Subject: Recombinant Human Bone Morphogenetic Protein (rhBMP) for Bone Fusion

Overview: Bone morphogenetic proteins can positively influence bone formation at several points along the developmental and healing pathway. As graft material, BMP overcomes some disadvantages of both autografts and bone allografts.

Policy and Coverage Criteria:

NOTE: Prior Authorization is NOT required

Harvard Pilgrim Healthcare covers rhBMP-2:
- As an alternative to autograft in recalcitrant long bone non-unions where use of autograft is unfeasible and alternative treatments have failed;
- For spinal fusion procedures at one or more levels in skeletally mature patients with degenerative disc disease from L2-S1; or
- For the treatment of acute, open fracture of the tibial shaft.

*(Unfeasible is defined as autograft is no longer available because of prior use or insufficient tissue or the candidate is unacceptable because of any of the following reasons - obesity, over 65 years of age, morbidity preventing harvesting at autograft donor site (infection, fracture), excessive risk of anatomic disruption from harvesting, osteoporosis, concurrent medical conditions and co-morbidities that increase risk of autograft.)*

Harvard Pilgrim does NOT cover the use of rhBMP-7 for bone healing and/or fusion. It is considered investigational/experimental and unproven.


Supporting Information:

1. Technology Assessment: BMPs belong to a family of growth factors and play an important role in bone and cartilage formation, fracture healing, and repair of other musculoskeletal tissues. The function of this osteoinductive protein is to attract and promote differentiation of pluripotential mesenchymal cells into chondrocytes and osteoblasts, promote differentiation of osteoprogenitors into osteoblasts, and influence skeletal pattern formation. BMPs can positively influence bone formation at several points along the developmental and healing pathway. BMP overcomes many disadvantages of both autografts and bone allografts. In order to remain confined within the region of repair, rhBMP must be used in conjunction with a suitable carrier. Collagen is currently the most common carrier. The approved technique for using INFUSE involves reconstituting the powdered rhBMP-2 with sterile water, drawing it into a syringe, and distributing it on an absorbable bovine tendon type I collagen sponge, which is placed in a cage that serves as the fusion device. OP-1 Putty is composed of rhBMP-7, bovine collagen, and a putty additive that is mixed with sterile saline solution to form a paste, which is applied directly to bone at the fusion site.
rhBMP-2: Marketed in the U.S. as INFUSE® Bone Graft (Medtronic Sofamor Danek) as an alternative to autogenous bone graft in certain types of spinal surgery, acute tibia fracture treatment, and some oral maxillofacial procedures.

rhBMP-7: Marketed in the U.S. as OP-1® Putty (Stryker Biotech) it is aimed at an alternative to autogenous bone graft in some spinal and trauma procedures. The FDA approved the OP-1 Implant and the OP-1 Putty for use in specifically defined patients under a humanitarian device exemption (HDE).

2. Literature Review: Numerous clinical publications demonstrate the use and acceptance of rhBMP-2 for the treatment of long-bone unions and spinal fusions.

**Spinal Fusion:**

**rhBMP-2:**

Early trials of rhBMP-2 use in spinal fusion surgery showed acceptable safety and effectiveness and, overall, increased fusion success with the use of the BMP compared to those of a control group who received autograft bone (Burkus, et al. 2002; Baskin, et al., 2003; Burkus, et al. 2005; Glassman, et al., 2005). However, recent studies have cautioned the original studies had design bias and the risk of adverse events associated with rhBMP-2 is much higher than the original estimates (Carragee, et al. 2011). A 2014 study by Goode et al. reviewed complications following cervical fusions and found patients receiving BMP were 29% more likely to have a complication and a nervous system complication.

