



Bone graft substitutes

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Policy contains: Bone graft substitutes; recombinant human bone morphogenetic protein-2.

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Coverage policy

The following bone graft substitutes are clinically proven and, therefore, may be medically necessary for enhancement of bone healing (Fischer, 2013; Laurencin, 2006; McNamara, 2015; Papageorgiou, 2016):

- Autograft based materials, used alone.
- Allograft-based, allograft bone used alone or in combination with other materials, including demineralized bone matrix.
- Ceramic or polymer-based synthetic bone graft substitutes, used alone or in combination with other materials.
- Bone graft substitutes containing an organic bone material (e.g., bovine or coral) when used alone or combined with another medically necessary bone graft substitute.

Recombinant human bone morphogenetic protein-2 is clinically proven and, therefore, may be medically necessary when used in accordance U.S. Food and Drug Administration-approved indications and labeling instructions:

- INFUSE® Bone Graft (Medtronic Inc., Minneapolis, Minnesota) for:

- Primary treatment for skeletally mature members with acute, open tibial shaft fractures stabilized with intramedullary nail fixation after appropriate wound management, if applied within 14 days after the initial fracture (U.S. Food and Drug Administration, 2004).
- Dental localized alveolar ridge augmentation for defects associated with extraction sockets and sinus augmentation (U.S. Food and Drug Administration, 2007).
- INFUSE® Bone Graft LT-CAGE (Medtronic, Inc., Minneapolis, Minnesota) when used only with the INFUSE Bone Graft for single-level lumbar spinal fusion and all of the following criteria (U.S. Food and Drug Administration, 2002):
 - When autologous iliac crest bone graft is not feasible.
 - Skeletally mature members (older than 18 years of age or no radiographic evidence of epiphyseal closure) with degenerative disc disease from L4 to S1; grade I spondylolisthesis at the involved level may be present.
 - At least six months of non-operative treatment.
 - Using an anterior open or laparoscopic approach.

Limitations

All other uses of bone graft substitutes are investigational/not clinically proven and, therefore, not medically necessary.

Mesenchymal stem cell therapy is investigational/not clinically proven and, therefore, not medically necessary for all orthopedic applications, including, but not limited to, use in repair or regeneration of musculoskeletal tissue (Killington, 2018).

Allograft bone products containing viable stem cells are investigational/not clinically proven and, therefore, not medically necessary for all orthopedic applications, including, but not limited to, demineralized bone matrix with stem cells.

All other uses of recombinant human bone morphogenetic protein-2 are not medically necessary.

Contraindications to the INFUSE Bone Graft include, but are not limited to:

- Known hypersensitivity to the components of the formulation or the titanium cage.
- Near a resected or extant tumor, any active malignancy, or a malignancy undergoing treatment.
- Active infection at the operative site.
- Inadequate neurovascular status.
- Compartment syndrome of the affected limb.
- Pregnancy.

Alternative covered services

No alternative covered services were identified during the writing of this policy.

Background

Bone grafting is a surgical procedure that replaces missing bone with material from the patient's own body (autograft), or with an artificial, synthetic, or natural substitute. Bone grafting exploits the bone tissue's ability to regenerate completely if provided the space into which to grow. As natural bone grows, it generally replaces the graft material completely, resulting in a fully integrated region of new bone.

Autologous cancellous bone graft remains the gold standard, because it provides the three elements required for bone regeneration: osteoconduction, osteoinduction, and osteogenic cells (Grabowski, 2013). Harvesting

autologous bone has caused complications and morbidity, which led to the search for reliable and safe bone graft substitutes (Giannoudis, 2005).

Bone graft substitutes include cancellous and cortical allograft bone, ceramics, demineralized bone matrix, bone marrow, and composite grafts. Currently, no single alternative graft material provides all three elements for bone regeneration. Synthetic bone substitutes or xenografts can be used as an alternative to autologous graft to overcome problems of additional surgeries or limited graft availability, but synthetic grafts, often made of hydroxyapatite or other naturally occurring and biocompatible substances, lack osteoinductive or osteogenic properties. Composite grafts combine scaffolding properties with biological elements, such as demineralized bone matrix or bone derivatives, to stimulate cell proliferation and differentiation and, eventually, osteogenesis. Xenografts, such as a bovine species, are used as a calcified matrix (Grabowski, 2013).

