BONE MORPHOGENETIC PROTEIN

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INSTRUCTIONS:

“Medical Policy assists in administering UCare benefits when making coverage determinations for members under our health benefit plans. When deciding coverage, all reviewers must first identify enrollee eligibility, federal and state legislation or regulatory guidance regarding benefit mandates, and the member specific Evidence of Coverage (EOC) document must be referenced prior to using the medical policies. In the event of a conflict, the enrollee’s specific benefit document and federal and state legislation and regulatory guidance supersede this Medical Policy. In the absence of benefit mandates or regulatory guidance that govern the service, procedure or treatment, or when the member’s EOC document is silent or not specific, medical policies help to clarify which healthcare services may or may not be covered. This Medical Policy is provided for informational purposes and does not constitute medical advice. In addition to medical policies, UCare also uses tools developed by third parties, such as the InterQual Guidelines®, to assist us in administering health benefits. The InterQual Guidelines are intended to be used in connection with the independent professional medical judgment of a qualified health care provider and do not constitute the practice of medicine or medical advice. Other Policies and Coverage Determination Guidelines may also apply. UCare reserves the right, in its sole discretion, to modify its Policies and Guidelines as necessary and to provide benefits otherwise excluded by medical policies when necessitated by operational considerations.”
POLICY DESCRIPTION:

This policy describes the use of bone morphogenetic protein (BPM), also referred to as recombinant human bone morphogenetic proteins (rhBMPs), for the promotion of bone growth and enhancement of healing. Bone morphogenetic proteins are growth factors that stimulate bone formation; they are used in formulations containing materials that the body converts to solid bone. BMP can be used as a replacement for bone autografts which is material typically obtained from the posterior iliac crest. The disadvantages of autografts include the possibility of pain at the graft donor site, injury to local nerves or vessels, postoperative infection or hematoma, and gait disturbances.

COVERAGE RATIONALE / CLINICAL CONSIDERATIONS:

A. InFUSE Bone Graft (Bone Morphogenic Protein-2 or rh-BMP-2)

The use of recombinant human bone morphogenetic protein-2 (rhBMP-2) may be considered MEDICALLY NECESSARY in adult patients for ANY of the following clinical situations:

1. As an adjunct to spinal fusion of the lower region of the spine (L4-S1) in cases of degenerative disc disease after a failure of at least 6 months of non-operative therapy (see Policy Number 2015M0052A, Spinal Fusion Surgery):
   - Instrumented anterior lumbar interbody or LT-cage fusion procedures for patients in whom autologous bone and bone marrow harvest are not feasible, not expected to promote fusion, or contraindications to harvesting of bone autograft exist, OR
   - Instrumented posterolateral intertransverse spinal fusion procedures when use of autograft is unfeasible,

2. As an adjunct to treatment of open fracture of the tibial shaft which has been stabilized with intramedullary nail fixation after appropriate wound management.

B. Osteogenic Protein-1 (OP-1) (rh-BMP-7)

The use of Osteogenic Protein-1 (Humanitarian Device Exemption (HDE) may be considered MEDICALLY NECESSARY for the following indications:

1. As an alternative to autologous bone graft in “compromised” patients undergoing revision of a prior spinal fusion. Compromised patients include those with osteoporosis, tobacco use, diabetes, etc.

2. As an alternative to autograft in recalcitrant long bone nonunions where use of autograft is unfeasible, other treatments have failed and the remaining alternative is amputation or no treatment.

NOT MEDICALLY NECESSARY:

The use of recombinant human bone morphogenetic protein-2 is considered EXPERIMENTAL and/or INVESTIGATIONAL and NOT MEDICALLY NECESSARY for conditions that do not meet the above criteria, including but not limited to:
• As an adjunct to cervical or thoracic spinal fusion procedures,
• As treatment of multiple levels of spinal fusion (multiple levels not noted in other policies),
• As an adjunct to posterior lumbar interbody fusion (PLIF) or transforaminal lumbar interbody fusion (TLIF),
• As management of early stages of osteonecrosis of the vascular head or femoral shaft,
• As an adjunct to distraction osteogenesis (Ilizarov procedure),
• Craniofacial applications including, but not limited to, periodontal defect regeneration, cleft palate repair, cranial defect repair, restoration and maintenance of the alveolar dental ridge.

