



Cigna Medical Coverage Policy

Subject Bone Graft Substitutes for Use in Bone Repair

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Coverage Policy

Please refer to the applicable plan document to determine benefit availability and the terms, conditions and limitations of coverage.

Dental implants are specifically excluded under many benefit plans. When coverage for dental implants is excluded, the use of bone graft materials in conjunction with a dental implant, including sinus and/or alveolar ridge augmentation, is similarly not covered.

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)
- ceramic or polymer-based synthetic bone graft substitutes
- bone graft substitutes containing anorganic bone material (e.g., bovine, coral) when used alone or combined with another covered bone graft substitute
- rhBMP-2 (i.e., INFUSE® Bone Graft) for EITHER of the following:

- in combination with a fusion device for a single-level anterior interbody lumbar or lumbosacral fusion* surgery when **ALL** of the following criteria have been met:
 - degenerative disc disease at one level from L2–S1
 - no more than Grade I spondylolisthesis at the involved level
- in surgical repair of an acute, open tibial shaft fractures when **BOTH** of the following criteria are met:
 - fracture is stabilized with intramedullary (IM) nail fixation
 - rhBMP–2 is applied within 14 days of the fracture

***Note: For specific medical necessity criteria for lumbar fusion please reference the Cigna Lumbar Fusion for Spinal Instability and Degenerative Disc Conditions Coverage Policy.**

Cigna does not cover rhBMP–2 for ANY other indication, including the following because it is considered experimental, investigational or unproven:

- rhBMP–2 (i.e., INFUSE® Bone Graft) when used for spinal fusion procedures other than single-level anterior spinal fusion (e.g., posterior lumbar fusion, transforaminal lumbar fusion, more than single-level fusion)
- rhBMP–2 (i.e., INFUSE® Bone Graft) as an alternative or adjunct treatment for sinus augmentation and/or localized alveolar ridge augmentation
- rhBMP–2 (i.e., INFUSE® Bone Graft) for the treatment of cervical spine conditions

Cigna does not cover ANY of the following bone graft substitutes for the enhancement of bone healing because each is considered experimental, investigational or unproven:

- rhBMP-7 (i.e., OP-1™)
- human amniotic membrane bone graft substitute
- cell-based substitutes (e.g., mesenchymal stem cell therapy) when used to enhance bone healing
- human growth factors (e.g., fibroblast growth factor, insulin-like growth factor) when used to enhance bone healing
- platelet rich plasma (e.g., autologous platelet derived growth factor) when used to enhance bone healing
- bone graft substitutes containing anorganic bone material (e.g., bovine, coral) when combined with any non-covered bone graft substitute
- allograft bone graft substitutes used exclusively as stand-alone stabilization devices for fusion (e.g., TruFuse® for isolated facet fusion, NuFix™ for isolated facet fusion, BacFast® HD for isolated facet fusion)
- bone graft substitutes used to reduce donor site morbidity (e.g., iliac crest donor site reconstruction)

General Background

Bone grafts can be harvested from the patient (autograft), a cadaver (allograft), or they can be synthetic. The composition of allograft and synthetic bone graft substitutes and their mechanism of action can vary widely. Bone graft materials are often combined to extend graft availability and enhance healing. Used alone or in combination, bone graft substitutes may be utilized for many orthopaedic applications including spinal fusion, for enhancement of fracture healing, for filling cavities and defects, bridging joints, establishing the continuity of long bone and providing bone blocks. For most of these indications there is sufficient evidence to support safety and effectiveness, although for some indications clinical studies are limited, and for some types of materials, clinical studies are not required.

Autografts

Autografts are considered the established standard and are typically retrieved from the patient's tibia, fibula, 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 disadvantages associated with autografts are that the

amount of autogenous bone available for grafting is limited; autografts are associated with increased morbidity; increased anesthesia time and blood loss; and post-operative donor site complications.

