# Molina Clinical Policy
# Bone Graft Substitutes for Bone Fusion: Policy No. 218

**Last Approval: 4/10/2024**
**Next Review Due By: April 2025**

## DISCLAIMER

This Molina Clinical Policy (MCP) is intended to facilitate the Utilization Management process. Policies are not a supplementation or recommendation for treatment; Providers are solely responsible for the diagnosis, treatment, and clinical recommendations for the Member. It expresses Molina's determination as to whether certain services or supplies are medically necessary, experimental, investigational, or cosmetic for purposes of determining appropriateness of payment. The conclusion that a particular service or supply is medically necessary does not constitute a representation or warranty that this service or supply is covered (e.g., will be paid for by Molina) for a particular Member. The Member's benefit plan determines coverage – each benefit plan defines which services are covered, which are excluded, and which are subject to dollar caps or other limits. Members and their Providers will need to consult the Member's benefit plan to determine if there are any exclusion(s) or other benefit limitations applicable to this service or supply. If there is a discrepancy between this policy and a Member's plan of benefits, the benefits plan will govern. In addition, coverage may be mandated by applicable legal requirements of a State, the Federal government or CMS for Medicare and Medicaid Members. CMS's Coverage Database can be found on the CMS website. The coverage directive(s) and criteria from an existing National Coverage Determination (NCD) or Local Coverage Determination (LCD) will supersede the contents of this MCP and provide the directive for all Medicare members. References included were accurate at the time of policy approval and publication.

## OVERVIEW

**Recombinant human bone morphogenetic protein (rhBMP)** is a key factor in bone healing, regeneration, and function that is used as a replacement for or adjunct to autologous bone grafts (autografts). rhBMP is most commonly used in spinal fusion surgery for degenerative disc disease to promote bone growth that results in fusion, as well as in the treatment of bone fractures. Recombinant DNA techniques have been used to produce BMP2 and BMP7 as alternatives to bone grafts to improve healing of bony defects and fractures when autograft bone harvest is not possible or is contraindicated.

### *Regulatory*

rhBMPs that have received Food and Drug Administration (FDA) approval* include:

- *rhBMP-2*: INFUSE® Bone Graft (Medtronic Sofamor Danek) received premarket approval for fusion of the lumbar spine in skeletally mature patients with degenerative disc disease at one level from L4-S1 and for healing of acute, open tibial shaft fractures stabilized with an intramedullary nail and treated within 14 days of the initial injury in 2002 ([1]FDA 2002). INFUSE® Bone Graft has subsequently been approved for use with multiple associated lumbar fusion carriers and delivery systems as supplements to the original PMA, including devices that can be placed at a single level from L2-S1. The Infuse™ Bone Graft/Medtronic Interbody Fusion Device consists of a spinal fusion cage, the rhBMP solution, and a carrier or scaffold for the rhBMP and resulting bone ([2]FDA 2002). Infuse Bone Graft for treatment of tibial shaft fractures consists of two components: the rhBMP and a carrier or scaffold. For each of the indications, the components must be used as a system and cannot be used alone (Medtronic 2020).

- *rhBMP-7:* The OP-1® Implant & Putty (Stryker Biotech) received humanitarian device exemption approval as an alternative to autograft in recalcitrant long bone nonunions where use of autograft is unfeasible and alternative treatments have failed. It is also approved as an alternative to autograft in compromised patients requiring revision posterolateral (intertransverse) lumbar spinal fusion for whom autologous bone and bone marrow harvest are not feasible or are not expected to promote fusion. Examples of compromising factors include osteoporosis, smoking and diabetes (FDA 2001; FDA 2004). The rhBMP-7 product is no longer marketed in the United States.

The FDA released a Public Health Notification in 2008 warning that use of rhBMP for cervical spinal fusion can cause life-threatening complications such as airway compression, compression of neurological structures, and difficulty swallowing, breathing, or speaking (FDA, 2008).

**i-Factor Protein** is biologic compound developed by Cerapedics, for use in spinal fusion surgery. i-Factor is an artificial blend of organic bone mineral infused with bioactive synthetic peptide (P-15), engineered to replicate the cellular environment of the natural bone matrix.

