



CIGNA MEDICAL COVERAGE POLICY

The following Coverage Policy applies to all plans administered by CIGNA Companies including plans administered by Great-West Healthcare, which is now a part of CIGNA.

Subject **Bone Graft Substitutes for Use in Bone Repair**

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Coverage Policy

Dental implants are specifically excluded under many benefit plans; therefore, recombinant bone morphogenetic proteins used in connection with dental implants, including sinus and/or alveolar ridge augmentation, are generally not covered. Please refer to the applicable plan document to determine benefit availability and the terms, conditions and limitations of coverage.

CIGNA covers the following bone graft materials, alone or in combination, as medically necessary for enhancement of bone healing:

- autografts
- allograft-based, including demineralized bone matrix (DBM)
- synthetic bone graft substitutes

CIGNA covers recombinant bone morphogenetic proteins (rhBMP) as medically necessary when ANY of the following criteria are met:

- rhBMP–2 in combination with a fusion device for single-level anterior interbody lumbar fusion surgery
- rhBMP–2 in surgical repair of acute, open tibial shaft fractures
- rhBMP–7 when provided in accordance with the FDA Humanitarian Device Exemption (HDE) specifications in the revision of posterolateral lumbar fusion surgery when an autograft is not feasible
- rhBMP–7 when provided in accordance with the FDA HDE specifications in surgical repair of long bone nonunion when conservative treatments have failed and an autograft is not feasible

CIGNA does not cover ANY of the following because each is considered experimental, investigational or unproven:

- rhBMP for the treatment of cervical spine conditions
- mesenchymal stem cell therapy or human growth factors (e.g., platelet rich plasma, autologous platelet derived growth factor) when used to enhance bone healing
- rhBMP–2 (i.e., INFUSE® Bone Graft) as an alternative or adjunct treatment for sinus augmentation and/or localized alveolar ridge augmentation

General Background

More than three million musculoskeletal procedures are performed annually in the United States and approximately half of those involve bone grafting with either an autograft or allograft (American Academy of Orthopedic Surgeons [AAOS], 2008). Bone grafts can be harvested from the patient (autograft), a cadaver (allograft), or they can be synthetic. Worldwide, autografts or allografts are used for an average of 2.2 million orthopedic procedures annually. In general, cortical bone grafts are used for structural support and cancellous bone grafts are used for osteogenesis. However, bone graft materials are often combined to extend graft availability and enhance healing. For example, during spinal fusion demineralized bone matrix is commonly used to augment grating material and increase the rate of fusion.

Autografts are considered the gold standard and are typically retrieved from the patient's own tibia, fibula or ileum or iliac crest, by way of a surgical procedure and are then placed at the injury site. The advantage of autograft is the high probability of success—autograft possesses all of the necessary characteristics such as osteoconductivity, osteogenicity, and osteoinductivity. The amount of autogenous bone available for grafting is limited. Furthermore, autografts are associated with increased morbidity, increased anesthesia time and blood loss, and post operative donor site complications.

An alternative to autograft is the use of allografts. Allograft offers the advantage of precluding a second surgery and is frequently used during procedures such as spinal fusion, for enhancement of fracture healing, for filling cavities and defects, bridging joints, establishing the continuity of long bone and providing bone blocks. Allograft substitutes may be used alone or in combination with other materials. Allografts are readily available from bone banks and provide both osteoinductive properties and structural support. However, allografts may give less consistent clinical results, 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 the processing removes osteogenic cells and reduces mechanical strength. AlloGro® Demineralized Bone Matrix (Wright Medical, Arlington, TN); Dynagraft-D™ (Citagenix, Laval, Quebec, Canada); Opteform® (Exactech, Inc., Gainesville, FL); Grafton® (Osteotech, Eatontown, NJ) are examples of allograft-based bone graft substitutes.

Demineralized bone matrix (DBM) is a type of allograft. It is produced through a process that involves the decalcification of cortical bone; this substantially decreases the structural strength. However, it is more osteoinductive than ordinary allograft. Although the reason for this is not completely understood, it has been speculated that the osteoinductive growth factors contained in the extracellular bone matrix are more easily accessed once the mineral phase of the bone has been removed. Various DBM preparations are available for use (e.g., Osteotech's Grafton®, Regeneration Technology's Osteofil®). These preparations differ in shape and size of DBM particles, the amount of residual minerals and the type of carrier materials.

Due to the limitations of autogenous bone and allograft material, and the number of surgeries that require grafting, investigators have developed grafting alternatives, some of which are available for current use and others which are still in developmental stages. Bone graft substitutes have overlapping properties and are made of a variety of materials such as polymers (degradable and nondegradable), ceramics and composites (calcium phosphate, calcium sulfate, and bioactive glass), factor-based techniques (recombinant growth factors) and cell-based techniques (mesenchymal stem cells). Some authors classify bone graft substitutes according to these materials. However, these substitutes can also be classified based on their characteristics, such as osteoconduction (e.g., calcium sulfate, ceramics, calcium phosphate, cements, collagen), osteoinduction (e.g., DMB, rhBMPs, growth factors), osteogenesis (e.g., bone marrow aspirate), or combined (composites). Nonetheless, the ideal bone graft substitute must provide scaffolding for osteoconduction, growth factors for osteoinduction and progenitor cells for osteogenesis. In addition, the bone graft substitute must be able to integrate with the host.

The role of bone graft substitutes is one of structural support only; they do not impart any osteoinductive properties (Urist, 1965; Szpalski and Gunzburg, 2002). Some materials may be combined with autograft or allograft and are considered bone graft extenders (e.g., demineralized bone matrix). These materials appear to be safe when used according to FDA indications; however each type of product is under varying degrees of regulation and in some cases safety and efficacy of these products remain unproven through human trials. For the intent of this coverage policy, bone graft substitutes are described as those that are cell-based, ceramic-based, polymer-based and factor-based. Synthetic substitutes generally consist of ceramic and polymer based materials.

- **Cell-based:** Bone graft substitutes that are cell-based use cells to generate new tissue either alone or seeded onto a support matrix. Mesenchymal stem cells are a type of cell-based bone graft substitute. Mesenchymal stem cells are multipotent stem cells that express a variety of different cell surface proteins and can differentiate into a variety of cell types. Obtained from bone marrow, they have been shown to differentiate into osteoblasts, chondrocytes, myocytes, adipocytes, and neuronal cells. Theoretically, these cells are responsive to osteogenic growth factors (e.g., gene therapy techniques) (Helm and Gazit, 2005). The use of mesenchymal stem cells has been and continues to be investigated for various procedures, including spinal fusion and for intervertebral disc regeneration. Although encouraging, data published in the medical literature is preliminary and primarily in the form of nonhuman trials.
- **Ceramic-based:** Ceramic-based bone graft substitutes include materials such as calcium phosphate, calcium sulfate and bioactive glass, used alone or in combination with other grafts. Several types of calcium phosphates, including tricalcium phosphate, synthetic hydroxyapatite, and coralline hydroxyapatite are available in pastes, putties, solid matrices, and granules. When used, calcium sulfate is less desirable for weight bearing applications due to loss of mechanical properties during degradation. When implanted into living tissue, bioactive glass forms a bond with pre-existing bone, however there are only a few products commercially available and use is primarily in dental applications. Synthetic hydroxyapatite (e.g., ProOsteon[®] Implant 500 [Interpore Cross, Int., Irvine, CA]) is brittle, has little tensile strength and is typically used for bone defects with internal fixation. A pure beta-tricalcium phosphate scaffold, Vitoss[®] Synthetic Cancellous Bone Filler (Orthovita, Inc., Malvern, PA) is intended for use in small defects in the extremities, pelvis, and spine. Other ceramic-based materials include Osteograft[®] (Ceramed, Lakewood, CO); Norian SRS (Skeletal Repair System) (Synthes, Inc., West Chester, PA); and Osteoset[®] (Wright Medical, Arlington, TN) and Actifuse[™] (ApaTech Limited, Elstree, Hertfordshire, UK).
- **Polymer-based:** Polymer-based substitutes are polymers that are either degradable or nondegradable and may be used alone or in combination with other materials. Degradable polymers are resorbed by the body allowing it to heal itself without foreign bodies remaining. Types of polymer-based substitutes include Cortoss[®] (Orthovita, Inc., Malvern, PA); OPLA (TMH Biomedical, Inc., Duluth, MN), Immix (Osteobiologics, Smith and Nephew, Memphis, TN).
- **Factor-based:** Factor-based bone graft substitutes consist of human growth factors and recombinant growth factors used alone or in combination with other materials. Recombinant bone morphogenetic

proteins (rhBMP), fibroblast growth factor, and transforming growth factor are types of factor-based bone graft substitutes. RhBMP is a unique subgroup of graft substitutes and many published trials support safety and efficacy. The effects of growth factors such as fibroblast growth factor and insulin-like growth factors on fracture healing have been investigated primarily in animal trials.