The iliac crest is frequently used as autogenous bone graft. Once the actual bone graft is obtained the site is allowed to heal independently without backfilling. However, there is often post-operative harvest site pain associated with this procedure. The use of various bone graft substitutes are being investigated for backfilling of iliac crest harvest sites, particularly when used for spinal surgery, as a method of reducing pain and for improving cosmesis. Despite this proposed use there is insufficient data in the peer-reviewed published scientific literature supporting the effectiveness of iliac reconstruction with any type of graft material. Most of the published studies involve small sample populations with inconsistent clinical outcomes for reducing donor site morbidity. The use of bone graft substitutes for this indication is not recommended at this time due to lack of data supporting safety, efficacy and improved clinical outcomes.

Autologous bone marrow aspirate obtained from the iliac crest is also commonly used during orthopedic procedures as an adjunct to other graft materials to enhance bone healing. Freshly harvested bone marrow aspirate contains osteogenic precursor cells (mesenchymal stem cells, growth factors) and once aspirated may be injected directly into defects or mixed with other grafting materials. It has been suggested that stem cell concentration is directly related to overall effectiveness and as a result, in order to increase the concentration of osteoprogenitor cells various cell retention processing methods (e.g., centrifugation) are employed. Although the amount of aspirate required and proposed indications and techniques may vary, this process may also be referred to as bone marrow nucleated cell concentrate (BMAC) or autologous bone marrow mononuclear cells (BMMC). In theory, combining bone marrow aspirate with an osteoconductive and osteoinductive bone graft material may avoid associated disadvantages of iliac crest graft harvest and improve healing. Although using bone marrow aspirate is commonly performed and generally considered integral to the procedure, published evidence supporting efficacy is limited. Furthermore, evidence for the use of concentrated bone marrow aspirate to enhance healing is also lacking.

Allografts

An alternative to autograft is the use of allografts. Allograft offers the advantage of avoiding additional surgery and potential complications associated with harvesting host bone during the primary procedure. Allograft materials are frequently used during various orthopedic procedures, and may also 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); OrthoBlast (IsoTis Orthobiologics, Irvine, CA); TruFuse[®] (minSURG[™] Corp., Clearwater, FL); and NuFix[™] (Nutech Medical, Birmingham, AL) 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; substantially decreasing 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. Allograft DBM preparations available for use include Osteotech's Grafton[®], Regeneration Technology's Osteofil[®] and Medtronic's Magnifuse to name a few. These preparations differ in shape and size of DBM particles, the amount of residual minerals and the type of carrier materials.

Stand-alone Stabilization Devices: Several types of bone graft substitutes have been developed for use as stand-alone stabilization devices as well as adjuncts to enhance bone healing (e.g., TruFuse dowels, NuFix bone dowels, BacFast[®] HD [hyper-demineralization] facet stabilization dowel). Since some of these devices are regulated by the FDA as human cells, tissue and cellular and tissue based products, they are generally processed by licensed tissue banks. Due to differences in requirements for regulation for many of these bone graft substitutes, published clinical studies supporting safety and efficacy of these products as stand alone stabilization devices are not available. Additionally, clinical studies supporting safety and efficacy for some of the techniques in which the product is used (e.g., facet stabilizing dowels, TruFuse procedure) are not available. As

such, there is no data to support that these products either provide additional stabilization or promote secondary bone healing or fusion of the spine when used in conjunction with or as an alternative to standard spinal fusion (e.g., isolated facet fusion). Until published clinical trials are available supporting long-term clinical outcomes, safety, and efficacy, their use cannot be recommended.

Anorganic Bone Graft Materials

Anorganic bone graft materials are a type of xenograft bone graft substitute made from other than human material, such as cow (i.e., bovine) or coral, and is typically used in combination with other types of bone graft materials, for example with collagen or a calcified matrix. The animal bone is processed to remove any organic components (i.e., anorganic bone material) reducing concerns of disease transmission or immunogenic reactions. Some of the anorganic type xenograft materials (e.g., Bio-Oss) may be used as stand-alone graft material to enhance healing, such as when used for dental implants. When used according to U.S. Food and Drug Administration (FDA) approved indications, either alone or combined with other bone graft materials proven effective, anorganic bone graft materials are considered safe and effective for promoting bone formation.

Bone Graft Substitutes

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 to provide a medium for osteoconduction rather than osteoinduction and can provide variable levels of structural support. 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. Support matrix may include xenograft (i.e., bovine) or human type I collagen. Cell-based substitutes that are available include mesenchymal and other cell based products.

