LEADER (U.S.)

Medtronic Product Linked to Surgery Problems

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A potent substance used in spine-repair surgery to promote bone growth has been linked to life-threatening complications in dozens of patients.

Many of the complications involving the product, Medtronic Inc. 's "Infuse Bone Graft," have occurred during "off label" uses, when surgeons use it in ways that haven't been approved by the Food and Drug Administration.

See a whistleblower lawsuit filed last year alleging Medtronic was improperly paying doctors to get them to use this spinal fusion product.

See the response of the doctors, who want the lawsuit dismissed.

The FDA warned surgeons in July that it had received reports of life-threatening complications associated with using the product in surgeries on the cervical spine, around the neck. The agency said it received 38 reports over four years of side effects, mainly swelling of neck and throat tissue, which resulted in compression of the airway and other structures in the neck. Patients reported difficulty swallowing, breathing and speaking. Several required emergency treatment, including tracheotomies and the insertion of feeding tubes, as well as second surgeries, according to reports filed with the agency.

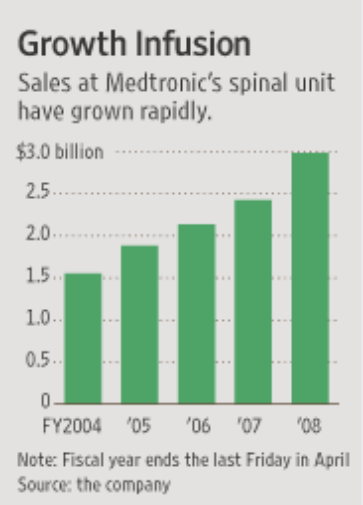
Medtronic says it takes the reports of complications seriously and has been active in warning doctors of certain problems related to use of the bone graft. At the same time, the company says the rate of complications is low and that reports to the FDA of problems represent one-tenth of 1% of the units sold.

Each year, an estimated half-million people undergo spinal-fusion procedures to repair and stabilize damaged discs, and to correct conditions like scoliosis, a curvature of the spine. Infuse Bone Graft, a biologically engineered liquid, has become a best seller for Minneapolis-based Medtronic. One analyst estimates the product notched sales of about $815 million in the fiscal year ended in April.

The problems with Infuse follow an episode several years ago involving Medtronic's leading business, heart pacemakers and defibrillators. In 2005, the company issued a recall of many of its defibrillators because they were prone to early battery depletion. It also recalled many of a line of defibrillator wires because they were prone to fracturing, which triggered multiple shocks in some patients and possibly deaths. Medtronic has agreed to settle more than 2,600 battery-depletion cases for $114 million.

The FDA's alert about Infuse was specific to neck surgeries. But a review of FDA records and medical literature shows there have been scores of other cases in which serious complications arose after the

product was used in other off-label situations. Many of these cases involve unwanted bone growths near nerves or in areas outside targeted fusion sites. That can lead to pain, repeat surgeries and, in some cases, emergency intervention.



Medtronic says it abides by federal regulations that prohibit it from promoting Infuse for off-label purposes. But doctors paid by Medtronic are under no such restriction. They are free to discuss unapproved uses of the product. Surgeons can use the product as they see fit.

Spine surgeons say Infuse is used widely off-label. At least three-quarters of the roughly 200 "adverse events" reported to the FDA involve off-label uses of Infuse. Medtronic says it doesn't track off-label usage.

Doctors with financial relationships with Medtronic have written favorably about off-label uses of Infuse on Web sites, in medical journals and at educational meetings. Some of the most influential spine surgeons in the country are consultants to the company. Several of them benefit from sales of the product through royalty deals, according to disclosures they have made in professional journals and at medical meetings.

Three "whistleblower" lawsuits brought by former employees have alleged illegal marketing, seeking refunds for the federal government on Medicare and Medicaid payments to the company. The former employees, who share in any recovery under federal law, asserted in the suits that the company paid inducements to doctors to use Infuse and other Medtronic spine products. Medtronic agreed to pay $40 million to settle two of the cases, which were filed in federal district court in Memphis, Tenn., without admitting wrongdoing. One of the whistleblowers has challenged the company's agreement with the federal government, saying the sum is too small.