### *i-Factor Regulatory*

- i-Factor Peptide Enhanced Bone Graft received premarket approval for use in skeletally mature patients with

degenerated cervical discs at one level from C3-C4 to C6-C7 following single-level discectomy, experiencing intractable radiculopathy, neck pain, or myelopathy. It must be used in combination with an allograft ring and metallic anterior cervical plate (FDA 2015).

## COVERAGE POLICY

A. *Recombinant human bone morphogenetic protein (rhBMP-2) Infuse Bone Graft* **may be considered medically necessary** and may be authorized when **ALL** of the following criteria have been met for the applicable procedure:

1. For use in conjunction with lumbar spinal fusion procedures when **ALL** of the following are met:
   a. Medical necessity criteria for lumbar fusion are met
   b. Single level degenerative disc disease at one level from L2-S1
   c. No more than Grade 1 spondylolisthesis or retrolisthesis at the involved level
   d. Used for single-level lumbar fusion in combination with a cage/device approved for use with INFUSE by the FDA
   e. Skeletally mature (Age 18 years or greater with radiographic evidence of epiphyseal closure)
   f. Absence of contraindications listed below

2. For the treatment of acute, open fracture of the tibial shaft **ALL** of the following must be met:
   a. Stabilized with intramedullary nail fixation
   b. Wound management performed
   c. Applied within 14 days after the initial fracture
   d. Skeletally mature (Age 18 years or greater with radiographic evidence of epiphyseal closure)

B. *rhBMP-2 Infuse Bone Graft* **is considered experimental, investigational, and unproven** for cervical spinal fusion, multilevel fusions, and any other indication not listed above due to insufficient evidence in the peer reviewed medical literature that indicate long term benefit on health outcomes

C. *rhBMP-7 OP-1® Implant & Putty* **is considered experimental, investigational, and unproven** for any indication due to insufficient evidence in the peer reviewed medical literature that indicate long term benefit on health outcomes

D. *i-Factor protein* **is considered experimental, investigational, and unproven** for any indication due to insufficient evidence in the peer reviewed medical literature that indicate long term benefit on health outcomes

**Contraindications**

1. Allergy or hypersensitivity to the rhBMP product, collagen, or materials contained in the device
2. Known or suspected malignancy, or a history of malignancy
3. Infection near the area of the surgical incision
4. Not skeletally mature
5. Pregnant or may become pregnant
6. Known autoimmune disease or immunodeficiency, including chronic steroid treatment
7. Should not be used in the vicinity of a resected or extant tumor

**DOCUMENTATION REQUIREMENTS.** Molina Healthcare reserves the right to require that additional documentation be made available as part of its coverage determination; quality improvement; and fraud; waste and abuse prevention processes. Documentation required may include, but is not limited to, patient records, test results and credentials of the provider ordering or performing a drug or service. Molina Healthcare may deny reimbursement or take additional appropriate action if the documentation provided does not support the initial determination that the drugs or services were medically necessary, not investigational or experimental, and otherwise within the scope of benefits afforded to the member, and/or the documentation demonstrates a pattern of billing or other practice that is inappropriate or excessive.

## SUMMARY OF MEDICAL EVIDENCE

The **Agency for Healthcare Research and Quality (AHRQ)** published *Bone Morphogenetic Protein: The State of the Evidence of On-Label and Off-Label Use*. The report assessed the available evidence addressing the use of bone

morphogenetic protein. Overall, the report concluded that the available data addressing the safety and efficacy of rhBMP2 and rhBMP7 for both on-label and off-label indications is moderate at best, and significant questions still exist regarding the benefits and drawbacks of its use in the clinical setting (Ratko et al. 2010).

**rhBMP-2 Infuse Bone Graft for Tibial Fracture**

There is low to moderate quality of evidence from a large multinational randomized controlled trial (RCT) (n=450) by Govender et al. (2002) and a smaller U.S. study by Jones et al. (2006) with 30 participants that suggest 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 (n=60) results suggest that this benefit may be greatest in patients with severe-grade fractures (Swiontkowski et al. 2006). The small study also demonstrated a benefit of rhBMP-2 for staged reconstruction of tibial shaft fractures (Jones et al. 2006). None of the studies focused on rhBMP-2 for the treatment of fresh closed tibial fractures or nonunion. Follow-up was 1 year.

