

CLINICAL AND ECONOMIC
VALUE DOSSIER

AUGMENT[®]

Bone Graft

THE **FIRST** AND **ONLY**
PROVEN ALTERNATIVE TO
AUTOGRAFT IN ANKLE AND
HINDFOOT ARTHRODESIS

 **WRIGHT**
FOCUSED EXCELLENCE



The Time Has Come to Augment Your Fusion.

AUGMENT® Bone Graft is the first and only **proven** alternative to autograft in ankle and hindfoot arthrodesis.

Proven

Level 1 evidence of safety and effectiveness as a replacement to autograft in the largest F&A clinical trial ever conducted

Labeled

Approved by the US FDA, Health Canada, Australia TGA, New Zealand Ministry of Health, Saudi Food and Drug Authority, and Mexico COFEPRIS as a safe and effective alternative to autograft in ankle and hindfoot fusion procedures

Unique

The only biologic product specifically engineered, proven, and approved for ankle and hindfoot fusions

Safe

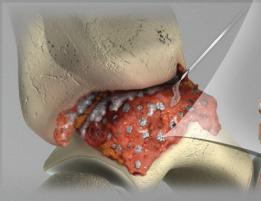
Proven safe through multiple clinical trials and successful commercial use since 2009 in Canada and 2011 in Australia and New Zealand, while eliminating the proven risks, morbidities, and costs associated with autograft harvest

Fast Facts

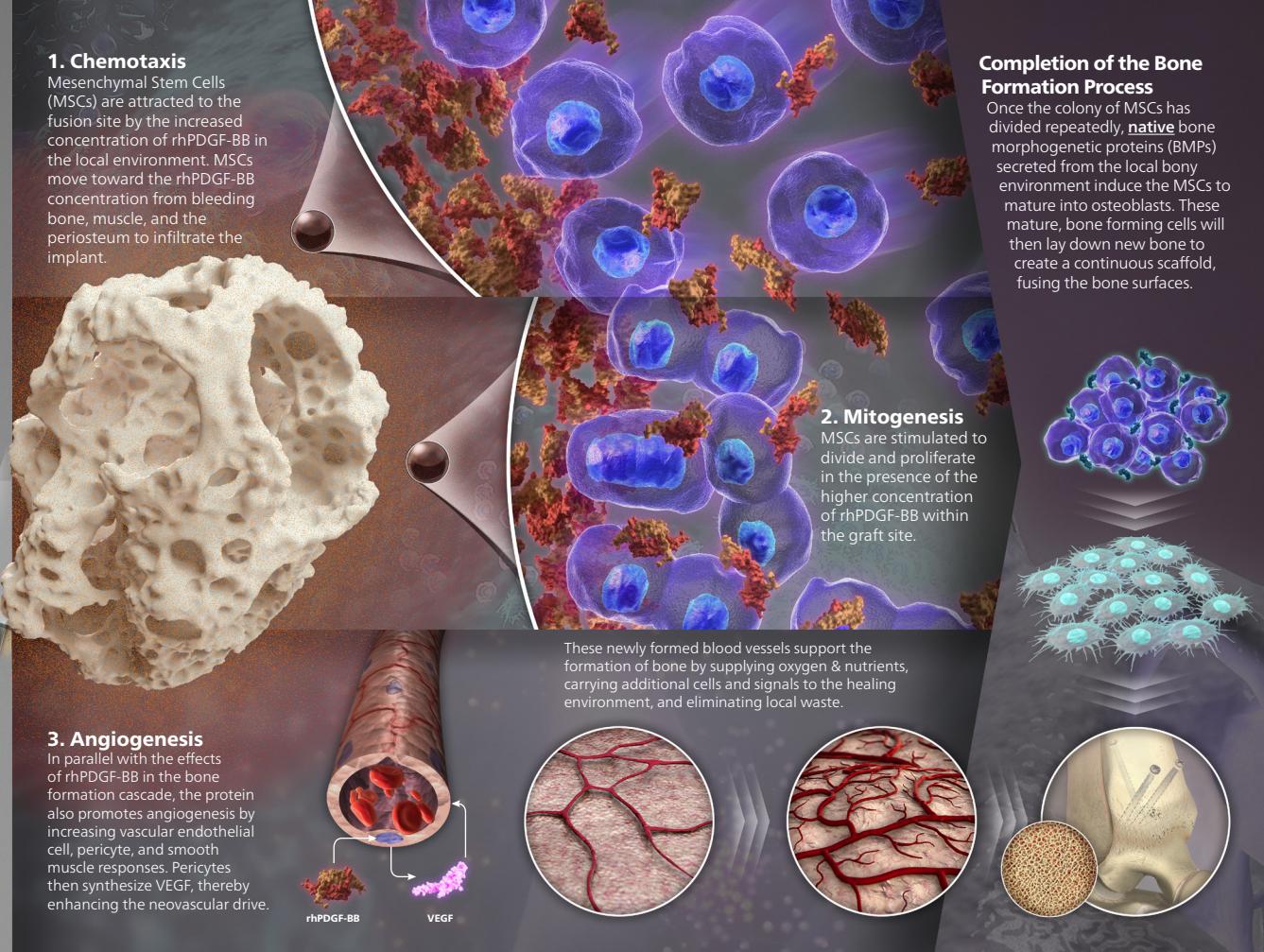
- » The only Class III US FDA-approved alternative to autograft bone for fusion procedures of the ankle and hindfoot.³⁰
- » Rigorously studied in over 500 patients, across 4 human clinical trials conducted in the US and Canada including the largest Level 1 clinical trial ever conducted in the foot and ankle.^{36,37,38}
- » Approved, and safely used in Canada beginning in 2009, and in Australia and New Zealand beginning in 2011, with no serious device-related adverse events,⁷ no significant immunologic responses,^{7,10,36} or any other negative reactions reported to date^{39,40,41} in its use for foot and ankle.
- » Clinically proven to offer comparable clinical success to the gold standard of autograft bone in foot and ankle fusion procedures.³⁶
- » Spares patients all risk for complications, postoperative morbidity, increased surgical time, longer hospital stays, short- and long-term impact on patient quality of life, and interference with routine activities of daily living associated with autograft bone harvest.^{10,14,15,16,17,18,19,20,21,22,23}
- » The rhPDGF-BB biologic component is engineered via recombinant DNA technology, as an exact replica of endogenous human PDGF-BB, thus eliminating risk of disease transmission or immune response possible with allogeneic bone.⁷
 - » rhPDGF-BB triggers the tissue healing and bone repair cascade.
- » The β-TCP matrix component allows targeted delivery of the rhPDGF-BB, fills the bone defect, provides an osteoconductive matrix, prevents soft tissue prolapse, and provides the environment necessary for the stability of a newly forming callus at the wound healing site.^{5,7,42}
 - » β-TCP is resorbed and replaced with bone during healing.

