

Patient Safety Alert

Veterans Health Administration Warning System
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February 20, 2009

Item: **Medtronic InFuse Recombinant Human Bone Morphogenetic Protein in Cervical Spine Fusion**

Specific Information: The FDA has received at least 38 reports of life-threatening complications during the last four years with recombinant human Bone Morphogenetic Protein (rhBMP) when used in the cervical spine (off-label use).

General Information: The attached FDA Public Health Notification describes life-threatening complications (usually swelling of the neck and throat tissues) associated with the use of recombinant human bone morphogenetic protein (rhBMP) when used in the cervical spine. When airway complications occurred, medical or surgical intervention was frequently necessary. The Notification mentions the Medtronic InFuse product as well as the Stryker OP-1 Putty product, (approved for humanitarian device exception).

The Notification includes the statement “**Note that the safety and effectiveness of rhBMP in the cervical spine have not been demonstrated and these products are not approved by FDA for this use.**”

- Actions:**
1. By Close of business (COB) February 23, 2009, the Facility Director will ensure that the neurosurgeons and orthopedic surgeons are informed of this issue.
 2. By COB February 24, 2009, Surgeons who used the product within the last 30 days in the cervical spine shall increase the frequency and depth of monitoring for their patients following surgery in order to improve their ability to detect complications.
 3. By COB February 24, 2009, patients who have been implanted with the product within the last 30 days must be instructed about:
 - a) the signs and symptoms of airway complications, including difficulty breathing or swallowing, or swelling of the neck, tongue, mouth, throat and shoulders or upper chest area, b)
 - b) that they need to seek medical attention immediately at the first sign of an airway complication, and c)
 - c) that they need to be especially watchful 2-14 days after the procedure when airway complications are more likely to occur.
 4. In light of the serious adverse events, by COB February 27, 2009, surgeons shall either use approved alternative treatments

or demonstrate there is sound scientific evidence for such use set forth in peer-reviewed medical literature and/or by recognized medical organizations or enroll as investigators in approved clinical studies.

5. By COB February 27, 2009, the Patient Safety Manager (PSM) shall assure that this Alert has been addressed and the action status updated on the VA's Hazardous Recalls/Alerts website, <http://vaww.nbc.med.va.gov/visn/recalls/index.cfm>.

Additional Information: Regulatory Status of rhBMP

FDA has approved the use of two rhBMPs for well-defined medical conditions in limited patient populations. These conditions do not include cervical spine fusion.

1. rhBMP-2 (contained in InFuse Bone Graft) has received premarket approval for fusion of the **lumbar** spine in skeletally mature patients with degenerative disc disease (DDD) at one level from L₂-S₁ and for healing of acute, open tibial shaft fractures stabilized with an IM nail and treated within 14 days of the initial injury. rhBMP-2 is also approved for certain oral and maxillofacial uses.
2. rhBMP-7 (referred to as OP-1 and contained in OP-1 Implant and OP-1 Putty) has received humanitarian device exemption approval as an alternative to autograft in recalcitrant long bone nonunions where use of autograft is unfeasible and alternative treatments have failed. It is also approved as an alternative to autograft in compromised patients requiring revision posterolateral (intertransverse) **lumbar** spinal fusion for whom autologous bone and bone marrow harvest are not feasible or are not expected to promote fusion. Examples of compromising factors include osteoporosis, smoking and diabetes.

Both rhBMPs are contraindicated for all uses in patients who are skeletally immature (<18 years of age) or pregnant, and in those with a known hypersensitivity to the specific rhBMP, bovine Type 1 collagen or to other components of the formulations.

Source: VA Medical Center

Attachment: FDA Public Health Notification: Life-threatening Complications Associated with Recombinant Human Bone Morphogenetic Protein in Surgical Spine Fusion, July 1, 2008

Contacts: Dr. William Gunnar, National Director of Surgery, (202) 461-7148; or Thomas Bauld, Biomedical Engineer, NCPS, (743) 930-5890

Attachment: FDA Public Health Notification: Life-threatening Complications Associated with Recombinant Human Bone Morphogenetic Protein in Cervical Spine Fusion

Issued: July 1, 2008

Dear Healthcare Practitioner:

This is to alert you to reports of life-threatening complications associated with recombinant human Bone Morphogenetic Protein (rhBMP) when used in the cervical spine. **Note that the safety and effectiveness of rhBMP in the cervical spine have not been demonstrated and these products are not approved by FDA for this use.**

The following information provides the adverse events reported to the FDA, the risks associated with the use of rhBMP products in the cervical spine, recommendations for mitigating those risks and the current regulatory status of rhBMP products in the U.S.

