BlueCross BlueShield of Alabama

Name of Policy:
Bone Morphogenetic Protein

Policy #: 189
Category: Surgery

Latest Review Date: May 2018
Policy Grade: A

Background/Definitions:

As a general rule, benefits are payable under Blue Cross and Blue Shield of Alabama health plans only in cases of medical necessity and only if services or supplies are not investigational, provided the customer group contracts have such coverage.

The following Association Technology Evaluation Criteria must be met for a service/supply to be considered for coverage:

1. *The technology must have final approval from the appropriate government regulatory bodies;*
2. *The scientific evidence must permit conclusions concerning the effect of the technology on health outcomes;*
3. *The technology must improve the net health outcome;*
4. *The technology must be as beneficial as any established alternatives;*
5. *The improvement must be attainable outside the investigational setting.*

Medical Necessity means that health care services (e.g., procedures, treatments, supplies, devices, equipment, facilities or drugs) that a physician, exercising prudent clinical judgment, would provide to a patient for the purpose of preventing, evaluating, diagnosing or treating an illness, injury or disease or its symptoms, and that are:

1. *In accordance with generally accepted standards of medical practice; and*
2. *Clinically appropriate in terms of type, frequency, extent, site and duration and considered effective for the patient's illness, injury or disease; and*
3. *Not primarily for the convenience of the patient, physician or other health care provider; and*
4. *Not more costly than an alternative service or sequence of services at least as likely to produce equivalent therapeutic or diagnostic results as to the diagnosis or treatment of that patient's illness, injury or disease.*

Description of Procedure or Service:

One recombinant human bone morphogenetic protein (rhBMP) is commercially available, rhBMP-2 applied with an absorbable collagen sponge (InFUSE®). rhBMP has 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.

Bone Morphogenetic Protein and Carrier and Delivery Systems

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. The recombinant human bone morphogenetic proteins (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, 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 provide mechanical support.

Applications

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 (posterior lumbar interbody fusion [PLIF] or transforaminal lumbar interbody fusion [TLIF]; see Appendix). 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.

Policy:

Effective for dates of service on or after October 25, 2017:

Use of recombinant human bone morphogenetic protein-2 (rhBMP-2, InFUSE) meets Blue Cross and Blue Shield of Alabama's medical criteria for coverage in **skeletally mature patients**:

- For anterior lumbar interbody fusion procedures when use of autograft is not feasible; or
- For instrumented posterolateral intertransverse spinal fusion procedures when use of autograft is not feasible*; or
- For the treatment of acute, open fracture of the tibial shaft, when use of autograft is not feasible.

***As of 2014, rhBMP-7 is no longer marketed in the United States**.

Use of bone morphogenetic protein (rhBMP-2) does not meet Blue Cross and Blue Shield of Alabama's medical criteria for coverage for all other indications, including but not limited to spinal fusion and craniomaxillofacial surgery when use of autograft is feasible.

*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 ICBGH than available (e.g., for multi-level fusion).
**A recalcitrant nonunion would thus be considered to be a non-union with a larger fracture gap (e.g., greater than 1 cm) or a non-union that has persisted for a longer duration of time with no response to conservative treatment (e.g., 3 months of ultrasound or electrical stimulation).

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;
- Are skeletally immature.

*FDA approved for one level
**FDA approved indication
***FDA approved under a Humanitarian Device Exemption (HDE)

Effective for dates of service January 31, 2014 through October 24, 2017:

Use of recombinant human bone morphogenetic protein-2 (rhBMP-2, InFUSE) meets Blue Cross and Blue Shield of Alabama's medical criteria for coverage in **skeletally mature patients**:

- For anterior lumbar interbody fusion procedures when use of autograft is not feasible; or
- For instrumented posterolateral intertransverse spinal fusion procedures when use of autograft is not feasible*; or
- For the treatment of acute, open fracture of the tibial shaft, when use of autograft is not feasible.

