MEDICAL POLICY

POLICY TITLE	BONE MORPHOGENETIC PROTEIN
POLICY NUMBER	MP-1.117

Original Issue Date (Created):	**1/1/2010**
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I. POLICY

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

- For anterior spinal interbody fusion procedures, when use of autograft is not feasible (see policy guidelines).
- For instrumented posterolateral intertransverse spinal fusion procedures, when use of autograft is not feasible (see policy guidelines).
- For the treatment of acute, open fracture of the tibial shaft, when use of autograft is not feasible (see policy guidelines).

Use of recombinant human bone morphogenetic protein (rhBMP-2) is considered **not medically necessary** for all other indications, including but not limited to spinal fusion when use of autograft is feasible and craniomaxillofacial surgery.

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).

Cross-references:

MP-2.033 Recombinant and Autologous Platelet-Derived Growth Factors as a Treatment of Wound Healing and Other Non-Orthopedic Conditions
MP-1.024 Electrical Bone Growth Stimulation of the Appendicular Skeleton
MP-1.150 Electrical Stimulation of the Spine as an Adjunct to Spinal Fusion Procedures
MP-6.021 Ultrasound Accelerated Fracture Healing Device

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II. PRODUCT VARIATIONS TOP

This policy is applicable to all programs and products administered by Capital BlueCross unless otherwise indicated below.

FEP PPO- Refer to FEP Medical Policy Manual MP 7.01.00, Bone Morphogenetic Protein. The FEP Medical Policy Manual can be found at: https://www.fepblue.org/benefit-plans/medical-policies-and-utilization-management-guidelines/medical-policies

III. DESCRIPTION/BACKGROUND TOP

Two recombinant human bone morphogenetic proteins (rhBMPs) have been extensively studied: rhBMP-2, applied with an absorbable collagen sponge (Infuse) and rhBMP-7, applied in putty (OP-1). These products have been investigated as alternatives 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 are members of the transforming growth factors family. At present, some 20 bone morphogenetic proteins 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 (e.g., long-bone nonunion, 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. Also, interbody fusion of the lumbar spine can be approached from an anterior (anterior lumbar interbody fusion), lateral, or posterior direction (posterior lumbar interbody fusion or transforaminal lumbar interbody fusion; see Appendix). Surgical procedures may include decompression of the spinal canal and insertion of pedicle screws and rods to increase the stability of the spine.

Posterior approaches (posterior lumbar interbody fusion, transforaminal lumbar interbody fusion) allow decompression (via laminotomies and facetectomies) for treatment of spinal canal pathology (eg, spinal stenosis, lateral recess and foraminal stenosis, synovial cysts, hypertrophic ligamentum flavum) along with spine stabilization. Such approaches are differentiated from instrumented or noninstrumented 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

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). FDA product code: NEK.

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."

FDA product code: MPW.

> "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."

FDA product code: MPY.

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.

IV. RATIONALE

TOP

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 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-level 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 (eg, oral and maxillofacial, hip arthroplasty, distraction osteogenesis) who receive rhBMP, the evidence includes a health technolgoy 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.

V. DEFINITIONS TOP

N/A

VI. BENEFIT VARIATIONS TOP

The existence of this medical policy does not mean that this service is a covered benefit under the member's contract. Benefit determinations should be based in all cases on the applicable contract language. Medical policies do not constitute a description of benefits. A member's individual or group customer benefits govern which services are covered, which are excluded, and which are subject to benefit limits and which require preauthorization. Members and providers should consult the member's benefit information or contact Capital BlueCross for benefit information.

VII. DISCLAIMER TOP

Capital BlueCross's medical policies are developed to assist in administering a member's benefits, do not constitute medical advice and are subject to change. Treating providers are solely responsible for medical advice and treatment of members. Members should discuss any medical policy related to their coverage or condition with their provider and consult their benefit information to determine if the service is covered. If there is a discrepancy between this medical policy and a member's benefit information, the benefit information will govern. Capital BlueCross considers the information contained in this medical policy to be proprietary and it may only be disseminated as permitted by law.