- 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).
- Trinity[®] Evolution[™] (Orthofix[®], Inc., Lewisville, TX) is a viable cell allograft that according to the manufacturer contains active adult mesenchymal stem cells. Trinity Evolution contains osteoprogenitor cells, mesenchymal stem cells, and demineralized cortical bone to promote osteoconduction, osteogenesis, and osteoinduction for successful bone grafting.
- Osteocel[®] Plus (NuVasive, Inc, San Diego, CA) is an allograft cellular matrix that contains viable stem cells. The manufacturer suggests this material promotes fusion in cervical, thoracic, and lumbar procedures. According to the manufacturer, Osteocel Plus mimics the biologic properties of autograft and contains mesenchymal cells, cancellous bone, and demineralized bone matrix. Osteocel Plus also provides a scaffold for new bone to grow on, theoretically avoiding limitations of other more traditional bone graft alternatives.
- Amniotic membrane, the innermost layer of the fetal membrane, is considered a source of collagen that acts as a scaffold for the attachment of cells. Recently, amniotic membrane allografts have been

investigated for various uses including use as bone void fillers during spinal and other orthopedic surgeries to enhance bone healing. Classifications of these products differ depending on the specific product but are generally classified as human tissue and/or cell-based products. Some are claimed to be non-immunogenic by the manufacturer. Amniotic membrane allografts currently under investigation include NuCel® (Nutech Medical, Birmingham, AL, USA), Ovation® cellular repair matrix (Osiris Therapeutics, Inc., Columbia, MD, USA) derived from placental mesenchyme to name a few.

The use of mesenchymal and other cell-based bone graft substitutes has been and continues to be investigated for various procedures, including spinal fusion and for intervertebral disc regeneration. Although currently under investigation, data published in the medical literature evaluating cell-based substitutes is in preliminary stages and mainly in the form of nonhuman trials or case reports; data supporting safety and efficacy for these indications are lacking.

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. Some ceramic-based products (e.g., calcium phosphate-collagen composites, beta-tricalcium phosphate) are combined with collagen to augment healing; collagen composites may include bovine material similar to that used with cell-based products. 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 but are not limited to:

- Osteograft® (Ceramed, Lakewood, CO)
- Norian SRS (Skeletal Repair System) (Synthes, Inc., West Chester, PA)
- Osteoset® (Wright Medical, Arlington, TN)
- Actifuse™ (ApaTech Limited, Elstree, Hertfordshire, UK)
- Integra MOZAIK™ Osteoconductive Scaffold (Integra LifeSciences, Plainsboro, NJ)
- PRO-DENSE® Bone Graft Substitute paste (Wright Medical Technology, Inc., Arlington, TN)

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 but are not limited to:

- 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. RhBMP is a unique subgroup of graft substitutes and many published trials support safety and efficacy. The effects of human growth factors such as fibroblast growth factor and insulin-like growth factors on fracture healing have been investigated primarily in animal trials. Factor-based bone graft substitutes include but are not limited to:

- human growth factors (e.g., fibroblast growth factor, insulin-like growth factor, transforming growth factor)
- recombinant bone morphogenetic proteins (rhBMP)

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.

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.

RhBMP–2 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, BMP 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.

The benefits of rhBMP 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 early 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.

Although early evidence supports safety and efficacy when used according to FDA indications, adverse events have been reported which include ectopic bone formation, bone resorption or remodeling at the graft site, hematoma, neck swelling, and painful seroma (Benglis, et al., 2008). Dural tears, bowel/bladder and sexual dysfunction, failure to fuse and paralysis have also been reported (Epstein, 2011), as well as carcinogenicity and teratogenic effects. Recently there has been concern more specifically safety and efficacy of rhBMP–2 used in spinal fusion surgeries. According to Carragee, et al. (2011), who in a systematic review compared conclusions regarding safety and efficacy published in the original rhBMP–2 industry-sponsored trials when used for spinal fusion, to data published following the FDA approval, the risk of adverse events associated with rhBMP–2 for spinal fusion was found to be “10 to 50 times the original estimates calculated from the industry-sponsored peer-reviewed publications.”