Classification of bone grafts is based on material, grouped as follows (Laurencin, 2006):

- Autograft-based — used alone. Properties of action are osteoconductive, osteoinductive, and osteogenic.
- Allograft-based — allograft bone used alone or in combination with other materials. Properties of action are osteoconductive and osteoinductive.
- Natural and recombinant growth factor-based — used alone or in combination with other materials. Properties of action are osteoinductive and both osteoconductive and osteoinductive with carrier materials.
- Cell-based — used to generate new tissue alone or seeded onto a support matrix. Properties of action are osteogenic and both osteogenic and osteoconductive with carrier materials.
- Ceramic-based — calcium phosphate, calcium sulfate, and bioactive glass used alone or in combination. Properties of action are osteoconductive and limited osteoinductive when mixed with bone marrow.
- Polymer-based — degradable and nondegradable polymers used alone and in combination with other materials. Properties of action are osteoconductive and bioresorbable in degradable polymer.
- Miscellaneous — materials such as coral hydrogel-hydroxyapatite granules, blocks, and composite.

Findings

Clinical guidelines

For spinal fusion, the North American Spine Society (2014) evaluated four randomized controlled trials (n = 577) and found insufficient evidence to recommend either autologous bone grafts or substitutes for posterolateral fusion in degenerative lumbar spondylolisthesis. The largest trial (n = 335) reported no significant differences in clinical outcomes between recombinant human bone morphogenetic protein-7 putty and iliac crest harvest, though the putty led to less bridging bone formation, it reduced operative time and blood loss. Smaller trials showed comparable fusion rates, function, and safety for calcium sulfate with local bone or coral hydroxyapatite versus iliac crest harvest, with one suggesting marginally better fusion with harvest. These findings suggest that bone graft substitutes may reduce complications associated with pelvic bone harvest while achieving similar effectiveness in this context.

Regulatory status varies by product type. Some bone graft substitutes are cleared through the U.S. Food and Drug Administration 510(k) pathway as Class II devices, such as resorbable calcium salt bone void fillers and synthetic dental bone grafting materials, while recombinant human bone morphogenetic protein-2 products are regulated through premarket approval pathways. A 510(k) clearance indicates substantial equivalence to a legally marketed predicate device and should not be interpreted as evidence of clinical superiority over other graft materials.

As of April 2026, FDA premarket approval records for INFUSE™ Bone Graft identify two clinically relevant labeling expansions during the preceding five years. In 2023, FDA approved expanded use of INFUSE® Bone Graft with additional Medtronic interbody fusion devices, including specified Anteralign LS and TL devices. In 2026, FDA approved INFUSE™ Bone Graft for transforaminal lumbar interbody fusion at one or two adjacent levels from L2 to S1 for symptomatic degenerative disc disease confirmed by history and radiographic studies, after at least six months of nonoperative treatment, when used with an FDA-cleared intervertebral body fusion device and metallic screw-and-rod system.

In pediatric congenital pseudarthrosis of the tibia, the consensus panel (Song, 2025) recommends operative management for individuals over 2 years old, involving complete excision of the pseudarthrosis site, sufficient autogenous bone grafting, and fixation using combined external and intramedullary methods (e.g., Ilizarov with intramedullary rods). Based on a systematic review of 74 studies (n = 1513 participants, 1525 tibias), this approach achieved a primary union rate of 84% and a final union rate of 93.3%, with a refracture rate of 22.3%. Vascularized fibular grafts and cross-union techniques were identified as viable alternatives to corticocancellous autografts, though no consensus was reached on adjuvants like recombinant human bone morphogenetic proteins due to inconclusive benefits. These recommendations underscore autogenous grafts as the standard while supporting substitutes in complex cases where traditional grafting may be challenging.

For foot and ankle conditions, the American Orthopaedic Foot & Ankle Society (2022) endorses osteochondral autograft and allograft transplantation as non-experimental options for treating osteochondral lesions of the talus, particularly in cases with large defects, cysts, or prior surgical failures. This guideline supports the use of both autogenous and allogeneic grafts to restore cartilage and bone integrity, highlighting their established role in addressing significant talar defects. Similarly, the American Academy of Orthopaedic Surgeons (2023) guideline on Osteochondritis Dissecans recommends surgical options, including grafting, for symptomatic individuals with unstable or displaced lesions, regardless of skeletal maturity. Based on limited evidence, this guideline supports grafting to stabilize lesions and promote healing, though specific graft types are not prioritized, indicating flexibility in choosing autografts or allografts based on clinical context.