Protocols followed by four studies of lumbar fusion involved a posterolateral or PLIF approach, neither of which is included in the FDA approval of INFUSE (Boden et al., 2002; Haid et al., 2004; Glassman et al., 2005; Singh et al., 2006). In Boden et al. (n=25), rhBMP-2 was used with or without an internal fixation device, the Texas Scottish Rite Hospital pedicle screw instrumentation (TSRH), and compared with autogenous iliac crest bone graft (AlCBG) in conjunction with TSRH. The rhBMP carrier was not collagen but rather granules of hydroxyapatite/tricalcium phosphate (HA/TCP). At 1-year follow-up, there was fusion in 100% of each investigational arm and in only 40% of the control group. The very small number of patients (n=5) in the control group precluded a reliable estimate of fusion success rate. Pain and disability were considered secondary outcomes in this study. However, the rhBMP-2-alone group had consistently and substantially superior clinical outcomes than either the rhBMP-2 with TSRH- or AlCBG with TSRH-group. These measures included the OLBPDQ, back and leg pain, the SF-36 PCS, and patient assessment of whether the outcome was good/excellent. The authors did not see a clear explanation for the difference in clinical outcomes between the two investigational groups. They speculated that this had to do with the more extensive retraction and prolonged operative time necessitated by internal fixation. There were a few adverse events in the two investigational arms and none in the control group, but again, the size of the control group limits conclusions about safety differences.

Haid et al. (2004) (n=67) used Inter Fix cages for PLIF and randomized patients to the INFUSE product or AlCBG within the cages. They found that the fusion rate was much higher in the rhBMP-2 group (97.3% patients) than in the control group (77.8%). However, a more clinically relevant measure of fusion success comparable with that used by Burkus et al. (2002 and 2005) was nearly identical in the two groups (82.4% and 81.8%). The use of rhBMP-2 appeared to result in substantially greater improvement of neurological symptoms, although the differences were statistically significant only for back pain. Patients in the rhBMP-2 group had somewhat better functional improvement, as measured by the OLBPDQ and the SF-36 PCS, but differences were not tested statistically. rhBMP-2 appeared to be more successful in enabling patients to work (an increase of 8.8% working at 2 years compared with a decrease of 3.1% of patients in the control group) or return to work (at 43 versus 137 days). However, patient satisfaction was slightly higher (nonsignificant) in the control group. There were no safety differences other than a significantly greater incidence of bone formation outside the disc space in the rhBMP-2 group (70% versus 12%). The study was suspended due to this finding, but it did not appear to have any relationship to increased leg pain. A limitation of this study was a 10.4% loss to follow-up or dropout rate at 24 months in the rhBMP group; there was no loss to follow-up after this interval in the control group.

Glassman et al. (2005) (n=74) reported interim fusion results at one of multiple sites participating in a randomized controlled trial approved by the FDA as an investigational device exemption (IDE) protocol (G00137) to evaluate the CD Horizon® Spinal System (Medtronic Sofamor Danek) for instrumented posterolateral fusion. 
This fusion system applies rhBMP-2 to a bovine collagen/HA-TCP compression resistant matrix (CRM). Patients were randomized to the CD-Horizon system or AlCBG. A significant difference in fusion grade was observed as early as 6 months. After 1 year, the mean fusion grade (on a scale of 1 for no fusion to 5 for solid bilateral fusion) was 4.62 for the rhBMP-2 group and only 3.77 (P<0.0023) for the control group. The proportions of patients with grade 4 or 5 were 89% and 66%, respectively. The authors’ scheme for grading fusion was not part of the IDE protocol, and no clinical outcomes were presented.

Singh et al. (2006) (n=52) designed a study to test the osteoconductivity of a reduced dose of rhBMP-2 on absorbable collagen sponge combined with autogenous bone as a bulking agent. Patients enrolled for the study underwent instrumented posterolateral lumbar fusion. rhBMP-2 was used as an adjunct to AlCBG, with laminectomy bone added to the collagen sponge; all three graft materials were placed on either side of the spine at each affected level. Results were compared with those of 11 sex-matched patients who had undergone the same procedure without the addition of rhBMP-2 (AlCBG, with laminectomy bone plus collagen sponge). No serious adverse events were observed. The rhBMP-2 group exhibited more probable fusion, higher quality fusion, and earlier fusion according to interpretation of computed tomography (CT) scans. Differences were substantial.