As a result of reported complications and the recent concern regarding safety and efficacy, use of RhBMP–2 product should be limited to the FDA-approved labeling indications. Evidence in the peer-reviewed scientific literature is insufficient and does not provide strong support to safety and efficacy of rhBMP–7 to enhance bone healing.

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.

Anterior Lumbar 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. According to the FDA approval, safety and effectiveness for approaches other than anterior have not been established. In December 2003 the approval was broadened 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 L2–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, many of which demonstrate safety and efficacy for the use of rhBMP-2 during spinal fusion (Burkus, et al., 2005; Glassman, et al., 2005; Baskin, et al., 2003; Burkus, et al., 2002; Kleeman, et al., 2002). In general, 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 has demonstrated similar results.

Posterior Spinal Fusion: RhBMP-2 has been used as part of posterior fusion techniques for treating both single and multi-level spinal deformity, either alone or combined with other osteoconductive scaffolds, and some authors have reported improved clinical outcomes (e.g., earlier and higher fusion rates) compared to iliac crest bone graft (Dawson, et al., 2009; Dimar, et al., 2009; Mulconrey, et al., 2008; Luhmann, et al., 2005). However, this represents an off-label use as it is not FDA-approved for posterolateral, posterior lumbar interbody fusion or multilevel fusion.

Cervical Spinal Fusion: 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 (=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. Further clinical trials are required to support safety and efficacy for treatment for cervical spine conditions.

Fracture Repair: RhBMP-2 has also been studied in patients with tibial fractures; 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

Published clinical studies evaluating the use of rhBMP–2 in patients with tibial fractures support safety and efficacy (Swiontkowski, et al., 2006; Jones, et al., 2006; Govender, yet al., 2002).

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 evaluating rhBMP–2 for oral maxillofacial surgery consists of few published clinical trials (Esposito, et al., 2007; Boyne, et al., 2005; Fiorellini, et al., 2005; Jung, et l., 2003). 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).

Posterolateral Lumbar 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."

Some of the outcomes reported for osteoinductive properties and fusion rates are comparable to those of autograft, and the use of rhBMP-7 does avoid the need for autogenous bone graft harvest. Overall, a paucity of studies have assessed rhBMP-7 in spine fusion surgery (Delawi, et al., 2010; Vaccaro, et al., 2008; Kanayama, et al., 2006; Vaccaro, et al., 2004; Vaccaro, et al., 2003; Johnsson, et al., 2002). Limitations to these available studies such as use of combined materials, small sample size and short-term follow-up does not lead to formation of evidence-based conclusions regarding safety, efficacy and improved clinical outcomes. Additionally these trials evaluated primary fusion surgery and not revision surgery as mentioned in the HDE approval, and are therefore not in agreement with FDA limitations. Studies evaluating safety and efficacy of on-label use in the peer-reviewed published scientific literature are lacking. Other variables precluding generalizations include inconsistency with regard to instrumentation; some procedures were instrumented while others were not. Additional studies are needed to assess clinical outcomes.

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

Similar to posterolateral lumbar fusion surgery, studies evaluating the use of rhBMP-7 for nonunion of long bones are limited by small sample size and short term follow-up. Although there is some evidence of successful clinical outcomes resulting from the use of rhBMP-7 for the treatment of nonunion in the published scientific literature (Ronga, et al., 2006; Maniscalco, et al., 2002; Friedlaender, et al., 2001; Geesink, et al., 1999) evidence is insufficient to draw strong conclusions regarding safety and efficacy.