Recombinant Bone Morphogenetic Proteins (rhBMP)

The function of BMP is to promote differentiation of mesenchymal cells into chondrocytes and osteoblasts, to promote differentiation of osteoprogenitors into osteoblasts, and to influence skeletal pattern formation. Part of this process involves the release of growth factors and cytokines, which in turn recruit inflammatory cells, macrophages, and fibroblasts to the bone injury site. The formation of cartilage, induction of osteoblasts, and formation of woven and lamellar bone follows. During this final stage, the hematopoietic marrow is also formed (Rengachary, 2002). BMPs can positively influence bone formation at several points along the developmental pathway and along the healing pathway (Lieberman, et al., 2002).

Recombinant human bone morphogenetic proteins act as an adjunct to autogenous bone grafts, and are used commonly with spinal instrumentation devices (i.e., cages) during lumbar fusion and for fracture repair. According to the FDA, (FDA, 2008) safety and effectiveness of rhBMP for the treatment of cervical spine conditions has not been demonstrated.

Both rhBMP–2 and rhBMP–7 appear to be safe when used appropriately, placed accurately, not allowed to come into contact with decompressed areas (i.e., rhBMP carrier must be protected from compression to avoid the forcing out of implant into surrounding tissues) and contained in the region of surgical fusion. BMPs must be used with caution in the presence of defects in the dura. In spinal fusion surgery, BMPs cannot resist compression or shear forces within a vertebral motion segment; thus, they cannot be used as stand-alone devices. RhBMP–2 must be used with a cage or some type of supportive structure within the vertebral interspace.

Although evidence supports safety and efficacy when used according to FDA indications, adverse events associated with rhBMPs include ectopic bone formation, bone resorption or remodeling at the graft site, hematoma, neck swelling, and painful seroma (Benglis, et al., 2008). Carcinogenicity and teratogenic are also potential concerns.

The benefits of rhBMPs versus autogenous iliac crest bone graft (AICBG) are the decreases in operating room time, blood loss, and morbidity due to the avoidance of an additional procedure to harvest AICBG. None of the studies utilizing rhBMP–2 or rhBMP–7 documented any adverse systemic effects occurring as a result of their use. A small percentage ($\leq 10\%$) of patients develops antibodies to rhBMPs, although there has been no documented evidence of harm resulting from this. Carreon et al. (2008) studied wound related and anaphylactic related adverse events in a case series of patients (n=90) who were re-exposed to rhBMP-2 and reported that multiple exposures from either a secondary primary surgery or revision (through the same approach or a different approach) does not increase the risk of those adverse events.

RhBMP–2/ INFUSE[®] Bone Graft

RhBMP–2 is marketed in the U.S. as INFUSE[®] Bone Graft in conjunction with specific spinal and non-specific tibial fusion devices, as an alternative to autogenous bone graft for sinus augmentation, and for localized alveolar ridge augmentation for defects associated with extraction sockets.

Spinal Fusion: The FDA gave new device approval to the InFuse[™] Bone Graft/LT-CAGE[™] (Medtronic Sofamor Danek, Memphis, TN) in July 2002. The InFuse Bone Graft /LT Cage is intended to be implanted via an anterior open or an anterior laparoscopic approach. The approval was broadened in December 2003 to include additional fusion cages, specifically the INTER FIX[™] Threaded Fusion Device and the INTER FIX[™] RP Threaded Fusion Device (FDA, 2004). The device is to be used by surgeons experienced in spinal fusion surgery and adequately trained in the use of the device.

The use of these devices in conjunction with surgical spinal fusion has been approved by the FDA (2004) for patients who meet all of 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 the 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

Evidence in the published peer-reviewed scientific literature consists of case series, randomized control trials, and literature reviews. Of the evidence reviewed, sample populations vary in size from 11 subjects to as many as 279 subjects and follow-up periods range from six to 24 months. Most of the patients have single-level lumbar disc disease. The approach to lumbar fusion and the use of instrumentation varies among clinical trials. Most of the control groups had standard lumbar fusion using autograft bone from the iliac crest. The results of early clinical trials (Boden, et al., 2000; Boden, et al, 2002; Burkus, et al., 2005) demonstrate that patients who received rhBMP–2 during spinal fusion surgery had shorter operating room times, shorter length of stay, and less blood loss compared to patients who received autogenous bone graft. Several studies published since that time have demonstrated similar results.

Evidence in the form of prospective, randomized controlled trials (RCT) has demonstrated safety and efficacy for the use of rhBMP–2 during spinal fusion (Burkus, et al, 2002; Baskin, et al., 2003; Burkus, et al., 2005; Glassman, et al., 2005). Strong supporting evidence is provided by Burkus and colleagues (2002) who reported the two year results of a multicenter RCT involving 279 patients in whom the rhBMP–2 study group showed similar clinical and quality-of-life outcomes compared to the autograft study group. According to the authors the major advantages of using rhBMP–2 rather than harvested autograft included reduction in morbidity, shorter operating room time and reduced blood loss. Kleeman et al., (2002) published interim results of a larger study that tested the laparoscopic placement of rhBMP–2 in spinal fusion surgery and reported there were no adverse events and that solid fusion was evident on radiographs at six months follow-up for all patients available. Baskin et al., (2003) reported slightly increased improvements in neck disability and arm pain for a group of subjects who underwent lumbar fusion using threaded cortical bone dowels and rhBMP–2 when compared to a control group who received autograft. All of the patients evaluated in this study group had solid fusions at 6, 12 and 24 months post-surgery. Burkus et al. (2005) reported significantly less back and leg pain and lower disability scores for patients who underwent lumbar fusion using rhBMP–2 when compared to the control group. Overall, increased fusion success with the use of rhBMP–2 compared to those of a control group who received autograft bone has been consistently reported in the literature (Burkus, et al., 2005; Glassman, et al., 2005).

Although it is an off-label use, rhBMP–2 has been evaluated for use in cervical spinal fusion. In 2006, Smucker et al. conducted a retrospective case-control study comparing the incidence of perioperative cervical swelling complications after anterior cervical fusion with (n=69) or without the use of rhBMP–2 (n=165). The authors found that rhBMP–2 was significantly associated with increased cervical swelling and reported that 27.5% (19 of 69) of the rhBMP–2 group had a clinically significant swelling event compared to 3.6% in the non-rhBMP–2 group. The results were statistically significant (p<0.001).

Boakye et al. (2005) retrospectively reviewed outcomes in 24 consecutive patients who had undergone anterior cervical discectomy and fusion of one to three levels using polyetheretherketone (PEEK) spacers filled with rhBMP–2. Fusion was documented by radiograph in all cases, and clinical outcomes were rated as good to excellent in 95% of cases. Complications included transient recurrent laryngeal nerve injury in one case, transient C–5 paresis in one, cerebrospinal fluid leakage in one, and transient dysphagia in two. Although the study is promising, it is limited by retrospective data, lack of controls and lack of blinding.

Fracture Repair: RhBMP–2 has also been studied in patients with tibial fractures, and this application received premarket approval from the FDA in April 2004. It is marketed as the INFUSE[®] Bone Graft device (Wyeth Pharmaceuticals, Inc., Philadelphia, PA) and consists of rhBMP–2 in an absorbable collagen sponge.

The FDA approval for this device is for the treatment of patients with acute, open tibial shaft fractures when all of the following criteria are met:

- The fracture must be stabilized with intramedullary (IM) nail fixation after appropriate wound management.
- The rhBMP-2 must be applied within 14 days after the initial fracture.
- The prospective patient should be skeletally mature.

The FDA notes the following contraindications to use of the product:

- possible or confirmed pregnancy
- sensitivity to titanium, titanium alloy, cow (bovine) Type I collagen, or rhBMP-2
- infection near the area of the surgical incision
- previous or current tumor at the site of use
- high risk of amputation of the affected leg
- compartment syndrome of the affected leg

Clinical studies evaluating the use of rhBMP-2 in patients with tibial fractures have supported safety and efficacy. Govender et al. (2002) conducted a prospective, controlled, randomized, multicenter study with 450 patients who had open tibial fractures. The authors compared standard care (i.e., IM nail fixation and soft tissue management) with an implant of rhBMP-2 applied with an absorbable collagen sponge. The primary outcome measure was the proportion of patients requiring secondary interventions due to delayed union or nonunion within 12 months post-surgery. When 1.5 mg/mL of rhBMP-2 was used, the intervention was superior to standard care in reducing frequency of secondary interventions ($p=0.0005$), reducing the overall invasiveness of the procedures ($p=0.0264$), accelerating fracture- and wound-healing ($p=0.0022$, $p=0.0010$, respectively) and reducing the infection rate ($p=0.0219$) in patients with open fractures of the tibia.