Use of recombinant human bone morphogenetic protein-7 (rhBMP-7, OP-1) meets Blue Cross and Blue Shield of Alabama's medical criteria for coverage in **skeletally mature patients**:

- As an alternative to autograft in compromised patients (e.g., 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.***

As of 2014, rhBMP-7 is no longer marketed in the United States.

Bone morphogenetic protein (rhBMP-2 or rhBMP-7) does not meet Blue Cross and Blue Shield of Alabama's medical criteria for coverage for all other indications, including but not limited to spinal fusion when use of autograft is feasible.

*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 ICBGH than available (e.g., for multi-level fusion).
**A recalcitrant nonunion would thus be considered to be a non-union with a larger fracture gap (e.g., greater than 1 cm) or a non-union that has persisted for a longer duration of time with no response to conservative treatment (e.g., 3 months of ultrasound or electrical stimulation).
***FDA approved under a Humanitarian Device Exemption (HDE). OP-1 is no longer sold in the United States.

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;
- Are skeletally immature.

*FDA approved for one level
**FDA approved indication
***FDA approved under a Humanitarian Device Exemption (HDE)

Blue Cross and Blue Shield of Alabama does not approve or deny procedures, services, testing, or equipment for our members. Our decisions concern coverage only. The decision of whether or not to have a certain test, treatment or procedure is one made between the physician and his/her patient. Blue Cross and Blue Shield of Alabama administer benefits based on the member's contract and corporate medical policies. Physicians should always exercise their best medical judgment in providing the care they feel is most appropriate for their patients. Needed care should not be delayed or refused because of a coverage determination.

Key Points:

This policy has been updated regularly with searches of the MEDLINE database. The most recent literature update was performed through March 8, 2018.

Evidence reviews assess the clinical evidence to determine whether the use of a technology improves the net health outcome. Broadly defined, health outcomes are length of life, quality of life, and ability to function- including benefits and harms. Every clinical condition has specific outcomes that are important to patients and to managing the course of that condition. Validated outcome measures are necessary to ascertain whether a condition improves or worsens; and whether the magnitude of that change is clinically significant. The net health outcome is a balance of benefits and harms.

To assess whether the evidence is sufficient to draw conclusions about the net health outcome of a technology, 2 domains are examined: the relevance and the quality and credibility. To be relevant, studies must represent one or more intended clinical use of the technology in the intended population and compare an effective and appropriate alternative at a comparable intensity. For some conditions, the alternative will be supportive care or surveillance. The quality and credibility of the evidence depend on study design and conduct, minimizing bias and confounding that can generate incorrect findings. The randomized controlled trial (RCT) is preferred to assess efficacy; however, in some circumstances, nonrandomized studies may be adequate. RCTs are rarely large enough or long enough to capture less common adverse events and long-term effects. Other types of studies can be used for these purposes and to assess generalizability to broader clinical populations and settings of clinical practice.

At the time this policy was created, randomized clinical trials (RCTs) supported the use of recombinant human bone morphogenetic protein-2 (rhBMP-2) in the treatment of anterior interbody spinal fusion when used in conjunction with a tapered cage and also in the treatment of open tibial fractures. In addition, a randomized study supported the use of rhBMP-7 in the treatment of recalcitrant nonunions of the long bones. 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 The proposed advantage of rhBMP is the elimination of a separate incision site to harvest autologous bone graft and the associated pain and morbidity. However, a 2011 study by Howard et al raised questions about the magnitude of pain observed with iliac crest bone graft (ICBG) harvesting. 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. ICBG was harvested in 53 patients (47.3%) through the midline incision used for lumbar fusion and 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 to 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).

Lumbar Spinal Fusion

Systematic Reviews

In 2013, 2 systematic reviews on the effectiveness and harms of recombinant human bone morphogenetic protein-2 (rhBMP-2) in spine fusion were published. 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. 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 (total N=1408), regardless of spinal level or surgical approach, and adverse event data from an additional 35 observational studies. 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 (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 36-Item Short-Form Health Survey Physical Component Summary score (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 rate 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 (total N=1981) and 31 cohort studies. 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 trial, 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 to 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 to 6.0), and at 48 months, there was a smaller increase that did not reach statistical significance (RR: 1.82, 95% CI: 0.84 to 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 individual publications consistently reported higher 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 rhBMP-2 was associated with a non-significantly 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 also noted 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, multi-center, randomized controlled trial of AMPLIFY (N=463). 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 two years there were 15 new cancer events in 11 patients in the rhBMP-2 group compared with two 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.

