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Lilly Announces New Data Further Exploring Mechanistic Differences Between FORTEO® (teriparatide [rDNA origin] injection) and Zoledronic Acid

INDIANAPOLIS, Oct. 15, 2012 /PRNewswire/ -- Eli Lilly and Company (NYSE: LLY) today presented data comparing the effects of FORTEO and zoledronic acid on transiliac crest bone biopsies at six months in postmenopausal women with osteoporosis, based on additional analysis of data from the SHOTZ trial. Results, which were presented in an oral presentation at the 2012 Annual Meeting of the American Society for Bone and Mineral Research (ASBMR) in Minneapolis, MN, clearly differentiate the mechanism of action of FORTEO as anabolic and that of zoledronic acid as antiresorptive.

The data show that the contrasting effects of FORTEO and zoledronic acid on bone remodeling are evident on all three bone surfaces: cancellous, endocortical and periosteal. The effects on mineralizing surface (MS/BS) and bone formation rate (BFR/BS) — dynamic indices of bone formation and turnover — provided clear differentiation of the mechanism of action of the two drugs at six months.[1]

"This study continues to differentiate these two established osteoporosis treatments with different mechanisms of action and further contrasts the anticatabolic action of zoledronic acid and the anabolic action of teriparatide on all three bone surfaces," said David W. Dempster, PhD, professor of clinical pathology, Columbia University. "It is important to understand the effect of antifracture drugs on cortical bone, which makes up 80 percent of the adult skeleton."

Previously, researchers used dynamic histomorphometry, a technique to measure cellular activities of remodeling at the bone tissue level, to explore the mechanisms of action of FORTEO and zoledronic acid in the cancellous compartment of bone biopsies. In this study, researchers extended their observations to the outer and inner surfaces of cortical bone.

In a typical bone sample, the internal meshwork, or cancellous bone, is surrounded with cortical bone. The cortical bone has two surfaces; the endocortical (inner) surface is adjacent to cancellous bone, and the periosteal (outer) surface forms the external bone surface.

These study results showed that the contrasting effects of FORTEO and zoledronic acid on bone remodeling were evident on all three bone envelopes measured. The dynamic index of bone formation, mineralizing surface (MS/BS), was a striking differentiator between the drugs:

- cancellous (median: 5.6 percent [FORTEO] vs. 0.16 percent [zoledronic acid]);
- endocortical (median: 18.64 percent [FORTEO] vs. 0.30 percent [zoledronic acid]); and
- periosteal (median: 0.71 percent [FORTEO] vs. 0.0 percent [zoledronic acid]).

Similar results were observed for other histomorphometric indices such as bone formation rate (BFR), mineral apposition rate (MAR), osteoid surface (OS/BS), osteoid thickness (O.Th) and wall thickness (W.Th); all of which were significantly higher in the FORTEO than the zoledronic acid group in both cancellous and endocortical envelopes. Conversely, in both envelopes, eroded surface (ES/BS) was lower in the zoledronic acid than the teriparatide group. Periosteal MS/BS and BFR/BS were greater with FORTEO than with zoledronic acid treatment.[1]

Although the effect of FORTEO was smaller on the periosteal surface than the endocortical surface, the greater values for dynamic indices relative to the zoledronic acid group suggests the possibility of periosteal expansion, and possibly an increase in bone size with FORTEO treatment. Further, in FORTEO samples, MS/BS and BRF/BS were higher in the endocortical than the cancellous envelope which, coupled with an increase in wall thickness, provides a mechanism for cortical thickening with FORTEO treatment.[1]

In the study, the overall safety profile was consistent with the known FORTEO safety profile seen in this patient population. The overall incidence of serious adverse events, treatment-emergent adverse events and adverse events leading to discontinuation were similar between the FORTEO and zoledronic acid treatment groups.[1]

"We believe these data help further explain the growing body of evidence supporting the mechanism of action of FORTEO," said Anthony Beardsworth, M.D., senior medical director, Eli Lilly and Company. "The results may help healthcare professionals better determine osteoporosis treatment for their individual patients."

FORTEO is used in both men and postmenopausal women with osteoporosis who are at high risk for having broken bones (fractures). FORTEO is used in both men and women with osteoporosis due to use of glucocorticoid medicines, such as prednisone, for several months, who are at high risk for having broken bones (fractures). FORTEO can be used by people who have had a fracture related to osteoporosis, or who have several risk factors for fracture, or who cannot use other osteoporosis treatments.[2]

During the drug testing process, the medicine in FORTEO caused some rats to develop osteosarcoma, which, in humans, is a serious but rare bone cancer. Osteosarcoma has been reported rarely in people who took FORTEO®, and it is unknown if people who take FORTEO have a higher chance of getting the disease. Before patients take FORTEO, patients should tell their healthcare provider if they have Paget's disease of bone, are a child or young adult whose bones are still growing or have had radiation therapy.[2] For more information about FORTEO, please see the important safety information, including Boxed Warning regarding osteosarcoma, below.

About the Study[1]

Results from this study were taken from the SHOTZ (**S**keletal **H**istomorphometry in Patients **O**n **T**eriparatide or **Z**oledronic Acid Therapy) Trial. The study was a 12-month, randomized, double-blind, active comparator-controlled study that compared, at six months, histomorphometric indices in the cancellous, endocortical and periosteal bone envelopes from bone biopsies obtained from 58 postmenopausal women with osteoporosis at high risk for fracture. Participants received either 20 mg/d teriparatide (TPTD, n=28) or 5 mg/y zoledronic acid (ZOL, n=30).