Swiontkowski et al. (2006) combined results of the previous RCT by Govender with a smaller randomized trial conducted in the U.S. ($n=60$). The U.S. trial followed a study design similar to that of the Govender trial. Raw data from the two studies were combined for two subgroup analyses (severe fracture treated with rhBMP-2 [$n=131$] and rhBMP-2 with reamed nailing [$n=113$], compared to a control group of standard treatment). The patients were followed for 12 months. The first subgroup (i.e., severe fractures) demonstrated improvements in the rhBMP-2 group, with less bone grafting procedures ($p=0.0005$), fewer patients requiring intensive secondary interventions ($p=0.0065$), and lower rates of infection ($p=0.0234$) when compared to the control group. The second subgroup analysis (reamed nailing) demonstrated no significant difference between the control and the rhBMP-2 group.

Jones et al. (2006) conducted an RCT assessing the efficacy of rhBMP-2 combined with allograft in the form of callous bone chips for the treatment of tibial diaphyseal fractures ($n=30$). The control group of this study ($n=15$) received treatment with autograft (iliac crest bone graft). Both groups of patients received prior treatment with intermedullary nail or external fixation at the time of initial injury, and were treated with grafting on average six to twelve weeks post-injury. Follow-up was conducted every six to eight weeks, with a final follow-up at one year. The evaluation of fracture healing included assessment of pain, full weight-bearing and fracture site tenderness. The Short Musculoskeletal Function Assessment (SMFA) was administered before and after treatment. Union, the presence of extracortical bridging callus, and incorporation of bone graft material were documented using radiographs. Success rates and blood loss were better in the rhBMP-2 group compared to the control group. Limitations noted by the authors of the study included small sample size, high loss to follow-up (only 24 patients completed the study, six were lost to follow-up), and differences in bone graft size.

Sinus Augmentation/Alveolar Ridge Augmentation: In March 2007 the INFUSE[®] Bone Graft (Medtronic Sofamor Danek, Memphis, TN) was granted premarket approval from the FDA for use in oral surgical procedures, (i.e., sinus augmentation and localized alveolar ridge augmentation for defects associated with extraction sockets), as an alternative to autograft. According to the FDA, INFUSE Bone Graft is used to fill space where bone is needed in order to place endosseous dental implants. Dental implants should be placed if there is sufficient bone to stabilize them. When the sinus wall is thin, there is not enough bone to place dental implants. In a procedure known as sinus augmentation, a sinus graft is inserted into the floor of the sinus (i.e., the roof of the upper jaw). Dental implants can then be inserted and stabilized in the new sinus bone. The

alveolar ridge of the jaw is the bone that surrounds the roots of the teeth. When a tooth is extracted, a socket remains which later heals; however, typically, previous height and width are not restored. Alveolar ridge augmentation is a procedure performed to increase bone volume, making treatment with dental implants possible.

The FDA notes the following contraindications to use for oral surgical procedures:

- in patients with an active infection at the operative site
- in patients who are pregnant
- in patients who are hypersensitive to rhBMP-2 or bovine type I collagen
- in an area where there was a tumor

Evidence in the published scientific literature supporting rhBMP-2 for oral maxillofacial surgery is limited, Jung and colleagues (2003) studied if the addition of rhBMP-2 to a xenogenic bone substitute mineral (Bio-Oss[®]) would improve guided bone regeneration therapy regarding bone volume, density and maturation. The authors conducted a prospective, controlled, randomized, double-masked clinical trial involving 11 patients who were in need of dental implant treatment. Test and control defects were both augmented with xenogenic bone substitute and a restorable collagen membrane. The test sites also received rhBMP-2. Clinical evaluation was based on measurement with a periodontal probe at insertion and six months afterwards. Reduction in defect height from baseline to reentry at six months for both test sites and control sites were statistically significant ($p < 0.01$). Test sites showed an average area density of 37% of newly formed bone, compared to 30% at control sites upon histomorphometric analysis. At the rhBMP-2 sites 57% of the surface bone substitute particles were in contact with newly formed bone compared to 30% at the control sites. This study was limited by small sample size and short-term outcomes.

Boyne et al. (2005) reported the results of a phase II study evaluating two concentrations of rhBMP-2 for safety and efficacy in inducing bone formation for dental implants. Patients were treated with rhBMP-2 via an absorbable sponge at concentrations 0.75 mg/ml ($n=18$), 1.50 mg/ml ($n=17$), or with bone graft ($n=13$). Bone induction was assessed by alveolar ridge height, width, and density measurements from computed tomography scans that were obtained before treatment, at four months after treatment, and six months post-functional loading of dental implants. Clinical success was based on the survival rate of the dental implants. At four months postoperatively, the mean changes in bone height from baseline were 11.29 mm, 9.47 mm, and 10.16 mm in the 0.75 mg/ml, 1.50 mg/ml, and bone graft treatment groups, respectively. Ridge width at four months was also statistically different among treatment groups: 4.7 mm, 2.0 mm, and 2.0 mm, respectively, in the bone graft 0.75 mg/ml and 1.5 mg/ml groups. Bone density was statistically different among treatment groups: 350 mg/cc, 84 mg/cc and 134 mg/cc for the bone graft, 0.75 mg/ml and 1.5 mg/ml treatment groups, respectively. The dental implant survival rate, regardless of loading status, was 81%, 88%, and 79% for the bone graft, 0.75 mg/ml, and 1.50 mg/ml groups, respectively. Limitations of the study included small sample size and measurement of short-term outcomes.

Fiorellini et al. (2005) reported on the efficacy of two doses of rhBMP-2 in 80 patients requiring extraction socket augmentation. Two sequential cohorts of 40 patients each were randomized in a double-masked manner to receive 0.75 mg/ml rhBMP-2 or 1.50 mg/ml, rhBMP-2, placebo, or no treatment in a 2:1:1 ratio. Computed tomography was used to determine efficacy by measuring bone induction, adequate volume for dental implant, and bone density. Biopsies were obtained at the time of dental implant insertion. The results showed patients treated with 1.50 mg/ml rhBMP-2 had significantly greater bone augmentation compared to the controls ($p \leq 0.05$). Increases in ridge height and median width in the rhBMP-2 group was also noted. Additionally, the adequacy of bone for dental implant insertion was almost two times greater in the rhBMP-2 groups compared to no treatment or placebo group. Histology on bone biopsies showed no differences between the rhBMP-2 induced bone and the native bone. A total of 250 adverse events were reported, including oral edema, mouth pain, and oral erythema.

Esposito et al. (2007) published a Cochrane review assessing the success, function, morbidity and patient satisfaction among different bone augmentation techniques for dental implant treatments. The review included 13 RCTs out of 30 potentially eligible trials reporting on a total of 332 patients. Regarding enhancing bone formation, the authors concluded that bone morphogenetic proteins may enhance bone formation around implants grafted with Bio-Oss (an osteoconductive bone substitute), but there was no reliable evidence

supporting the efficacy of other active agents, such as platelet-rich plasma, in conjunction with implant treatment.

Although the study results suggest that this technique may be a promising treatment option, the evidence in the published, peer-reviewed, scientific literature is insufficient to allow strong conclusions regarding the long-term effectiveness of rhBMP-2 for sinus augmentation and alveolar ridge augmentation. Published studies have been small in sample size, and data on long-term outcomes are lacking. Patient selection criteria are not well-defined. Some studies have indicated that rhBMP-2 is safe and enhances bone maturation. However, additional well-designed clinical trials assessing long-term health outcomes are needed to validate these results.

RhBMP-7/ OP-1™ Putty

A second type of human bone morphogenetic protein is rhBMP-7, marketed in the United States as OP-1™ Implant for use in healing fractures of the long bones, and OP-1™ Putty for use in spinal fusion. The FDA approved the OP-1 Implant and the OP-1 Putty for use in specifically-defined patients under a humanitarian device exemption (HDE).