Zadegan et al conducted a systematic review and meta-analysis investigating the off-label uses of rhBMP. Reviewers evaluated the evidence for rhBMP-2 and rhBMP-7 in anterior cervical spine fusions. A literature search returned 18 articles (total N=4782 patients). Reviewers specifically assessed rhBMP for fusion rates, adverse events and complication rates. The fusion rate was higher in rhBMP than in alternative treatments such as bone grafting. However, serious complications (e.g., cervical swelling, dysphagia/dysphonia, ossification) occurred more frequently in rhBMP procedures than in any other treatment alternative.

Observational Studies

In a retrospective cohort study, Khan et al investigated the effectiveness and safety of using rhBMP-2 in transforaminal lumbar interbody fusions. The authors compared rhBMP-2 with bone autograft by reviewing data on 191 patients undergoing anteroposterior instrumented spinal fusion with transforaminal lumbar interbody fusion from 1997 to 2014 at a single institution. Patients were separated into 2 treatment groups: 83 patients were treated with rhBMP-2 (BMP group) and 104 patients were treated with bone grafting (non-BMP group. Results were similar between groups; fusion rates were 92.7% and 92.3% for BMP and non-BMP patients, respectively. Seven patients in the BMP group and 2 patients in the non-BMP group experienced

radiculitis. Seroma was observed in 2 patients in the BMP group; it was not observed in any patients in the non-BMP group. Given these very small differences, the authors concluded that rhBMP-2 is a comparable treatment option to bone grafting in transforaminal lumbar interbody fusion procedures.

Section Summary: Lumbar Spinal Fusion
The evidence on the effectiveness and potential harms of rhBMP-2 and rhBMP-7 in spinal fusion consists of RCTs, systematic reviews, meta-analyses, and observational studies. The fusion rates with the use of rhBMP are comparable to bone autograft. There is evidence that specific complication rates are higher with rhBMP.

Tibial Fractures and Nonunions
In 2015, Dai et al published a meta-analysis on rhBMP for the healing of acute tibial fractures (4 RCTs, 868 patients) and non-unions (4 RCTs, 245 patients). For acute tibial fractures, three RCTs were conducted with rhBMP-2 and one with rhBMP-7. All of the included studies were conducted over a decade ago. rhBMP was associated with a higher rate of union (RR=1.16) and a lower rate of revision (RR=0.68) compared with controls (three trials with soft-tissue management andone1 with intramedullary nail [IM] plus autograft). There was no significant difference between the BMP and control groups for hardware failure or infection. For tibial fracture non-unions, three trials used rhBMP-7 and the fourth trial did not state which formulation. The RR=0.98, and there was no significant difference between the BMP and IM plus autograft groups in the rate of revision or infection. Interpretation of these results is limited by the different control groups and different formulations of rhBMP, one of which is no longer marketed in the U.S.

A 2010 Cochrane review evaluated the effectiveness and costs of rhBMP on fracture healing in acute fractures and nonunions compared with standards of care. The literature was searched to October 2008, and 11 RCTs (976 participants) and four 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 efficacy of rhBMP for treating nonunion remains uncertain (RR: 1.02).

In 2014, Lyon et al reported a manufacturer-funded randomized double-blind trial of injectable rhBMP-2 in a calcium phosphate matrix for closed tibial diaphyseal fractures. The study had a target enrollment of 600 patients but was stopped after interim analysis with 387 patients enrolled. Addition of the injectable rhBMP-2 paste to the standard of reamed intramedullary nail fixation did not shorten the time to fracture healing, resulting in the study termination due to futility.