Clinical Considerations:
In the studies reviewed in detail for this report, neither rhBMP-2 nor rhBMP-7 appeared to be associated with any serious adverse events.

Professional labeling states that rhBMP-2 and rhBMP-7 should not be used in patients who have any of the following conditions (Medtronic Inc., 2010b):
• Allergy or hypersensitivity to the rhBMP product, collagen, or materials contained in the device,
• Known or suspected active malignancy, or undergoing treatment for a malignancy,
• Active infection near the area of the surgical incision,
• Not skeletally mature (< 18 years of age or no radiographic evidence of closure of epiphyses),
• Pregnancy,
• Known autoimmune disease or immunodeficiency, including chronic steroid treatment,
• Prior exposure to products containing OP-1.

BACKGROUND:
It is estimated that 1.5 million bone-grafting operations are performed annually in the United States. Bone grafts can be harvested from the patient (autograft), obtained from bone banks (cadaver allograft), or composed of synthetic material. An autograft, also referred to as autogenic or autologous bone, is the usual material for spinal fusion and is typically obtained from the posterior iliac crest. The potential disadvantages of autografts include pain at the graft donor site, injury to local nerves or vessels, postoperative infection or hematoma, and gait disturbances.

Allografts, also referred to as allogeneic bone, provide less consistent clinical results than autografts, and there is an increased risk of disease transmission and immunogenic response. When allografts are intensively processed to decrease these risks, the osteoinductive potential is lessened and mechanical strength is reduced. In some cases, bone marrow from the patient may be harvested and used with the allograft to provide additional osteoinductive capability. This procedure is known as bone marrow aspirate with allograft (BMAA). The design of structural allografts for spinal fusion has progressed from femoral rings to threaded cortical bone dowels. Unlike femoral rings, which act as intradiscal spacers, bone dowels do not require additional fixation because they resist expulsion and thus may be used as stand-alone implants. Demineralized bone (DMB) is another type of allograft. It is produced through a process that involves the decalcification of cortical bone. This substantially decreases the structural strength, but the resulting product is more osteoinductive than ordinary allograft. Researchers have speculated that the osteoinductive growth factors contained in the extracellular bone matrix are more easily accessed once the
Recombinant human bone morphogenetic proteins (rhBMPs) are growth factors that stimulate bone formation; they are being evaluated as replacements for bone grafting in formulations containing materials that the body converts to solid bone. rhBMP serves as an alternative or adjunct to autologous bone grafts (autografts). It is used to promote bone growth and enhance healing. rhBMPs are being investigated as replacements for bone autografts, to avoid the pain and other potential complications associated with harvesting of bone. Since rhBMPs are water-soluble, they readily diffuse in body fluids. In order to stay confined within the region of repair, rhBMP must be used in conjunction with a suitable carrier. Collagen and ceramics are currently the most common carriers. Type I collagen can be obtained from bone, tendons, or ligaments. Bone collagen binds rhBMP more tightly than tendon or ligament collagen and therefore provides a good matrix for rhBMP. Moreover, collagen—both as a powder and as an absorbable sponge—is approved by the FDA for use in several clinical applications, suggesting that it has a favorable safety profile and is effective in specific applications. Infuse kits are available in several different sizes; however, the rhBMP-2 concentration is always 1.5 milligrams per milliliter (mg/mL). One or 2 sponges, depending on the size of the cage, are placed in each cage. The cages are then placed around the appropriate area in the lumbar spine and are left there to become part of the permanently fused spine. The sponges expand once in place so that they adhere to the host bone. Infuse has also been used with allograft dowels rather than cages, and in this case, the sponge adheres to the inside of the bone dowel. OP-1 Putty is composed of osteogenic protein-1 (rhBMP-7), bovine collagen, and a putty additive, all mixed with sterile saline solution to form a thick paste, which is applied directly to the fusion site where the vertebral bone has been decorticated (Boden et al., 2000; Kleeman et al., 2001; Lieberman et al., 2002; Baskin et al., 2003; Burkus et al., 2005; Carlisle and Fischgrund, 2005; Medtronic Inc., 2010a).