Spinal Fusion: The FDA granted HDE approval in April 2004 for the use of OP-1™ Putty (Stryker Biotech, Hopkinton, MA) for use as an alternative to autograft in compromised patients requiring revision posterolateral spinal fusion of the lower back. OP-1 Putty is made from a manufactured human protein powder and bovine collagen that is mixed with a saline solution and a thickening agent to form a putty-like material. During surgery, the putty is placed on each side of the spinal levels to be fused. The FDA approval 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

The data presented to the FDA for consideration of approval is contained in the FDA Summary of Safety and Probable Benefit (FDA, 2004). Forty-eight patients with single-level degenerative lumbar spondylolisthesis and spinal stenosis received rhBMP-7 alone, rhBMP-7 combined with autograft, or autograft alone. The patients receiving rhBMP-7 alone demonstrated superior success, as evidenced by radiograph and clinical improvement, over those receiving autograft alone.

The FDA decision is based on the clinical data, as well as the following rationale provided in the approval summary:

“When revision of a failed fusion is required, most patients are limited to either living with pain and altered function or repeating the original procedure with additional autologous bone, which may result in depletion of the bone stock and further risk to the patient. Allograft bone and bone graft substitutes are not considered feasible alternatives to autograft in revision surgery due to their lack of osteogenic potential. For certain patients, e.g., those with implanted leads, bone growth stimulators would not be considered as feasible options. OP-1 Putty has the potential to eliminate the risk and complications associated with these treatment alternatives while providing a feasible and beneficial alternative treatment.”

Few studies have assessed rhBMP-7 in spine fusion surgery. An uncontrolled prospective study used rhBMP-7 together with carboxymethylcellulose and type I bone collagen as an adjunct to AICBG; all were mixed together into a paste and applied to the lateral aspects of the vertebrae (Vaccaro, et al., 2003). However, the combined use of these materials precludes a determination of the effect of rhBMP-7. A randomized, controlled efficacy trial compared the use of AICBG implants to rhBMP-7 implants (Johnsson, et al., 2002). Results were similar for patients treated with AICBG and those treated with rhBMP-7.

More recently, Kanayama et al. (2006) conducted a prospective RCT evaluating the osteoinductive properties and fusion rates of OP-1 (i.e., BMP-7) in instrumented posterolateral lumbar fusion. A total of 19 patients underwent posterolateral lumbar fusion for degenerative spondylolisthesis of L3-L4, or L4-L5. The patients were randomized to receive either OP-1 (n=9) or a local autograft with ceramic granules (n=10). Both groups underwent instrumentation with a pedicle screw. Fusion status was evaluated using plain radiographs and computerized tomography (CT) scans. After a minimum of at least one year follow-up, the patients who showed radiographic evidence of fusion underwent instrument removal and exploration of the fusion site. Biopsies were taken and evaluated histologically. The authors reported that radiographic fusion rate was 7 out of 9 in the OP-1 group and 9 out of 10 in the control group. Solid fusion was observed in more autograft patients when compared to OP-1 patients. Furthermore, during open exploration, the entire control group demonstrated viable bone and fibrous tissue surrounding ceramic granules histologically, and six of the seven OP-1 patients demonstrated viable bone. Limitations of the study included discrepancies between radiographs and surgical findings regarding fusion status; the possibility that the use of pedicle screw fixation led to overestimates of fusion status; and variable timing of biopsies, including sampling error bias in addition to small sample size.

Vaccaro et al. (2008) published the results of a prospective, randomized controlled multicenter clinical pilot trials evaluated the intermediate-term safety and efficacy of OP-1 Putty as an alternative to autogenous bone. The authors assessed subjects by comparing radiograph, clinical and safety data at four-year follow-up post surgery. All patients in the study group underwent decompression and un-instrumented fusion with either OP-1 Putty (n=24) or iliac crest autograft (n=12). The authors reported that the rates of radiograph fusions, clinical improvement and overall success with OP-1 Putty was at least comparable to that of autograft at 48 months post surgery.

Fracture Repair: The FDA gave HDE approval for the use of rhBMP-7 to treat nonunion of long bones. It is a powder that is mixed with normal saline to form a paste which is applied during surgery. The substance is marketed in the U.S. as OP-1™ Implant (Stryker Biotech, Hopkinton, MA).

The FDA approval indicates that the substance is appropriate for use in the surgical repair of long bone nonunion when both of the following patient selection criteria are met:

- autograft is not feasible
- alternative treatments have failed

The use of the product is contraindicated in patients with the following conditions:

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

The BMP-7 Italian Observational Study Group (Ronga, et al., 2006) reported on 105 consecutive patients treated with BMP-7 graft between May 2002 and September 2005 for nonunion in various anatomical long bone sites. Mean follow-up was 29.2 months and consisted of radiographic and clinical assessments throughout various time intervals. The study consisted of patients who received BMP-7 alone, BMP-7 with an osteoconductive agent, or BMP-7 with an autograft. The authors stated that successful outcomes were reported in 88 patients, and the average healing time was 7.9 months.

Three studies evaluated rhBMP-7 as an aid to promoting bone repair in fractures of the tibia (Friedlaender, et al., 2001; Maniscalco, et al., 2002) or in critically-sized defects of fibular bone (Geesink, et al., 1999). Of the two fracture repair studies, Friedlaender et al. (2001) presented the best evidence in a prospective, partially-blinded, multicenter RCT. The control was IM fixation with AICBG, and the intervention was IM fixation with rhBMP-7 implantation in a type I collagen carrier. At nine months follow-up, clinical success, physician satisfaction, and bone bridging were slightly better in the control group, but there were also more adverse events in this group (e.g., acute/subacute osteomyelitis, leg edema, mechanical complications, and hematoma). 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 nine months); however, 68% of the patient population (control group, 31 of 38; study group, 37 of 45) had greater than 82% continued clinical success at two years.

The other fracture repair study (Maniscalco, et al., 2002) 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. The study protocol involved randomizing patients with closed fractures of the tibial shaft to monolateral external fixation (control) and monolateral external fixation with rhBMP-7 applied at the fracture site. 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. This study was limited by the small number of patients (seven per group) and short follow-up period (five months).

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).

Platelet Rich Plasma (PRP)

The use of platelet rich plasma (plasma having a platelet concentration above baseline) is an approach being investigated for the treatment of bone healing. PRP is also referred to as autologous platelet derived growth factor, platelet enriched plasma, platelet-rich concentrate, and autogenous platelet gel or platelet releasate. When activated in the body, platelets release growth factors which accelerate healing, including platelet-derived growth factor, transforming growth factor beta (TGF- β) and insulin-like growth factor to name a few. It is hypothesized that a concentrated preparation of platelets, which contain higher concentrations of growth factors, may promote more rapid healing. Platelet concentrates are not osteoinductive however, since they do not include BMPs (Marx, 2004), although in theory they promote osteoblast proliferation and differentiation (Veillette, McKee, 2007). During the procedure, a small amount of the patient's blood is drawn and centrifuged to separate red blood cells from the platelet rich plasma. The platelet rich plasma is then mixed with the patients bone graft material. Theoretically, the growth factors signal the local mesenchymal and epithelial cells to migrate, divide, and increase collagen and matrix synthesis increasing bone regeneration. Overexposure of cells to PRP yields many cells but limited differentiation of those cells into appropriate cell lines. It has been suggested that the inability to control differentiation is a reason to not use PRP for healing of tissue (Mehta, Watson, 2008).

Platelet concentration devices are approved by the FDA as part of the 510(k) approval process for preparation of platelet rich plasma. Examples of devices that are FDA approved include PCCS(TM) Platelet Concentrate Separation Kit (3i [Implant Innovations Inc.] and Magellan(TM) Autologous Platelet Separator System (Medtronic Perfusion Systems).

Evidence in the published scientific literature is inconsistent and does not lend strong support to the clinical utility of using PRP to augment bone grafting. There are few randomized controlled trials with comparison groups available to support routine use of PRP. Some authors have reported PRP successfully promotes graft incorporation in oral and maxillofacial surgery (Marx, 2004; Kassoulis, Reynolds, 2005; Camargo, et al., 2005). For other applications, such as spinal fusion the studies are encouraging but limited in quantity and quality, therefore no conclusions can be drawn. Additionally, there is a lack of controlled clinical trials to support safety and efficacy of platelet rich plasma for the treatment of long bone nonunion or delayed union. In a recent prospective case series published by Mariconda and colleagues (2008) the authors failed to demonstrate the clinical utility of platelet gel supplementation in the treatment of long bone nonunions. Calorie et al. (2008) conducted a prospective randomized clinical study comparing efficacy of rhBMP-7 and PRP in the treatment of fracture nonunions and reported that rhBMP-7 resulted in superior clinical and radiological efficacy when compared to PRP. In a review published by Veillette and McKee (2008) the authors noted that there was a lack of evidence evaluating the efficacy of PRP in management of acute fractures, to assess the effect of PRP on new bone formation for long bone defects and nonunions, and that there is no clinical evidence to support the

use of PRP to augment spinal fusion. Currently, whether or not platelet rich plasma facilitates osteoinduction remains unproven in the published scientific literature. (Please refer to CIGNA Coverage Policy: Tissue Engineered Skin Substitutes and Growth Factors for further detail regarding autologous platelet derived growth factor.)

