

**Proposed Risk Evaluation and
Mitigation Strategy
(REMS)**

FORTEO® NDA: 21-318/S-012

Teriparatide (rDNA origin) Injection
Osteoporosis

United States Food and Drug Administration
Division of Reproductive and Urologic Products

Eli Lilly and Company

Indianapolis, IN 46285



NDA 21-318/S-012 FORTEO®

Eli Lilly and Company

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PROPOSED RISK EVALUATION AND MITIGATION STRATEGY (REMS)

I. Goals

A. Risk Mitigation

To mitigate the potential risk of osteosarcoma associated with FORTEO by:

- i. alerting and warning healthcare providers and patients about the potential risk
- ii. informing healthcare providers of the 2-year maximum lifetime duration of treatment with FORTEO and proper patient selection
- iii. informing and educating healthcare providers and patients about the voluntary FORTEO Patient Registry.

II. REMS Elements

A. Medication Guide

A Medication Guide will be dispensed with each FORTEO prescription in accordance with 21 CFR 208.24. The Medication Guide is enclosed within each FORTEO carton at the time of final product assembly along with the Prescribing Information and User Manual.

Please see the appended Medication Guide.

B. Communication Plan

In accordance with FDCA 505-1(e)(3), Lilly will implement the following elements of a communication plan to healthcare providers (HCP) likely to prescribe FORTEO:

- i. **A Dear HCP (DHCP) Letter** will be mailed at the time of launch of the GIOP indication. The intended audience for this DHCP letter will be all healthcare professionals who are likely to prescribe FORTEO. Lilly has identified these providers as any HCP who has prescribed FORTEO in the last 12 months. These include physicians, nurse practitioners, and physicians' assistants, predominantly in the specialties of Rheumatology, Endocrinology, Internal Medicine, and Family Practice.

Please see the appended DHCP Letter.

- ii. **A Direct Mail Letter** containing the elements of the DHCP letter will also be mailed once per year for an additional two years post launch to all prescribers who newly prescribe FORTEO. These prescribers will be

defined as any HCP individuals who prescribe FORTEO in a 12-month period and who had not prescribed FORTEO in the previous 12-month period.

Please see the appended Direct Mail Letter.

- iii. **The Highlighted Information for Prescribers** will be provided by Lilly representatives during the first discussion of the new GIOP indication with all HCPs visited during the first six months after this indication's launch. This will also be sent with the Direct Mail Letter.

Please see the appended Highlighted Information for Prescribers.

Lilly will make the REMS, the DHCP letter, the Medication Guide, the Highlighted Information for Prescribers, and professional labeling available via a REMS-specific linkage from the FORTEO website. The Medication Guide, the Highlighted Information for Prescribers, and professional labeling will also be available via hardcopy from Lilly sales specialists, through Lilly's medical information department, and by calling The Lilly Answers Center.

C. Elements to Assure Safe Use

Elements to Assure Safe Use are not required.

D. Implementation System

An Implementation System is not required.

E. Timetable for Submission of Assessments

REMS Assessments will be submitted to the FDA at 18 months, 3 years and 7 years according to the following timetable:

1 st Assessment (18 months)	January 2011
2 nd Assessment (3 years)	July 2012
3 rd Assessment (7 years)	July 2016

The reporting interval covered by each assessment will conclude no earlier than 60 days before the submission date for that assessment time interval.

Attachments

- Medication Guide
- Dear Healthcare Professional Letter
- Direct Mail Letter
- Highlighted Information for Prescribers

Medication Guide

FORTEO® (for-TAY-o) teriparatide (rDNA origin) injection

Read this Medication Guide before you start taking FORTEO and each time you get a refill. There may be new information. Also, read the User Manual that comes with the FORTEO delivery device (pen) for information on how to use the device to inject your medicine the right way. This Medication Guide does not take the place of talking with your healthcare provider about your medical condition or your treatment.

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

- 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.
- You should not take FORTEO for more than 2 years over your lifetime.
- 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.rti.org.

What is FORTEO?

- FORTEO is a prescription medicine that is like a hormone made by the body called parathyroid hormone or PTH. FORTEO may help to form new bone, increase bone mineral density and bone strength.
- FORTEO can lessen the number of fractures of the spine and other bones in postmenopausal women with osteoporosis.
- The effect on fractures has not been studied in men.
- FORTEO is used in both men and postmenopausal women with osteoporosis who are at high risk for having 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 can not use other osteoporosis treatments.
- 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). These include men and women with either a history of broken bones, who have several risk factors for fracture, or who can not use other osteoporosis treatments.