Definitions:

Anterior lumbar interbody fusion (ALIF): A spinal fusion surgery procedure where the surgeon approaches the surgical site through the abdominal cavity and the site of fusion is between the vertebral bodies; this is one of the most common approaches to spinal fusion.

Degenerative disc disease: A disease of a vertebral disc where the intervertebral disc breaks down, resulting in pain and disability.

Electrical bone growth stimulation: A medical device that uses an electric field or current to stimulate the growth of bone tissue. These devices may be worn on the outside of the body or can be surgically implanted around the area requiring treatment.

Instrumented fusion: A fusion procedure involving the use of plates, screws, cages or rods to increase the stability of the joint during the healing process.

Intramedullary nail fixation (also known as IM nail fixation or intramedullary rod fixation): A surgical method of stabilizing a broken bone in order to prevent movement and promote proper healing.

Posterolateral intertransverse fusion of lumbar vertebrae (also known as TIF): A spinal fusion surgery procedure where the surgeon approaches the surgical site from the back and side, and the sites of fusion are the transverse processes. This is one of the most common approaches to spinal fusion.

Posterior lumbar interbody fusion (PLIF): A spinal fusion surgery procedure where the surgeon approaches the surgical site from the back and the site of fusion is between the vertebral bodies.
**Spinal fusion**: A surgical procedure where two or more spinal vertebrae (spine bones) are surgically attached together.

**Transforaminal lumbar interbody fusion (TLIF)**: A spinal fusion surgery procedure where the surgeon approaches the surgical site through the vertebral foramen and the site of fusion is between the vertebral bodies.

**Transverse process**: A bony protrusion on either side of the arch of a vertebra which functions as an anchor point and lever for attached muscles.

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### REGULATORY STATUS:

1. **U.S. FOOD AND DRUG ADMINISTRATION (FDA):**
   
   Medtronic Sofamor Danek received a New Device Approval from the FDA on July 2, 2002, for the Infuse Bone Graft (recombinant human bone morphogenetic protein-2) (rhBMP-2)/LT-Cage Lumbar Tapered Fusion Device for use in spinal fusion procedures in skeletally mature patients with degenerative disc disease at 1 level from L4-S1. Degenerative disc disease is defined as discogenic back pain with degeneration of the disc and is confirmed by patient history, function deficit and/or neurological deficit, and radiographic studies. These patients may also have up to grade I spondylolisthesis at the involved level. Subsequently (in December 2003), FDA approval was granted for the use of rhBMP-2 combined with other types of interbody fusion devices, including the Inter Fix Threaded Spinal Fusion Device and Inter Fix RP Threaded Fusion Device (Medtronic Sofamor Danek). The Infuse Bone Graft/LT-Cage Lumbar Tapered Fusion device is to be implanted via an anterior open or a laparoscopic approach. The Infuse Bone Graft/Inter Fix Threaded Spinal Fusion Device and the 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 with interbody fusion devices should have had inadequate response to at least 6 months of prior nonoperative treatment. The FDA extended approval to the level L2-S1 on July 29, 2004. Several other minor changes in design and labeling have been approved since 2002. No other devices under product code NEK have been approved.

   On October 17, 2001, the FDA approved a Humanitarian Device Exemption (HDE) (H010002) for the OP-1 Implant (Stryker Biotech), which had previously received a Humanitarian Use Device (HUD) designation. An approved HDE authorizes marketing of an HUD, which may only be used after Institutional Review Board (IRB) approval has been obtained for the use of the device for the FDA-approved indication. The labeling for an HUD must state that the device is a humanitarian use device and, although the device is authorized by federal law, that the effectiveness of the device for the specific indication has not been demonstrated. The OP-1 Implant is made of recombinant human osteogenic protein-1 (OP-1, or rhBMP-7) and bovine bone collagen, and is indicated for use instead of autograft in recalcitrant long bone nonunions where use of autograft is unfeasible and conservative treatments have failed.

