Complications rise along with off-label use of BMP-2

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When the U.S. Food and Drug Administration in 2002 approved a product many thought would revolutionize back surgery, the agency did so despite concerns the product might cause serious side effects.

Six years later the FDA warned doctors that this remarkable product, known as bone morphogenetic protein-2, was causing life-threatening complications.

What caused the product to go from revolutionary advance to public health alert?

A series of complications and side effects have piled up since 2002. Many of them have occurred when BMP-2 was used in an unapproved or so-called off-label manner, now about 85 percent of the time.

The concerns are so serious that Medicare is weighing whether to stop covering BMP-2, which is made by Medtronic, and a similar product made by another company. Advisers to the program will hold a hearing on that question Sept. 22.

Medical studies have found a variety of problems since Infuse was approved:

Trial halted: Because bone morphogenetic proteins are powerful promoters of new bone growth, there has been concern that BMP-2 could cause bone to form outside the fusion area in places where it could

be harmful. The phenomenon is known as ectopic bone formation.

Ectopic bone formation is of special concern when BMP-2 is used off-label, such as in surgery that uses an approach from the back, or posterior method.

In 1999, a Medtronic-funded clinical trial of BMP-2 in an unapproved type of fusion surgery was halted because CT scans showed troubling bone formation in the spinal canal of 75 percent of the BMP-2 patients.

However, it was not until 2004 that a paper on the trial finally was published in the Spine Journal.

The trial, which involved an off-label posterior surgical technique, had planned to enroll hundreds of people but was stopped at 67 patients, 34 who got BMP-2 and 33 who got a hip bone graft. The authors said the trial was stopped "out of abundant caution."

Three of the paper's four authors worked as consultants to Medtronic and had financial relationships related to the research. They concluded that "although not desirable," the bone formation in the spinal canal did not appear to have an ill effect on the patients.

In 2008 a different group of doctors in Denver reported on ectopic bone forming in the spinal canals of five patients who had undergone similar fusion surgery, again in an off-label use of BMP-2.

In those cases, neurological impairment occurred, challenging the finding of the surgeons with Medtronic financial ties. The authors of that article said they did not have any financial relationship or direct conflict involving Medtronic.

Cervical spine fusion: In July 2008, the FDA warned doctors of life-

threatening complications with BMP when it was used in unapproved cervical spine fusions. The warning came after 38 cases involving swelling in the neck and throat resulting in compression of the airway and neurological structures of the neck. Some of the cases required emergency tracheotomies and surgery to drain the swelling site.

In 2006, doctors writing in a medical journal reported on 69 patients who underwent off-label cervical spine fusion with BMP-2, 28 percent of whom had significant swelling, compared with only 4 percent of those who did not get BMP-2.

In June 2009, a large study in the Journal of the American Medical Association found that BMP-2 was associated with a 43 percent higher rate of in-hospital complications in cervical fusions. It also added substantially to the cost of those fusions, adding 42 percent to hospital charges, or about $15,000.

Fueling cancer: BMP-2 and other proteins from that family are known as growth factors, substances that encourage cells to proliferate. There still is debate about whether BMP-2 stimulates or inhibits the growth of cancer cells.

Cancer got a lot of attention in July at an FDA advisory panel hearing over whether to approve another Medtronic fusion product known as Amplify, which uses higher doses of BMP-2.

Five years after surgery, there were 13 cancers in the BMP-2 group and four in the control group, a difference it said was not statistically significant. The trial involved 463 patients, split evenly between those who got BMP-2 and those who got a hip bone graft.

Advisory panel members, including Raj Rao, a professor of orthopedic surgery at the Medical College of Wisconsin, expressed concern about

the higher cancer numbers.

"It raises concerns about the long-term effects of using BMP, particularly with the higher doses being used," Rao said.

Rao said concerns about cancer and other side effects, flaws in the way the study was done and the marginal effectiveness of the product caused him to vote against approval. The panel voted 6-5 that its benefits outweighed its risks. The FDA is expected to make a decision in the next few months.

Immune response: BMPs are produced naturally in people and other animals, especially in embryos where the proteins are involved in the development of most organs and tissue.

In a 2001 memo, the FDA said it was concerned that implanted BMP-2 could cross the placental barrier and effectively "knock out" a developing baby's own BMP-2 during a critical stage of development.

Still another concern is that fetal BMP-2 could stimulate the immune system of a woman who previously had an immune response to implanted BMP-2.

Medtronic says women of childbearing age should not become pregnant within a year of being implanted with BMP-2.

Leg pain: In March 2008, doctors reported on post-operative, radiating leg pain occurring in 23 percent of patients undergoing fusion with BMP-2, compared with 3 percent of patients who had the same surgery with a traditional hip bone graft.

The study by doctors at Thomas Jefferson University used an off-label surgical approach known as transforaminal lumbar interbody fusion.

The study, which involved 39 patients, found that the radiating leg pain, known as radiculitis, was 8.4 times more likely to occur in the BMP-2 patients, especially women. James Sanfilippo, an orthopedic surgeon in New Jersey and lead author of the study, said BMP-2 is a good technology when it is used properly.

But, he added, "the adverse effects of BMP-2 are worrisome. Potentially, we are overusing it."

Medtronic spokeswoman Marybeth Thorsgaard said the company is strongly committed to preventing the promotion of its products for unapproved uses and has implemented corporate policies and training to prevent that.

In addition, she said the package label for BMP-2 covers all safety concerns that the FDA believes the public needs to know.