It is not known if FORTEO is safe and effective in children.

FORTEO should not be used in children and young adults whose bones are still growing.

Who should not use FORTEO?

Do not use FORTEO if you:

- are allergic to any of the ingredients in FORTEO. See the end of this Medication Guide for a complete list of the ingredients in FORTEO.

What should I tell my healthcare provider before taking FORTEO?

Before you take FORTEO, tell your healthcare provider if you:

- have the condition listed in the section “Who should not use FORTEO?”
- have Paget’s disease or other bone disease
- have cancer in your bones
- have trouble injecting yourself and do not have someone who can help you
- are a child or young adult whose bones are still growing
- have or have had kidney stones
- have had radiation therapy
- have or had too much calcium in your blood

- 52 • have any other medical conditions
- 53 • are pregnant or thinking about becoming pregnant. It is not known if FORTEO will harm your unborn
- 54 baby.
- 55 • are breast-feeding or plan to breast-feed. It is not known if FORTEO passes into your breast milk. You
- 56 and your doctor should decide if you will take FORTEO or breast feed. You should not do both.

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58 **Tell your healthcare provider about all the medicines you take** including prescription and non-prescription
59 medicines, vitamins, and herbal supplements. Your healthcare provider needs this information to help keep you from
60 taking FORTEO with other medicines that may harm you.

- 61 • Especially tell your doctor if you take medicines that contain digoxin (Digoxin, Lanoxicaps, Lanoxin).

62 **How should I use FORTEO?**

- 63 • Inject FORTEO one time each day in your thigh or abdomen (lower stomach area). Talk to a healthcare
- 64 provider about how to rotate injection sites.
- 65 • Before you try to inject FORTEO yourself, a healthcare provider should teach you how to use the
- 66 FORTEO delivery device to give your injection the right way.
- 67 • Read the detailed User Manual at the end of this Medication Guide.
- 68 • You can take FORTEO with or without food or drink.
- 69 • The FORTEO delivery device has enough medicine for 28 days. It is set to give a 20 microgram dose of
- 70 medicine each day. Do not inject all the medicine in the FORTEO delivery device at any one time.
- 71 • Do not transfer the medicine from the FORTEO delivery device to a syringe. This can result in taking
- 72 the wrong dose of FORTEO. If you do not have pen needles to use with your FORTEO delivery device,
- 73 talk with your healthcare provider.
- 74 • FORTEO should look clear and colorless. Do not use FORTEO if it has particles in it, or if it is cloudy
- 75 or colored.
- 76 • Inject FORTEO right away after you take the delivery device out of the refrigerator.
- 77 • After each use, safely remove the needle, recap the delivery device, and put it back in the refrigerator
- 78 right away.
- 79 • You can take FORTEO at any time of the day. To help you remember to take FORTEO, take it at about
- 80 the same time each day.
- 81 • If you forget or can not take FORTEO at your usual time, take it as soon as you can on that day. Do not
- 82 take more than one injection in the same day.
- 83 • If you take more FORTEO than prescribed, call your healthcare provider. If you take too much
- 84 FORTEO, you may have nausea, vomiting, weakness or dizziness.

85
86 Follow your healthcare provider's instructions about other ways you can help your osteoporosis, such as exercise,
87 diet, and reducing or stopping your use of tobacco and alcohol. If your healthcare provider recommends calcium and
88 vitamin D supplements, you can take them at the same time you take FORTEO.

89 **What are the possible side effects of FORTEO?**

90
91 FORTEO can cause serious side effects including:

- 92 • See "What is the most important information I should know about FORTEO?"
- 93 • **Decrease in blood pressure when you change positions.** Some people feel dizzy, get a fast heartbeat, or feel
- 94 faint right after the first few doses. This usually happens within 4 hours of taking FORTEO and goes away
- 95 within a few hours. For the first few doses, take your injections of FORTEO in a place where you can sit or lie
- 96 down right away if you get these symptoms. If your symptoms get worse or do not go away, stop taking
- 97 FORTEO and call your healthcare provider.
- 98 • **Increased calcium in your blood.** Tell your healthcare provider if you have nausea, vomiting, constipation,
- 99 low energy, or muscle weakness. These may be signs there is too much calcium in your blood.

100
101 Common side effects of FORTEO include:

- 102 • nausea
- 103 • joint aches
- 104 • pain

105

106 Your healthcare provider may take samples of blood and urine during treatment to check your response to FORTEO.
107 Also, your healthcare provider may ask you to have follow-up tests of bone mineral density.

