Bone Morphogenetic Protein

Description

Two recombinant human bone morphogenetic proteins (rhBMPs) are now commercially available, rhBMP-2, applied with an absorbable collagen sponge (InFUSE®, Medtronic, Memphis, TN) and rhBMP-7, applied in putty (OP-1®). These products have been investigated as an alternative to bone autografting in a variety of clinical situations, including spinal fusions, internal fixation of fractures, treatment of bone defects, and reconstruction of maxillofacial conditions.

Background

Bone morphogenetic proteins (BMPs) are members of the family of transforming growth factors. At present, some 20 different BMPs have been identified, all with varying degrees of tissue stimulating properties. RhBMPs are delivered to the bone grafting site as part of a surgical procedure; a variety of carrier and delivery systems has been investigated. Carrier systems, which are absorbed over time, function to maintain the concentration of the rhBMP at the treatment site; provide temporary scaffolding for osteogenesis; and prevent extraneous bone formation. Carrier systems have included inorganic material, synthetic polymer, natural polymers, and bone allograft. The rhBMP and carrier may be inserted via a delivery system, which may also function to provide mechanical support.

The carrier and delivery system are important variables in the clinical use of rhBMPs, and different clinical applications, such as long bone nonunion, or interbody or intertransverse fusion, have been evaluated with different carriers and delivery systems. For example, rhBMP putty with pedicle and screw devices are used for instrumented intertransverse fusion (posterolateral fusion; PLF), while rhBMP in a collagen sponge with bone dowels or interbody cages are used for interbody spinal fusion. In addition, interbody fusion of the lumbar spine can be approached from an anterior (anterior lumbar interbody fusion; ALIF), lateral (XLIF), or posterior direction (PLIF or TLIF). Surgical procedures may include decompression of the spinal canal and insertion of pedicle screws and rods to increase stability of the spine.

Posterior approaches (PLIF and TLIF) allow decompression (via laminotomies and facetectomies) for treatment of spinal canal pathology (e.g., spinal stenosis, lateral recess and foraminal stenosis, synovial cysts, hypertrophic ligamentum flavum) along with stabilization of the spine and are differentiated from instrumented or noninstrumented posterolateral intertransverse fusion (PLF), which
involves the transverse processes. Due to the proximity of these procedures to the spinal canal, risks associated with ectopic bone formation are increased (e.g., radiculopathies). Increased risk of bone resorption around rhBMP grafts, heterotopic bone formation, epidural cyst formation, and seromas has also been postulated.

**Regulatory Status**

At the present time, two rhBMPs and associated carrier/delivery systems have received approval from the U.S. Food and Drug Administration (FDA). The InFUSE® system consists of rhBMP-2 on an absorbable collagen sponge carrier. The labeled indications for these devices are summarized here. OP-1® consists of rhBMP-7 and bovine collagen, which is reconstituted with saline to form a paste. The addition of carboxymethylcellulose forms putty.

1. **InFUSE Bone Graft in conjunction with 1 of 2 interbody fusion devices, i.e., either the LT-Cage Lumbar Tapered Fusion Device or the Inter Fix RP Threaded Fusion device.** This device received FDA approval through the premarket approval (PMA) process:
   - The device is indicated for spinal fusion procedures in skeletally mature patients with degenerative disc disease (DDD) at 1 level from L2-S1. DDD is defined as discogenic back pain with degeneration of the disc confirmed by patient history, function deficit, and/or neurologic deficit and radiographic studies. These DDD patients may also have up to grade I spondylolisthesis at the involved level or retrolisthesis. The InFUSE™ Bone Graft/LT-CAGE™ devices are to be implanted via an anterior open or a laparoscopic approach. The InFUSE™ Bone Graft/INTER FIX™ Threaded Fusion Device; and InFUSE™ Bone Graft/INTER FIX™ RP Threaded Fusion Device are to be implanted via an anterior open approach only. Patients receiving the InFUSE™ Bone Graft/Interbody Fusion Device should have had at least 6 months of nonoperative treatment prior to treatment with the InFUSE™ Bone Graft/Interbody Fusion Device. (Note: A collagen sponge consists of the carrier, while the interbody fusion device is a delivery system. Use with posterior or transforaminal lumbar interbody fusion is considered off-label.)
   - For the treatment of acute, open fractures of the tibial shaft
   - For sinus augmentations, and for localized alveolar ridge augmentations for defects associated with extraction sockets (P050053, March 2007)

