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Drug Suits Raise Questions for Doctors, and Juries

By NATASHA SINGER
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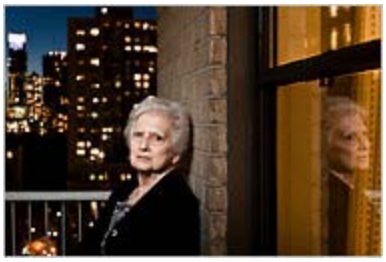

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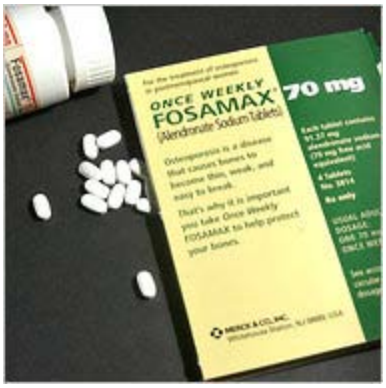

The F.D.A. said the optimal period for using drugs like Fosamax was unknown.

In a civil trial now under way in Manhattan, Mrs. Graves is suing Merck, the maker of Fosamax. Her lawyer, Timothy M. O'Brien, told the jury that Fosamax had caused such debilitating jawbone deterioration that Mrs. Graves required five major operations, including a lengthy surgery to replace her broken jaw with bone from her left arm.

Merck has argued that Fosamax is not the culprit. In its defense, Merck contends that Mrs. Graves took other prescriptions — like steroids to treat rheumatoid arthritis — that weakened her immune system, leading to her jaw infection and healing problems, said Paul F. Strain, outside counsel for the company.

The lawsuit is one of a handful of bellwether cases against Merck representing litigation involving about 1,400 people across the country who say they developed jawbone ailments after taking Fosamax, Mr. O'Brien said. Merck won an earlier case; but in another, a judge proposed to reduce a plaintiff's jury award to $1.5 million from $8 million (both sides plan to appeal).

In Mrs. Graves's case, the trial is providing a palpable backdrop for a broadening debate among many doctors and researchers who are rethinking Fosamax and similar bone medications known as oral bisphosphonates, particularly as a treatment for women who have not yet developed osteoporosis.

An advisory issued last month by the Food and Drug Administration, which first approved Fosamax in the 1990s to treat and prevent osteoporosis, along with reports in medical journals linking

bisphosphonates with some rare medical problems including unusual thigh fractures, has heightened scrutiny of the long-term use of these medications.

While the F.D.A. cautioned that it was not clear that oral bisphosphonates had caused the rare thigh breaks, it said these kinds of bone fractures might be related to lengthy treatments with the drugs. The agency will now require the labels on Fosamax, Actonel, Boniva, Reclast and Atelvia and generic alternatives to state that the optimal period for using the drugs is unknown.

That uncertainty has shadowed the debate over how and when to prescribe these bone drugs, especially because they have been successful, by most accounts, in significantly reducing fractures over several years in postmenopausal women with osteoporosis. From 1999 to 2009, Fosamax and a newer drug, Fosamax Plus D, had worldwide sales of more than $23.8 billion, according to IMS Health, a health information company that tracks drug sales.

But the drugs' popularity and effectiveness for generally healthy women without osteoporosis or broken bones have become a source of increasing argument in doctors' offices and in courtrooms.

Doctors had already started to review the unlimited use of oral bisphosphonates, said Dr. Elizabeth Shane, a professor of medicine at Columbia University College of Physicians and Surgeons. Fifteen years ago, she said, the medical community hoped that if women took the drugs before they developed osteoporosis, they would be protected from breaking bones later in life. But doctors have begun waiting longer before prescribing the drugs, she added.

"We are moving much more to targeting people later in the development of osteoporosis when they are at high risk of fracture, since we're not entirely clear yet how long is the most appropriate length of time to treat a person," said Dr. Shane, who has received research grants from Merck, Eli Lilly and Novartis.