The lawsuit that hasn't been settled was filed last year in federal district court in Boston by two former Medtronic employees. It alleges that the company illegally marketed Infuse for off-label purposes through doctors who were paid inflated consulting fees and bogus royalty payments. Marketing off-label uses is not allowed under FDA regulations.

Medtronic says all payments to doctors are "fully compliant with the law," and that the company has "rigorous processes" to ensure that all physician compensation is fair and at market value.

The lawsuit says the doctors promoted the off-label use through training sessions and educational meetings, and during "VIP" visits by physicians to Memphis, where the spine unit of Medtronic is located. The federal government has declined to intervene in the matter. A large group of doctors named in the lawsuit have moved to have it dismissed.

Before Infuse

Before Infuse was approved in 2002, most spinal fusions were performed with bone taken from patients' hips. It required two surgeries, and many patients complained of hip pain for months afterward. An alternative involves using bone from cadavers.

Infuse surgery uses a potent version of a growth agent produced in the body, called bone morphogenetic protein. A thimblelike metallic cage is placed between spinal vertebrae, and a spongy material soaked in the genetically engineered protein is placed inside the cage. That causes bone growth, which fuses the

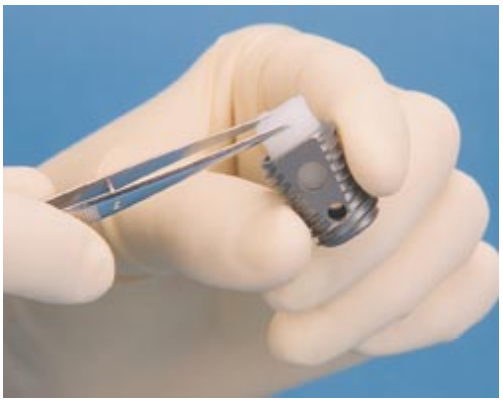
vertebrae. Some studies show the procedure causes spinal bones to fuse faster than with previous methods, and fails less often.

But the artificial protein also can inflame nearby tissue. If the material isn't inserted properly, or if it leaks, it can cause bone growth in areas outside the surgical site, according to surgeons and reports to the FDA.

That's one reason the FDA approved Infuse only for some forms of spine surgery: operations that approach the spine through an incision in the abdomen and fuse a narrow range of vertebrae in the lower back. Using it on the neck area, or operating from the back side, is considered off-label.

A favorable buzz about off-label use began shortly after the product was approved. In May 2003, four surgeons wrote a report for the Web site Spine Universe, which provides educational material for spine surgeons. The report, "New Technologies in Anterior Cervical Spine Fixation," cited favorable results from using Infuse in the neck area and for fusing larger numbers of vertebrae.

The authors, who included Atlanta surgeon Regis W. Haid Jr. and Emory University surgeon Gerald Rodts, wrote that they had used Infuse "in the cervical spine with very good results." The doctors did not provide data related to the cervical-spine results. The report, like many others like it, is accessible on the Internet.



To use the 'Infuse Bone Graft,' a metallic cage containing a spongy material is placed between spinal vertebrae. *Medtronic*

At least three of the four authors have financial relationships with Medtronic, according to disclosures they have made in medical journals and at conferences, although that was not noted in the report.

Dr. Haid said there were no rules about disclosing financial ties at the time, and that the group disclosed detailed data in a later report. Dr. Rodts declined to comment.

Other surgeons were experiencing complications. In September 2004, Medtronic sent spine doctors a note saying it had received reports of soft-tissue swelling following the use of Infuse in cervical-spine fusions. The company told doctors "it is unknown whether those incidents are solely related to the use of Infuse Bone Graft," and that the product has an "excellent safety record."