Section Summary: Tibial Fractures and Nonunions
The evidence for the use of rhBMP in long-bone fractures and nonunions consists of RCTs, systematic reviews, and meta-analyses. Two systematic reviews have concluded that rhBMP can

reduce reoperations rates compared with soft-tissue management with or without intramedullary nailing.

Oral and Maxillofacial Procedures

A 2010 Agency for Healthcare Research and Quality (AHRQ) technology assessment on the state of the evidence of on-label and off-label use of rhBMP 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 moderate evidence that oral sensory loss associated with autograft bone harvest can be avoided by use of rhBMP2.

Additional Applications

Limited research has evaluated the use of rhBMP for 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). The literature regarding these applications consists of small case series; no controlled trials have been identified.

Section Summary: Other Surgical Procedures

There is little evidence supporting the use of rhBMP in surgical procedures or interventions other than spinal fusion and acute long fractures. Conclusions cannot be drawn on the utility of rhBMP for other surgical indications.

Summary of Evidence

For individuals who are undergoing anterior or posterolateral lumbar spinal fusion and in whom autograft is not feasible who receive rhBMP, the evidence includes randomized controlled trials (RCTs), systematic reviews, and meta-analyses. Relevant outcomes are symptoms, morbid events, functional outcomes, and treatment-related morbidity. In 2013, 2 systematic reviews of rhBMP-2 trials using manufacturer-provided individual patient data were published. Overall, these reviews found little to no benefit of rhBMP-2 over iliac crest bone graft for all patients undergoing spinal fusion, with an uncertain risk of harm. The small benefits reported do not support the widespread use of rhBMP-2 as an alternative to iliac crest autograft. However, the studies do establish that rhBMP-2 has efficacy in promoting bone fusion and will improve outcomes for patients for whom use of iliac crest bone graft is not feasible. The overall adverse event rate was low, though concerns remain about increased adverse event rates with rhBMP-2, including cancer. The evidence is sufficient to determine that the technology results in a meaningful improvement in the net health outcome.

For individuals who are undergoing surgery for acute tibial shaft fracture and in whom autograft is not feasible who receive rhBMP, the evidence includes RCTs and systematic reviews of the RCTs. Relevant outcomes are symptoms, morbid events, functional outcomes, and treatment-related morbidity. Two systematic reviews have concluded that rhBMP can reduce reoperations rates compared with soft-tissue management with or without intramedullary nailing. The evidence is sufficient to determine that the technology results in a meaningful improvement in the net health outcome.

For individuals undergoing other surgical procedures (e.g., oral and maxillofacial, hip arthroplasty, distraction osteogenesis) who receive rhBMP, the evidence includes a health technology assessment and small case series. Relevant outcomes are symptoms, morbid events, functional outcomes, and treatment-related morbidity. The evidence does not permit conclusions about the effect of rhBMP for craniomaxillofacial surgery or tibial shaft fracture nonunion. The evidence is insufficient to determine the effects of the technology on health outcomes.

Practice Guidelines and Position Statements
Guidelines on lumbar spinal fusion from the American Association of Neurological Surgeons (AANS) and the Congress of Neurological Surgeons were updated in 2014. AANS/CNS gave a Grade B recommendation (multiple level II studies) for the use of rhBMP-2 as a substitute for autologous iliac crest bone for anterior lumbar interbody fusion and single-level posterolateral instrumented fusion. Grade C recommendations were made for rhBMP-2 as an option for PLIF and TLIF, posterolateral fusion in patients older than 60 years, and as a graft extender for either instrumented or noninstrumented posterolateral fusions. AANS/CNS also gave a Grade C recommendation (based on multiple level IV and V studies) that the use of rhBMP-2 as a graft option has been associated with a unique constellation of complications of which the surgeon should be aware when considering the use of this graft extender/substitute.

U.S. Preventive Services Task Force Recommendations
Not applicable.

