or effectiveness were observed between the elderly and younger patients, but greater sensitivity of some older individuals cannot be ruled out.

8.6 Hepatic Impairment

No special considerations or dosage adjustments are recommended when WELCHOL is administered to patients with hepatic impairment.

8.7 Renal Impairment

Type 2 Diabetes Mellitus: Of the 1128 patients enrolled in the four diabetes studies, 696 (62%) had mild renal insufficiency (creatinine clearance [CrCl] 50-80 mL/min), 53 (5%) had moderate renal insufficiency (CrCl 30-50 mL/min), and none had severe renal insufficiency (CrCl <30 mL/min), as estimated from baseline serum creatinine using the Modification of Diet in Renal Disease (MDRD) equation. No overall differences in safety or effectiveness were observed between patients with CrCl \leq 50 mL/min (n=53) and those with a CrCl \geq 50 mL/min (n=1075).

10 OVERDOSAGE

Doses of WELCHOL in excess of 4.5 g/day have not been tested. Because WELCHOL is not absorbed, the risk of systemic toxicity is low. However, excessive doses of WELCHOL may cause more severe local gastrointestinal effects (e.g., constipation) than recommended doses.



The decision to continue bisphosphonate treatment long term must be individualized.

DR. BLACK

rate of morphometric vertebral fractures, compared with stopping alendronate.

The new zoledronic acid findings came from an extension of the Health Outcomes and Reduced Incidence With Zoledronic Acid Once Yearly (HORIZON) Pivotal Fracture Trial, which compared a single, annual infusion of zoledronic acid with placebo in postmenopausal women with osteoporosis during 3 years of treatment (N. Engl. J. Med. 2007;356:1809-22).

Dr. Black and his associates randomized 1,233 women who completed the zoledronic acid arm of the study to either continue with another 3 years of annual infusions of 5 mg zoledronic acid or switch to placebo. Their average age was 76, and about 55% had a femoral neck T score of less than -2.5.

At the end of the study, the percent change in femoral neck bone mineral density, compared with the level at entry into the study, averaged 1% higher in patients treated with zoledronic acid, a statistically significant difference in the study's primary end point. Femoral neck bone mineral density in the zoledronic acid-treated patients increased by an average of 1.4% over their baseline 6 years earlier (when they started on the drug), compared with those who switched off the bisphosphonate after 3 years, also a statistically significant difference.

Six years of annual zoledronic acid treatment appeared safe, with no excess of adverse events or serious adverse events compared with the patients on 3 years of placebo.

The HORIZON Pivotal Fracture Trial was funded by Novartis, which markets zoledronic acid (Aclasta). Dr. Black said that he has served as a consultant and done teaching for Amgen Inc. and Nycomed, and that he has received research contracts from Amgen, Merck & Co., Novartis, and Roche/Genentech. ■

Welchol
(colesevelam HCl)

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