Christopher B. Shields, chairman of neurological surgery at the University of Louisville, says it was apparent by late 2004 that using Infuse in the neck area could cause serious problems. He thinks some problems in his hospital stemmed from surgeons using dosages that were too high. "It wasn't every patient that had these problems," he says. "But it would come up every couple of weeks."

Some of his hospital's patients suffered hemorrhages at surgical sites serious enough to require another operation. In a 2006 report in Spine, Dr. Shields and his colleagues wrote about "a significant rate of

complications" after high-dose use of Infuse. They reported that 35 patients, or 23% of their total, had to be readmitted to the hospital, or had prolonged hospital stays because of difficulty breathing or swallowing, or "dramatic swelling." Medtronic says that a high dosage could explain the reactions.

Susan Levine, a vice president at Hayes Inc., which evaluates medical technologies for insurers, says she has reviewed the research work on Infuse, and finds it "really distressing to see something like this used in a potentially harmful way and without adequate evidence." Ms. Levine says when used properly, Infuse can be "good for a patient."

Early Concerns

Questions about off-label use cropped up before the product was approved. In early 2002, one member of an FDA advisory committee reviewing Infuse asked agency staff for recommendations on "guarding against off-label use of this product."

Scott Boden, director of the Emory University Orthopaedics & Spine Center, helped present the committee with clinical trial data on behalf of Medtronic. He said discussion about off-label use was "outside the scope of what we ought to be focusing on today," according to a transcript of the meeting.

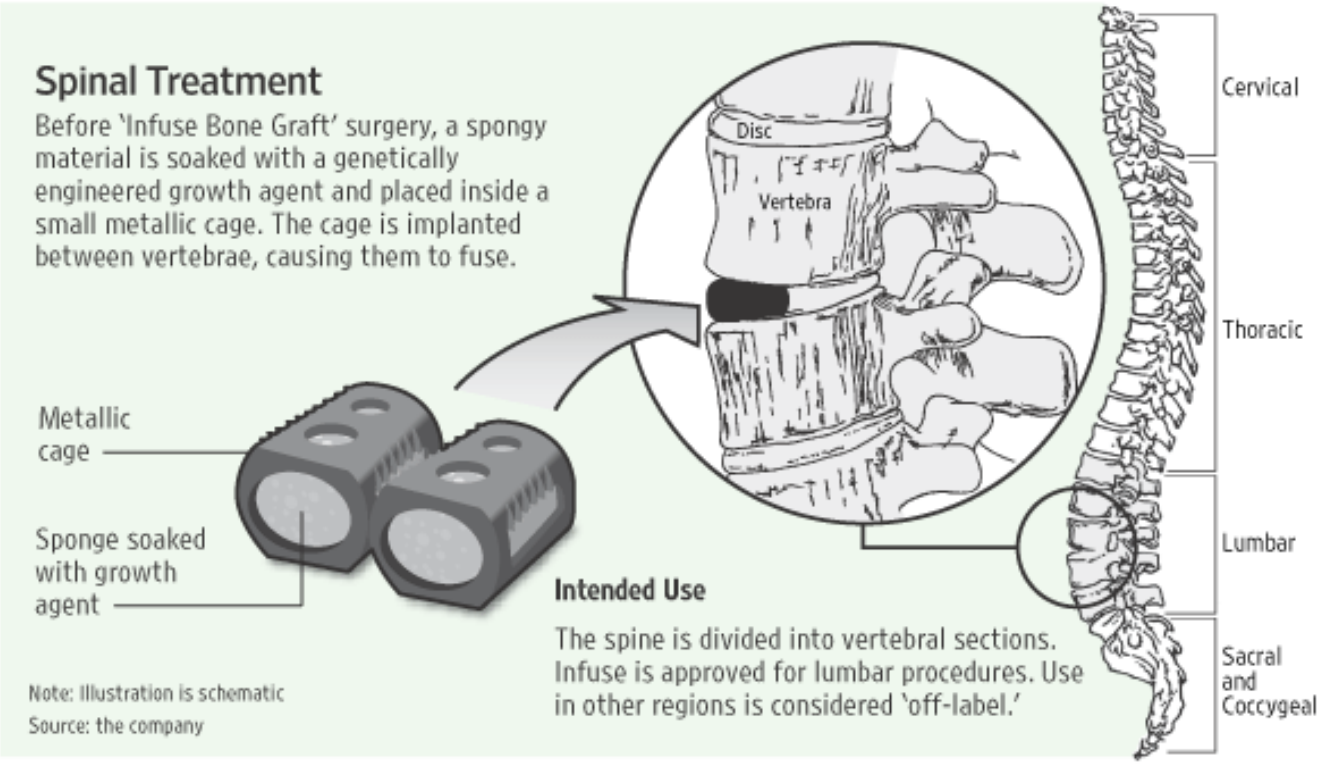
Committee Chairman Maureen Finnegan said the concern was valid. "Actually, I'll take a little bit of exception to that, because you know that in the skilled hands of the people who did your trial, that was placed where it was supposed to be placed," she said. "But if it goes out into the free market, it's going to be probably placed close to nerve roots, and I think that's a really valid question."