In knee reconstruction, the American Academy of Orthopaedic Surgeons (2022) provides robust guidance for Anterior Cruciate Ligament reconstruction, issuing a strong recommendation based on high-quality evidence to prefer autografts over allografts in young or active individuals due to lower graft failure rates and potentially better outcomes (Brophy, 2023). For skeletally mature patients, a moderate recommendation suggests selecting between bone-patellar tendon-bone or hamstring autografts by balancing lower risks of graft failure and infection with bone-patellar tendon-bone against reduced anterior or kneeling pain with hamstring grafts. The guideline also strongly advocates reconstruction over repair for Anterior Cruciate Ligament tears requiring surgery, citing lower revision risks. These recommendations emphasize the superiority of autografts in Anterior Cruciate Ligament reconstruction while acknowledging allografts as viable in less active or older patients, guiding graft selection to optimize functional outcomes.

The use of orthobiologics, particularly cell-based therapies, is approached with significant caution. A consensus conference convened by the American Academy of Orthopaedic Surgeons and National Institutes of Health (Chu, 2019) raised concerns about the widespread use of unproven biologic treatments, particularly minimally manipulated cell products marketed as "stem cells." These products do not meet scientific criteria for stem cells and should be termed "cell therapy," with clear patient communication about their unproven status. The consensus recommends adopting minimum standards for characterizing biologics (e.g., checklists), establishing high-quality patient registries, and conducting rigorous clinical trials to evaluate safety and efficacy before broad adoption. Consequently, mesenchymal stem cell therapies and allograft products containing

viable stem cells are considered investigational for most orthopedic applications, highlighting the need for robust evidence to support their use over established grafting techniques.

Regulatory oversight ensures the safety of allograft substitutes. To address risks of antigenicity and disease transmission, the U.S. Food and Drug Administration mandates that manufacturers of human allograft products, including bone, adhere to strict registration and processing standards (Campana, 2014). This framework supports the safe integration of allografts as alternatives to autografts in various orthopedic applications, reinforcing their role in clinical practice while ensuring patient safety.

Systematic reviews

Systematic reviews synthesize evidence on the safety and efficacy of bone graft substitutes across spinal, foot and ankle, dental, maxillofacial, and other orthopedic applications, providing insights into their clinical utility and limitations. In spinal fusion, Fitzgerald (2025) reviewed 21 studies ($n = 3,321$ participants), including three randomized controlled trials, one cohort study, and four case series on Infuse™ (recombinant human bone morphogenetic protein-2) and 10 studies on other grafts for lumbar interbody fusion in degenerative disc disease. The review found comparable fusion rates between Infuse™ (90.9–100%) and iliac crest bone graft (66.7–95.8%, $P=0.102$ – 0.903 , $n = 266$ across two randomized controlled trials), with Infuse™ reducing operative time (1.4–1.9 hours vs. 2.0–3.3 hours, $P<0.001$ – 0.006 , $n = 282$) and blood loss (95–109.8 ml vs. 153.1–167 ml, $P=0.017$ – 0.400 , $n = 282$), though high risk of bias and limited comparative data for non-Infuse™ grafts were noted.

Ambrosio (2025) conducted a systematic review and network meta-analysis of 43 randomized controlled trials ($n = 3,823$) comparing osteobiologics with autologous iliac crest bone graft in lumbar spinal fusion. Recombinant human bone morphogenetic protein-2 was associated with significantly higher fusion rates (odds ratio 3.71; 95% confidence interval 2.59 to 5.32; $P < .0001$), lower complication rates (odds ratio 0.30; 95% confidence interval 0.13 to 0.68; $P < .0001$), shorter operative time, and lower blood loss. Evidence certainty was moderate for recombinant human bone morphogenetic protein-2 but low to very low for most other osteobiologics, limiting conclusions for non-recombinant human bone morphogenetic protein-2 products.