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VIII. CODING INFORMATION TOP

Note: This list of codes may not be all-inclusive, and codes are subject to change at any time. The identification of a code in this section does not denote coverage as coverage is determined by the terms of member benefit information. In addition, not all covered services are eligible for separate reimbursement.

Covered when medically necessary:

CPT Codes®								
20930	20999							

ICD-10-CM Diagnosis Code	Description
M51.06	Intervertebral disc disorders with myelopathy, lumbar region
M51.16	Intervertebral disc disorders with radiculopathy, lumbar region
M51.17	Intervertebral disc disorders with radiculopathy, lumbosacral region
M51.36	Other intervertebral disc degeneration, lumbar region
M51.37	Other intervertebral disc degeneration, lumbosacral region
M96.0	Pseudarthrosis after fusion or arthrodesis
M96.1	Post-laminectomy syndrome, not elsewhere classified
S82.221B	Displaced transverse fracture of shaft of right tibia, initial encounter for open fracture type I or II
S82.221C	Displaced transverse fracture of shaft of right tibia, initial encounter for open fracture type IIIA, IIIB, or IIIC
S82.221B	Displaced transverse fracture of shaft of right tibia, initial encounter for open fracture type I or II
S82.221C	Displaced transverse fracture of shaft of right tibia, initial encounter for open fracture type IIIA, IIIB, or IIIC
S82.223B	Displaced transverse fracture of shaft of unspecified tibia, initial encounter for open fracture type I or II
S82.223C	Displaced transverse fracture of shaft of unspecified tibia, initial encounter for open fracture type IIIA, IIIB, or IIIC
S82.224B	Nondisplaced transverse fracture of shaft of right tibia, initial encounter for open fracture type I or II
S82.224C	Nondisplaced transverse fracture of shaft of right tibia, initial encounter for open fracture type IIIA, IIIB, or IIIC
S82.225B	Nondisplaced transverse fracture of shaft of left tibia, initial encounter for open fracture type I or II
S82.225C	Nondisplaced transverse fracture of shaft of left tibia, initial encounter for open fracture type IIIA, IIIB, or IIIC
S82.226B	Nondisplaced transverse fracture of shaft of unspecified tibia, initial encounter for open fracture type I or II

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ICD-10-CM Diagnosis Code	Description
S82.226C	Nondisplaced transverse fracture of shaft of unspecified tibia, initial encounter for open fracture type IIIA, IIIB, or IIIC
S82.231B	Displaced oblique fracture of shaft of right tibia, initial encounter for open fracture type I or II
S82.231C	Displaced oblique fracture of shaft of right tibia, initial encounter for open fracture type IIIA, IIIB, or IIIC
S82.232B	Displaced oblique fracture of shaft of left tibia, initial encounter for open fracture type I or II
S82.232C	Displaced oblique fracture of shaft of left tibia, initial encounter for open fracture type IIIA, IIIB, or IIIC
S82.233B	Displaced oblique fracture of shaft of unspecified tibia, initial encounter for open fracture type I or II
S82.233C	Displaced oblique fracture of shaft of unspecified tibia, initial encounter for open fracture type IIIA, IIIB, or IIIC
S82.234B	Nondisplaced oblique fracture of shaft of right tibia, initial encounter for open fracture type I or II
S82.234C	Nondisplaced oblique fracture of shaft of right tibia, initial encounter for open fracture type IIIA, IIIB, or IIIC
S82.235B	Nondisplaced oblique fracture of shaft of left tibia, initial encounter for open fracture type I or II
S82.235C	Nondisplaced oblique fracture of shaft of left tibia, initial encounter for open fracture type IIIA, IIIB, or IIIC
S82.236B	Nondisplaced oblique fracture of shaft of unspecified tibia, initial encounter for open fracture type I or II
S82.236C	Nondisplaced oblique fracture of shaft of unspecified tibia, initial encounter for open fracture type IIIA, IIIB, or IIIC
S82.241B	Displaced spiral fracture of shaft of right tibia, initial encounter for open fracture type I or II
S82.241C	Displaced spiral fracture of shaft of right tibia, initial encounter for open fracture type IIIA, IIIB, or IIIC
S82.242B	Displaced spiral fracture of shaft of left tibia, initial encounter for open fracture type I or II
S82.242C	Displaced spiral fracture of shaft of left tibia, initial encounter for open fracture type IIIA, IIIB, or IIIC
S82.243B	Displaced spiral fracture of shaft of unspecified tibia, initial encounter for open fracture type I or II
S82.243C	Displaced spiral fracture of shaft of unspecified tibia, initial encounter for open fracture type IIIA, IIIB, or IIIC
S82.244B	Nondisplaced spiral fracture of shaft of right tibia, initial encounter for open fracture type I or II
S82.244C	Nondisplaced spiral fracture of shaft of right tibia, initial encounter for open fracture type IIIA, IIIB, or IIIC