Key Words:
Bone morphogenetic protein, BMP, InFUSE®, OP-1, bone morphogenetic protein-2, rhBMP-2, bone morphogenetic protein-7, rhBMP-7, InFUSE™ Bone Graft/LT-CAGE™, InFUSE™ Bone Graft/INTER FIX™ Threaded Fusion Device, OP-1 Implant, OP-1 Putty, osteobiologics, BMP-7, BMP, Recombinant human bone morphogenetic protein

Approved by Governing Bodies:
The INFUSE® Bone Graft product (Medtronic) consists of rhBMP-2 on an absorbable collagen sponge carrier; it is used in conjunction with several carrier and delivery systems. The INFUSE® line of products has been approved by the U.S. Food and Drug Administration (FDA) through the premarket approval process (PMA) (see summary of key approvals in Table 1).

In 2008, FDA issued a public health notification on life-threatening complications associated with rhBMP in cervical spine fusion, based on reports of complications with use of rhBMP in cervical spine fusion.1 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 efficacy of rhBMP in the cervical spine have not been demonstrated. These products are not approved by FDA for this use.

In 2011, Medtronic received a "nonapprovable letter" from FDA for AMPLIFY™. The AMPLIFY™ rhBMP-2 Matrix uses a higher dose of rhBMP (2.0 mg/mL) with a compression-resistant carrier.

OP-1® Putty (Stryker Biotech), which consists of rhBMP-7 and bovine collagen and carboxymethylcellulose, forms a paste or putty when reconstituted with saline. OP-1® Putty was initially approved by FDA through the humanitarian device exemption process (H020008) for 2 indications:

> "OP-1 Implant is indicated for use as an alternative to autograft in recalcitrant long-bone nonunions where use of autograft is unfeasible 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 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."

Stryker Biotech sought FDA permission to expand the use of OP-1® Putty to include uninstrumented posterolateral lumbar spinal fusion for the treatment of lumbar spondylolisthesis. In 2009, FDA Advisory Committee voted against the expanded approval. Olympus Biotech (a subsidiary of Olympus Corp.) acquired OP-1® assets in 2010. In 2014, Olympus closed Olympus Biotech operations in the United States and discontinued domestic sales of Olympus Biotech products. The rhBMP-7 product is no longer marketed in the United States.

Table 1. rhBMP Products and Associated Carrier and Delivery Systems Approved by FDA

Systems	Manufacturer	Approved	PMA No.
INFUSE® Bone Graft • Alternative to autogenous bone graft for sinus augmentations • For localized alveolar ridge augmentations in extraction socket defects	Medtronic	03/07	P050053
INFUSE® Bone Graft • Expanded indication for spinal fusion procedures in skeletally mature patients with degenerative disc disease at 1 level from L4 to S1 • Expanded indication for acute, open tibial shaft fractures stabilized with nail fixation		10/09	P050053/S012
INFUSE™ Bone Graft/LT-CAGE™ Lumbar Tapered Fusion Device • Indicated for spinal fusion procedures in skeletally mature patients with degenerative disc disease at 1 level from L4 to S1 • Up to grade 1 spondylolisthesis at involved level • Implantation via anterior open or anterior laparoscopic approach	Medtronic Sofamor Danek USA[a]	07/02	P000058
INFUSE™ Bone Graft/LT-CAGE™ Lumbar Tapered Fusion Device • Extension of device use from L2 to S1 • May be used with retrolisthesis		07/04	P000058/S002
INFUSE™ Bone Graft/LT-CAGE™ Lumbar Tapered Fusion Device • Indicated for acute, open tibial shaft fractures stabilized with nail fixation • Alternative to autogenous bone graft for sinus augmentations • For localized alveolar ridge augmentations in extraction socket defects		10/09	P000058/S033

INFUSE™ Bone Graft/Medtronic Interbody Fusion Device (Marketing name change) • Expanded indication for 2 additional interbody fusion devices • Perimeter Interbody Fusion Device implanted via retroperitoneal ALIF L2 to S1 or OLIF L5 to S1 • Clydesdale Spinal System implanted via OLIF at single level from L2-S5	12/15	P000058/S059
INFUSE™ Bone Graft/Medtronic Interbody Fusion Device • Expanded indication for 2 additional interbody fusion devices: o Divergence-L Anterior/Oblique Lumbar Fusion System o Pivox™ Oblique Lateral Spinal System	09/17	P000058/S065

ALIF: anterior lumbar interbody fusion; FDA: Food and Drug Administration; OLI: oblique lateral interbody fusion; rhBMP: recombinant human bone morphogenetic protein; S: supplement.
[a] Medtronic is the manufacturer for all of the INFUSE bone graft and carrier systems.