Platelet Rich Plasma (PRP) for Bone Healing

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 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 patient's 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) and there is a growing body of evidence evaluating the safety and efficacy of PRP as a treatment for knee osteoarthritis and other degenerative conditions (Kon, et al., 2010; Filardo, et al., 2010; Vidriero, et al., 2010; Sanchez, et al., 2009). However, the outcomes of these reports are variable and the utility of PRP for use in bone repair is debatable. 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 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. In 2009 Miyazaki et al. published a systematic review regarding bone graft substitutes for spinal fusion and reported that the evidence for autologous platelet concentrates is weak and the clarity of risk/benefit is unclear. In addition, a formal position statement supporting platelet rich plasma for enhancement of bone healing from the American Academy of Orthopaedics (AAOS) could not be found. The AAOS does provide general information regarding PRP and suggests that further studies are needed to define the role of PRP and to determine for which settings PRP may be valuable. Currently, whether or not platelet rich plasma facilitates osteoinduction and improves clinical outcomes remains unproven in the published scientific literature. (Please refer to CIGNA Coverage Policy: Tissue Engineered Skin Substitutes and Platelet-Derived 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. 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 and do not require clinical trials or FDA approval for marketing, such as some of the DBM products and cell-based materials.

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.

Technology Assessments

Technology assessments evaluating the safety and efficacy of bone graft substitutes in general were not found in the medical literature. Although the American Academy of Orthopaedic Surgeons does not have a formal position statement, the Orthopaedic Device Forum initially published a document addressing the use of bone graft substitutes in 2001 (Greenwald, et al., 2001). The forum noted at that time, and again in 2006 and 2008, that the currently marketed products vary in their composition and their claimed mechanisms of action—not all substitutes perform the same. Selection should be based on reasoned burdens of proof which include the examination of the product claims and whether or not they are supported by preclinical and human studies in site specific locations, where they are to be utilized in surgery. The AAOS noted it is imperative to appreciate the level of evidence claimed in the latter studies.

In 2010 the Agency for Healthcare Research and Quality (AHRQ) published a technology assessment evaluating on and off-label use of bone morphogenetic protein (AHRQ, 2010). A total of 41 articles, which included RCTs, nonrandomized comparative studies, and other observational studies, met inclusion criteria and were reviewed as part of the assessment. For on-label use, the evidence gave moderate support to clinical benefit from the use of rhBMP–2 for fusion of the lumbar-sacral spine, rhBMP–2 improved outcomes when used for the treatment of acute open tibial fractures, rhBMP–2 did not provide an advantage in prosthesis implantation and functional loading when used for sinus augmentation. The evidence was insufficient to evaluate the use of rhBMP–7 for fusion of the spine. There was low strength evidence to support rhBMP–7 improved outcomes for recalcitrant long bone nonunion. Regarding off-label use, the strength of evidence that rhBMP–2 improved radiographic fusion success was moderate, however no conclusion could be drawn regarding the potential impact of off-label components on fusion success. The evidence was insufficient to draw conclusions regarding off-label use of rhBMP–7 in fusion of the lumbar spine. There was moderate support that off-label use of rhBMP–2 in anterior cervical spinal fusion increased cervical swelling and related complications. There was insufficient evidence to draw conclusions about radiographic fusion success or associated changes in neck disability scores.

Although there are no recent updates, several other technology assessments specifically evaluating rhBMP are available in the medical literature. 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 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, human growth factors, 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. Additionally, although using bone marrow aspirate is generally considered integral to various orthopedic procedures, published evidence supporting efficacy is limited; and evidence for the use of concentrated bone marrow aspirate to enhance healing is lacking. 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 rhBMP–2, 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 anterior lumbar fusion surgery and in the repair of tibial fractures when conducted according to the indications documented by the FDA. There is insufficient evidence to support the use of rhBMP–7 as a paste for long bone fracture repair and as putty in spinal fusion revision. Additionally, 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: 1) This list of codes may not be all-inclusive.

2) Deleted codes and codes which are not effective at the time the service is rendered may not be eligible for reimbursement.

Most bone graft substitutes used to enhance bone healing do not have a specific CPT or HCPCS code to represent the material. However, there are specific CPT codes to differentiate by type of graft. For all other procedures, coverage will be considered based on the clinical indication and type of material for the procedure requested.