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ICD-10-CM Diagnosis Code	Description
S82.245B	Nondisplaced spiral fracture of shaft of left tibia, initial encounter for open fracture type I or II
S82.245C	Nondisplaced spiral fracture of shaft of left tibia, initial encounter for open fracture type IIIA, IIIB, or IIIC
S82.246B	Nondisplaced spiral fracture of shaft of unspecified tibia, initial encounter for open fracture type I or II
S82.246C	Nondisplaced spiral fracture of shaft of unspecified tibia, initial encounter for open fracture type IIIA, IIIB, or IIIC
S82.251B	Displaced comminuted fracture of shaft of right tibia, initial encounter for open fracture type I or II
S82.251C	Displaced comminuted fracture of shaft of right tibia, initial encounter for open fracture type IIIA, IIIB, or IIIC
S82.252B	Displaced comminuted fracture of shaft of left tibia, initial encounter for open fracture type I or II
S82.252C	Displaced comminuted fracture of shaft of left tibia, initial encounter for open fracture type IIIA, IIIB, or IIIC
S82.253B	Displaced comminuted fracture of shaft of unspecified tibia, initial encounter for open fracture type I or II
S82.253C	Displaced comminuted fracture of shaft of unspecified tibia, initial encounter for open fracture type IIIA, IIIB, or IIIC
S82.254B	Nondisplaced comminuted fracture of shaft of right tibia, initial encounter for open fracture type I or II
S82.254C	Nondisplaced comminuted fracture of shaft of right tibia, initial encounter for open fracture type IIIA, IIIB, or IIIC
S82.255B	Nondisplaced comminuted fracture of shaft of left tibia, initial encounter for open fracture type I or II
S82.255C	Nondisplaced comminuted fracture of shaft of left tibia, initial encounter for open fracture type IIIA, IIIB, or IIIC
S82.256B	Nondisplaced comminuted fracture of shaft of unspecified tibia, initial encounter for open fracture type I or II
S82.256C	Nondisplaced comminuted fracture of shaft of unspecified tibia, initial encounter for open fracture type IIIA, IIIB, or IIIC
S82.261B	Displaced segmental fracture of shaft of right tibia, initial encounter for open fracture type I or II
S82.261C	Displaced segmental fracture of shaft of right tibia, initial encounter for open fracture type IIIA, IIIB, or IIIC
S82.262B	Displaced segmental fracture of shaft of left tibia, initial encounter for open fracture type I or II
S82.262C	Displaced segmental fracture of shaft of left tibia, initial encounter for open fracture type IIIA, IIIB, or IIIC
S82.263B	Displaced segmental fracture of shaft of unspecified tibia, initial encounter for open fracture type I or II