108
109 Tell your healthcare provider if you have any side effect that bothers you or that does not go away.

110
111 These are not all the possible side effects of FORTEO. For more information, ask your doctor or pharmacist.

112
113 Call your doctor for medical advice about side effects. You may report side effects to FDA at 1-800-FDA-1088.

114 **How should I store FORTEO?**

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

120 **Keep FORTEO and all medicines out of the reach of children.**

121 **General information about FORTEO**

122 Medicines are sometimes prescribed for purposes other than those listed in a Medication Guide. Do not use
123 FORTEO for a condition for which it was not prescribed. Do not give FORTEO to other people, even if they have
124 the same condition you have.

125
126 This Medication Guide summarizes the most important information about FORTEO. If you would like more
127 information, talk with your healthcare provider. You can ask your pharmacist or healthcare provider for information
128 about FORTEO that is written for healthcare professionals. For more information, go to www.FORTEO.com or call
129 Lilly at 1-866-436-7836.

130 **What are the ingredients in FORTEO?**

131
132 Active ingredient: teriparatide

133
134 Inactive ingredients: glacial acetic acid, sodium acetate (anhydrous), mannitol, metacresol, and water for injection.
135 In addition, hydrochloric acid solution 10% and/or sodium hydroxide solution 10% may have been added to adjust
136 the product to pH 4.

137 **What is Osteoporosis?**

138 Osteoporosis is a disease in which the bones become thin and weak, increasing the chance of having a broken bone.
139 Osteoporosis usually causes no symptoms until a fracture happens. The most common fractures are in the spine
140 (backbone). They can shorten height, even without causing pain. Over time, the spine can become curved or
141 deformed and the body bent over. Fractures from osteoporosis can also happen in almost any bone in the body, for
142 example, the wrist, rib, or hip. Once you have had a fracture, the chance for more fractures greatly increases.

143
144 The following risk factors increase your chance of getting fractures from osteoporosis:

- 145 • past broken bones from osteoporosis.
- 146 • very low bone mineral density (BMD).
- 147 • frequent falls.
- 148 • limited movement, such as using a wheelchair.
- 149 • medical conditions likely to cause bone loss, such as some kinds of arthritis.
- 150 • taking steroid medicines called glucocorticoids, such as prednisone.
- 151 • other medicines that may cause bone loss, for example: seizure medicines (such as phenytoin), blood
152 thinners (such as heparin), high doses of vitamin A.

153
154 *This Medication Guide has been approved by the U.S. Food and Drug Administration.*

155 Medication Guide revised Month XX, YYYY

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162 PA 9411 FSAMP

IMPORTANT PRESCRIBING INFORMATION

Dear Healthcare Professional:

Eli Lilly and Company (Lilly) wishes to inform you of important safety information and updates to the Prescribing Information for FORTEO (teriparatide [rDNA origin] injection). FORTEO is indicated for treatment of postmenopausal women with osteoporosis at high risk for fracture and increase of bone mass in men with primary or hypogonadal osteoporosis at high risk for fracture.

The label includes information regarding the new indication for the treatment of men and women with glucocorticoid-induced osteoporosis (GIO) at high risk for fracture and appropriate patient selection. The label has included a boxed warning concerning the potential risk of osteosarcoma since the approval of FORTEO in 2002. Because patients with GIO may be younger than those currently receiving FORTEO, the language in the boxed warning has been updated to reinforce that FORTEO should not be used in pediatric and young adult patients with open epiphyses.

Cases of bone tumor and osteosarcoma have been reported rarely in the post marketing period. The causality to FORTEO use is unclear. Osteosarcoma is a serious but rare cancer. The incidence in the general population over the age of 60 in the United States is approximately 4 per million per year. The incidence of osteosarcoma in patients taking FORTEO is unknown.

Also included in the label is information regarding the new voluntary patient registry. Patients should be encouraged to enroll in the voluntary FORTEO Patient Registry, which is designed to collect information about any potential risk of osteosarcoma in patients who have taken FORTEO.

Potential Risk of Osteosarcoma

- In male and female rats, teriparatide caused an increase in the incidence of osteosarcoma (a malignant bone tumor) that was dependent on dose and treatment duration. The effect was observed at systemic exposures to teriparatide ranging from 3 to 60 times the exposure in humans given a 20-mcg dose. The clinical relevance of the rat osteosarcoma finding to humans is unknown.
- FORTEO should be prescribed only to patients for whom the potential benefits are considered to outweigh the potential risk. FORTEO should not be prescribed for patients at increased baseline risk for osteosarcoma, including those with Paget's disease of bone, unexplained elevations of alkaline phosphatase, pediatric patients or young adults with open epiphyses, or prior external beam or implant radiation therapy involving the skeleton. Additionally, patients with bone metastases or a history of skeletal malignancies, metabolic bone diseases other than osteoporosis, or pre-existing hypercalcemia should not receive FORTEO.