Benefit Application:

Coverage is subject to member's specific benefits. Group specific policy will supersede this policy when applicable.
ITS: Home Policy provisions apply
FEP contracts: Special benefit consideration may apply. Refer to member's benefit plan.

Current Coding:

There is not CPT or HCPCS code for bone morphogenic protein. In 2011, CPT code 20930 was revised to include BMP-type materials used in spine surgery.

CPT:

20930	Allograft, morselized, or placement of osteopromotive material, for spine surgery only (List separately in addition to code for primary procedure)

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Policy History:

Medical Policy Group, July 2004 **(2)**
Medical Policy Administration Committee, August 2004
Available for comment August 11-September 24, 2004
Medical Policy Group, July 2006 **(1)**
Medical Policy Group, July 2008 **(1)**
Medical Policy Panel, June 2009
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Medical Policy Group, October 2010
Medical Policy Panel, November 2012
Medical Policy Group, January 2013 **(2):** Policy statement excluding coverage for cervical fusion added. Key Points, Approved by Governing Bodies, References updated to reflect changes. Information regarding high-risk patients for fusion added to Key Points
Medical Policy Administration Committee, February 2013
Available for comment February 21 through April 7, 2013
Medical Policy Panel, September 2013
Medical Policy Group, September 2013 **(2):** Policy statement changed to coverage when harvesting of iliac crest bone graft bone is unfeasible. Description, Key Points, References updated to support policy changes. CPT code added. ICD-10-PC code added. Deleted coverage statements prior to 2009
Medical Policy Group, October 2013 **(2):** Removed ICD-9 Procedure codes; no change to policy statement.
Medical Policy Administration Committee, October 2013
Available for comment October 16 through November 30, 2013
Medical Policy Panel, November 2013
Medical Policy Group, November 2013 **(2):** Policy updated with literature review through October 2013. Added coverage for treatment of tibial shaft with BMP-2 (when autograft is unfeasible). Returned to use of FDA language regarding treatment of noninstrumented revision posterolateral intertransverse lumbar spinal fusion with BMP-7 where use of autograft is unfeasible. Additional instructions added to Coding section. Key Points and References updated to support policy changes.
Medical Policy Administration Committee, December 2013
Available for comment December 17, 2013 through January 30, 2014
Medical Policy Panel, November 2014
Medical Policy Group **(4)**: Added to Policy that OP-1 is no longer sold in United States. Update to Description, Key Points, and References. Added Appendix section.
Medical Policy Panel, April 2016
Medical Policy Group, April 2016 **(7)**: Note added to Policy Statement that rhBMP-7, OP-1 no longer being marketed in the US as of 2014; Description, Key Points, Approved by Governing Bodies, and References.
Medical Policy Panel, October 2017

Medical Policy Group, October 2017 **(7)**: 2017 Updates to Key Points, Approved by Governing Bodies and References. Updated policy statement- rhBMP-7, OP-1 removed from policy statement due to rhBMP-7, OP-1 no longer being marketed in the US as of 2014. Craniomaxillofacial surgery added to "included, but not limited…" to statement as not meeting medical criteria for coverage.
Medical Policy Panel, April 2018
Medical Policy Group, May 2018 **(7)**: Updates to Key Points and References. No change in Policy Statement.

Appendix

Procedures used for lumbar interbody fusion differ primarily in the direction of approach to the spine, i.e., from the front (anterior), from the back (posterior or transforaminal) or from the side (lateral). An alternative approach to interbody fusion is arthrodesis of the transverse processes alone (posterolateral), which does not fuse the adjoining vertebral bodies. Circumferential fusion fuses both the adjacent vertebral bodies and the transverse processes, typically using both an anterior and posterior approach to the spine.