Dimar et al. (2009) reported on a multi-center RCT comparing results of patients with degenerative disc disease treated with either AlCBG or rhBMP-2. 224 control patients underwent AlCBG and 239 underwent rhBMP. The ODI, SF-36, and back and leg pain scores were determined preoperatively and at 1.5, 3, 6, 12, and 24 months postoperatively. Radiographs and computed tomography scans were made at 6, 12, and 24 months postoperatively to evaluate for fusion. Results found both groups had similar improvements in pain and disability scores. At 24 months, results suggested rhBMP-2 patients had more successful fusion than those in the control group.

Lee et al. (2010) conducted a retrospective review of patients who underwent either AlCBG or rhBMP-2 fusion. Three groups of patients were analyzed. Group A consisted of 34 patients, 65 and older, treated with rhBMP-2 and allograft. Group B included 52 patients under 65 treated with rhBMP-2 and allograft. Group C included 41 patients 65 and older treated with autograft. Fusion rate, fusion time, clinical outcome, VAS, perioperative complications and revision rate between each group.

Pimenta et al. (2013) published results of an RCT comparing rhBMP-2 with synthetic silicate calcium phosphate as bone graft substitutes and their effect of fusion rates and clinical outcomes in patients undergoing single-level lumbar stand-alone extreme lateral interbody fusion. 15 patients underwent the procedure with rhBMP-2 and 15 with the silicate material. Clinical and radiographic results were compared between the two groups. Clinical outcomes were similar improved between the two groups from baseline to 36 months postoperatively. Complication rates between the two were similar, though with slightly more instances of subsidence in the silicate group and high rates of excessive bone formation and adjacent segment disease in the rhBMP-2 group. Additional studies have evaluated complications related to the use of rhBMP-2 used in posterior lumbar spinal fusion and did not identify a significant increase in complication rates (Cahill et al. 2011; Williams et al. 2011; Glassman et al. 2011).

Studies evaluating the FDA-approved rhBMP-2 fusion system and some small to mid-sized randomized controlled trials or comparison studies of off-label uses or non-approved components suggest that rhBMP-2 in lumbar fusion is safe and provides equivalent, if not better, fusion success, improvement in symptoms and function, and patient satisfaction compared with AlCBG.

rhBMP-7:

In evaluating the available evidence for the use of rhBMP-7 in spinal fusion surgery, there are three randomized controlled trials (Johnsson et al., 2002; Vaccaro et al., 2005a; Kanayama et al., 2006; Vaccaro et al., 2008) and one prospective study with historical controls (Vaccaro et al., 2005b) that evaluated posterolateral procedures. However, none selected patients according to the FDA’s HDE criteria, i.e., these were primary rather than revision fusions and inclusion criteria did not include the compromising patient characteristics identified in the HDE. In fact, both studies by Vaccaro et al. specifically excluded smokers.
Johnsson et al. (2002) (n=20) compared OP-1 Implant (not approved for spinal fusion) and AlCBG; results were very similar in the two groups.

Vaccaro et al. (2005a) (n=36) compared OP-1 Putty with AlCBG and found that both radiographic fusion success and clinical success, defined as 20% improvement in OLBPDQ score, were superior in the rhBMP group: 55% versus 40% fusion success and 85% versus 64% clinical success when analysis was limited to evaluable patients. The study was not large enough to demonstrate statistical significance for these results. Differences were diminished but still positive (in favor of rhBMP) when patients who were lost to follow-up, dropped out, or had poor film quality were included in the analysis and counted as failures. General function, as measured by the SF-36 PCS and MSC scores, also improved to a greater degree, and scores were more likely to be comparable with population age-matched norms in the rhBMP group; differences were especially striking with respect to PCS scores (46.2 versus 29 at 24 months, compared with norms of 46 for ages 55 to 64 and 43 for ages 65 to 74). Kanayama et al. (2006) (n=20) used OP-1 Putty alone in the interventional group and added local autograft to a ceramic bone substitute in the comparison group. Local autograft consisted of decorticated bone at the fusion site. Decorticated bone was discarded in the intervention group. Both groups also underwent instrumentation with a pedicle screw. Fusion success was greater in the comparison group, both in radiographic results (78% of rhBMP group versus 90% comparison group) and when confirmed surgically in patients undergoing instrumentation removal (57% versus 78%). However, there were no differences in OLBPDQ score changes, which at 24 months were approximately 50% of baseline values in both groups. The authors note that fusion was difficult to assess in the comparison group due to the slow resorption of radiodense molecules in the ceramic bone graft substitute and since the rates may be overestimated for both groups due to the immediate stability afforded by pedicle screw fixation. A much higher mean age in the OP-1 Putty group (70) than in the comparison group (59) may have diminished any treatment effect that might otherwise have been observed. Thus, the validity of results from this study was compromised.

