

Proposed Package Insert

Augment™ Bone Graft

Augment™ Bone Graft (rhPDGF-BB/ β -TCP) is a completely synthetic graft substitute composed of recombinant human platelet-derived growth factor BB and beta-tricalcium phosphate granules.

- Beta-tricalcium phosphate (β -TCP) is a highly porous, resorbable and osteoconductive scaffold that provides a framework for bone ingrowth, aids in preventing soft tissue infiltration and promotes stabilization of the blood clot.
- The particle size ranges from approximately 1000 to 2000 microns in diameter.
- Recombinant human platelet-derived growth factor BB (rhPDGF-BB), also known as becaplermin, acts by stimulating the recruitment and proliferation of a variety of cell types, including bone cells and mesenchymal stem cells, while also promoting revascularization. rhPDGF-BB is a synthetic protein that is produced using recombinant DNA technology. rhPDGF-BB is similar in structure and activity to endogenous PDGF-BB that is naturally found in the body.

The components of Augment™ Bone Graft are provided in two sterile trays:

- The vial tray contains one, two or three vials, dependent on the kit configuration, aseptically filled with rhPDGF-BB solution (0.3mg/ml). The vial tray is sterilized by ethylene oxide.
- The cup tray contains a sealed cup filled with dry β -TCP granules. The volume of granules will vary depending upon the kit configuration. The cup tray is sterilized by gamma radiation.

At time of use, the two primary components are combined in entirety, mixed and applied to the surgical site.

STORAGE CONDITIONS:

Augment™ Bone Graft must be stored at refrigerated temperature (2°- 8°C, 36°- 46°F). Do not freeze.

INDICATIONS FOR USE:

Augment™ Bone Graft is indicated for use as an alternative to autograft in hindfoot and ankle fusion procedures that require supplemental graft material, including tibiotalar, tibiocalcaneal, talonavicular and calcaneocuboid fusions.

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.
- Augment™ Bone Graft should not be used in the vicinity of a resected or active tumor.
- Augment™ Bone Graft should not be used in patients who are skeletally immature (<18 years of age or no radiographic evidence of closure of epiphyses).
- Augment™ Bone Graft should not be used in pregnant women. The potential effects of rhPDGF-BB on the human fetus have not been evaluated.
- Augment™ Bone Graft should not be implanted in patients with an active infection at the operative site.
- Augment™ Bone Graft should not be used in situations where soft tissue coverage is not achievable.
- Augment™ Bone Graft should not 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.
- Augment™ Bone Graft should not be used as a substitute for structural graft.

WARNINGS:

- Women of childbearing potential should be advised that antibody formation to rhPDGF-BB or its influence on fetal development have not been assessed. In clinical studies to support

the safety and effectiveness of Augment™ Bone Graft, 26 patients were evaluated for the presence of antibodies to rhPDGF-BB. Antibodies were detected in 3 out of 26 (12%) patients. However, none of the antibodies were found to be neutralizing. The clinical significance of these non-neutralizing anti-bodies is 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.
- Women of childbearing potential should be advised to avoid becoming pregnant for one year following treatment with Augment™ Bone Graft.
- The safety and effectiveness of Augment™ Bone Graft has not been established in anatomical locations other than the foot or ankle, used in surgical techniques other than open surgical approaches, or combined with autogenous bone or other bone grafting materials.
- Augment™ Bone Graft does not have any biomechanical strength and must be used in conjunction with standard orthopedic hardware to achieve rigid fixation.

PRECAUTIONS:

- Augment™ Bone Graft should only be used by surgeons who are familiar with bone grafting techniques used in foot and ankle surgery.
- In order to enhance the formation of new bone, Augment™ Bone Graft should be placed in direct contact with well-vascularized bone. Cortical bone may be perforated prior to placement of the material. In order to optimize bony fusion, Augment™ Bone Graft should be implanted such that it does not prevent bony apposition of the articular surfaces intended for fusion.
- The β -TCP component is radiopaque, which must be considered when evaluating radiographs as it may mask underlying pathological conditions.
- The safety and effectiveness of repeat applications of Augment™ Bone Graft has not been established.
- Careful consideration should be given to alternative therapies prior to performing bone grafting in patients who have severe endocrine-induced bone diseases (e.g. hyperparathyroidism); who are receiving immunosuppressive therapy; or who have known

conditions that may lead to bleeding complications (e.g. hemophilia).

- The safety and effectiveness of Augment™ Bone Graft in pediatric patients below the age of 18 years has not been established.
- Augment™ Bone Graft is supplied as a single use only kit. Discard any unused material. The individual components of this product should not be used separately. Use a new device for subsequent applications.
- Prior to use, inspect the packaging, vial and stopper for visible damage. If damage is visible, do not use the product. Retain the packaging and contact a representative of BioMimetic Therapeutics, Inc.
- Do not use after the expiration date located on the product carton. The product expires on the last day of the month indicated on the carton label.
- **IMMUNOGENICITY:** 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 study for foot and ankle fusions. In this study population of a total of 356 patients treated with Augment, anti-rhPDGF-BB antibodies were detected in 46 patients (12.9%). However, there were no antibodies that were found to be neutralizing antibodies.

The clinical significance of these binding non-neutralizing antibodies is not known. In 33 of the 46 patients, the antibody levels returned to baseline by the 6 month follow-up visit. The incidence of antibody detection is highly dependent on the sensitivity and specificity of the assay. Additionally the incidence of antibody detection may be influenced by several factors including sample handling, 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.