The largest study (BESTT Trial) randomized 450 individuals with open tibial shaft fractures to receive initial irrigation and debridement followed by treatment with a locked intramedullary nail either alone or with additional rhBMP-2 on an absorbable collagen sponge placed over the fracture at the time of definitive wound closure. The primary outcome measure was the proportion of individuals requiring secondary intervention due to delayed union or nonunion at 12 months. A total of 58% of individuals treated with rhBMP-2 were healed compared with only 38% in the control group. The rhBMP-2 group also had fewer hardware failures, fewer infections and faster wound healing (Govender et al. 2002).

A Cochrane Review highlights a paucity of data on the use of BMP in fracture healing as well as considerable industry involvement in the currently available evidence. There is limited evidence to suggest that BMP may be more effective than controls for acute tibial fracture healing; however, the use of BMP for treating nonunion remains unclear. The limited available economic evidence indicates that BMP treatment for acute open tibial fractures may be more favorable economically when used in patients with the most severe fractures (Garrison et al. 2010).

**rhBMP-2 Infuse Bone Graft for Spinal Fusion**

The key clinical trial of rhBMP-2 as part of the FDA approval process consisted of 279 individuals undergoing single-level lumbar fusion via an open anterior approach who were randomized to receive either the LT (e.g., lumbar tapered)-Cage with rh-BMP-2 or the same cage filled with iliac crest autograft. In a non-randomized portion of the trial, an additional 136 individuals underwent a single level laparoscopic lumbar interbody fusion with rhBMP-2. There were no differences in fusion success rates, Oswestry Disability Index scores, or back pain between the randomized groups. The group treated laparoscopically also had similar fusion rates. The operative time and blood loss were significantly lower in those receiving the rh-BMP-2, and obviously, these individuals did not experience the pain and morbidity associated with the harvesting of autologous bone from the iliac crest. The results were similar in a similarly designed trial of posterior lumbar interbody fusion. In addition, the rhBMP-2 group had a shorter hospital stay of 3.4 days compared to 5.1 days for the control group (Boden et al. 2002).

Several systematic reviews and meta-analyses reported that rhBMP-2 was superior to the iliac crest bone graft (ICBG) for achieving fusion success and avoiding reoperation (Chen et al. 2012) and that at 24 months, rhBMP-2 increases fusion rates (Galimberti et al. 2015), reduces pain by a clinically insignificant amount, and increases early postsurgical pain compared with ICBG (Simmonds et al. 2013). Evidence of increased cancer incidence is inconclusive (Simmonds et al. 2013; Vavken et al. 2016a; Dettori et al. 2016). However, the risk of adverse events associated with rhBMP-2 is higher than the original estimates reported in the industry-sponsored peer-reviewed publications (Carragee et al. 2011; Vavken et al. 2016a; Vavken et al. 2016b; Stiel et al. 2016). The clinical efficiency of rhBMP-2 is equal or superior to that of allogenic or autologous bone graft in respect to fusion success rate, low back pain disability, patient satisfaction and rate of re-operations (Liu et al. 2020).

A health technology assessment analyzed 19 studies that evaluated rhRMP-2 for spinal fusion. Thirteen randomized controlled trials, 4 retrospective registry analyses, a prospective trial, and a retrospective comparative cohort study were included. When compared with an autograft, evidence suggests that rhBMP-2 lumbar spinal fusions lead to quicker fusion and a somewhat greater likelihood of achieving fusion. However, rhBMP-2 does not seem to offer significant improvements in pain, disability, or quality of life over autografts. Few statistically significant differences were found between rhBMP-2 and bone autographs regarding complication rates. In lumbar spinal fusions, rhBMP-2

was associated with increased postoperative pain but insignificant long-term pain reduction. For cervical fusion, rhBMP-2 was linked to higher rates of wound complications and dysphagia. Another analysis on cervical fusion procedures revealed that rhBMP-2 was correlated with increased risks of dysphagia, dysphonia, neurological complications, and hematoma or seroma formation, but also with a decreased need for tracheostomy tube insertion. The quality of evidence for rhBMP-2 in lumbar spinal fusion was deemed moderate, while for cervical fusion, it was considered low. Consequently, the health technology assessment suggests the necessity for additional studies with extended follow-up periods to ascertain whether the benefits of rhBMP-2 outweigh its associated risks (Hayes 2022).