Vaccaro et al. (2005b) prospectively enrolled 12 patients for a trial of OP-1 Putty plus AlCBG. At 24 months, fusion success was observed in 50% of patients and clinical success (20% improvement in OLBPDQ score) was observed in 89% of patients. These rates were reduced to 42% and 67% when patients who were lost to follow-up, dropped out, or had poor film quality were included in the analysis and counted as failures. A group of historical controls exhibited a 50% fusion success rate.

Vaccaro et al. (2008) published the results of a randomized controlled multicenter trial comparing the safety and clinical radiographic efficacy of OP-1 (rhBMP-7) Putty with an iliac crest bone autograft control in uninstrumented, single-level posterolateral spinal arthrodesis. 335 patients were randomized 2:1 to receive either OP-1 Putty or autograft. Radiographs, clinical examinations, and appropriate clinical indicators, including ODI, SF-36 and VAS scores were observed serially. Serum samples were also measured at regular intervals to assess the presence of antibodies to OP-1. Overall success was evaluated at 24 months. The study was then extended to include additional imaging data and long-term clinical follow-up at 36+ months. Results found OP-1 Putty demonstrated statistical equivalency to autograft with respect to the primary end point of overall success. OP-1 Putty has statistically lower intraoperative blood loss and shorter operative times. Vaccaro et al. concluded OP-1 to be a safe and effective alternative to autograft in the setting of uninstrumented posterolateral spinal arthrodesis performed for degenerative spondylolisthesis and symptomatic spinal stenosis.

Tibial fusion:

rhBMP-2:

Clinical studies evaluating the use of rhBMP-2 in patients with tibial fractures have supported safety and efficacy. Govender et al., (2002); Jones et al., (2006); Swiontkowski et al., (2006) reviewed the use of BMP-2 in patients with tibial fractures. In order to partially compensate for the lack of surgeon blinding, overall treatment success was defined in terms of both blinded radiographic assessment and unblinded clinical assessment. Govender et al. (2002) conducted a multicenter randomized controlled trial involving 49 centers in 11 countries, referred to as the BMP-2 Evaluation in Surgery for Tibial Trauma (BESST) Trial. The study group consisted of 450 patients with open tibial fractures. Both treatment groups underwent standard primary treatment (intramedullary nail fixation). The trial compared the addition of an rhBMP-2 implant (rhBMP-2 on collagen sponge) at two different concentrations (0.75 mg/mL and the approved concentration of 1.5 mg/mL) with standard treatment alone, based on earlier evidence that the osteoinductive effect of rhBMP-2 is driven by concentration rather than dose. The primary outcome measure was the proportion of patients requiring secondary interventions due to delayed
union or nonunion within 12 months postsurgery. Patients with rhBMP implants were substantially less likely to require secondary intervention (37% at 0.75 mg/mL and 26% at 1.5 mg/mL) than patients receiving nail fixation alone (46%), and a statistically significant dose-response relationship was demonstrated (P=0.0004). This difference, however, did not meet the authors’ a priori definition of clinical significance (difference of 30%). Compared with standard treatment alone, rhBMP-2 at 1.5 mg/mL reduced the risk of secondary procedure by 44%. rhBMP-2 implants also reduced the invasiveness of procedures, promoted faster healing, and resulted in greater overall treatment success (54% and 65% for the lower-dose and higher-dose rhBMP-2 implants, 47% for nail fixation alone; P=0.0028). The authors did not offer an explanation for the modest treatment success observed in all groups. Adverse events were substantially less frequent in patients who received the rhBMP-2 implants; differences in infection rates were observed only in the more severe fractures. Multivariate analysis of potential predictors of the need for secondary procedure revealed rhBMP-2 implant and the use of reaming to be independent predictors. Reaming involves enlargement of the intramedullary canal to facilitate the insertion of a nail larger than the intramedullary canal. Differences in use of reaming (used more frequently in the two rhBMP-2 groups) do not fully explain outcome differences since both rhBMP-2 and reaming had independent effects in multivariate analysis. However, the role that reaming played in this study is difficult to assess since the authors do not report the values of the relative risks associated with rhBMP-2 and reaming in multivariate analysis; they also do not identify the other variables included in the model.