Public health concerns: Adverse events and risks to health

FDA has received at least 38 reports of complications during the last 4 years with the use of rhBMP in cervical spine fusion. These complications were associated with swelling of neck and throat tissue, which resulted in compression of the airway and/or neurological structures in the neck. Some reports describe difficulty swallowing, breathing or speaking. Severe dysphagia following cervical spine fusion using rhBMP products has also been reported in the literature.

Anatomical proximity of the cervical spine to airway structures in the body has contributed to the seriousness of the events reported and the need for emergency medical intervention. The mechanism of action is unknown, and characteristics of patients at increased risk have not been identified.

Most complications occurred between 2 and 14 days post-operatively with only a few events occurring prior to day 2. When airway complications occurred, medical intervention was frequently necessary. Treatments needed included respiratory support with intubation, anti-inflammatory medication, tracheotomy and most commonly second surgeries to drain the surgical site.

Mitigating the risks

Since the safety and effectiveness of rhBMP for treatment of cervical spine conditions has not been demonstrated, and in light of the serious adverse events described above, **FDA recommends that practitioners either use approved alternative treatments or consider enrolling as investigators in approved clinical studies.**

Attachment (cont.)

Patients treated with rhBMP in the cervical spine should know:

- the signs and symptoms of airway complications, including difficulty breathing or swallowing, or swelling of the neck, tongue, mouth, throat and shoulders or upper chest area
- that they need to seek medical attention immediately at the first sign of an airway complication
- that they need to be especially watchful 2 -14 days after the procedure when airway complications are more likely to occur

Regulatory Status of rhBMP

FDA has approved the use of two rhBMPs for well-defined medical conditions in limited patient populations:

3. rhBMP-2 (contained in InFuse Bone Graft) has received premarket approval for fusion of the lumbar spine in skeletally mature patients with degenerative disc disease (DDD) at one level from L₂-S₁ and for healing of acute, open tibial shaft fractures stabilized with an IM nail and treated within 14 days of the initial injury. rhBMP-2 is also approved for certain oral and maxillofacial uses.
4. rhBMP-7 (referred to as OP-1 and contained in OP-1 Implant and OP-1 Putty) has received humanitarian device exemption approval as an alternative to autograft in recalcitrant long bone nonunions where use of autograft is unfeasible and alternative treatments have failed. It is also approved as an alternative to autograft in compromised patients requiring revision posterolateral (intertransverse) lumbar spinal fusion for whom autologous bone and bone marrow harvest are not feasible or are not expected to promote fusion. Examples of compromising factors include osteoporosis, smoking and diabetes.

Both rhBMPs are contraindicated for all uses in patients who are skeletally immature (<18 years of age) or pregnant, and in those with a known hypersensitivity to the specific rhBMP, bovine Type 1 collagen or to other components of the formulations.

Reporting to FDA

FDA requires hospitals and other user facilities to report deaths and serious injuries associated with the use of medical devices. If you suspect that a reportable adverse event was related to the use of rhBMP, you should follow the reporting procedure established by your facility.

Reporting adverse events is everyone's responsibility, even if the event involves off-label use of medical devices.

Attachment (cont.)

To report your experience regarding the devices in this Notification, please use MedWatch, the FDA's voluntary reporting program. You may submit reports to MedWatch by phone at 1-800-332-1088; by FAX at 1-800-332-0178; by mail to MedWatch, Food and Drug Administration, 5600 Fishers Lane, Rockville, MD 20852-9787; or online at <http://www.fda.gov/medwatch/report.htm>.

If you have questions about this notification, please contact Julia Marders, RN, MS, Office of Surveillance and Biometrics (HFZ-510), 1350 Piccard Drive, Rockville, Maryland, 20850, by Fax at 240-276-3356, or by e-mail at phann@cdrh.fda.gov. You may also leave a voicemail message at 240-276-3357, and we will return your call as soon as possible.

FDA medical device Public Health Notifications are available on the Internet at <http://www.fda.gov/cdrh/safety.html>. You can also be notified through email on the day the safety notification is released by subscribing to our list server. To subscribe, visit: http://service.govdelivery.com/service/subscribe.html?code=USFDA_39.

Sincerely,

Daniel G. Schultz, MD
Director
Center for Devices and Radiological Health
Food and Drug Administration

Updated July 8, 2008