Biddau (2024) evaluated 27 studies ($n = 66,027$ participants) on anterior lumbar interbody fusion, with 18 studies focusing on recombinant human bone morphogenetic protein-2, reporting high fusion rates (88.5–100%) but increased complications like retrograde ejaculation (6.3% vs. 1.2%, $P=0.001$) and pseudoarthrosis (odds ratio 1.44, 95% confidence interval: 1.16–1.76). Allografts (84.2–96%), synthetics (77.78–100%), and peptide-based grafts (93.6%) showed promise but lacked robust data. Mariscal (2020) affirmed the efficacy of synthetic ceramics and morphogenetic proteins in spinal fusion, though specific quantitative data were not reported. Cicciu (2018) and Killington (2018) confirmed the safety and effectiveness of recombinant human bone morphogenetic protein-2 in spinal applications, aligning with current policies, without detailing participant numbers.

In foot and ankle surgery, Hoveidaei (2024) conducted a systematic review and meta-analysis of eight studies ($n = 894$ patients, $n = 497$ synthetic grafts, $n = 397$ autologous grafts), finding no significant differences in Computed Tomography fusion rates (odds ratio 0.95, 95% confidence interval: 0.69–1.31, $I^2 = 0\%$), American Orthopaedic Foot & Ankle Society functional scores (standardized mean difference 0.03, 95% confidence interval: -0.13–0.18, $I^2 = 27\%$), or surgical complications (odds ratio 1.03, 95% confidence interval: 0.59–1.78, $I^2 = 60\%$) between synthetic and autologous grafts. Hartman (2025) reviewed 13 non-randomized studies ($n = 363$ patients, $n = 397$ procedures) on demineralized bone matrix, reporting osseous union rates of 85.6% ($n =$

238/278) in fusion cohorts and 100% in fifth metatarsal and calcaneal fracture cohorts, with complication rates of 27.2% (n = 99) and failure rates of 10.8% (n = 43). Non-union rates were comparable between demineralized bone matrix (12.9%, n = 4/31) and non-demineralized bone matrix cohorts (14.8%, P = 0.83), though low evidence quality and study heterogeneity were limitations.

In dental and maxillofacial applications, Al-Moraissi (2020), Avila-Ortiz (2019), Dragonas (2019), Liu (2019), and Stumbras (2019) supported the effectiveness of xenografts and recombinant protein-enhanced grafts for maxillary sinus and alveolar ridge augmentation, though participant numbers were not specified. Deandra (2024) reviewed seven studies (n = 83 participants) on regenerative periodontal surgery, finding comparable clinical attachment level outcomes between early (4 weeks) and later (6 months) orthodontic treatment initiation, with autografts, allografts, xenografts (e.g., deproteinized bovine bone mineral), and alloplasts (e.g., β -tricalcium phosphate) all demonstrating success. Mohanasatheesh (2024) examined biphasic calcium phosphate for dental extraction socket preservation in two randomized controlled trials (n = 74 participants, n = 26 from Mardas, n = 48 from Uzeda), reporting significantly increased bone density ($p < 0.05$) with a 60% hydroxyapatite and 40% β -tricalcium phosphate ratio after 6 months, though limited trial numbers prevented meta-analysis.

Thomas (2026) systematically reviewed 18 clinical studies comparing alloplastic and biologic grafts for maxillary sinus augmentation. Autografts demonstrated the highest effectiveness, followed by xenografts and allografts. Alloplastic grafts had lower new bone formation and regenerative potential than biologic grafts but showed acceptable safety, high implant survival, and potential utility when avoiding donor-site morbidity, immunologic risk, or infection-related concerns is clinically important.

Saghiri (2025) performed a systematic review and meta-analysis comparing bioactive glass with autogenic bone grafts in maxillofacial reconstruction. Bioactive glass showed greater total bone volume retention at six months, lower graft resorption, and higher residual biomaterial retention, while new bone formation was comparable to autogenic grafts. The authors concluded that bioactive glass may be a viable alternative when autograft harvesting is impractical or associated with high donor-site morbidity, though small sample sizes, heterogeneous indications, and limited long-term outcomes warrant cautious interpretation.

Across general orthopedic applications, Fischer (2013), McNamara (2015), and Papageorgiou (2016) supported bone graft substitutes in alveolar ridge augmentation, sinus lift procedures, and long-bone defect repair, without reporting specific participant counts. Vaishya (2019) endorsed substitutes for bony defects caused by giant cell tumors, also without quantitative details. Limitations across reviews include high risk of bias, inconsistent fusion definitions, reliance on retrospective or industry-funded studies, and small sample sizes, underscoring the need for standardized reporting and well-designed trials to strengthen evidence for bone graft substitutes.