Treatment Duration

The safety and efficacy of FORTEO have not been evaluated beyond 2 years of treatment. Consequently, use of the drug for more than 2 years **during a patient's lifetime** is not recommended.

INTRODUCTION OF NEW FORTEO[®] PATIENT REGISTRY

A new voluntary FORTEO Patient Registry has been implemented to supplement ongoing long-term safety studies. We ask that you encourage patients that you are treating with FORTEO to enroll in the registry. Patients can enroll themselves and the burden of enrolling is minimal (3 to 5 minutes). No further action is required of you, beyond encouraging patients to participate.

RTI International (RTI), a nonprofit research organization, is conducting the registry study. All information collected as part of the registry will be kept strictly confidential by RTI, and information that can identify patients will not be shared with Eli Lilly and Company (Lilly), the sponsor of this registry, or with anyone outside of the research team.

Targeted patient information including name, address, date of birth, and last 4 digits of social security number will be provided by patients one time only for entry into the registry. Each year for 12 years, information provided by patients to RTI will be linked by a secure process to participating state cancer registries that capture information on newly diagnosed cases of cancer. The information will be analyzed along with information from other studies to help evaluate whether FORTEO users have an increased risk for developing osteosarcoma compared to the general population.

The success of the evaluation is dependent on a high participation rate among FORTEO users, so we ask that you encourage your patients to participate. The results will be made publicly available after completion of the study. Patients who do not wish to participate in the registry can still receive FORTEO treatment.

Participation of patients is voluntary and will involve only three steps:

Step 1: Patient completes brief information on the pre-enrollment form.

Step 2: After the pre-enrollment form is received, RTI will mail the patient a two-page informed consent document, the short registration form, and \$5 as a token of our appreciation for the patient's time in completing the forms.

Step 3: Patient completes and mails the informed consent document and registration back to RTI and his/her involvement ends.

Pre-enrollment forms are available:

- in the FORTEO prescription package
- from sales representatives
- by calling the RTI registry hotline at 1-866-382-6813
- by visiting www.forteoregistry.rti.org.

If you have any questions about the registry or these materials, please call the RTI registry hotline at 1-866-382-6813 or visit www.forteoregistry.rti.org.

To report adverse events among patients taking FORTEO, please call 1-800-LillyRx (1-800-545-5979). Alternatively, adverse event information may be reported to FDA's MedWatch Reporting System by:

- phone at 1-800-FDA-1088 (1-800-332-1088)
- by facsimile at 1-800-FDA-0178 (1-800-332-0178)
- by mail using FDA Form 3500 at <http://www.fda.gov/medwatch/index.html>.

We urge you to contact our Medical Information department at 1-866-4FORTEO (1-866-436-7836) or visit www.FORTEO.com if you have any questions about the information contained in this letter or the safe and effective use of FORTEO.

Thank you in advance for encouraging patients to enroll in this important registry!

Sincerely,

Donald Therasse, M.D.
Vice President, Global Patient Safety
Eli Lilly and Company

Enclosure: FORTEO Full Prescribing Information

Date

Dear Healthcare Professional:

Eli Lilly and Company (Lilly) wishes to remind you of important information for FORTEO® (teriparatide [rDNA origin] injection) related to the following topics:

- potential risk of osteosarcoma
- proper patient selection and 2-year maximum lifetime duration of treatment
- the voluntary FORTEO Patient Registry.

Please take time to read the attached document entitled:

Highlighted Information for Prescribers,
Potential Risk of Osteosarcoma and the Voluntary FORTEO Patient Registry

Please refer to the Full Prescribing Information for further product information.

We invite you to contact our Medical Information Department at 1-866-4FORTEO (1-866 436-7836) or visit www.FORTEO.com if you have any questions about the information contained in this letter or in the attached overview.

Sincerely,

Appropriate Lilly signee and department
Eli Lilly and Company

Enclosure: Highlighted Information for Prescribers; Full Prescribing Information

FORTEO[®] (teriparatide rDNA origin) injection

Highlighted Information for Prescribers

Potential Risk of Osteosarcoma and the Voluntary FORTEO Patient Registry

This information is being provided to prescribers of FORTEO as part of the Risk Evaluation and Mitigation Strategy (REMS) plan for FORTEO. REMS plans have been required for certain drugs with serious risks since 2008 by the U.S. Food and Drug Administration to ensure that the benefits of the drug outweigh the risks of the drug.