A phase IV, national, multicenter, retrospective study aimed to assess the utilization of rhBMP-2 in spine fusion surgery. Analysis encompassed four hundred patients exhibiting a spectrum of primary diagnostic indications, including degenerative disc disease (32.3%), spondylolisthesis (29.8%), deformity (14.8%), and pseudoarthrosis (7.3%). Fusion, the primary outcome, exhibited success rates in 48.4% of patients, with 13.7% experiencing fusion failure. Fusion status remained undetermined in 12.4% of cases, and 25.4% of patients did not undergo fusion assessment. Notably, 12.4% lacked a determinable fusion status, and 25.4% lacked fusion assessments. At the 12-month mark, fusion success reached 94.5% among the assessed subset of 127 patients. Secondary outcomes included adverse events of interest (AEI) and secondary spine interventions, with 31 AEIs observed in 27 patients, only one of which was deemed related to rhBMP-2. Common AEIs comprised device displacement (7 patients) and fluid collection at the implant site (5 patients), necessitating unplanned secondary spine interventions in 4 patients. Limitations arose from the retrospective design and variations in patient follow-up protocols, resulting in over half lost to follow-up at 12 months. Despite limitations, this study offers valuable insights into the safety and efficacy of rhBMP-2 as a treatment option for spine fusion surgery, underlining its potential in clinical practice (Vincentelli et al. 2019).

**iFactor Protein for Spinal Fusion**

A prospective, randomized, controlled, parallel, single-blinded FDA Investigational Device Exemption trial was conducted to assess the effectiveness and safety of i-Factor Bone Graft compared to local autograft in a single-level anterior cervical discectomy and fusion (ACDF) for cervical radiculopathy. The study included 319 patients, receiving autograft (n = 154) or i-Factor (n = 165) in a cortical ring allograft. Primary outcomes, such as fusion rates, Neck Disability Index (NDI), and neurological success rates, were measured. Secondary outcomes included VAS pain, SF-36v2, and Odom outcomes. At 12-months, fusion rates were 88.97% for i-Factor and 85.82% for autograft ($p = 0.0004$), with NDI scores improving significantly by 28.75 points in the i-Factor group and 27.40 points in the autograft group ($p < 0.0001$). A high neurological success rate was seen in both groups ($p < 0.001$), with no difference in the rate of adverse events between groups ($p = 0.8814$). VAS pain and SF-36v2 scores showed similar improvements between groups. A substantial proportion of patients reported good or excellent Odom outcomes (81.4% in both groups). i-Factor met all four FDA-mandated noninferiority success criteria, demonstrating safety and efficacy in single-level ACDF for cervical radiculopathy. Both i-Factor and autograft groups exhibited significant improvement post-surgery and high fusion rates (Arnold et al. 2016).

At the two-year follow-up, the study compared outcomes between subjects who received i-Factor and those who underwent autograft procedures. Fusion rates were similar between the two groups (97.30% for i-Factor™ and 94.44% for autograft, $p = 0.2513$), as were neurological success rates (94.87% for i-Factor™ and 93.79% for autograft, $p = 0.7869$). Improvement in various measures such as the Neck Disability Index ($p = 0.1448$), Visual Analog Scale scores for arm ($p = 0.2763$) and neck ($p = 0.1652$) pain, and Short Form-36 (SF-36v2)( scores were observed in both groups, with no significant differences between them. The composite endpoint of overall success, which included factors like fusion, Neck Disability Index improvement, neurological success, and absence of re-operations, was higher in i-Factor subjects compared to autograft subjects (69.83% vs. 56.35%, respectively, $p = 0.0302$). Reoperation rates were similar between the i-Factor (7.45%) and autograft (10.53%) groups ($p = 0.3411$). No allergic reactions were reported in i-Factor subjects. The study concluded, at the two-year mark post-surgery, i-Factor in anterior cervical discectomy and fusion is both effective and safe. The outcomes achieved are comparable to those obtained using local autograft bone (Arnold et al. 2018).