Participants aged 55 to 89 years were enrolled based on bone mineral density (BMD) and fracture criteria as assessed by the investigators.

Important Safety Information about FORTEO

What is the most important information I should know about FORTEO?

WARNING: POTENTIAL RISK OF OSTEOSARCOMA

During the drug testing process, the medicine in FORTEO caused some rats to develop a bone cancer called osteosarcoma. In people, osteosarcoma is a serious but rare cancer. Osteosarcoma has been reported rarely in people who took FORTEO. It is not known if people who take FORTEO have a higher chance of getting osteosarcoma. Before you take FORTEO, you should tell your healthcare provider if you have Paget's disease of bone, are a child or young adult whose bones are still growing, or have had radiation therapy.

Who should not take FORTEO?

- You should not take FORTEO for more than 2 years over your lifetime.
- Do not use FORTEO if you are allergic to any of the ingredients in FORTEO. Serious allergic reactions have been reported.

What should I tell my healthcare provider before taking FORTEO?

- Before you take FORTEO, you should tell your healthcare provider if you have a bone disease other than osteoporosis, have cancer in your bones, have trouble injecting yourself and do not have someone who can help you, have or have had kidney stones, have or have had too much calcium in your blood, take medications that contain digoxin (Digoxin, Lanoxicaps, Lanoxin), or have any other medical conditions.
- You should also tell your healthcare provider, before you take FORTEO, if you are pregnant or thinking about becoming pregnant. It is not known if FORTEO will harm your unborn baby. If you are breastfeeding or plan to breastfeed, it is not known if FORTEO passes into your breast milk. You and your healthcare provider should decide if you will take FORTEO or breastfeed. You should not do both.

What are the possible side effects of FORTEO?

- FORTEO can cause serious side effects including a decrease in blood pressure when you change positions. Some people feel dizzy, get a fast heartbeat, or feel faint right after the first few doses. This usually happens within 4 hours of taking FORTEO and goes away within a few hours. For the first few doses, take your injections of FORTEO in a place where you can sit or lie down right away if you get these symptoms. If your symptoms get worse or do not go away, stop taking FORTEO and call your healthcare provider. FORTEO may also cause increased calcium in your blood. Tell your healthcare provider if you have nausea, vomiting, constipation, low energy, or muscle weakness. These may be signs there is too much calcium in your blood.
- Common side effects of FORTEO include nausea, joint aches, pain, leg cramps, and injection site reactions including

injection site pain, swelling and bruising. These are not all the possible side effects of FORTEO. You are encouraged to report negative side effects of Prescription drugs to the FDA. Visit www.fda.gov/medwatch or call 1-800-FDA-1088.

Additional safety information about FORTEO

- There is a voluntary patient registry for people who take FORTEO. The purpose of the registry is to collect information about the possible risk of osteosarcoma in people who take FORTEO. For information about how to sign up for this patient registry, call 1-866-382-6813 or go to www.forteoregistry.org.
- The FORTEO Delivery Device has enough medicine for 28 days. It is set to give a 20-microgram dose of medicine each day. Before you try to inject FORTEO yourself, a healthcare provider should teach you how to use the FORTEO Delivery Device to give your injection the right way. Inject FORTEO one time each day in your thigh or abdomen (lower stomach area). Do not inject all the medicine in the FORTEO Delivery Device at any one time. Do not transfer the medicine from the FORTEO Delivery Device to a syringe. This can result in taking the wrong dose of FORTEO. If you take more FORTEO than prescribed, call your healthcare provider. If you take too much FORTEO, you may have nausea, vomiting, weakness, or dizziness.

How should I store FORTEO?

- Keep your FORTEO Delivery Device in the refrigerator between 36 degrees F to 46 degrees F (2 degrees C to 8 degrees C). Do not freeze the FORTEO Delivery Device. Do not use FORTEO if it has been frozen. Do not use FORTEO after the expiration date printed on the delivery device and packaging. Throw away the FORTEO Delivery Device after 28 days even if it has medicine in it (see the User Manual).

For more safety information, please see Medication Guide (http://pi.lilly.com/us/forteo-medguide.pdf) and Prescribing Information (http://pi.lilly.com/us/forteo-pi.pdf), including Boxed Warning regarding osteosarcoma. Please see full user manual that accompanies the delivery device.

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About Eli Lilly and Company

Eli Lilly and Company, a leading innovation-driven company, is developing a growing portfolio of pharmaceutical products by applying the latest research from its own worldwide laboratories and from collaborations with eminent scientific organizations. Headquartered in Indianapolis, Ind., Lilly provides answers — through medicines and information — for some of the world's most urgent medical needs. Information about Lilly is available at www.lilly.com. P-LLY

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This press release contains forward-looking statements about Forteo for the treatment of osteoporosis. It reflects Lilly's current beliefs; however, as with any such undertaking, there are substantial risks and uncertainties in the process of drug development and commercialization. There is no guarantee that future study results and patient experience will be consistent with study findings to date or that Forteo will continue to be commercially successful. For further discussion of these and other risks and uncertainties, please see Lilly's latest Forms 10-Q and 10-K filed with the U.S. Securities and Exchange Commission. Lilly undertakes no duty to update forward-looking statements.

[1] Dempster, D., et al. "Differential Effects of Teriparatide and Zoledronic Acid on the Outer and Inner Surfaces of Cortical Bone in Postmenopausal Women with Osteoporosis: Results from the SHOTZ Trial." Abstract presented at the ASBMR 2012 Annual Meeting, Oct.15, 2012, 10:15 AM.

[2] FORTEO PI. Available at http://pi.lilly.com/us/forteo-pi.pdf.

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