   OP-1 Putty (Stryker Biotech) received an HDE (H020008) on April 7, 2004, for application to lumbar fusion. OP-1 Putty consists of the recombinant human osteogenic protein (rhOP-1, or rhBMP-7) mixed with bovine type I bone collagen matrix (collagen matrix) and a separate vial of the putty additive, carboxymethylcellulose (CMC). OP-1 Putty is intended to be reconstituted with sterile saline (0.9%) solution. Federal law authorizes its use as a substitute for autograft in compromised patients requiring...
revision posterolateral (intertransverse) lumbar spinal fusion, or for patients in whom autologous bone and bone marrow harvest are not feasible or are not expected to promote fusion. “Revision” refers to repeat fusion in cases of pseudarthrosis. Examples of compromising factors include osteoporosis, smoking, and diabetes. The effectiveness of OP-1 Putty for this use has not been demonstrated.

In 2008, the FDA released a Public Health Notification regarding the use of rhBMP in cervical spine fusion. During the period of 2004 to 2008, the FDA received 38 reports of complications related to swelling of the neck and throat tissue. There were reports of airway compression; compression of neurological structures; and difficulty swallowing, breathing, or speaking. Some of these complications were life threatening. The use of rhBMP in cervical spine fusion has not been approved by the FDA.

2. CENTERS FOR MEDICARE AND MEDICAID SERVICES (CMS):

CMS has not established a National Coverage Determination (NCD) that addresses bone morphogenetic protein (BMP).

In 2010, CMS published a technology assessment of the on-label and off-label use of rhBMP, which came to the following conclusions (Ratko et al., 2010):

- Strength of the body of evidence supporting improved outcomes with on-label use of rhBMP-2 (Infuse) was graded as moderate.
- Strength of the body of evidence supporting improved radiographic fusion success with off-label use of rhBMP-2 in fusion of the lumbar sacral spine was graded as moderate; the strength of other outcomes was graded as low.
- There was insufficient evidence to reach conclusions concerning radiographic fusion or associated changes in neck disability scores with the off-label use of rhBMP-2 in anterior cervical spinal fusion.
- There was insufficient evidence to reach conclusions concerning outcomes with on-label use of rhBMP-7 (OP-1) or with off-label use of rhBMP-7 in fusion of the lumbar sacral spine.
- Evidence on BMP-specific adverse events is insufficient to draw conclusions of safety in most settings; however, there is moderate evidence that off-label use of rhBMP-2 in anterior cervical spinal fusion increases cervical swelling and related complications.
- Quality of reporting in the studies reviewed was variable and inconsistent, in particular with respect to attribution of adverse events to BMP use and the use of standardized or validated instruments to collect adverse events.

Local Coverage Determinations (LCDs) do not exist at this time.

3. MINNESOTA DEPARTMENT OF HUMAN SERVICES (DHS):

No information on bone morphogenetic protein was identified in the MHCP Provider Manual.

CLINICAL EVIDENCE:

Efficacy of rhBMP-2 for Lumbar Spinal Fusion: A total of 12 RCTs and 4 retrospective cohort studies compared rhBMP-2 with autograft and consistently found that rhBMP-2 accelerated fusion and/or increased the incidence of solid fusion. However, most of the studies found that rhBMP-2 and autograft provided essentially identical relief of pain and disability and improvement of quality of life. Some studies found that rhBMP-2 provided minor benefits, such as shorter operative time and less estimated blood loss.
Additional preliminary evidence suggests that harvesting pelvic bone for autograft may not increase long-term pain and that rhBMP-2 may be no better than autograft at overcoming risk factors for nonunion.

**Efficacy of rhBMP-2 for Cervical Spinal Fusion:** Two RCTs evaluated rhBMP-2 versus autograft for cervical spinal fusion. One of these studies found that rhBMP-2 decreased the mean time to fusion but was not associated with increased likelihood of fusion, reduced pain, or improved function. The other study found that despite attainment of fusion in all patients in both treatment groups, rhBMP-2 was associated with statistically significant improvements in neck disability and arm pain.