2. **OP-1 (Stryker Biotech, Hopkinton, MA) has received 2 FDA approvals through the Humanitarian Device Exemption (HDE) process.** HDE is available to devices intended for fewer than 4,000 patients per year. As part of this process, the manufacturer is not required to demonstrate unequivocal benefit but only “probable” benefit. OP-1 received the following labeled indications:
   - “OP-1 Implant is indicated for use as an alternative to autograft in recalcitrant long bone nonunions where use of autograft is uneconomic and alternative treatments have failed.”
   - “OP-1 Putty is indicated for use as an alternative to autograft in compromised patients requiring revision posterolateral (intertransverse) lumbar spinal fusion, for which 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.”
Stryker Biotech recently sought FDA permission to expand use of OP-1 Putty to include use in uninstrumented posterolateral lumbar spinal fusion for the treatment of lumbar spondylolisthesis. In March 2009, an FDA advisory committee voted 6-1 against recommending the expanded approval.

Both OP-1 and InFUSE Bone Graft/LT-Cage Lumbar Tapered Fusion device are contraindicated in patients who are pregnant, may be allergic to any of the materials contained in the devices, have an infection near the area of the surgical incision, have had a tumor removed from the area of the implantation site or currently have a tumor in that area, or who are skeletally immature.

In July 2008, the FDA issued a public health notification regarding life-threatening complications associated with recombinant human bone morphogenetic protein in cervical spine fusion. The FDA had received reports of complications with the use of rhBMP in cervical spine fusion. (1) These complications were associated with swelling of neck and throat tissue, which resulted in compression of the airway and/or neurologic structures in the neck. Some reports described difficulty swallowing, breathing, or speaking. Severe dysphagia following cervical spine fusion using rhBMP products has also been reported in the literature. As stated in the public health notification, the safety and effectiveness of rhBMP in the cervical spine have not been demonstrated, and these products are not approved by the FDA for this use.

In 2011 Medtronic received a “nonapprovable letter” from the FDA for AMPLIFY. The AMPLIFY rhBMP-2 Matrix utilizes a higher dose of rhBMP (2.0 mg/mL) with a compression-resistant carrier and is being evaluated for posterolateral fusion of single level lumbar (L2-S1) degenerative disc disease.

Related Policies
1.01.05 Ultrasound Accelerated Fracture Healing Device
2.01.16 Recombinant and Autologous Platelet-Derived Growth Factors as a Treatment of Wound Healing and Other Conditions
7.01.07 Electrical Bone Growth Stimulation of the Appendicular Skeleton
7.01.85 Electrical Stimulation of the Spine as an Adjunct to Spinal Fusion Procedures

Policy
*This policy statement applies to clinical review performed for pre-service (Prior Approval, Precertification, Advanced Benefit Determination, etc.) and/or post-service claims.

Use of recombinant human bone morphogenetic protein-2 (rhBMP-2, InFUSE) may be considered medically necessary in skeletally mature patients:

- For anterior lumbar interbody fusion procedures when use of autograft is unfeasible.
- For instrumented posterolateral intertransverse spinal fusion procedures when use of autograft is unfeasible.
- For the treatment of acute, open fracture of the tibial shaft, when use of autograft is unfeasible.

Use of recombinant human bone morphogenetic protein-7 (rhBMP-7, OP-1) may be considered medically necessary in skeletally mature patients:
As an alternative to autograft in compromised patients (eg, osteoporosis, tobacco use, or diabetes) requiring noninstrumented revision posterolateral intertransverse lumbar spinal fusion, for whom autologous bone and bone marrow harvest are not feasible or are not expected to promote fusion.*

For recalcitrant long-bone nonunions where use of autograft is unfeasible and alternative conservative treatments have failed.*

Bone morphogenetic protein (rhBMP-2 or rhBMP-7) is considered not medically necessary for all other indications, including but not limited to spinal fusion when use of autograft is feasible.

*FDA approved under a Humanitarian Device Exemption (HDE).

**Policy Guidelines**

Use of iliac crest bone graft (ICBG) may be considered unfeasible due to situations that may include, but are not limited to, prior harvesting of ICBG or need for a greater quantity of ICBG than available (e.g., for multi-level fusion).

There is not a consensus for the definition of nonunions. One proposed definition is failure of progression of fracture healing for at least 3 consecutive months (and at least 6 months following the fracture) accompanied by clinical symptoms of delayed/nonunion (pain, difficulty weight bearing). (2)

The following patient selection criteria are described for policies No. 1.01.05 (ultrasound) and 7.01.07 (electrical stimulation) in the treatment of nonunions:

- At least 3 months have passed since the date of the fracture, AND
- Serial radiographs have confirmed that no progressive signs of healing have occurred, AND
- The fracture gap is 1 cm or less, AND
- The patient can be adequately immobilized and is of an age when he/she is likely to comply with non-weight bearing.