Autograft, Allograft (non rhBMP)/Synthetic (Ceramic/Polymer)

Covered when medically necessary:

CPT [®] * Codes	Description
20900	Bone graft, any donor area; minor or small (eg, dowel or button)

20902	Bone graft, any donor area; major or large
20930	Allograft, morselized, or placement of osteopromotive material, for spine surgery only (List separately in addition to code for primary procedure)
20931	Allograft, structural, for spine surgery only (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)
20999	Unlisted procedure, musculoskeletal system, general
27899	Unlisted procedure, leg or ankle

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
C9362	Porous purified collagen matrix bone void filler (Integra Mozaik Osteoconductive Scaffold Strip), per 0.5 cc
L8699	Prosthetic implant, not otherwise specified

Factor-based (rhBMP-2)

Covered when medically necessary when used to report rhBMP–2 utilized in combination with a fusion device for single-level anterior interbody lumbar fusion surgery or for surgical repair of acute, open tibial fracture:

CPT®* Codes	Description
20930	Allograft, morselized, or placement of osteopromotive material, for spine surgery only (List separately in addition to code for primary procedure)
20999	Unlisted procedure, musculoskeletal system, general
27899	Unlisted procedure, leg or ankle

HCPCS Codes	Description
L8699	Prosthetic implant, not otherwise specified

Not Covered

Experimental/Investigational/Unproven/Not Covered when used to report rhBMP–2 for any other indication:

CPT®* Codes	Description
20930	Allograft, morselized, or placement of osteopromotive material, for spine surgery only (List separately in addition to code for primary procedure)
21208	Osteoplasty, facial bones; augmentation (autograft, allograft, or prosthetic implant)
21210	Graft, bone; nasal, maxillary or malar areas (includes obtaining graft)
21499	Unlisted musculoskeletal procedure, head
31299	Unlisted procedure, accessory sinuses

HCPCS Codes	Description
D4264	Bone replacement graft—each additional site in quadrant)
D4265	Biologic materials to aid in soft and osseous tissue regeneration
D7950	Osseous, osteoperiosteal, or cartilage graft of the mandible or maxilla—autogenous or nonautogenous, by report
D7951	Sinus augmentation with bone or bone substitutes
D7953	Bone replacement graft for ridge preservation, per site
L8699	Prosthetic implant, not otherwise specified

Experimental/Investigational/Unproven/Not Covered when used to report recombinant human bone morphogenetic protein (rhBMP-7), human amniotic membrane bone graft substitute, cell-based/mesenchymal stem cell used as bone graft substitute, or synthetic or allograft substitute following autograft harvest for iliac crest reconstruction (i.e., back fill grafting of an iliac crest donor site):

CPT* Codes	Description
20930	Allograft, morselized, or placement of osteopromotive material, for spine surgery only (List separately in addition to code for primary procedure)
27299	Unlisted procedure, pelvis or hip joint
20999	Unlisted procedure, musculoskeletal system, general

HCPCS Codes	Description
L8699	Prosthetic implant, not otherwise specified

Experimental/Investigational/Unproven/Not Covered for allograft bone graft substitutes used exclusively as stand-alone stabilization devices for fusion (e.g., TruFuse® for isolated facet fusion, NuFix™ for isolated facet fusion, BacFast® HD for isolated facet fusion):

CPT* Codes	Description
0219T	Placement of a posterior intrafacet implant(s), unilateral or bilateral, including imaging and placement of bone graft(s) or synthetic device(s), single level; cervical
0220T	Placement of posterior intrafacet implant(s), unilateral or bilateral, including imaging and placement of bone graft(s) or synthetic device(s), single level; thoracic
0221T	Placement of posterior intrafacet implant(s), unilateral or bilateral, including imaging and placement of bone graft(s) or synthetic device(s), single level; lumbar
0222T	Placement of a posterior intrafacet implant(s), unilateral or bilateral, including imaging and placement of bone graft(s) or synthetic device(s), single level; each additional vertebral segment (List separately in addition to code for primary procedure)

HCPCS Codes	Description
L8699	Prosthetic implant, not otherwise specified

Experimental/Investigational/Unproven/Not Covered when used to report platelet rich plasma for bone healing:

CPT* Codes	Description
0232T	Injection(s), platelet rich plasma, any site, including image guidance, harvesting and preparation when performed

HCCPS Codes	Description
P9020	Platelet rich plasma, each unit
S9055	Procuren or other growth factor preparation to promote wound healing

***Current Procedural Terminology (CPT®) ©2013 American Medical Association: Chicago, IL.**

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