Swiontkowski et al. (2006) combined results from the randomized controlled trial reported by Govender et al. (2002) with a smaller trial (n=60) in U.S. centers only. The U.S. study followed a design identical to that of the BESTT trial. Data for the 0.75 mg/mL treatment group in the BESTT trial were excluded. This analysis was published partly in response to criticisms of the earlier study, including the claim that the study group was not representative of the U.S. population due to differences in the use of reaming, which was left up to the discretion of the surgeon. The U.S.-only study group did, indeed, have a higher rate of reaming (50% and 53% in interventional and control groups) than the BESTT trial study group (40% and 26%). Since reaming had been shown by Govender et al. to have an independent effect in preventing the need for secondary procedure, the results from that study would not be entirely generalizable to the U.S. Swiontkowski et al. also intended to further explore the earlier finding that the effect of rhBMP-2 on infection rates was stronger in patients with severe fractures. Raw data from the two studies were combined for two subgroup analyses: (1) severe (Gustilo-Anderson type IIIA-IIIB) fractures and (2) reamed nailing. The severe fracture subgroup analysis showed that rhBMP-2 reduced the risk of secondary procedure by 68% (compared with 44% in the entire BESTT trial study group), improved time to full weight bearing from 126 to 95 days, and reduced infection by 47% (about the same as in the severe fracture subgroup of the BESTT trial). In the reamed nailing subgroup of the combined analysis, these outcomes were only modestly and non-significantly superior in the rhBMP-2 treatment group compared with standard treatment. Thus, the greater benefit of rhBMP-2 for severe fractures than for mild-to-moderate fractures and the confounding effect of reamed nailing were corroborated.

Jones et al. (2006) conducted a small, randomized controlled trial (n=30) to assess the efficacy of rhBMP-2 combined with allograft in the form of cancellous bone chips. The control group received morselized autogenous iliac crest bone graft (AICBG) (autograft). In contrast to the other two studies and in contrast to the protocol specified in the FDA approval, the patients had already received primary treatment with intramedullary (IM) nail or external skeletal fixation 6 to 12 weeks earlier and met the clinical criteria for reconstruction with staged bone grafting. Overall treatment success was defined somewhat differently from the definition used by the other two studies. Success rates were significantly greater in the rhBMP-2 group (87%) than in the control group (67%), and the difference was judged to be clinically meaningful. Difference in healing time was minimal. A disease-specific health status measurement tool, the Short Musculoskeletal Function Assessment (SMFA), was used to assess improvements in function and the extent to which the patient was affected by disability. Improvements between the two treatment groups were both substantial (changes in the range of 20 to 25 points out of total possible scores of 100) but did not differ between groups. Adverse events were more frequent in the rhBMP-2 group but were not serious in nature. A high loss to follow-up and/or dropout rate seriously weakened the conclusions from this study.