A recalcitrant nonunion would thus be considered to be a nonunion with a larger fracture gap (eg, greater than 1 cm) or a nonunion that has persisted for a longer duration of time with no response to conservative treatment (eg, 3 months of ultrasound or electrical stimulation).

**Rationale**

At the time of the writing of this policy, randomized clinical trials supported the use of recombinant human bone morphogenetic protein-2 (rhBMP-2) in the treatment of interbody spinal fusion when used in conjunction with a tapered cage and also in the treatment of open tibial fractures. (3) In addition, a randomized study supported the use of rhBMP-7 in the treatment of recalcitrant nonunions of the long bones. (4) It should be noted that the majority of trials were designed to show that use of rhBMP is equivalent (not superior) to autologous bone grafting. Although the proposed advantage of rhBMP is the elimination of a separate incision site required for harvesting of autologous bone graft and the associated pain and morbidity secondary to this procedure, a 2011 study by Howard and colleagues raises questions about the magnitude of pain observed with iliac crest bone graft (ICBG) harvesting. (5)
In this study, 112 patients who had an instrumented posterolateral lumbar fusion at 1 or 2 levels were seen at a tertiary spine center for a routine postoperative visit. Iliac crest bone graft was harvested in 53 patients (47.3%) through the midline incision used for lumbar fusion and recombinant human bone morphogenetic protein (rhBMP-2) was used in 59 patients (52.7%) with no graft harvest. An independent investigator who was not directly involved in the care of the patient and was unaware of the type of bone graft used in the fusion examined the patient for tenderness over the surgical site, as well as the left and right posterior iliac crest. At a mean follow-up of 41 months (range 6-211 months), there was no significant difference between the groups in the proportion of patients complaining of tenderness over either iliac crest (3.8 vs. 3.6 on a 10-point scale). While 54% of patients complained of tenderness over one or both iliac crests, only 10 patients (9% of 112) had pain over the same crest from which the graft was harvested (mean pain score of 4.4).

**Spinal Fusion**

In 2013, 2 systematic reviews on the effectiveness and harms of recombinant human bone morphogenetic protein-2 (rhBMP-2) in spine fusion were published. (6, 7) These 2 systematic reviews of patient-level data followed a 2011 U.S. Senate investigation of industry influence on Infuse clinical studies and a systematic review by Carragee and colleagues of emerging safety concerns with rhBMP-2. (8, 9) The systematic review by Carragee et al. compared conclusions regarding safety and efficacy from the 13 published rhBMP-2 industry-sponsored trials with available U.S. Food and Drug Administration (FDA) data summaries, subsequent studies, and databases. Evaluation of the original trials suggested methodologic bias against the control group in the study design (discarding local bone graft and failure to prepare facets for arthrodesis) and potential bias (overestimation of harm) in the reporting of iliac crest donor site pain. Comparison between the published studies and FDA documents revealed internal inconsistencies and adverse events that were not reported in the published articles.

Both of the 2013 studies conducted meta-analyses on individual patient data, both published and unpublished, that was provided by the manufacturer through the Yale University Open Data Access (YODA) Project. One meta-analysis was conducted by Simmonds and colleagues from the University of York in the United Kingdom; the other was by Fu and colleagues from the Oregon Health and Science University.

The meta-analysis by Simmonds et al. included patient-level data from 12 randomized controlled trials (RCTs, n=1,408), regardless of spinal level or surgical approach, and adverse event data from an additional 35 observational studies. (6) rhBMP-2 increased the rate of radiographic fusion by 12% compared to ICBG, with substantial heterogeneity across trials. A small improvement in the Oswestry Disability Index (ODI, 3.5 percentage points) did not reach the previously defined threshold for a clinically significant effect. The review also found a small improvement in back pain (1 point on a 20-point scale) and SF-36 physical component score (PCS, 1.9 percentage points). There was no significant difference between the groups for leg pain. There was a potential for bias in the pain and functional outcomes since outcomes were patient-reported and patients were not blinded to the treatment received. Overall, the increase in successful fusion at up to 24 months did not appear to be associated with a clinically significant reduction in pain.
The meta-analysis by Fu et al. included individual-patient data from 13 RCTs (n=1,981) and 31 cohort studies. (7) The review found moderate evidence of no consistent differences between rhBMP-2 and ICBG in overall success, fusion rates, or other effectiveness measures for anterior lumbar interbody fusion (ALIF) or posterolateral fusion (PLF). A small RCT and 3 cohort studies revealed no difference in effectiveness outcomes between rhBMP and ICBG for anterior cervical fusion. Reporting in the original published trials was found to be biased, with journal publications selecting analyses and results that favored rhBMP over ICBG.