U.S Food and Drug Administration (FDA)

The FDA classifies most orthobiologicals (e.g., rhBMP–2, Osteoset, Grafton) as Class II devices. Class II devices are those for which general controls alone are insufficient to ensure safety and effectiveness, and existing methods are available to provide such assurances. In addition to complying with general controls, Class II devices are also subject to special controls. Many of the bone graft substitutes are approved through the 510(k) process and are based on a predicate device clearance although some require premarket approval (i.e., Class III devices). In addition, some of the bone graft materials are regulated as human tissue, such as some of the DBM products.

Humanitarian Device Exemption (HDE) was granted by the FDA for the OP-1 Implant and the OP-1 Putty, also referred to as rhBMP–7, for use in specifically defined patients (FDA, H010002, H020008). According to the FDA, a humanitarian use device (HUD) is a device that is intended to benefit patients by treating or diagnosing a disease or condition that affects fewer than 4,000 individuals in the United States per year. An HDE application is not required to contain the results of scientifically valid clinical investigations demonstrating that the device is effective for its intended purpose. The application, however, must contain sufficient information for the FDA to determine that the device does not pose an unreasonable or significant risk of illness or injury and that the probable benefit to health outweighs the risk of injury or illness from its use, taking into account the probable risks and benefits of currently available devices or alternative forms of treatment. Additionally, the applicant must demonstrate that no comparable devices are available to treat or diagnose the disease or condition, and that they could not otherwise bring the device to market.

Technology Assessments

Technology assessments evaluating the safety and efficacy of bone graft substitutes in general were not found in the medical literature.

Several technology assessments evaluating rhBMP were located. A health technology assessment was conducted by Garrison et al. (2007) to assess the clinical- and cost- effectiveness of BMP for the treatment of spinal fusions and the healing of fractures compared to current standards of care under the National Health Service, England. All studies that reported on BMP for these indications were included; however, the authors focused primarily on evidence from RCTs because of the poor quality of data from the case series. The authors reviewed eight RCTs evaluating BMP for tibial fractures, one for scaphoid fractures, and 12 for spinal fusion. The authors noted several methodological weaknesses such as unreported randomization, incomparable baseline characteristics between groups, failure to perform intention-to-treat analysis, to use independent blinded assessors and failure to report reasons for dropouts. In some studies, secondary outcomes were not measured and/or reported. Data indicated that BMP increased fracture union for patients with acute tibial fractures and found that high-dose BMP is more effective than a lower dose for open tibial fractures. The evidence supporting safety of BMP for scaphoid nonunion was limited. Evidence indicated that BMP-2 is more effective than autogenous bone graft for radiographic fusion in patients with single-level degenerative disc disease, and that BMP was associated with a shorter hospital stay and reduced operating time compared to autograft.

The California Technology Assessment Forum (CTAF) (Feldman, et al., 2005) reviewed the literature to assess safety and effectiveness of rhBMP for spinal surgery and tibial fractures. The focus of the review was for rhBMP–2 for the promotion of bone fusion and to accelerate healing. The CTAF concluded that rhBMP–2 carried on a type-I collagen sponge meets CTAF criteria when used in conjunction with FDA- approved devices for the treatment of patients undergoing single-level spinal anterior lumbar interbody fusion for symptomatic single-level degenerative disc disease at L4–S1 of at least six months' duration that has not responded to nonoperative treatment.

In 2005, the Ontario Health Technology Advisory Committee published a report evaluating osteogenic protein–1 (OP–1) for long bone fracture nonunion. Based on level one evidence, the recommendation of the Committee stated that OP-1 was a reasonable alternative to autologous bone grafting in the treatment of long bone nonunions, and the decision to use it should be left to the discretion of treating physicians.

In 2004, the Ontario Health Technology Advisory published a report evaluating the safety and effectiveness of rhBMP (i.e., INFUSE) for spinal surgery as an alternative to autologous bone grafting. Their recommendations indicate that the Infuse device is safe. For spinal fusion, radiologic fusion occurs at a consistently faster rate among recipients of the BMP device than among recipients of autologous bone grafts. However, no differences in clinical outcomes were noted. Regardless of technique, improvements in pain and disability are reported by similar proportions of participants in all the arms of all the trials. At the time of the report, BMP devices for cervical fusion were not approved in Canada.

In 2003, the Washington Department of Labor and Industries conducted a technology assessment evaluating BMP for treatment of long bone fractures and for use in spinal fusion procedures. The authors reviewed several RCTs comparing BMP to autograft for the treatment of long bone fractures and concluded that patients with closed tibial fractures and patients with tibial nonunions had similar outcomes, regardless of treatment regimen. Patients who received BMP had shorter operative times and shorter hospital stays, although these results were not always statistically significant. Patients with BMP implants did not experience donor-site pain when compared to the autograft patients. Two case series that evaluated BMP for femoral nonunion had positive outcomes; however, the study did not have comparison groups. Additionally, RCTs of patients who underwent spinal fusion using BMP, when compared to autograft, had similar outcomes, regardless of treatment.

Summary

Many bone graft substitutes are emerging as new treatments for the repair, restoration or regeneration of bone. Much of the evidence in the peer-reviewed published scientific literature evaluating these materials consists of nonhuman trials, case reports and case series. Materials such as mesenchymal stem cells and platelet rich plasma remain under investigation and well designed trials, involving human subjects is necessary to support safety and efficacy when used for bone repair. While investigators continue to evaluate which materials yield optimal results, the American Academy of Orthopedic Surgeons (AAOS) emphasizes familiarity with orthobiologic products, knowledge regarding the proposed indications for use and the possible outcomes of the procedures along with informed patient consent.

The evidence in the published, peer-reviewed, scientific literature indicates that rhBMPs, when used as implants in the FDA-approved context, are at least as effective as autogenous iliac crest bone graft (AICBG) in achieving stable spinal fusion and healing of fracture nonunions. There is sufficient evidence to support the use of rhBMP-2 in a collagen sponge in combination with supportive devices for single-level spinal fusion surgery and in the repair of tibial fractures when conducted according to the indications documented by the FDA. There is also sufficient evidence to support the use of rhBMP-7 as a paste for long bone fracture repair and as a putty in spinal fusion revision when conducted in accordance with the humanitarian device exemption specifications of the FDA. However, the evidence regarding rhBMP-2 as an alternative to or adjunct to sinus augmentation and/or alveolar ridge augmentation is insufficient to support long-term effectiveness and improved health outcomes.

Coding/Billing Information

Note: This list of codes may not be all-inclusive.

Covered when medically necessary:

CPT® Codes	Description
20930	Allograft for spine surgery only; morselized (List separately in addition to code for primary procedure)
20931	Allograft for spine surgery only; structural (List separately in addition to code for primary procedure)
20936	Autograft for spine surgery only (includes harvesting the graft); local (eg, ribs, spinous process, or laminar fragments) obtained from same incision (List separately in addition to code for primary procedure)
20937	Autograft for spine surgery only (includes harvesting the graft); morselized

	(through separate skin or fascial incision) (List separately in addition to code for primary procedure)
20938	Autograft for spine surgery only (includes harvesting the graft); structural, bicortical or tricortical (through separate skin or fascial incision) (List separately in addition to code for primary procedure)
22851	Application of intervertebral biomechanical device(s) (eg, synthetic cage(s) threaded bone dowel(s), methylmethacrylate) to vertebral defect or interspace

HCPCS Codes	Description
C9359	Porous purified collagen matrix bone void filler (Integra Mozaik Osteoconductive Scaffold Putty, Integra OS Osteoconductive Scaffold Putty), per 0.5 cc

ICD-9-CM Diagnosis Codes	Description
715.90-715.98	Osteoarthritis, unspecified whether generalized or localized
722.52	Degeneration of lumbar or lumbosacral intervertebral disc
722.73	Intervertebral lumbar disc disorder with myelopathy, lumbar region
722.83	Postlaminectomy syndrome, lumbar region
724.9	Other unspecified back disorder
733.81	Malunion of fracture
733.82	Nonunion of fracture
806.4	Closed fracture of lumbar spine with spinal cord injury
823.0-823.92	Fracture of tibia and fibula
905.5	Late effect of fracture of multiple and unspecified bones

Experimental/Investigational/Unproven/Not Covered:

HCPCS Codes	Description
D7951 [†]	Sinus augmentation with bone or bone substitutes
D7953 [†]	Bone replacement graft for ridge preservation, per site
P9020	Platelet rich plasma, each unit

[†]**Note:** Experimental, investigational or unproven and not covered when used to report rhBMP-2 (i.e., INFUSE[®] Bone Graft) as an alternative or adjunct treatment for sinus augmentation and/or localized alveolar ridge augmentation.