A systematic review conducted by Hasan et al. (2023) aimed to assess the effectiveness and overall outcomes of iFactor/ABMP-15 in lumbar spine surgery. Five studies were included in the review. Primary outcomes evaluated included fusion rates and iFactor efficacy, while secondary outcomes encompassed patient-reported measures and complication rates. Across interbody approaches, fusion rates ranged from 92.7% to 97.9%, while in posterolateral, non-instrumental fusions, rates varied from 50% to 57%. iFactor/ABM/P-15 showed a significantly faster rate of fusion when compared to traditional grafts including allograft, autograft, DBM, and rhBMP-2. The review's limitations included small sample sizes, predominance of single-center studies, and variations in iFactor grafting methods. The review

concluded that iFactor/ABM/P-15 exhibited a significantly faster fusion rate with comparable patient-reported outcomes compared to alternative grafting methods in lumbar spine surgery.

**National and Specialty Organizations**

The **American Association of Neurological Surgeons (AANS)** and **Congress of Neurological Surgeons (CNS)** published a joint guideline in 2014 stating that the use of rhBMP-2 could be a substitute for AICB in lumbar fusion. The guideline also notes that although rhBMP-2 has been shown to have a positive effect on fusion rate, its use is associated with unique complications. Surgeons utilizing rhBMP-2 should be aware of the potential for these complications and be selective in their use. Further research on identifying patient populations that would best benefit from rhBMP-2 is warranted (Kaiser et al. 2014).

**The North American Spine Society (NASS)** published *Appropriate Use Criteria for Degenerative Lumbar Spondylolisthesis*, citing that BMP is a reasonable option for bone graft in patients who are at higher risk of nonunion due to smoking (NASS 2020).

The **International Society for the Advancement of Spine Surgery (ISASS)** published *Recommendations and Coverage Criteria for Bone Graft Substitutes used in Spinal Surgery*. The guidelines suggest that the P-15 peptide in the form of i-Factor is safe and effective based on its mechanism of action and clinical data from an IDE level 1 clinical study (Abjornson et al. 2018).

## CODING & BILLING INFORMATION

**CPT (Current Procedural Terminology) Codes**

| CPT | Description |
|---|---|
| **20930** | Allograft, morselized, or placement of osteopromotive material, for spine surgery only [when specified as recombinant human bone morphogenetic protein]. |
| **20999** | Unlisted procedure, musculoskeletal system, general [when specified as placement of recombinant human bone morphogenetic protein for tibial fracture] |

**CODING DISCLAIMER.** Codes listed in this policy are for reference purposes only and may not be all-inclusive. Deleted codes and codes which are not effective at the time the service is rendered may not be eligible for reimbursement. Listing of a service or device code in this policy does not guarantee coverage. Coverage is determined by the benefit document. Molina adheres to Current Procedural Terminology (CPT®), a registered trademark of the American Medical Association (AMA). All CPT codes and descriptions are copyrighted by the AMA; this information is included for informational purposes only. Providers and facilities are expected to utilize industry standard coding practices for all submissions. When improper billing and coding is not followed, Molina has the right to reject/deny the claim and recover claim payment(s). Due to changing industry practices, Molina reserves the right to revise this policy as needed.

## APPROVAL HISTORY

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| **04/10/2024** | Policy reviewed. Changed name to 'Bone Graft Substitutes for Bone Fusion'. Updated coverage criteria to include i-Factor protein. Updated Summary of Medical Evidence and References. |
| **04/13/2023** | Policy reviewed. No changes in criteria. Updated references. |
| **04/13/2022** | Policy reviewed. Overview, Summary of Evidence and References updated. Coverage criteria for use in lumbar fusion revised to include levels L2-3. |
| **04/05/2021** | Policy reviewed, no changes to criteria; literature review did not yield any new applications of the Infuse bone graft. |
| **06/17/2020** | Policy reviewed, no changes. |
| **06/19/2019** | Policy reviewed, no changes. |
| **07/10/2018** | Policy reviewed, no changes, updated references. In the Coding section, changed definition for code 20930; added "List separately in addition to code for primary procedure. According to 2018 Encoder Pro the following must be coded first: 22319, 22532-22533, 22548-22558, 22590-22612, 22630, 22633-22634, 22800-22812. |
| **09/19/2017** | Policy reviewed, no changes. |
| **09/15/2016** | Policy reviewed, no changes. |
| **12/16/2015** | Policy reviewed, no changes. |
| **12/08/2014** | New policy. |

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