AUGMENT® Bone Graft offers surgeons and patients a **better way** to achieve fusion, by eliminating the need for harvesting autograft bone.

AUGMENT® Bone Graft Works in a Unique Way to Stimulate Three Key Processes of Early Bone Healing.



Following preparation of the bone surfaces, the surgeon implants AUGMENT® Bone Graft into the fusion site. The rhPDGF-BB releases from the β-TCP, forming a concentration gradient as it migrates throughout the local environment.



| Figure 1 PDGF is the essential starting point for tissue healing, including bone formation following injury or repair. The osteogenesis processes triggered by PDGF guide the differentiation of progenitor cells into osteoblasts that, through remodeling processes, become new bone tissue.^{1,3,4,5,6,9}

Bone Healing Process

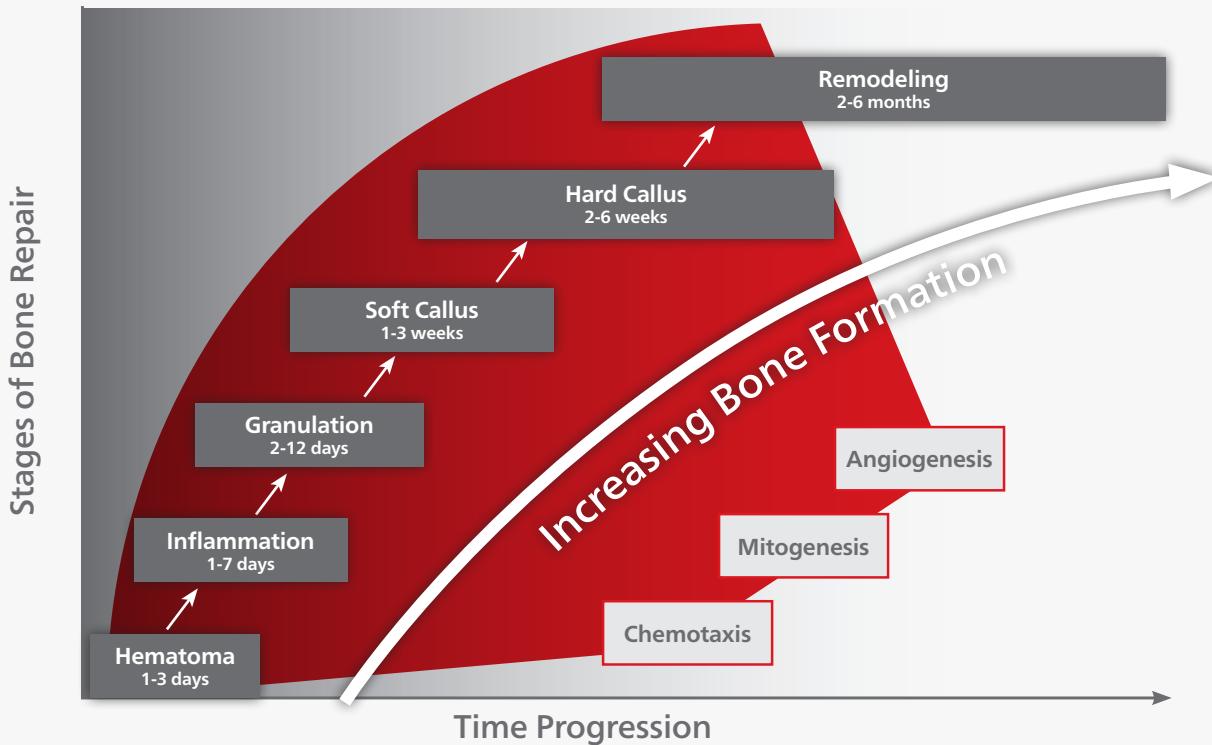
When bone is injured naturally or by surgical intervention, the body immediately responds by triggering a bone generation and repair cascade to heal the injury. **Platelet-derived growth factor (PDGF)** sits at the top of the wound healing cascade, and is responsible for triggering a variety of events critical for bone formation in the healing process.^{1,2}

Naturally occurring endogenous PDGF is released from platelets and macrophages during the earliest phase of the healing cascade.^{1,2} **PDGF acts in three important ways in bone formation:**^{1,2}

1. As an important chemotactic agent PDGF recruits reparative cells to the site of injury;
2. As a potent mitogenic agent, PDGF directs the proliferation of these reparative cells to form a repair blastema; the cells in this repair tissue respond to local factors and differentiate into a cartilaginous callus;
3. As an angiogenic stimulant, PDGF upregulates the expression of vascular endothelial growth factor (VEGF), which is responsible for initiating the proliferation of vasculature into the soft cartilaginous callus.

PDGF's secondary influence in the bone healing cascade is on the transition from a soft cartilaginous callus to a hard callus made of endochondral (woven) bone, and finally remodeling into mature lamellar bone by the balanced activity of osteoblasts (bone forming cells) and osteoclasts (bone resorbing cells), which gain access to the repair area through the newly-formed blood vessels at the fracture site.^{1,2,3,4,5,6} | Figures 1 and 2

Challenges To Optimal Bone Healing



| Figure 2 In the bone formation portion of tissue healing processes (remodeling), PDGF acts in a bi-phasic process. The first phase, triggered by the chemotactic and mitogenic properties of PDGF, results in the formation of a soft callus. The second phase, triggered by the angiogenic nature of PDGF, initiates formation of vasculature that is critical to tissue healing and the formation of bone. Secondarily, the PDGF effects result in matrix synthesis and eventual remodeling of bone.^{1,3,4,5,6,9}

The risk of non-union and delayed union is of concern to orthopaedic surgeons. Some foot and ankle experts suggest that supplementation of foot and ankle fusion procedures should be considered for all patients, but particularly those at high risk of non-union.⁷

The chances of adverse healing are increased by local and systemic risk factors. Local factors include poor blood supply, fracture comminution, open fractures with extensive soft tissue stripping, bone gap (segmental defects), infection and extensive soft tissue damage or contamination. Additional surgical risk factors affecting bone healing include a history of diabetes,^{2,7,8} smoking, osteoporosis and obesity which affect patient-specific levels of endogenous PDGF.^{7,8}

Current Practice In Foot and Ankle Fusion

Autograft bone is the gold standard for use in a wide variety of procedures from arthrodesis (fusion), to treatment of fractures and nonunions, because it naturally provides an osteoconductive scaffold, living cells, and numerous osteoinductive growth factors, essential characteristics necessary for bone healing.^{1,7} Autograft bone also does not pose any risk of disease transmission or immunologic reaction that is possible with allographic (allogeneic) material.^{7,10} Autograft for use in foot and ankle fusion procedures is routinely harvested from the iliac crest, the proximal tibia, distal tibia, and calcaneus.^{7,11,12}