ICD-9-CM Diagnosis Codes	Description
525.0-525.26	Exfoliation of teeth due to trauma, extraction, or periodontal loss

*Current Procedural Terminology (CPT[®]) ©2008 American Medical Association: Chicago, IL.

References

1. Acosta FL Jr, Lotz J, Ames CP. The potential role of mesenchymal stem cell therapy for intervertebral disc degeneration: a critical overview. *Neurosurg Focus*. 2005 Sep 15;19(3):E4.
2. Agency for Healthcare Research and Quality. Technology assessment: the role of bone growth stimulating devices and orthobiologics in healing nonunion fractures. Updated 2005 Sep 21. Accessed December 8, 2008. Available at URL address: <http://www.ahrq.gov/clinic/techix.htm>

3. American Academy of Orthopaedic Surgeons. Nonunions. Updated 2007 September. Accessed December 8, 2008. Available at URL address: <http://orthoinfo.aaos.org/topic.cfm?topic=A00374>
4. American Academy of Orthopaedic Surgeons. Spinal fusion. Updated 2007 September. Accessed December 8, 2008. Available at URL address: http://orthoinfo.aaos.org/fact/thr_report.cfm?Thread_ID=156
5. American Academy of Orthopaedic Surgeons. Research. Statistics on Orthopedic Patients and Conditions. 2006. Accessed December 8, 2008. Available at URL address: <http://www.aaos.org/Research/stats/patientstats.asp>
6. Apatech, Inc. Actifuse. Accessed December 2, 2008. Available at URL address: <http://www.apatech.com/index.html>
7. Baskin DS, Ryan P, Sonntag V, Westmark R, Widmayer MA. A prospective, randomized, controlled cervical fusion study using recombinant human bone morphogenetic protein-2 with the CORNERSTONE-SR allograft ring and the ATLANTIS anterior cervical plate. *Spine*. 2003;28(12):1219-25.
8. Beaman FD; Bancroft LW; Peterson JJ; Kransdorf MJ. Bone graft materials and synthetic substitutes. *Radiol Clin North Am*. 2006 May;44(3):451-61.
9. Benglis D, Wang MY, Levi AD. A comprehensive review of the safety profile of bone morphogenetic protein in spine surgery. *Neurosurgery*. 2008 May;62(5 Suppl 2):ONS423-31; discussion ONS431.
10. Block MS, Achong R. Bone morphogenetic protein for sinus augmentation. *Atlas Oral Maxillofac Surg Clin North Am*. 2006 Mar;14(1):99-105.
11. Boakye M, Mummaneni PV, Garrett M, Rodts G, Haid R. Anterior cervical discectomy and fusion involving a polyetheretherketone spacer and bone morphogenetic protein. *J Neurosurg: Spine*. 2005 May;2:521-5.
12. Boden SD, Zdeblick TA, Sandhu HS, Heim SE. The use of rhBMP-2 in interbody fusion cages. Definitive evidence of osteoinduction in humans: a preliminary report. *Spine*. 2000;25(3):376-81.
13. Boden SD, Kang J, Sandhu H, Heller JG. Use of recombinant human bone morphogenetic protein-2 to achieve posterolateral lumbar spine fusion in humans: a prospective, randomized clinical pilot trial: 2002 Volvo Award in clinical studies. *Spine*. 2002;27(23):2662-73.
14. Boyne PJ, Lilly LC, Marx RE, Moy PK, Nevins M, Spagnoli DB, Triplett RG. De novo bone induction by recombinant human bone morphogenetic protein-2 (rhBMP-2) in maxillary sinus floor augmentation. *J Oral Maxillofac Surg*. 2005 Dec;63(12):1693-707.
15. Burger EL, Patel V. Calcium phosphates as bone graft extenders. *Orthopedics*. 2007 Nov;30(11):939-42. (Abstract only)
16. Burkus JK, Gornet MF, Dickman CA, Zdeblick TA. Anterior lumbar interbody fusion using rhBMP-2 with tapered interbody cages. *J Spinal Disord Tech*. 2002;15(5):337-49.
17. Burkus JK, Sandhu HS, Gornet MF, Longley MC. Use of rhBMP-2 in combination with structural cortical allografts: clinical and radiographic outcomes in anterior lumbar spinal surgery. *J Bone Joint Surg Am*. 2005 Jun;87-A(6):1205-12.
18. Calori GM, Tagliabue L, Gala L, d'Imporzano M, Peretti G, Albisetti W. Application of rhBMP-7 and platelet-rich plasma in the treatment of long bone non-unions: A prospective randomised clinical study on 120 patients. *Injury*. 2008 Dec;39(12):1391-402. Epub 2008 Nov 22.

19. Camargo PM, Lekovic V, Weinlaender M, Vasilic N, Madzarevic M, Kenney EB. A reentry study on the use of bovine porous bone mineral, GTR, and platelet-rich plasma in the regenerative treatment of intrabony defects in humans. *Int J Periodontics Restorative Dent*. 2005 Feb;25(1):49-59.
20. Carreon LY, Glassman SD, Anekstein Y, Puno RM. Platelet gel (AGF) fails to increase fusion rates in instrumented posterolateral fusions. *Spine*. 2005 May 1;30(9):E243-6; discussion E247.
21. Carreon LY, Glassman SD, Brock DC, Dimar JR, Puno RM, Campbell MJ. Adverse events in patients re-exposed to bone morphogenetic protein for spine surgery. *Spine*. 2008 Feb 15;33(4):391-3.
22. Carlisle E, Fischgrund JS. Bone morphogenetic proteins for spinal fusion. *Spine*. 2005;5:240S-9S.
23. Dimar JR, Glassman SD, Burkus KJ, Carreon LY. Clinical outcomes and fusion success at 2 years of single-level instrumented posterolateral fusions with recombinant human bone morphogenetic protein-2/compression resistant matrix versus iliac crest bone graft. *Spine*. 2006 Oct 15;31(22):2534-9; discussion 2540.
24. Einhorn TA. Clinical applications of recombinant human BMPs: early experience and future development. *J Bone Joint Surg Am*. 2003;85-A(Suppl 3):82-8.
25. Esposito M; Grusovin MG; Coulthard P; Worthington HV. Interventions for replacing missing teeth: bone augmentation techniques for dental implant treatment. *The Cochrane Database of Systematic Reviews* 2007 Issue 4, Copyright © 2007 The Cochrane Collaboration.
26. Feiz-Erfan I, Harrigan M, Sonntag VK, Harrington TR. Effect of autologous platelet gel on early and late graft fusion in anterior cervical spine surgery. *J Neurosurg Spine*. 2007 Nov;7(5):496-502 (Abstract only).
27. Feldman MD. Recombinant human bone morphogenetic protein-2 for spinal surgery and treatment of open tibial fractures. February 16, 2005. Accessed December 8, 2008. Available at URL address: <http://ctaf.org/content/general/detail/568>
28. Fiorellini JP, Howell TH, Cochran D, Malmquist J, Lilly LC, Spagnoli D, Toljanic J, Jones A, Nevins M. Randomized study evaluating recombinant human bone morphogenetic protein-2 for extraction socket augmentation. *J Periodontol*. 2005 Apr;76(4):605-13.
29. Friedlaender GE, Perry CR, Cole JD, Cook SD, Cierny G, Muschler GF, et al. Osteogenic protein-1 (bone morphogenetic protein-7) in the treatment of tibial nonunions: a prospective, randomized clinical trial comparing rhOP-1 with fresh bone autograft. *J Bone Joint Surg Am*. 2001;83-A(Suppl 1 Pt 2):S151-8.
30. Freymiller EG, Aghaloo TL. Platelet-rich plasma: ready or not? *J Oral Maxillofac Surg*. 2004 Apr;62(4):484-8.
31. Garrison KR, Donell S, Ryder J, Shemilt I, Mugford M, Harvey I, Song F. Clinical effectiveness and cost-effectiveness of bone morphogenetic proteins in the non-healing of fractures and spinal fusion: a systematic review. *Health Technol Assess*. 2007 Aug;11(30):1-150, iii-iv.
32. Gautschi OP, Frey SP, Zellweger R. Bone morphogenetic proteins in clinical applications. *ANZ J Surg*. 2007 Aug;77(8):626-31.
33. Geesink RG, Hoefnagels NH, Bulstra SK. Osteogenic activity of OP-1 bone morphogenetic protein (BMP-7) in a human fibular defect. *J Bone Joint Surg Br*. 1999;81-B(4):710-8.
34. Glassman SD, Dimar JR 3rd, Burkus K, Hardacker JW, Pryor PW, Boden SD, Carreon LY. The efficacy of rhBMP-2 for posterolateral lumbar fusion in smokers. *Spine*. 2007 Jul 1;32(15):1693-8.

