

rhPDGF-BB/ $\beta$ -TCP

HOW TO CATEGORIZE  
**AUGMENT<sup>®</sup>**  
Bone Graft

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



# Choosing an Appropriate Graft for Hindfoot and Ankle Fusion Surgery

With the myriad of bone graft options available and continuing to grow, it has become increasingly difficult for surgeons and hospitals to avoid confusion and maintain a clear understanding of the clinical value, specific features, benefits, and appropriate uses of available graft choices.

	CATEGORIZATION	CHARACTERISTICS	REGULATORY PATHWAY AND CLINICAL BURDEN OF PROOF	EXAMPLES
Recombinant Growth Factors	Proven alternative to Autograft <sup>1</sup>	True biologic: Combination products with consistent, highly active signal proteins that drive bone regeneration <sup>4</sup>	Pre-Market Approval (PMA)  Safety and Efficacy in large pivotal clinical trial <sup>5</sup>	AUGMENT® Bone Graft (rhPDGF-BB/β-TCP)  INFUSE® Bone Graft (rhBMP-2/ACS)
Allograft Tissue	Bone Void Fillers <sup>2</sup>	Osteoconductive and weakly osteoinductive putties with variable handling  Cell-containing products include various claims of cell viability at point of use	Human tissue products (361 HCT/Ps) – No proof needed <sup>6</sup>  Devices containing human tissue (351 HCT/Ps - more than minimally manipulated) – 510(k) <sup>7</sup>	DBX®, TRINITY® Elite, ACCELL®, ALLOMATRIX®, OSTEOCEL® Plus, GRAFTON®, BIO4®, OSTEOSPONGE®, FUSIONFLEX®, Allograft chips, femoral head allograft, ALLOPURE® wedges
Synthetic Scaffolds	Bone Void Fillers <sup>3</sup>	Passive osteoconduction and fills space	Synthetics – 510(k) <sup>7</sup>	VITOSS® BA, HYDROSET®, NORIAN® Drillable Inject, OSTEOSET®

1. Combination Growth Factor products composed of biologically active signals that promote chemotaxis, mitogenesis, angiogenesis, and/or osteoinductivity, rigorously reviewed by FDA and proven to be non-inferior to the Gold Standard, autograft in specific approved indications (see back page).

2. Void fillers with mineralized or demineralized bone, with or without cryopreserved cells from same donor intended for treatment of musculoskeletal defects.

3. Physical scaffolds composed of synthetic materials (e.g. calcium phosphate) intended to be used to fill bone voids.

4. Platelet-derived growth factor (rhPDGF-BB) and bone morphogenetic protein-2 (rhBMP-2) have been tested, reviewed and established as alternatives to autograft in multiple clinical studies for specific indications in foot & ankle (rhPDGF-BB only), spine/orthopaedic trauma (rhBMP-2 only) and dental (rhPDGF-BB & rhBMP-2).

5. Multiple clinical trials culminating in a large pivotal trial are typically required to prove that the combination device is both safe and efficacious in the specified indications.

6. Human tissues designated as 361 HCT/Ps are not regulated as medical devices and do not require a submission and/or review for commercialization. Tissue processors are required to register with FDA and follow Good Tissue Practices (GTP) per 21 CFR 1271.

7. A 510(k) clearance demonstrates that the device is substantially equivalent to a legally marketed device.



This Guide is intended to offer some perspective on how to better understand the three basic categories of commercially available bone graft products, and to offer a method of applying four simple, overarching questions that will allow you to make better informed purchasing decisions:

1

What Is the Evidence?

2

How Was It Approved?

3

How Should It Be Used?

4

How Does It Work?

# What Is the Evidence?

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

- The role of PDGF in bone repair and regeneration is documented in at least ten peer-reviewed publications including two large-scale randomized, controlled clinical trials involving rhPDGF-BB/β-TCP.
- This Level-I clinical data is considered the most reliable quality of data based upon standards for peer-reviewed evidence.



# How Was It Approved?

**AUGMENT® Bone Graft** was approved via the rigorous PMA pathway by the U.S. FDA as a Class III combination medical device/drug product.



- The PMA application was supported by two pilot clinical trials, the largest prospective, randomized controlled clinical trial in foot and ankle history, and numerous preclinical studies.



# How Should It Be Used?

Among the criteria for which patients undergoing hindfoot and ankle arthrodesis should receive **AUGMENT® Bone Graft**, the following factors should be considered:

- In the Randomized, controlled pivotal trial conducted to support U.S. FDA approval of AUGMENT® Bone Graft, 75% of the treated patients had one or more risk-factors for non-union. AUGMENT® Bone Graft treated patients were found to have equivalent clinical and radiographic outcomes and a better overall safety profile versus autograft (due to the elimination of harvest site pain and morbidity).<sup>1</sup>
- A natural deficiency in PDGF-BB has been found to be correlated with non-union and poor bone formation in clinical and preclinical studies involving subjects with diabetes, osteoporosis and smokers.<sup>2,3,4</sup>
- 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.<sup>5</sup>

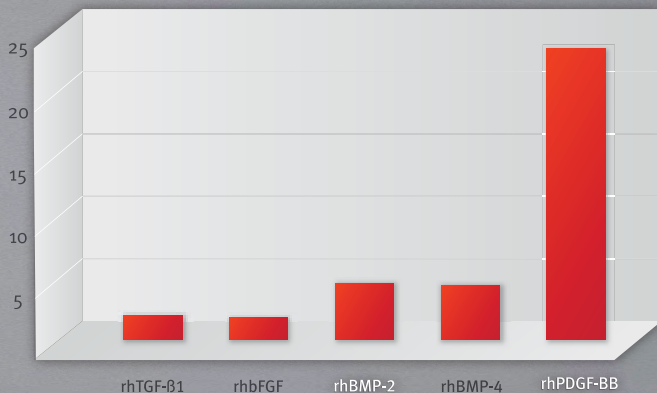
\* FDA did not base its approval of AUGMENT® Bone Graft on radiologic findings from the pivotal study, but instead relied on clinical outcomes.