**Efficacy of rhBMP-7 for Lumbar Spinal Fusion:** A total of 5 RCTs evaluated rhBMP-7 versus autograft for lumbar spinal fusion. Although the largest RCT found that autograft was associated with a statistically significant increase in likelihood of fusion compared with rhBMP-7 at 24 months, differences in fusion were no longer significant at 36 months and the other studies found that autograft and rhBMP-7 provided essentially identical likelihood of fusion. The 5 RCTs also found that rhBMP-7 and autograft provided essentially equal improvements in pain and disability.

**Open tibial fractures:** Open tibial shaft fractures often take longer to heal and healing rates are lower than for other long bone fractures. These factors contribute to a high rate of delayed union or nonunion; estimates of the rate of delayed union of tibial fracture range from 43% to 100% for severe fractures. Slow or failed fracture healing is associated with significant morbidity, reduction in quality of life, delay in return to work, and often the need for secondary interventions. Bone grafts may be used in the treatment of severe open fresh tibial fractures to reduce the risk of delayed or nonunion, and are often used if a secondary intervention is required for slow or unsuccessful bone healing.

**SUMMARY:**
The best available evidence suggests that compared with autograft, rhBMP-2 increases the rate or overall incidence of solid fusion. However, this improvement in fusion was not found to have a significant effect on patient pain, disability, or QOL. A very large multinational RCT (n=450) demonstrated the safety of rhBMP-2 implants and superior efficacy compared with standard treatment for the FDA-approved indication of primary open tibial fracture treatment, although the clinical significance of the effect of rhBMP-2 in this study remains unclear. This study left open the question of whether the results might have been inflated by the use of reaming. Subgroup analyses with combined data from this and a smaller identically designed U.S. study revealed that rhBMP-2 improved safety, as well as clinical success, to an even greater degree in patients with severe-grade fractures than in a population with a range of fracture severity. The combined data also showed that the benefits of nail reaming diminished the gains to be had from using rhBMP-7. A third, small, trial weakened by dropouts and/or loss to follow-up suggested that in planned staged reconstruction of tibial fractures, rhBMP-2 combined with allograft and administered several weeks after primary treatment (unapproved protocol) leads to greater clinical success than standard AICBG but does not improve health status.

There is low to moderate quality of evidence from a very large multinational randomized controlled trial (RCT) and a smaller U.S. study that recombinant human bone morphogenetic protein (rhBMP)-2 is safe and, when combined with standard fracture treatment, may reduce the need for secondary intervention in patients with fresh open tibial fractures, compared with standard care alone. Subgroup analysis of the study results suggests that this benefit may be greatest in patients with severe-grade fractures. One small
study also demonstrated a benefit of rhBMP-2 for staged reconstruction of tibial shaft fractures. None of the studies focused on rhBMP-2 for the treatment of fresh closed tibial fractures or nonunion.

There is also low- to moderate-quality evidence from a few RCTs evaluating rhBMP-7 in combination with external fixation for primary treatment of fresh closed fractures of the tibia and as an adjunct to intramedullary (IM) nail fixation for tibial nonunions. The results of the studies of fresh fractures were conflicting. One small randomized trial found no benefit, while another reported an increase in healing rate and speed of healing. Most of the patients in these studies had closed fractures; therefore, there is no evidence regarding the effect of rhBMP on fresh open fractures. For tibial nonunion, two randomized studies found that rhBMP-7 may improve healing rates compared with platelet-rich plasma and may provide similar bone healing success compared with autograft, without the morbidity associated with graft harvesting, and with a reduced risk of osteomyelitis.

### APPLICABLE CODES:

The Current Procedural Terminology (CPT®) codes and HCPCS codes listed in this policy are for reference purposes only. Listing of a service or device code in this policy does not imply that the service described by this code is a covered or non-covered health service. The inclusion of a code does not imply any right to reimbursement or guarantee claims payment. Other medical policies and coverage determination guidelines may apply.

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