ADVERSE EVENTS:

- No serious adverse events (SAE's) attributable to Augment™ Bone Graft have been reported in clinical studies with the product, however patients may experience any of the following

adverse events that have been reported in the literature with regard to the use of autograft or bone graft substitute products: swelling, pain, bleeding, hematoma, superficial or deep wound infection, cellulitis, wound dehiscence, incomplete or lack of osseous ingrowth, transient hypercalcemia, neuralgia and loss of sensation locally and peripherally and anaphylaxis.

- Occurrence of one or more of these conditions may require an additional surgical procedure and may also require removal of the grafting material.
- The following table (Table 1) was compiled using data obtained from a multi-center clinical study of Augment™ Bone Graft conducted in the United States and Canada (randomized, controlled 2:1 with autologous bone graft) in patients undergoing foot and ankle fusion procedures. This table contains all of the reported events that were available as of August 2009.

Table 1 – Summary of Adverse Events for All Patients

Body System	Augment™ N=272	Autograft N=142
Cardiac Disorders	2 (0.7%)	5 (3.5%)
Gastrointestinal Disorders	32 (11.8%)	17 (12%)
General disorders and administration site condition	31 (11.4%)	17 (12%)
Immune System Disorders	10 (3.7%)	2 (1.4%)
Infections and Infestations	55 (20.2%)	26 (18.3%)
Investigations	5 (1.8%)	3 (2.1%)
Musculoskeletal and connective tissue disorders	100 (36.8%)	43 (30.3%)
Neoplasms benign, malignant and unspecified	4 (1.5%)	1 (0.7%)
Nervous system disorders	40 (14.7%)	14 (9.9%)
Psychiatric disorders	8 (2.9%)	5 (3.5%)
Renal and urinary disorders	13 (4.8%)	11 (7.7%)

Reproductive system and breast disorders	1 (0.4%)	2 (1.4%)
Respiratory, thoracic and mediastinal disorders	13 (4.8%)	11 (7.7%)
Skin and subcutaneous tissue disorders	39 (14.3%)	20 (14.1%)
Surgical and medical procedures	7 (2.6%)	6 (4.2%)
Vascular disorders	17 (6.3%)	8 (5.6%)

DIRECTIONS FOR USE:

- 1) Using sterile technique, transfer the cup (containing the β -TCP granules) and the vial(s)(containing the rhPDGF-BB solution) to the sterile field.
- 2) Open the cup and transfer the β -TCP granules to a sterile surgical bowl.
- 3) Using a syringe and needle, draw up the contents of the vial(s) in entirety and transfer all of the fluid to the surgical bowl containing the β -TCP granules. If multiple kits are used (not to exceed 9cc), the contents may be combined.
- 4) Gently stir the two components together for approximately 30 seconds using a spatula, curette or similar instrument.
- 5) The mixture should be left undisturbed for 10 minutes before being implanted to ensure optimal saturation the β -TCP particles.
- 6) The product should be implanted within one (1) hour after mixing the two components.
- 7) Any unabsorbed rhPDGF-BB solution should be drawn into a sterile syringe and applied to the surgical site prior to the release of the tourniquet to ensure the graft remains hydrated.

RECOMMENDED TECHNIQUE:

- Debride and decorticate the joint surfaces to expose viable bone.
- Where practical, complete surgical manipulations of the graft site prior to implanting the graft material.
- Irrigate the surgical site.
- Manually pack Augment™ Bone Graft into all subchondral voids and surface irregularities throughout the joint. NOTE: Overfilling of the osseous defect(s) should be avoided in order to achieve adequate fixation, closure and containment of the material.
- Reduce the joint and apply rigid fixation.

- Pack any remaining Augment™ Bone Graft around the perimeter of the joint.
- Apply all remaining rhPDGF-BB solution to the surgical site to ensure the graft remains hydrated.
- Carefully layer the periosteal and overlying soft tissue to enclose and contain the graft material. NOTE: Do not irrigate the graft site following implantation of Augment™ Bone Graft.
- Apply the self-adhesive labels that indicate the lot number of each device to the patient's permanent records.

CLINICAL EXPERIENCE:

In a multi-center clinical study conducted in the United States and Canada, 434 patients requiring ankle or hindfoot fusion surgery were treated with Augment™ Bone Graft to facilitate bony healing and union. The study employed a 2 Augment to 1 autograft randomization. Success rates for clinical and radiographic endpoints are shown in Table 2 below. The primary endpoint was CT fusion at six months defined as $\geq 50\%$ osseous bridging. CT results are given for both a full complement (FC) of joints (all treated joints in a patient fused) as well as for all individual joints (AJ). Clinical success is the number and percentage of subjects judged to have complete clinical union.

Table 2 – Summary Foot/Ankle Fusion Study Results

	Augment™	Autograft	
CT for FC	61.2%	62.0%	p=0.038
CT for AJ	66.5%	62.6%	p<0.001
Clinical Success for FC	82.3%	83.5%	p=0.011
Clinical Success for AJ	83.5%	83.3%	p<0.001

SYMBOLS:

	Attention, See Instructions for Use
	Single Use Only
	Expiration Date
	Prescription Only
	Store at Refrigerated Temperature
	Reorder Number
	Lot Number
	Sterilized by Irradiation
	Sterilized by Ethylene Oxide

This product is covered by one or more of the following US patents: 4,845,075, 5,045,633, 5,124,316, 7,473,678. Other patents pending.

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