The purpose of this information is to inform prescribers of FORTEO about the following:

- Proper patient selection and 2 years maximum lifetime duration of treatment
- Potential risk of osteosarcoma
- Voluntary FORTEO Patient Registry

Refer to the Full Prescribing Information for further product information.

INDICATIONS AND USAGE

FORTEO is indicated:

- for the treatment of postmenopausal women with osteoporosis at high risk for fracture
- to increase bone mass in men with primary or hypogonadal osteoporosis at high risk for fracture
- for the treatment of men and women with glucocorticoid-induced osteoporosis at high risk for fracture.

These patients include women and men with a history of osteoporotic fracture, or who have multiple risk factors for fracture, or who have failed or are intolerant of previous osteoporosis therapy, based upon physician assessment.

TREATMENT DURATION

The use of FORTEO for more than 2 years during a patient's lifetime is not recommended.

POTENTIAL RISK OF OSTEOSARCOMA

FORTEO labeling contains a boxed warning describing the potential risk of osteosarcoma:

- In male and female rats, teriparatide caused an increase in the incidence of osteosarcoma (a malignant bone tumor) that was dependent on dose and treatment duration. The effect was observed at systemic exposures to teriparatide ranging from 3 to 60 times the exposure in humans given a 20-mcg dose.

- Because of the uncertain relevance of the rat osteosarcoma finding to humans, teriparatide should be prescribed only to patients for whom the potential benefits are considered to outweigh the potential risk.
- FORTEO should not be prescribed for patients who are at increased baseline risk for osteosarcoma including those with:
 - Paget's disease of bone or unexplained elevations of alkaline phosphatase
 - Pediatric and young adult patients with open epiphyses
 - Prior external beam or implant radiation therapy involving the skeleton

Additional warnings in the label state that patients with the following conditions should not receive FORTEO:

- Bone metastases or a history of skeletal malignancies
- Metabolic bone diseases other than osteoporosis
- Pre-existing hypercalcemia

POSTMARKETING EXPERIENCE: OSTEOSARCOMA

Cases of bone tumor and osteosarcoma have been reported rarely in the post marketing period. The causality to FORTEO use is unclear.

Osteosarcoma is a serious but rare cancer. The incidence in the general population over the age of 60 in the United States is approximately 4 per million per year. The incidence of osteosarcoma in patients taking FORTEO is unknown. The first report of osteosarcoma in a patient treated with FORTEO has been published (*J Bone Miner Res.* 2007;22:334).

VOLUNTARY FORTEO PATIENT REGISTRY

A voluntary FORTEO Patient Registry has been established to collect information about any potential risk of osteosarcoma in patients who have taken FORTEO. Prescribers of FORTEO should encourage patients to enroll in the registry. The time burden for the patient is minimal (3-5 minutes). Beyond encouraging patients to participate, no further action is necessary for prescribers of FORTEO.

The voluntary FORTEO Patient Registry is being conducted by RTI International (RTI), a nonprofit research organization. All information collected as part of the registry will be kept strictly confidential by RTI, and information that can identify patients will not be shared with Eli Lilly and Company (the sponsor of this registry) or with anyone outside of the research team.

Targeted patient information including name, address, date of birth, and last 4 digits of social security number will be provided by patients one time only for entry into the registry. Annually for 12 years, this information will be linked by a secure process to participating state cancer registry databases. Currently, state cancer registries capture newly diagnosed cases of cancer.

Data from this linkage will be analyzed along with information from other studies to help evaluate whether FORTEO patients have an increased risk for developing osteosarcoma.

The results will be published after the last linkage. Patients who do not wish to participate in the registry can still receive FORTEO treatment.

Patient participation is voluntary and involves a three-step process:

- Step 1: Patient completes a short pre-enrollment form and mails to RTI.
- Step 2: After receiving the pre-enrollment form, RTI mails the patient an informed consent form, a short registration form, and a modest reimbursement for the patient's time in completing the forms.
- Step 3: Patient completes and mails the informed consent and registration back to RTI. Patient involvement is completed.

Pre-enrollment forms are available to patients in each filled FORTEO prescription and may also be obtained from FORTEO prescribers. Healthcare providers may obtain further information about the registry or request pre-enrollment forms by calling the RTI registry hotline at 1-866-382-6813 or visiting www.FORTEORegistry.rti.org.

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/s/

George Benson

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