35. Glassman SD, Dimar JR, Carreon LY, Campbell MJ, Puno RM, Johnson JR. Initial fusion rates with recombinant human bone morphogenetic protein-2/compression resistant matrix and a hydroxyapatite and tricalcium phosphate/collagen carrier in posterolateral spinal fusion. *Spine*. 2005;30(15):1694-8.
36. Govender S, Csimma C, Genant HK, Valentin-Opran A, Amit Y, Arbel R, et al; BMP-2 Evaluation in Surgery for Tibial Trauma (BESTT) Study Group. Recombinant human bone morphogenetic protein-2 for treatment of open tibial fractures: a prospective, controlled, randomized study of four hundred and fifty patients. *J Bone Joint Surg Am*. 2002;84-A(12):2123-34.
37. Granjeiro JM, Oliveira RC, Bustos-Valenzuela JC, Sogayar MC, Taga R. Bone morphogenetic proteins: from structure to clinical use. *Braz J Med Biol Res*. 2005 Oct;38(10):1463-73.
38. Hardenbrook MA, Lombardo SR. Silicate-substituted calcium phosphate as a bone void filler after kyphoplasty in a young patient with multiple compression fractures due to osteogenesis imperfecta variant: case report. *Neurosurg Focus*. 2006 Dec 15;21(6):E9 (Abstract only).
39. HAYES Medical Technology Directory™. Recombinant Human Bone Morphogenetic Protein For Use in Spinal Fusion. Lansdale PA: HAYES, Inc.; ©2007 Winifred S. Hayes, Inc. 2006 Sep. Updated search September 2007, July 2008.
40. HAYES Medical Technology Directory™. Recombinant Human Bone Morphogenetic Protein For Use in Tibia Repair. Lansdale PA: HAYES, Inc.; ©2007 Winifred S. Hayes, Inc. 2006 Sep. Updated search September 2007, September 2008.
41. HAYES Medical Technology Directory™. Beta-Tricalcium Phosphate Bone Void Filler. . Lansdale PA: HAYES, Inc.; ©2008 Winifred S. Hayes, Inc. September 2006. Updated search September 2008.
42. HAYES Search and Summary™. Actifuse™ ABX E-Z-fil Putty Bone graft. Lansdale PA: HAYES, Inc.; ©2008 Winifred S. Hayes, Inc. 2008 April.
43. HAYES Technology Brief. Autologous Platelet-rich Plasma to Aid Bone Fusion Following Ankle Surgery. Lansdale PA: HAYES, Inc.; ©2007 Winifred S. Hayes, Inc. 2007 July.
44. Helm GA, Gazit Z. Future uses of mesenchymal stem cells in spine surgery. *Neurosurg Focus*. 2005 Dec 15;19(6):E13.
45. Hing KA, Annaz B, Saeed S, Revell PA, Buckland T. Microporosity enhances bioactivity of synthetic bone graft substitutes. *J Mater Sci Mater Med*. 2005 May;16(5):467-75. (Abstract only).
46. Jahangir A, Nunley RM, Menta S, Sharan A, Washington Health Policy Fellows. Bone graft substitutes in orthopaedic surgery. *American Academy of Orthopaedic Surgeons*. January 2008, AAOS Now.
47. Jones AL, Bucholz RW, Bosse MJ, Mirza SK, Lyon TR, Webb LX, Pollak AN, Golden JD, Valentin-Opran A; BMP-2 Evaluation in Surgery for Tibial Trauma-Allgraft (BESTT-ALL) Study Group. Recombinant human BMP-2 and allograft compared with autogenous bone graft for reconstruction of diaphyseal tibial fractures with cortical defects. A randomized, controlled trial. *J Bone Joint Surg Am*. 2006 Jul;88(7):1431-41.
48. Johnsson R, Stromqvist B, Aspenberg P. Randomized radiostereometric study comparing osteogenic protein-1 (BMP-7) and autograft bone in human noninstrumented posterolateral lumbar fusion: 2002 Volvo Award in clinical studies. *Spine*. 2002;27(23):2654-61.
49. Jung RE, Glauser R, Schärer P, Hämmerle CH, Sailer HF, Weber FE. Effect of rhBMP-2 on guided bone regeneration in humans. *Clin Oral Implants Res*. 2003 Oct;14(5):556-68.
50. Kanayama M, Hashimoto T, Shigenobu K, Yamane S, Bauer TW, Togawa D. A prospective randomized study of posterolateral lumbar fusion using osteogenic protein-1 (OP-1) versus local autograft with

- ceramic bone substitute: emphasis of surgical exploration and histologic assessment. *Spine*. 2006 May 1;31(10):1067-74.
51. Kassolis JD, Reynolds MA. Evaluation of the adjunctive benefits of platelet-rich plasma in subantral sinus augmentation. *J Craniofac Surg*. 2005 Mar;16(2):280-7.
 52. Khan SN, Sandhu HS, Lane JM, Cammisa FP Jr, Girardi FP. Bone morphogenetic proteins: relevance in spine surgery. *Orthop Clin North Am*. 2002;33(2):447-63.
 53. Kleeman TJ, Ahn UM, Talbot-Kleeman A. Laparoscopic anterior lumbar interbody fusion with rhBMP-2: a prospective study of clinical and radiographic outcomes. *Spine*. 2001;26(24):2751-6.
 54. Lee YP, Jo M, Luna M, Chien B, Lieberman JR, Wang JC. The efficacy of different commercially available demineralized bone matrix substances in an athymic rat model. *J Spinal Disord Tech*. 2005 Oct;18(5):439-44. (Abstract only)
 55. Leung VY, Chan D, Cheung KM. Regeneration of intervertebral disc by mesenchymal stem cells: potentials, limitations, and future direction. *Eur Spine J*. 2006 Aug;15 Suppl 3:S406-13. Epub 2006 Jul 15.
 56. Lieberman JR, Daluiski A, Einhorn TA. The role of growth factors in the repair of bone. Biology and clinical applications. *J Bone Joint Surg Am*. 2002;84-A(6):1032-44.
 57. Maniscalco P, Gambera D, Bertone C, Rivera F, Crainz E, Urgelli S. Healing of fresh tibial fractures with OP-1. A preliminary report. *Acta Biomed Ateneo Parmense*. 2002;73(1-2):27-33.
 58. Mariconda M, Cozzolino F, Cozzolino A, D'Agostino E, Bove A, Milano C. Platelet gel supplementation in long bone nonunions treated by external fixation. *J Orthop Trauma*. 2008 May-Jun;22(5):342-5.
 59. Marx RE. Platelet-rich plasma: evidence to support its use. *J Oral Maxillofac Surg*. 2004 Apr;62(4):489-96.
 60. Marx RE, Carlson ER, Eichstaedt RM, Schimmele SR, Strauss JE, Georgeff KR. Platelet-rich plasma: Growth factor enhancement for bone grafts. *Oral Surg Oral Med Oral Pathol Oral Radiol Endod*. 1998 Jun;85(6):638-46.
 61. McKay WF, Peckham SM, Badura JM. A comprehensive clinical review of recombinant human bone morphogenetic protein-2 (INFUSE((R)) Bone Graft). *Int Orthop*. 2007 Dec;31(6):729-734. Epub 2007 Jul 17.
 62. Medtronic. Infuse Bone Graft. Oral-facial. Accessed December 8, 2008. Available at URL address: http://www.infusebonegraft.com/omf_about.html
 63. Mehta S, Watson JT. Platelet rich concentrate: basic science and current clinical applications. *J Orthop Trauma*. 2008 Jul;22(6):432-8.
 64. Minamide A, Yoshida M, Kawakami M, Okada M, Enyo Y, Hashizume H, Boden SD. The effects of bone morphogenetic protein and basic fibroblast growth factor on cultured mesenchymal stem cells for spine fusion. *Spine*. 2007 May 1;32(10):1067-71.
 65. Mussano F, Ciccone G, Ceccarelli M, Baldi I, Bassi F. Bone morphogenetic proteins and bone defects: a systematic review. *Spine*. 2007 Apr 1;32(7):824-30.
 66. Ontario Ministry of Health and Long-Term Care, Medical Advisory Secretariat. Osteogenic protein-1 for long bone nonunion. Health Technology Assessment Scientific Literature Review. Toronto, ON: Ontario Ministry of Health and Long-Term Care; April 2005. Accessed December 8, 2008. Available at URL address: <http://www.searchontario.gov.on.ca/cgi->

bin/e_search_results.pl?query=osteogenic+protein&offset=0&collection=50000gosp&owner_id=moh&language=en&url=http%3A%2F%2Fwww.health.gov.on.ca