A 2011 retrospective study by Tressler et al. investigated the results of rhBMP-2 compared to autologous iliac crest bone graft in the treatment of long-bone non-union. 19 patients with non-union received rhBMP-2 and 74 non-union patients received autologous iliac crest bone graft. Results showed no statistical difference in the rate
of healing between the two groups. rhBMP-2 patients had a lower incidence of postoperative infection and a shorter intraoperative time. The authors concluded the outcomes suggest rhBMP-2 may be a suitable alternative to iliac bone graft for long bone non-unions.

rhBMP-7:

There are few studies that have assessed rhBMP-7 in tibial fractures. Two randomized controlled trials evaluated rhBMP-7 as an aid to promoting bone repair in tibial fracture with nonunion (Friedlaender et al., 2001) or fresh tibial fracture (Maniscalco et al., 2002). Friedlaender et al. (n=122) followed a protocol consistent with the HDE for OP-1 Implant. Inclusion criteria included nonunion of a tibial fracture at ≥ 9 months following injury. The control was IM fixation with fresh bone autograft, and the intervention was IM fixation with implantation of rhBMP-7 in a type I collagen carrier. At 9-month follow-up (after treatment of nonunion), clinical success, physician satisfaction, and bone bridging were slightly better in the control group. Most adverse events were similar in the two groups, except for a much higher incidence of osteomyelitis in the control group. The advantage of using rhBMP-7 was that it gave similar results without the need for bone-harvesting surgery. The limitation to this study was the short follow-up (primary endpoint was 9 months). However, the clinical success rate at 2 years was 82% of patients in each group, nearly as high as at 9-month follow-up. Substantial loss to 2-year follow-up (38% of the control group and 26% of the investigational group) limits long-term conclusions. The other study (Maniscalco et al., 2002) (n=14) was designed to standardize the surgical procedure, to evaluate tolerance and toxicity to rhBMP-7, and to evaluate its potential to accelerate bone healing and functional recovery. It differed from both the study by Friedlaender et al. (2001) and the parameters defined by the HDE for OP-1 Implant in that treatment was for a recent fracture (mean time from injury < 1 week) rather than for nonunion. The study protocol involved randomizing patients with closed fractures of the tibial shaft to monolateral external fixation with rhBMP-7 applied at the fracture site (investigational group) or monolateral external fixation with fresh bone autograft (control group). The rhBMP-7 was well tolerated, and there were no adverse events associated with its use. However, there was no accelerated healing advantage conferred by the rhBMP-7, and its application required an extra incision. The authors concluded that rhBMP-7 is not indicated for fresh shaft fractures of the tibia. This study was limited by the small number of patients and short follow-up period (5 months).

Calori et al. (2008) reported results of an randomized clinical study comparing the efficacy of rhBMP-7 and platelet-rich plasma as bone-stimulating agents in the treatment of persistent fracture non-unions. 60 patients underwent treatment either rhBMP-7 or PRP. In the rhBMP-y group there were 15 tibial non-unions, 10 femoral, 15 humeral, 12 ulnar, and 8 radial. In the PRP group there were 19 tibial, 8 femoral, 16 humeral, 8 ulnar, and 9 radial non-unions. Both clinical and radiological union occurred in 86.7% of cases in the patients treated with rhBMP-7. 68.3% of the cases treated with PRP achieved clinical and radiological union. A lower median clinical and radiographic healing time was observed in the rhBMP-7 group. The researchers concluded the study supports the view that in the treatment of persistent long bone non-unions, the application of rhBMP-7 as a bone-stimulating agent is superior compared to that of PRP.

Ristiniemi et al. (2007) discussed a study where 20 patients with distal tibial fractures were treated with osteoinduction with rhBMP-7 and bovine collagen. Healing of the fracture was compared with that of 20 matched patients in whom treatment was similar except that rhBMP-7 was not used. Significantly more fractures had healed by 16 (p=0.039) and 20 weeks (p=0.022) in the BMP group compared with the matched group. The mean time to union (p=0.002), the duration of absence from work (p=0.018) and the time for which external fixation was required (p=0.037) were significantly shorter in the BMP group than in the matched group. Secondary intervention due to delayed healing was required in two patients in the BMP group and seven in the matched group. RhBMP-7 can enhance the union of distal tibial fractures treated by external fixation.