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ICD-10-CM Diagnosis Code	Description
S82.263C	Displaced segmental fracture of shaft of unspecified tibia, initial encounter for open fracture type IIIA, IIIB, or IIIC
S82.264B	Nondisplaced segmental fracture of shaft of right tibia, initial encounter for open fracture type I or II
S82.264C	Nondisplaced segmental fracture of shaft of right tibia, initial encounter for open fracture type IIIA, IIIB, or IIIC
S82.265B	Nondisplaced segmental fracture of shaft of left tibia, initial encounter for open fracture type I or II
S82.265C	Nondisplaced segmental fracture of shaft of left tibia, initial encounter for open fracture type IIIA, IIIB, or IIIC
S82.266B	Nondisplaced segmental fracture of shaft of unspecified tibia, initial encounter for open fracture type I or II
S82.266C	Nondisplaced segmental fracture of shaft of unspecified tibia, initial encounter for open fracture type IIIA, IIIB, or IIIC
S82.291B	Other fracture of shaft of right tibia, initial encounter for open fracture type I or II
S82.291C	Other fracture of shaft of right tibia, initial encounter for open fracture type IIIA, IIIB, or IIIC
S82.292B	Other fracture of shaft of left tibia, initial encounter for open fracture type I or II
S82.292C	Other fracture of shaft of left tibia, initial encounter for open fracture type IIIA, IIIB, or IIIC

IX. REFERENCES

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X. POLICY HISTORY

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MP-1.117	**CAC 11/24/09** New policy.
	CAC 4/26/11 Adopt BCBSA. No change to policy criteria language. Bullets re-formatted. Minor wording change only in 1st bullet of "investigational" statement.
	CAC 4/24/12 Added policy criteria from BCBSA to restrict use of rhBMP to cases where there is a high risk of fusion failure. Added cervical spinal fusion to list of "all other indications, including but not limited to" investigational indications. **7/9/12** FEP variation revised to refer to FEP policy manual.
	CAC 3/26/13 Consensus. No change to policy statements. References updated. Codes reviewed.
	CAC 01/28/14 Minor. For rhBMP-2, InFUSE – deleted the following from the **medically necessary** statements: • Used in conjunction with an FDA-approved interbody fusion device. • At one or more levels • Patients with degenerative disc disease from L2-S1. • Patients should have failed at least 6 months of conservative treatment. For rhBMP-2, InFUSE **Added** "when use of autograft is unfeasible" to medically necessary indications. For rhBMP-7, OP-1- deleted the following as **medically necessary.** • As an alternative to autograft in recalcitrant long bone nonunions, where use of autograft is unfeasible and alternative conservative treatments have failed. For rhBMP-7, OP-1 "for recalcitrant long-bone nonunions where use of autograft is unfeasible and alternative conservative treatments have failed. Deleted Information on high risk of fusion failure Deleted list of investigational indications. Added the following statement "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". Added policy guidelines. Codes reviewed
	CAC 1/27/15 Consensus review. References and rationale updated. No changes to the policy statements. Codes reviewed, not unranged.
	CAC 1/26/16 Consensus review. No changes to the policy statements. References and rationale updated**.** Coding reviewed.
	Admin Update 11/10/16 Variation Reformatting 1
	CAC 1/31/17 Minor review. FDA approval for rhBMP-2 in oblique lateral interbody fusion added. rhBMP-7 removed from policy statements – no longer manufactured in the United States. Coding Reviewed.

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	12/1/17 Consensus review. The term "unfeasible" changed to "not feasible" bullet points in the first medically necessary statement. The second statement (not medically necessary) was revised to say "Use of recombinant human bone morphogenetic protein (rhBMP-2) and added "craniomaxillofacial surgery" into statement. Intent of policy statements unchanged. Removed the paragraph in the policy guidelines addressing nonunion and Bone Growth Stimulators. Added Appendix.
	9/4/18 Consensus review. No change to the policy statements. Background and references updated. Rationale revised. **Retired**- Please refer to TurningPoint Healthcare for management of these services effective 1/1/2019.*

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