Clinical Implications of Autograft and Addressing the Unmet Need



Patient Implications

Autograft has well-documented clinical drawbacks, risk of complications, and long-term patient impacts:

- » In the largest clinical trial ever conducted in foot and ankle fusion, 18% of all autograft patients experienced persistent pain at up to 1 year.¹²
 - » Clinically-significant graft harvest site pain was reported in 8.5% of autograft harvest patients at 1 year post graft harvest.¹²
 - » Harvesting graft from the distal tibia, proximal tibia or calcaneous results in prolonged donor-site pain (24-52 weeks), equal to that of iliac crest bone.^{12,13}
- » Reported complication incidence rates for iliac crest, proximal tibia, distal tibia and calcaneous bone harvest range from 0% to 39% in the literature. Complications include harvest site fracture, infection, seroma formation, hematoma, wound complications, prolonged donor site pain, sensory loss, and scarring.^{7,10,14,15,16,17,18,19,20,21,22,23,24,25}
 - » 3 of 142 patients (2.1%) in the same clinical trial in foot and ankle fusion suffered a major complication incident related to bone graft harvest which required additional intervention. Major complications were observed in patients receiving graft harvest from the proximal tibia.²⁶
 - » In the same clinical trial in foot and ankle fusion, 13% of distal tibia harvest patients, 5.8% of proximal tibia harvest patients, and 20% of calcaneus harvest patients experienced clinically-significant, prolonged donor-site pain during the clinical follow-up period.¹²
 - » In the same clinical trial in foot and ankle fusion, 5.9% of iliac crest harvest patients experienced clinically-significant, prolonged donor-site pain during the clinical follow-up period.¹²
 - » A relatively large percentage of patients experience impairment of and interference with routine activities of daily living for one to three years post-surgery following iliac crest bone graft harvest.²⁷

» Autograft material harvested from different sites is histologically different across patients and harvest sites.²⁸ These variations may contribute to differences in fusion rates for autograft bone.^{7,8}

- » Both the quality and quantity of autograft material are known to vary with patient age, body mass index, gender, overall health status, and risk factors that can affect bone healing.^{7,8,28}
- » Bone graft harvest site selection is clinician driven, and fusion rates are affected by the site of autograft harvest due to variability in graft harvest composition.^{7,8,12,28}

Drawbacks to Autograft Bone Harvest

- » There is a finite amount of bone that can be safely and reasonably harvested.⁷
- » The amount of bone available to be harvested may be insufficient, depending on the size of the bone defect to be treated at the primary surgical site, the physical size of the patient, the number of joints to be fused.⁷
- » The presence of comorbidities such as osteoporosis can even further reduce the quantity of bone available for harvest.^{7,11}
- » Risk of nonunion during foot and ankle fusion surgery is of clinical concern to surgeons.^{7,11}
- » Some foot and ankle experts suggest that supplementation of foot and ankle fusion procedures should be considered for all patients.⁷

Autograft Bone Harvest is Not Free

The costs associated with bone graft harvest can be substantial when operating room time, instrument costs, anesthesia costs, physician fees, and management of postoperative complications are taken into account:

- » Harvesting bone graft may add an average of 26 minutes of operating room time (ranging from 17 to 35 minutes) to the overall fusion procedure.^{7,10,23}
- » Addressing associated complications from bone graft harvest, may add up to 2 additional days to the hospitalization length of stay.^{7,19,23,29}
- » Harvesting bone graft material can slow recovery time leading to lower levels of patient satisfaction, affect activities of daily living, and delay the return to work.²⁴

AUGMENT® Bone Graft

A Better Way

Approved For Use

AUGMENT® Bone Graft (combination of rhPDGF-BB and a β-TCP osteoconductive matrix) is a Class III, US FDA-approved³⁰ clinical alternative to autograft in fusion procedures of the hindfoot and ankle joints. AUGMENT® Bone Graft is also approved for use in ankle and hindfoot fusion procedures in Australia³¹, New Zealand³², Saudi Arabia³³, and Mexico³⁴, and for midfoot, ankle and hindfoot fusion procedures in Canada³⁵.