Meta-analyses

Meta-analyses provide quantitative evidence on the efficacy and safety of bone graft substitutes across spinal, maxillofacial, and orthopedic applications. Cottrill (2020) analyzed three randomized controlled trials and seven case series (n = 694 patients) on silicate-substituted calcium phosphate grafts in spinal fusion, reporting a 93% arthrodesis rate and significant improvements in back pain (visual analog score -3.3 points), leg pain (visual analog score -4.8 points), and Oswestry Disability Index (-31.6 points) by six to 36 months ($P < .001$ for each). Fusion rates were comparable to recombinant human bone morphogenetic protein-2 (odds ratio 1.11, $P = .83$). Ambrosio (2026) updated the network meta-analysis for posterior lumbar spinal fusion, including 35 randomized controlled trials (n = 2,298). Recombinant human bone morphogenetic protein-2 showed

significantly higher fusion rates than autologous iliac crest bone graft (odds ratio 3.86; 95% confidence interval 2.60 to 5.74; $P < .0001$) and lower osteobiologic-related complication risk (odds ratio 0.50; 95% confidence interval 0.34 to 0.73; $P = .0004$). Pain and disability outcomes were comparable across treatments. Other osteobiologics showed favorable trends but did not demonstrate consistent superiority, reinforcing recombinant human bone morphogenetic protein-2 as the best-supported biologic in posterior lumbar fusion while leaving uncertainty for other agents.

Lee (2024) evaluated five studies ($n = 598$ patients) on recombinant human bone morphogenetic protein-2 in posterior cervical fusion, finding a significantly lower risk of pseudarthrosis (odds ratio 0.44; 95% confidence interval, 0.21–0.92; $P = 0.03$) compared to autografts or allografts, with no significant increase in neurologic (odds ratio 1.86; $P = 0.08$) or immediate medical complications (odds ratio 0.77; $P = 0.28$). However, high-dose recombinant human bone morphogenetic protein-2 (>2.1 mg/level) increased wound infection risk ($P = 0.03$). Wu (2021) reported superior spinal fusion outcomes with recombinant human bone morphogenetic protein-2 compared to iliac crest autografts. Liu (2020) and Xiao (2020) confirmed equivalent outcomes for recombinant human bone morphogenetic protein-2 versus autologous grafts in lumbar fusion and cleft lip/palate reconstruction.

Alawami (2025) analyzed eight studies ($n = 154$ patients) on recombinant human bone morphogenetic protein-2 for alveolar cleft reconstruction in children, finding no significant difference in bone filling (mean difference - 1.24; 95% confidence interval, -4.14 to 1.67) between recombinant human bone morphogenetic protein-2 ($61.11\% \pm 24.6\%$) and iliac crest grafts ($59.12\% \pm 18.59\%$), though iliac crest grafts achieved higher bone height ($78.65\% \pm 14.38\%$ vs. $67.5\% \pm 5.45\%$). Trimmel (2021) found bovine xenograft with bone marrow concentrate (81%) outperformed autologous grafts (57%) in maxillary sinus augmentation. Amini (2021) supported decellularized xenograft scaffolds as effective alternatives. Mendes (2023) analyzed 22 studies ($n = 477$ patients), finding that growth factors like platelet-rich plasma increased new bone formation by 49% ($P = .004$) in maxillary sinus augmentation, with recombinant human bone morphogenetic protein-2 increasing connective tissue formation 1.85-fold ($P = .03$). Xie (2023) reviewed 14 studies ($n = 1,782$) on long bone non-union, finding recombinant human bone morphogenetic protein-2 had higher healing rates and shorter healing times than autologous grafts in moderate-quality studies. Xie (2022), reviewing five studies ($n = 394$), found no benefit in combining recombinant proteins with autologous grafts.