Geesink et al. (1999) tested the osteogenic potential of rhBMP-7 in 24 patients who underwent a high tibial osteotomy as a treatment for osteoarthritis of the knee. As a result of the tibial osteotomy, the patients had a bone gap at the site of the associated osteotomy of the fibula. The ability of three different materials, DMB, rhBMP-7, and collagen type I, to promote bridging of the fibular bone gap was evaluated. Results were similar for both DMB and rhBMP-7, while there was little effect from collagen. The authors concluded that further investigations are required to establish the efficacy of rhBMP-7 in various musculoskeletal disorders to determine the dose response profiles or effects of different carriers, and to confirm the biological and biomechanical characteristics of regenerated new bone. This study was limited by the small number of patients (12 per group).
Currently, the FDA only approves the use of rhBMP-7 under a Humanitarian Device Exemption.

3. Governmental/Regulatory Agencies:

FDA: InFuse™ Bone Graft/LT-CAGE™ received FDA approval in July 2002. It was approval broadened in December 2003 to include additional fusion cages, specifically the INTER FIX™ Threaded fusion Device and the INTER FIX™ RP Threaded Fusion Device. The FDA approves of the use of these devices in conjunction with spinal fusion surgery in patients who meet the following criteria:

- skeletally mature
- degenerative disc disease at one level from L4-S1
- no more than Grade I spondylolisthesis at the involved level
- failure of at least six months of nonoperative therapy

The device is contraindicated in patients with the following conditions:

- hypersensitivity to rhBMP-2, bovine Type I collagen or to other components of formulation
- resected or extant tumor at the operative site
- active infection at the operative site
- allergy to titanium or titanium alloy
- possible or confirmed pregnancy

INFUSE® Bone Graft (Medtronic Sofamor Danek) (rhBMP-2 on an absorbable collagen sponge), under product code MPW, was approved on April 30, 2004 for treating acute, open tibial shaft fractures that have been stabilized with IM nail fixation after appropriate wound management. INFUSE Bone Graft must be applied within 14 days after the initial fracture. Prospective patients should be skeletally mature. No other devices under MPW have been approved (FDA, 2006).

In March 2007, INFUSE Bone Graft received FDA approval for use in making enough bone in the sinus area to place endosseous dental implants in the upper jaw. It is also used to increase bone in extraction sites prior to implant placement. http://www.fda.gov/MedicalDevices/ProductsandMedicalProcedures/DeviceApprovalsandClearances/Recently-ApprovedDevices/ucm077024.htm

On October 17, 2001, the FDA approved a Humanitarian Device Exemption (HDE) (H010002) for the OP-1® Implant (Stryker Biotech). 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 as an alternative to autograft in recalcitrant long bone nonunions where use of autograft is unfeasible and alternative treatments have failed (FDA, 2001).

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 type 1 bovine 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 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. "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 (FDA, 2004).

The OP-1™ Implant and OP-1™ Putty products were acquired on February 1, 2011 by Olympus Biotech Corporation.

The FDA approval for the use of rhBMP-7/OP-1™ Putty specifies patient selection criteria as those who meet both of the following:

- failed previous spinal fusion surgery
- not candidates for autograft because of a condition such as osteoporosis, diabetes or smoking
The use of the product is contraindicated in patients with the following conditions:

- allergy to OP-1 or collagen
- existing tumor, tumor removed at or near the fracture, or history of malignancy
- previous history of cancer
- skeletal immaturity
- pregnancy

CMS: There is no NCD for this procedure/treatment

North American Spine Society: Based on the available evidence, rhBMP is indicated as an adjunct to spinal fusion in cases in which other alternatives are either not available or are not likely to lead to successful fusion. [https://www.spine.org/Documents/PolicyPractice/CoverageRecommendations/rhBMP.pdf](https://www.spine.org/Documents/PolicyPractice/CoverageRecommendations/rhBMP.pdf)

**Codes:**

20903 – Allograft, morselized, or placement of osteopromotive material, for spine surgery only (list separate in addition to code for primary procedure)

**References:**


Summary of Changes

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