Extensively Studied Clinically

AUGMENT® Bone Graft has been extensively studied as an alternative to autograft in foot and ankle fusion procedures that require supplemental graft material:

- » 434-patient, 37-center, North American prospective, randomized, controlled, non-inferiority trial.³⁶
- » 60-patient Canadian registration trial.³⁷
- » 20-patient United States pilot trial.³⁸
- » 11-patient Canadian pharmacokinetic trial.⁴²
- » In all of these trials there were no reported serious device-related adverse events⁷ no significant immunologic responses,^{7,10,36} or any other negative reactions directly attributable to the device in its use for foot and ankle.^{39,40,41}

A Unique Product for Foot and Ankle Fusion

- » The rhPDGF-BB component of AUGMENT® Bone Graft is a bioengineered replica of the naturally occurring (endogenous) PDGF-BB, the most active and universal isoform of PDGF because of its ability to bind to all known receptor isotypes of PDGF.^{2,36} The rhPDGF-BB isoform in AUGMENT® Bone Graft:
 - » Is an exact, bioactive replica of endogenous human PDGF-BB;
 - » Binds to both α and β cellular receptors, thus providing the optimal isoform of the PDGF molecule for therapeutic use;²
 - » Triggers the body's natural healing cascade the same as endogenous PDGF; | Figure 1
 - » Provides an essential, biologically active growth factor responsible for regulating natural tissue healing and regeneration processes, including bone growth and healing. | Figure 2

The β-TCP component of AUGMENT®

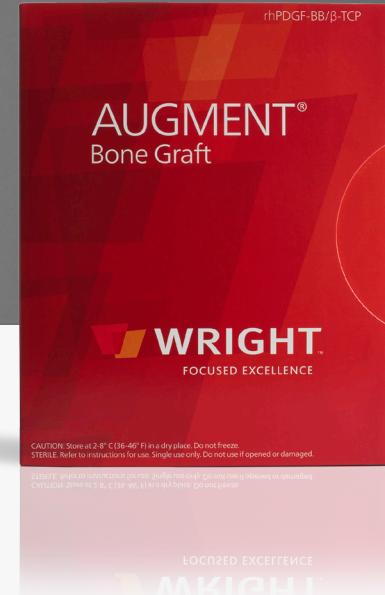
Bone Graft provides important functions in the bone healing process:

- » Adsorbs the rhPDGF-BB for targeted delivery at the fusion site;^{7,42}
- » Physically fills the bone defect;^{7,42}
- » Provides a biocompatible, resorbable osteoconductive scaffold that is of similar chemical composition to natural bone;^{7,42}
- » Prevents soft tissue prolapse;^{7,42} and
- » Provides a permissive environment for the stability of the healing callus.^{7,42}

AUGMENT® Bone Graft does not have any biomechanical strength, and must be used in conjunction with standard orthopedic hardware for rigid fixation of the fusion site.

AUGMENT® Bone Graft

A Better Way



A Safe Mechanism of Action

The rhPDGF-BB and β-TCP components are mixed at the time of surgery, and implanted only once during the fusion procedure.⁴³ **The rhPDGF-BB is released in a bi-phasic mode;** an initial burst release followed by a slower release over a period of approximately seven days, **identical to the natural biological release of endogenous PDGF in the natural tissue healing and regeneration processes.** | Figure 2

- » Local administration of rhPDGF-BB results in limited systemic exposure and is cleared rapidly from circulation, also when administered intravenously. Pharmacokinetic studies in animal models consistently demonstrated that 50% of the rhPDGF-BB is released from the implantation site in the first 60 minutes and 90% is released from the site after 72 hours. A human PK study demonstrated that the use of AUGMENT® Bone Graft is not associated with a detectable elevation of PDGF-BB in the serum of patients receiving the product.^{42,44}
- » AUGMENT® Bone Graft mimics the complete healing mechanism that is triggered by the body in response to injury. Other growth factors act at selective points further down the tissue healing process. For example, bone morphogenetic proteins (BMPs) act only on the portion of the healing process leading directly to bone formation by affecting the osteoblastic differentiation of cells at the implantation site. This selectivity in the point-in-time activity in the healing process has limitations and risks including ectopic bone formation.^{45,46,47,48} There are no reported incidences of ectopic bone formation in surrounding tissue with the use of AUGMENT® Bone Graft.^{34,35,36}
- » Economic models provide evidence of the hospital cost savings that may be realized with the use of AUGMENT® Bone Graft as a substitute for autograft in foot and ankle fusion. Interactive budgetary impact models for Canada, Australia and the US have been developed in accordance with ISPOR guidelines.⁴⁹ Based on the models' hospital cost estimates, AUGMENT® Bone Graft offers cost elimination of the incremental hospital costs associated with the harvesting of autograft, and the treatment of subsequent potential complications at the graft harvest site.^{24,25,50}