Other evidence

Other evidence, including narrative reviews and cohort studies, highlights emerging bone graft substitute options. Laurencin (2006) described the ideal substitute as biocompatible, bioresorbable, osteoconductive, osteoinductive, and structurally similar to bone, noting future biosynthetic implants may reduce reliance on autologous grafts. Zhang (2017) reviewed nacre (mother-of-pearl) as a biocompatible, osteoinductive, and biodegradable substitute with potential clinical applications. Fu (2013), Kelly (2016), Lin (2016), and Simmonds (2013) supported the use of INFUSE (recombinant human bone morphogenetic protein-2) for approved indications like tibial fractures and spinal fusion when autologous grafting is not feasible, despite reported adverse events (Krishnakumar, 2017; Poorman, 2017; Zadegan, 2017). Campana (2014) noted concerns with allografts, including antigenicity and disease transmission risks, emphasizing strict regulatory oversight by the U.S. Food and Drug Administration.

In 2026, we updated the findings section with new systematic reviews and network meta-analyses on lumbar spinal fusion, posterior lumbar fusion, maxillary sinus augmentation, and bioactive glass in maxillofacial reconstruction (Ambrosio, 2025; Ambrosio, 2026; Saghiri, 2025; Thomas, 2026). We also updated the background and coverage rationale to reflect recent U.S. Food and Drug Administration activity for INFUSE Bone

Graft and selected 510(k)-cleared bone graft substitute products (U.S. Food and Drug Administration, 2023; U.S. Food and Drug Administration, 2026).

References

On April 19, 2026, we searched PubMed and the databases of the Cochrane Library, the U.K. National Health Services Centre for Reviews and Dissemination, the Agency for Healthcare Research and Quality, and the Centers for Medicare & Medicaid Services. Search terms were “Bone Transplantation” (MeSH), “Bone Substitutes,” (MeSH), “allograft,” “autograft,” “bone reconstruction,” “bone repair,” “calcium sulphate,” “ceramic,” “hydroxyapatite,” “implant,” and “polymer.” We included the best available evidence according to established evidence hierarchies (typically systematic reviews, meta-analyses, and full economic analyses, where available) and professional guidelines based on such evidence and clinical expertise.

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Policy updates

5/2016: Initial review date and clinical policy effective date: 7/2016

7/2017: Policy references updated.

7/2018: Policy references updated. Coverage expanded to include recombinant human bone morphogenetic protein -2 (INFUSE) products.

5/2019: Policy references updated.

5/2020: Policy references updated.

5/2021: Policy references updated.

5/2022: Policy references updated.

5/2023: Policy references updated.

5/2024: Policy references updated.

5/2025: Policy references updated.

5/2026: Policy references updated.

Related codes

Below are the most commonly submitted codes for the service(s)/item(s) subject to this policy CCP.1232 This is not an exhaustive list of codes. Providers are expected to consult the appropriate coding manuals and bill accordingly.

Code	Code description
20900	CPT - Bone graft harvest/procedure, minor or small.
20902	CPT - Bone graft harvest/procedure, major or large.
20930	CPT - Spine add-on for morselized allograft or osteopromotive material.
20931	CPT - Spine add-on for structural allograft.

Code	Code description
20936-20939	CPT - Spine autograft and bone marrow aspirate add-on code family.
20999	CPT - Unlisted musculoskeletal procedure.
21208	CPT - Facial bone augmentation with graft or implant material.
21210	CPT - Bone graft to nasal, maxillary, or malar area.
21499	CPT - Unlisted musculoskeletal procedure, head.
22558	CPT - Anterior lumbar interbody arthrodesis context.
22585	CPT - Additional interspace for anterior interbody arthrodesis.
22630-22634	CPT - Posterior lumbar interbody or posterolateral arthrodesis code family.
22853	CPT - Interbody biomechanical device insertion add-on.
27759	CPT - Tibial shaft fracture treatment with intramedullary implant.
27899	CPT - Unlisted leg or ankle procedure.
31299	CPT - Unlisted accessory sinus procedure.
C1602	HCPCS - Antimicrobial-eluting absorbable bone void filler.
C1734	HCPCS - Orthopedic/device/drug matrix for bone-to-bone or soft tissue-to-bone use.
C1762	HCPCS - Human connective tissue, including fascia lata.
C1889	HCPCS - Implantable or insertable device, not otherwise classified.
C9359	HCPCS - Porous purified collagen matrix bone void filler, putty, per 0.5 cc.
C9362	HCPCS - Porous purified collagen matrix bone void filler, strip, per 0.5 cc.
L8699	HCPCS - Prosthetic implant, not otherwise specified.