Both studies found that cancer risk may be increased with rhBMP-2, although the number of events was low and there was heterogeneity in the types of cancer. In the Simmonds analysis, combined analysis revealed a relative risk of 1.84 for cancer in the BMP group, but this increased rate did not reach statistical significance (95% CI: 0.81-4.16). Fu et al. performed a combined analysis of cancer incidence at 24 months and 48 months post-treatment. At 24 months, there was a significant increase in cancer for the BMP group (risk ratio [RR]: 3.45, 95% CI: 1.98-6.0), and at 48 months, there was a smaller increase that did not reach statistical significance (RR: 1.82, 95% CI: 0.84-3.95).

Other adverse events were also increased for the BMP group. Simmonds et al. found a higher incidence of early back and leg pain with rhBMP-2 in the analysis of patient-level data. The studies consistently reported increased rates of heterotopic bone formation, leg pain/radiculitis, osteolysis and dysphagia, but combined analysis for these outcomes was not performed. The Fu study reported that BMP-2 was associated with a nonsignificantly increased risk for urogenital problems when used for anterior lumbar fusion and an increased risk for wound complications and dysphagia when used for anterior cervical spine fusion. Fu et al. documented that the information on adverse events in the published literature was incomplete in comparison to the total amount of information available.

Off-label use of BMP can include multiple levels and dosages greater than the FDA-approved dose of rhBMP-2 for single-level fusion. In 2013, Carragee et al. assessed cancer risk after high-dose rhBMP-2 (40 mg) using publicly available data from the pivotal, multicenter, randomized controlled trial of AMPLIFY (n=463).(10) The study found an increase in the incidence of cancer, a reduction in the time to first cancer, and a greater number of patients with multiple cancers. For example, at 2 years there were 15 new cancer events in 11 patients in the rhBMP-2 group compared with 2 new cancer events in 2 patients treated with autogenous bone graft, with an incidence rate ratio of 6.75. When calculated in terms of the number of patients with one or more cancer events 2 years after surgery, the incidence rate per 100 person-years was 2.54 in the rhBMP-2 group compared with 0.50 in the control group, and the incidence rate ratio was 5.04. The mean time to development of cancer was 17.5 months after use of rhBMP-2 compared with 31.8 months in the controls. Three patients in the rhBMP-2 group and none in the control group developed multiple new cancers.

Long-Bone Fractures and Nonunions

A 2010 Cochrane review evaluated the effectiveness and costs of rhBMP on fracture healing in acute fractures and nonunions compared with standards of care. (11) The literature was searched to October 2008, and 11 RCTs (976 participants) and 4 economic evaluations were included in the review. The times to fracture healing were comparable between the rhBMP and control groups. There was some evidence for increased healing rates, mainly for open tibial fractures without secondary procedures (risk ratio [RR]: 1.19). Three trials indicated that fewer secondary procedures were
required for acute fractures treated with rhBMP (RR: 0.65). The authors concluded that limited evidence suggests that rhBMP may be more effective than standard of care for acute tibial fracture healing; however, the use of rhBMP for treating nonunion remains unclear (RR: 1.02).

**Oral and Maxillofacial Procedures**

The 2010 AHRQ technology assessment on the state of the evidence of on-label and off-label use of rhBMP (7) included the following conclusions:

- The strength of the body of evidence on clinical outcomes is moderate that rhBMP-2 does not provide an advantage in prosthesis implantation and functional loading compared to autograft plus allograft bone.
- There is also moderate evidence that oral sensory loss associated with autograft bone harvest can be avoided by use of rhBMP2.

Through April 30, 2011, the FDA’s Manufacturer and User Facility Device Experience (MAUDE) received 83 reports of adverse events involving rhBMP-2 in oral and maxillofacial operations. (12) rhBMP-2 was used off-label in 66.3% of these cases and included reconstruction of the mandible after fracture or cancer and alveolar cleft repair. The most frequently reported adverse events were local edema/pain, surgical site infections/wound complications, and graft failure.

Overall, the evidence does not support a health benefit of rhBMP in oral and maxillofacial procedures.