Adults generally lose bone mass as they age. But the process accelerates in menopause when cells called osteoclasts start breaking down a larger amount of older bone than can be replaced by other cells, called osteoblasts. Bisphosphonates work by inhibiting that breakdown, thereby conserving bone density.

In one arm of a study called the Fracture Intervention Trial, or FIT, sponsored by Merck and involving about 2,000 women ages 55 to 81 with an existing vertebral fracture, Fosamax cut the risk of a new vertebral fracture by about half compared with a placebo.

"Before these drugs came on the market, we really had nothing," said Dr. Margaret Seton, a rheumatologist at the Massachusetts General Hospital in Boston. "When you have no drug and you've seen a patient and watched their spine crumble, that's heartbreaking."

But for those whose bones have not thinned enough to be classified as having osteoporosis, potential treatments are in real flux.

In the FIT trial, for example, Fosamax significantly reduced the risk of clinical fractures in women with osteoporosis but not among those with higher bone mineral density, according to an analysis published in 1998. In a separate analysis of the FIT data that year, Anthony Mucci, a statistical reviewer at the F.D.A. wrote that, for women without osteoporosis, there was no measurable benefit shown “for any category of fracture.”

Karen Riley, a spokeswoman for the F.D.A., said that the subgroup of women without osteoporosis in the FIT trial was too small to produce significant results, and that the Mucci report was one document in a much larger effort by the agency to assess the drug. She added that the F.D.A. approved Fosamax to prevent osteoporosis because it proved to conserve bone mineral density and had previously shown it could avert breaks.

Dr. Michael Rosenblatt, the chief medical officer at Merck and a former dean of Tufts University School of Medicine, pointed to the real goal: preventing osteoporosis, which carries a high risk of serious fractures, among people with thinning bones and stopping their progression from pre-osteoporosis, also known as osteopenia.

Dr. Shane of Columbia disputed the blanket use among patients without osteoporosis.

The drugs may indeed be appropriate, she said, for those with pre-osteoporosis who have other risk factors, like a broken bone, or a family history of hip fractures, or those taking steroids that can thin bones, or who are in their 70s. But the clinical benefit for a 51-year-old woman with osteopenia and no other risk factors cannot be assured, she said.

“As the field has evolved, we have learned that bisphosphonates don’t seem to reduce the fracture risk in people who are not at high risk for fracture,” Dr. Shane said.

As for long-term use of the drugs in light of some recent reports in medical journals about rare problems like jawbone death and unusual thigh fractures, Dr. Rosenblatt of Merck said there was not enough evidence to conclude that the drugs caused the conditions.

In a courtroom in Lower Manhattan, Mrs. Graves argues otherwise. In an interview, she said she did not have osteoporosis when her doctor prescribed Fosamax in 2001. After a tooth extraction in 2003, the left side of her lower jaw began to deteriorate.

She underwent several operations to replace her jaw, first with a titanium implant and bone from her left arm, and then, when that broke, with further implants. Now, she said, she can eat only soft foods, and only on the right side of her mouth.

In a statement, Merck said that Fosamax did not cause Mrs. Graves’s illnesses. The company said Mrs. Graves had other medical conditions that can impair the jaw, and listed other prescription drugs she took that can suppress the body’s immune system and inhibit wound healing.

For Dr. Seton of Massachusetts General, who is not involved in any of the lawsuits, the unusual jaw and thigh conditions pose a mystery. She theorized that perhaps these rare cases might be occurring in a

small subset of patients whose bodies absorb the drugs in a different way or whose bones have unique qualities that increase their risk for such problems. Two of her patients on bisphosphonates suffered the atypical thigh bone breaks, she said.

“While I think the benefits outweigh the risks in the elderly population being treated for osteoporosis, I’m not sure that that is so clear for a younger person or those with osteopenia,” Dr. Seton said, adding that she takes postmenopausal patients off the drugs after three to five years.

“I have great humility for what we don’t know,” Dr. Seton said. “And I don’t know that more bisphosphonates will prevent more fractures.”

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