67. Ontario Ministry of Health and Long-Term Care, Medical Advisory Secretariat. Bone morphogenetic proteins and spinal surgery for degenerative disc disease. Health Technology Scientific Literature Review. Toronto, ON: Ontario Ministry of Health and Long-Term Care; March 2004. Accessed December 8, 2008. Available at URL address: http://www.health.gov.on.ca/english/providers/program/ohtac/tech/techlist_2004.html
68. Papakostidis C, Kontakis G, Bhandari M, Giannoudis PV. Efficacy of autologous iliac crest bone graft and bone morphogenetic proteins for posterolateral fusion of lumbar spine: a meta-analysis of the results. *Spine*. 2008 Sep 1;33(19):E680-92.
69. Pradhan BB, Bae HW, Patel VV, Delamarter RB. Graft resorption with the use of bone morphogenetic protein: lessons from anterior lumbar interbody fusion using femoral ring allografts and recombinant human bone morphogenetic protein-2. *Spine*. 2006 May 1;31(10):E277-84.
70. Rengachary SS. Bone morphogenetic proteins: basic concepts. *Neurosurg Focus* [serial online]. 2002;13(6):1-6. *Neurosurg Focus* 13(6), 2002. © 2002 American Association of Neurological Surgeons.
71. Ronga M, Baldo F, Zappala G, Cherubino P; BMP-7 Italian Observational Study (BIOS) Group. Recombinant human bone morphogenetic protein-7 for treatment of long bone non-union: An observational, retrospective, non-randomized study of 105 patients. *Injury*. 2006 Sep;37(9 Suppl):S51-6.
72. Russell TA, Leighton RK; Alpha-BSM Tibial Plateau Fracture Study Group. Comparison of autogenous bone graft and endothermic calcium phosphate cement for defect augmentation in tibial plateau fractures. A multicenter, prospective, randomized study. *J Bone Joint Surg Am*. 2008 Oct;90(10):2057-61.
73. Singh K, Smucker JD, Boden SD. Use of recombinant human bone morphogenetic protein-2 as an adjunct in posterolateral lumbar spine fusion: a prospective CT-scan analysis at one and two years. *J Spinal Disord Tech*. 2006 Aug;19(6):416-23.
74. Smucker JD, Rhee JM, Singh K, Yoon ST, Heller JG. Increased swelling complications associated with off-label usage of rhBMP-2 in the anterior cervical spine. *Spine*. 2006 Nov 15;31(24):2813-9.
75. Swiontkowski MF, Aro HT, Donell S, Esterhai JL, Goulet J, Jones A, et al. Recombinant human bone morphogenetic protein-2 in open tibial fractures. A subgroup analysis of data combined from two prospective randomized studies. *Bone Joint Surg Am*. 2006 Jun;88(6):1258-65.
76. Szpalski M, Gunzburg R. Applications of calcium phosphate-based cancellous bone void fillers in trauma surgery. *Orthopedics*. 2002;25(5 Suppl):S601-9.
77. Takikawa S, Bauer TW, Kambic H, Togawa D. Comparative evaluation of the osteoinductivity of two formulations of human demineralized bone matrix. *J Biomed Mater Res A*. 2003 Apr 1;65(1):37-42. (Abstract only)
78. Termaat MF, Den Boer FC, Bakker FC, Patka P, Haarman HJ. Bone morphogenetic proteins. Development and clinical efficacy in the treatment of fractures and bone defects. *J Bone Joint Surg Am*. 2005 Jun;87-A(6):1367-78.
79. Urist MR. Bone: formation by autoinduction. *Science*. 1965;150(698):893-9.
80. U.S. Food and Drug Administration. INTER FIX Threaded Fusion Device: important medical information. Accessed Nov 28, 2005. Available at URL address: <http://www.fda.gov/cdrh/pdf/P970015c.pdf>

81. U.S. Food and Drug Administration. New device approval: INFUSE[®] bone graft-P000054. Updated May 17, 2004. Accessed December 5, 2008. Available at URL address: <http://www.fda.gov/cdrh/PDF/p000054.html>
82. U.S. Food and Drug Administration. New device approval: InFUSE[™] bone graft/LT-CAGE[™] lumbar tapered fusion device-P000058. Updated 2002 Sep 6. Accessed December 5, 2008. Available at URL address: <http://www.fda.gov/cdrh/pdf/P000058.html>
83. U.S. Food and Drug Administration. New humanitarian device approval: OP-1[™] - H010002. Updated 2001 Nov 30. Accessed December 5, 2008. Available at URL address: <http://www.fda.gov/cdrh/mda/docs/h010002.html>
84. U.S. Food and Drug Administration. New humanitarian device approval: OP-1 Putty- H020008. Updated 2004 Apr 27. Accessed December 5, 2008. Available at URL address: <http://www.fda.gov/cdrh/ode/H020008sum.html>
85. U.S. Food and Drug Administration. InFUSE[™] Bone Graft/LT-CAGE[™] Lumbar Tapered Fusion Device. PMA final decisions rendered for December 2003. Updated 2004 Jul 16. Accessed December 5, 2008. Available at URL address: <http://www.fda.gov/cdrh/pma/pmadec03.html>
86. U.S. Food and Drug Administration. Osteofil Allograft Paste. 510(k) summary K043420. Accessed December 2, 2008. Available at URL address: <http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfPMN/pmn.cfm?ID=17071>
87. Vaccaro AR, Patel T, Fischgrund J, Anderson DG, Truumees E, Herkowitz H, et al. A pilot safety and efficacy study of OP-1 putty (rhBMP-7) as an adjunct to iliac crest autograft in posterolateral lumbar fusions. *Eur Spine J.* 2003;12(5):495-500.
88. Vaccaro AR, Whang PG, Patel T, Phillips FM, Anderson DG, Albert TJ, Hilibrand AS, Brower RS, Kurd MF, Appannagari A, Patel M, Fischgrund JS. The safety and efficacy of OP-1 (rhBMP-7) as a replacement for iliac crest autograft for posterolateral lumbar arthrodesis: minimum 4-year follow-up of a pilot study. *Spine J.* 2008 May-Jun;8(3):457-65. Epub 2007 May 25.
89. Veillette CJ, McKee MD. Growth factors--BMPs, DBMs, and buffy coat products: are there any proven differences amongst them? *Injury.* 2007 Mar;38 Suppl 1:S38-48.
90. Wang JC, Alanay A, Mark D, Kanim LE, Campbell PA, Dawson EG, Lieberman JR. A comparison of commercially available demineralized bone matrix for spinal fusion. *Eur Spine J.* 2007 Aug;16(8):1233-40. Epub 2007 Jan 5. (Abstract only).
91. Washington Department of Labor and Industry. Office of the Medical Director. Bone morphogenic protein for the treatment of long bone fractures and for use in spinal fusion procedures. Olympia, WA: Washington State Department of Labor and Industries; September 29, 2003. Accessed December 8, 2008. <http://www.lni.wa.gov/ClaimsIns/Providers/Treatment/CovMedDev/TechAssess/default.asp>
92. Wood GW. General principles of fracture treatment. *Fracture Healing.* In: Canale & Beaty: *Campbell's Operative Orthopaedics*, 11th ed. CH 50. Copyright © 2007 Mosby.
93. Yoon ST, Boden SD. Spine fusion by gene therapy. *Gene Ther.* 2004;11(4):360-7.

Policy History

Pre-Merger Organizations	Last Review Date	Policy Number	Title
CIGNA HealthCare	1/15/2008	0118	Recombinant Human Bone Morphogenetic Protein (rhBMP) for Use in Bone Repair

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