**Additional Applications**

There has been research interest in the following applications: management of early stages of osteonecrosis of the vascular head, as an adjunct to hip arthroplasty to restore bone defects in the acetabulum or femoral shaft, and as an adjunct to distraction osteogenesis (i.e., Ilizarov procedure). (13, 14) The literature regarding these applications consists of small case series; no controlled trials have been identified.

**Ongoing Clinical Trials**

A search of online site clinicaltrials.gov in July 2013 identified several ongoing studies. Of particular interest is an industry-sponsored Phase II randomized controlled dose finding study of intra-articular BMP-7 for osteoarthritis of the knee (NCT01111045). The study lists an enrollment of 355 subjects and is described as completed as of January 2012. As of July 2013, no publications from this study have been identified.

**Practice Guidelines and Position Statements**

None identified
Summary

In 2013, 2 systematic reviews on recombinant human bone morphogenetic protein-2 (rhBMP-2) that used manufacturer-provided individual patient data were published. Overall, these systematic reviews found little to no benefit of rhBMP-2 over iliac crest bone graft for spinal fusion, with an uncertain risk of harm. The small benefits reported do not support the widespread use of rhBMP-2, but do leave the possibility that rhBMP-2 may lead to clinically significant improvements in selected subgroups, such as patients in whom use of iliac crest bone graft (ICBG) is unfeasible and have a high risk of fusion failure. While there was a low adverse event rate overall, concerns remain about the possibility of increased adverse event rates with rhBMP-2, including cancer. Based on this new evidence, it is not possible to conclude that the small benefits of rhBMP-2 outweigh the risks. Therefore, rhBMP-2 is considered to be not medically necessary when use of ICBG is feasible. In cases where use of ICBG is not feasible, such as when previous bone harvest has been performed, the benefit of rhBMP in promoting fusion will likely outweigh the adverse effects, and therefore rhBMP-2 may be considered medically necessary.

The U.S. Food and Drug Administration’s humanitarian device exemptions (HDE) for rhBMP-7 state that use is restricted to patients in whom autologous bone and bone marrow harvest are not feasible or are not expected to promote to promote fusion. Therefore, the policy on rhBMP-7 remains unchanged.

Use of rhBMP has not been shown to be as beneficial as the established alternative (iliac crest bone graft, ICBG) and evidence is insufficient to permit conclusions concerning the effect of rhBMP and is considered investigational for other indications, including (but not limited to):

- Cervical spinal fusions
- Posterior or transforaminal lumbar interbody spinal fusion (considered investigational because of safety concerns related to ectopic bone formation in the spinal canal);
- Treatment of noninstrumented posterolateral intertransverse spinal fusion when autograft is feasible and expected to promote fusion;
- An alternative or adjunct to bone grafting in other locations, (considered investigational due to the lack of controlled trials to support it efficacy).

Medicare National Coverage

The Centers for Medicare and Medicaid Services (CMS) has established an add-on to the diagnosis-related group (DRG) payment to cover a portion of the cost of new technologies during the 2-year period before charge data for the technologies are incorporated into the DRG weights. To qualify, a technology must be new, must provide verifiable improvement in the treatment or diagnosis of beneficiaries, and the mean standardized charge for treatment using the new technology must be at least 1 standard deviation above the mean standardized charge for treating the same case without the new technology. In 2004, CMS concluded that the InFUSE™ Bone Graft/LT-CAGE met these criteria and will receive an add-on payment to DRGs 497 or 498. Medtronic, the manufacturer of the InFUSE device, has applied for a new technology add-on payment for the FDA-approved indication of treatment of open acute fractures of the tibial shaft.
References


Policy History

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<tr>
<th>Date</th>
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<tbody>
<tr>
<td>June 2012</td>
<td>New Policy</td>
<td>Policy updated with literature review; references 49-51 added; policy statements unchanged.</td>
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<tr>
<td>March 2013</td>
<td>Update Policy</td>
<td>Policy updated with literature review, one FDA-approved indication that had been omitted was reinserted: Treatment of tibial shaft with BMP-2 (when autograft is unfeasible added); return to use of FDA language regarding treatment of noninstrumented revision posterolateral intertransverse lumbar spinal fusion with BMP-7 where use of autograft is unfeasible.</td>
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Keywords

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Infuse, Bone Morphogenetic Protein
OP-1, Bone Morphogenetic Protein
BMP, BMP-2, BMP-7
Infuse
Recombinant human bone morphogenetic protein

This policy was approved by the FEP® Pharmacy and Medical Policy Committee on March 14, 2014 and is effective April 15, 2014.

Signature on File
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