1. DiGiovanni CW, et al., JBJS (2013)  
2. Verma, et al., Curr Orthop Pract (2011)  
3. Hollinger, et al., JOR (2008)  
4. Al-Zube, et al., J Orthop Res (2009)  
5. Carragee EJ, et al., Spine J (2011)



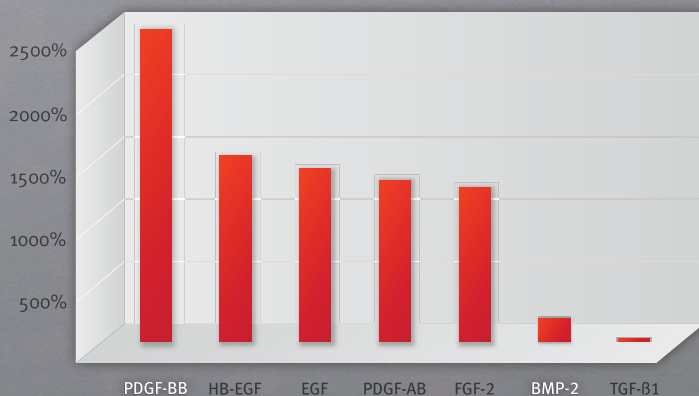
# How Does It Work?

**CHEMOTACTIC POTENTIAL OF rhPDGF-BB FOR MESENCHYMAL PROGENITOR CELLS**



**FIGURE 1 | PDGF-BB has been shown as the strongest identified chemotactic agent for MSCs.<sup>6</sup>**

**CELL PROLIFERATION ASSAY COMPARISON**



**FIGURE 2 | PDGF-BB has been shown as the most potent mitogen for MSCs.<sup>7</sup>**

**AUGMENT® Bone Graft** works in a unique way to stimulate the **key active processes** of early bone healing, as well as provide a scaffold to support new bone formation.

## ACTIVE EARLY HEALING SIGNALS

### Chemotaxis

rhPDGF-BB attracts Mesenchymal Stem Cells (MSCs) to the local fusion site.<sup>6</sup> | **FIGURE 1**

### Mitogenesis

MSCs are stimulated to divide and proliferate in the presence of the higher concentration of rhPDGF-BB within the graft site.<sup>7</sup> | **FIGURE 2**

### Angiogenesis

rhPDGF-BB promotes the formation of new blood vessels at the site of healing by increasing vascular endothelial cell, pericyte, and smooth muscle responses.

- PDGF-BB has been shown to upregulate VEGF production, leading to neoangiogenesis.<sup>8</sup>

## ACTIVE LATE HEALING SIGNALS

### Osteoinduction

Native endogenous factors, such as Bone Morphogenic Proteins (BMPs) are secreted from the local bony environment and induce the MSCs to mature into osteoblasts.<sup>9</sup> These mature, bone forming cells will then lay down new bone to create a continuous scaffold, fusing the bone surfaces.

## PASSIVE

### Osteoconductivity

The β-TCP component fills the surgical defect, reliably delivers the rhPDGF-BB over time, and provides a physical scaffold for new bone formation.

### Rigid Fixation

In order to allow for proper healing, rigid fixation is used to stabilize the fusion site and allow the biologically active and passive processes to take place.

6. Fiedler et al., J Cell Biochem (2002)  
 7. Wildemann et al., J Orthop Sur Res (2007)  
 8. Ozaki et al., J Stem Cells and Dev (2007)  
 9. Lieberman et al., JBJS Am (2002)

## 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.

### 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.

### 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

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  $\beta$ -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  $\beta$ -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.

Please refer to the full package insert for more information.

## Competitive Product Information

Vitoss®, Hydroset®, and Bio4® are registered trademarks of Stryker Corporation.

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Osteosponge® is a registered trademark of Bacterin.

### INFUSE® Bone Graft Indications for Use (Spine, Trauma, OMF)\*

The INFUSE® Bone Graft/Medtronic Interbody Fusion Device is indicated for spinal fusion procedures in skeletally mature patients with degenerative disc disease (DDD) at one level from L2-S1, who may also have up to Grade I spondylolisthesis or Grade 1 retrolisthesis at the involved level.

The INFUSE® Bone Graft is indicated for treating acute, open tibial shaft fractures that have been stabilized with IM nail fixation after appropriate wound management. INFUSE® Bone Graft must be applied within 14 days after the initial fracture. Prospective consumers should be skeletally mature.

INFUSE® Bone Graft is indicated as an alternative to autogenous bone graft for sinus augmentations, and for localized alveolar ridge augmentations for defects associated with extraction sockets.

\*For more information please refer to the full package inserts.



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