Open and Minimally Invasive Approaches to Lumbar Interbody Fusion

Procedures	Access	Approach	Visualization
Anterior (ALIF)	Open, MI, or laparoscopic	Transperitoneal or retroperitoneal	Direct, endoscopic or laparoscopic with fluoroscopic guidance Direct, endoscopic or microscopic, with fluoroscopic guidance
Posterior (PLIF)	Open or MI	Incision centered over spine with laminectomy/laminotomy and retraction of nerve	Direct, endoscopic or microscopic, with fluoroscopic guidance
Transforaminal (TLIF)	Open or MI	Offset from spine, through the intervertebral foramen via unilateral facetectomy	Direct, endoscopic or microscopic, with fluoroscopic guidance
Lateral Extreme lateral (XLIF) Direct Lateral (DLIV)	MI	Retroperitoneal through transpsoas	Direct, with neurologic monitoring and fluoroscopic guidance

LIF: lumbar interbody fusion; MI: minimally invasive

Anterior Lumbar Interbody Fusion

Anterior access provides direct visualization of the disc space, potentially allowing a more complete discectomy and better fusion than lateral or posterior approaches. An anterior approach avoids trauma to the paraspinal musculature, epidural scarring, traction on nerve roots, and dural tears. However, the retraction of the great vessels, peritoneal contents, and superior hypogastric sympathetic plexus with a peritoneal or retroperitoneal approach place these structures at risk of iatrogenic injury. Access to the posterior space for the treatment of nerve compression is also limited. Laparoscopic anterior lumbar interbody fusion has also been investigated.

Posterior Lumbar Interbody Fusion

Posterior lumbar interbody fusion (PLIF) can be performed through either a traditional open procedure with a midline incision or with a minimally invasive approach using bilateral paramedian incisions. In the open procedure, the midline muscle attachments are divided along the central incision to facilitate wide muscle retraction and laminectomy. In minimally invasive PLIF, tubular retractors may be used to open smaller central bilateral working channels to access the pedicles and foramen. Minimally invasive PLIF typically involves partial laminotomies and facetectomies. The decompression allows treatment of spinal canal pathology (e.g., spinal stenosis, lateral recess and foraminal stenosis, synovial cysts, hypertrophic ligamentum flavum), as well as stabilization of the spine through interbody fusion.

Transforaminal Lumbar Interbody Fusion
Transforaminal lumbar interbody fusion (TLIF) is differentiated from the more traditional bilateral PLIF by a unilateral approach to the disc space through the intervertebral foramen. In minimally invasive TLIF, a single incision about 2 to 3 cm in length is made approximately 3 cm lateral to the midline. A tubular retractor is docked on the facet joint complex and a facetectomy with partial laminectomy is performed. Less dural retraction is needed with access through the foramen via unilateral facetectomy, and contralateral scar formation is eliminated. TLIF provides access to the posterior elements along with the intervertebral disc space.

Lateral Interbody Fusion
Lateral interbody fusion (e.g., extreme lateral interbody fusion or direct lateral interbody fusion) uses specialized retractors in a minimally invasive, lateral approach to the anterior spine through the psoas. In comparison with ALIF, the lateral approach does not risk injury to the peritoneum or great vessels. However, exposure to the spine may be more limited, and dissection of the psoas major places the nerves of the lumbar plexus at risk. Electromyographic monitoring and dissection predominantly within the anterior psoas major may be utilized to reduce the risk of nerve root injury. These various factors decrease the ability to perform a complete discectomy and address pathology of the posterior elements.

Circumferential Fusion
Circumferential fusion is 360° fusion that joins vertebrae by their entire bodies and transverse processes, typically through an anterior and posterior approach.

Posterolateral Fusion
Posterolateral fusion is a procedure where the transverse processes of the involved segments are decorticated and covered with a mixture of bone autograft or allograft.