Conclusions

- » The documented clinical trial success, and defined mechanism of action, clearly establish the safety and efficacy of AUGMENT® Bone Graft in foot and ankle fusion procedures.^{36,37,38}
- » The role of PDGF, and the bioengineered replica rhPDGF-BB, in musculoskeletal repair and regeneration uniquely differentiates AUGMENT® Bone Graft from all other bone graft substitute products available for foot and ankle fusion.⁷
- » Unlike growth factors such as the bone morphogenetic proteins (BMPs), which lead solely to osteoblastic differentiation of cells at the implantation site, there are no reported incidences of ectopic bone formation with the use of AUGMENT® Bone Graft.^{39,40,41}
- » AUGMENT® Bone Graft eliminates all costs associated with autograft bone harvest, including additional operating room time and resources, harvest site complication risk, length of stay impact, in addition to graft harvest impact on patient satisfaction, quality of life, activities of daily living and return to work that may be associated with patient pain at their graft harvest site.^{24,25,50}

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Brief Summary of Important Product Information

Indications for Use

AUGMENT® Bone Graft is indicated for use as an alternative to autograft in arthrodesis (i.e., surgical fusion procedures) of the ankle (tibiotalar joint) and/or hindfoot (including subtalar, talonavicular, and calcaneocuboid joints, alone or in combination), due to osteoarthritis, post-traumatic arthritis, rheumatoid arthritis, psoriatic arthritis, avascular necrosis, joint instability, joint deformity, congenital defect, or joint arthropathy in patients with preoperative or intraoperative evidence indicating the need for supplemental graft material.

Warnings

As with all therapeutic recombinant proteins, there is a potential for immune responses to be generated to the rhPDGF-BB component of AUGMENT® Bone Graft. The immune response to rhPDGF-BB was evaluated in two pilot and one pivotal studies for ankle and hindfoot arthrodesis procedures. The detection of antibody formation is highly dependent on the sensitivity and specificity of the assay. Additionally, the observed incidence of antibody (including neutralizing antibody) positivity in an assay may be influenced by several factors including assay methodology, sample handling, timing of sample collection, concomitant medications, and underlying disease. For these reasons, comparison of the incidence of antibodies to AUGMENT® Bone Graft with the incidence of antibodies to other products may be misleading.

Women of childbearing potential should avoid becoming pregnant for one year

Contraindications

AUGMENT® Bone Graft should not:

- » be used in patients who have a known hypersensitivity to any of the components of the product or are allergic to yeast-derived products.
- » be used in patients with active cancer.
- » be used in patients who are skeletally immature (<18 years of age or no radiographic evidence of closure of epiphyses).
- » be used in pregnant women. The potential effects of rhPDGF-BB on the human fetus have not been evaluated.
- » be implanted in patients with an active infection at the operative site.
- » be used in situations where soft tissue coverage is not achievable.
- » be used in patients with metabolic disorders known to adversely affect the skeleton (e.g. renal osteodystrophy or hypercalcemia), other than primary osteoporosis or diabetes.
- » be used as a substitute for structural graft.

following treatment with AUGMENT® Bone Graft. The implantation of rhPDGF-BB in women and the influence of their development of anti-PDGF-BB antibodies, with or without neutralizing activity, on human fetal development are not known.

The safety and effectiveness of AUGMENT® Bone Graft in nursing mothers has not been established. It is not known if rhPDGF-BB is excreted in human milk.

The safety and effectiveness of AUGMENT® Bone Graft has not been established in anatomical locations other than the ankle or hindfoot, or when combined with autologous bone or other bone grafting materials.

The safety and effectiveness of repeat applications of AUGMENT® Bone Graft have not been established.

The safety and effectiveness of AUGMENT® Bone Graft in pediatric patients below the age of 18 years have not been established.

AUGMENT® Bone Graft does not have any biomechanical strength and must be used in conjunction with standard orthopedic hardware to achieve rigid fixation.

The β-TCP component is radiopaque, which must be considered when evaluating radiographs for the assessment of bridging bone. The radiopacity may also mask underlying pathological conditions. Over time, the β-TCP is intended to be resorbed at the fusion site and replaced by new bone. Under such circumstances, it would typically be indistinguishable from surrounding bone.



FOCUSED EXCELLENCE

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