Several cases of complications involving nerves being affected after the Infuse procedure have since been reported to the FDA.

John W. Lundquist, a Minneapolis lawyer who represents Dr. Boden, says his client doesn't specifically recall the exchange, but that "he was not in any way arguing with the panel against efforts to discourage off-label use." Mr. Lundquist says Dr. Boden routinely warns against unproven off-label use.

At the time he testified, Dr. Boden was being paid more than $100,000 a year by Medtronic, according to the whistleblower lawsuit filed last year. Those payments continued at least through 2006, when he received at least $75,000, according to the lawsuit. The lawsuit alleges the consulting payments to Dr. Boden and scores of other physicians were payments designed to get the doctors to use Infuse for unapproved procedures.

At Back.com, a Web site that says it is "brought to you by Medtronic," concern about bone growth outside targeted areas is downplayed by several surgeons who are paid by the company. Dr. Boden is quoted as saying Infuse "only works locally at the surgical site. If any leaks away or gets into your bloodstream it will not have any effects anywhere else."



Dr. Boden and scores of other doctors are defendants in the whistleblower litigation. Mr. Lundquist, who represents Dr. Boden and many of the other doctors named, says his client stands by that view. In court filings, the surgeons said they were the subject of claims "without factual support" that could unfairly damage their reputations. They are seeking to have the claims against them dismissed.

Reports filed with the FDA identify bone growth outside the surgical site as a problem. A Medtronic study was stopped early in 1999 because of unexpected bone growth. In that study, Medtronic researchers operated on patients from the back -- a procedure known as Posterior Lumbar Interbody Fusion, or PLIF. They compared results of patients receiving Infuse with those who received bone from their own hips. The use of Infuse in PLIF procedures is off-label.

Clinical Outcome

In a 2004 article in the Spine Journal, the researchers said 24 of the 32 patients receiving Infuse had new bone formation extending outside the disc space and into the spinal canal. Only four of the 31 patients in the group receiving hip bone had similar bone formation. The researchers said the new bone growth did not "affect clinical outcome."

Three of the four authors disclosed in the article that they are paid consultants to Medtronic. Lead author Dr. Haid, who wrote the earlier favorable report on the use of Infuse in cervical spine procedures, reported at the time that he owned stock in Medtronic. He is named as a defendant in whistleblower lawsuits.

In a commentary on the study, New Jersey surgeon Neil Kahanovitz criticized the positive conclusions of the study as unwarranted, and challenged the assertion that the bone growth was not clinically relevant. Last year, surgeons in Denver reported in a medical journal five cases of out-of-place bone growth in the spinal canal associated with off-label uses of Infuse.

In response to concern about the complications during PLIF procedures, Medtronic says, it has added a

warning to the Infuse label to advise surgeons not to put too much of the manufactured protein into the metal cage.

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