AUGMENT® Bone Graft
Instructions for Use

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

- 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 biosynthetic 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 (0.3 mg/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 varies depending upon the kit configuration. The cup tray is sterilized by gamma irradiation.

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

STORAGE CONDITIONS:

The 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 with malignancy. The product is regarded as carrying a carcinogenic risk based on the biological activities of rhPDGF-BB and clinical post-market data of REGRANEX® (see WARNINGS).
- 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 used in lactating women. It is not known if rhPDGF-BB is excreted in human milk.
- 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 has not been assessed. In clinical studies to support the safety and effectiveness of AUGMENT® Bone Graft and Autograft, 483 patients were evaluated for the presence of antibodies to rhPDGF-BB. Antibodies were detected in 48 out of 338 (14.2%) of the AUGMENT® Bone Graft patients and in 5 out of 145 (3.4%) of the Autograft patients. However, none of the antibodies were found to be neutralizing. The clinical significance of these non-neutralizing antibodies is not known but all were transient.
- In a retrospective post-marketing study, an increased rate of mortality secondary to malignancy was observed in patients with diabetic foot ulcers treated daily over 90 days with 3 or more tubes of REGRANEX® (rhPDGF-BB) Gel.
- 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 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 or breach of sterility. If damage is visible, do not use the product. Retain the packaging and contact a representative of BioMimetic Therapeutics, LLC.
- 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 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 483 patients receiving foot and ankle fusions in conjunction with application of the product or an Autograft control. In this study population, antibodies were detected in 48 out of 338 patients (14.2%) treated with AUGMENT® Bone Graft and in 5 out of 145 (3.4%) of the Autograft patients, but no antibodies were found to be neutralizing. The clinical significance of these non-neutralizing antibodies is not known but all were transient. Antibody levels returned to baseline at follow up visits. 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 pooled data obtained from three North American AUGMENT® Bone Graft studies of patients undergoing foot and ankle fusion procedures: two randomized, autograft-controlled, multi-center clinical studies in the United States and Canada and one open-label study in Canada. This table contains all of the reported events that were available as of May 5, 2010.

Table 1 – Summary of Adverse Events for All Patients in the Foot and Ankle Fusion Clinical Studies

Body System	Canadian Registration study	Pooled autograft-controlled studies	
	Augment™ N=60	Augment™ N=286	Autograft N=148
Blood and lymphatic system disorders	0 (0.0%)	1 (0.35%)	1 (0.68%)
Cardiac Disorders	1 (1.7%)	3 (1.0%)	6 (4.1%)
Congenital, familial and genetic disorders	0 (0.0%)	1 (0.35%)	1 (0.68%)
Ear and labyrinth disorders	0 (0.0%)	1 (0.35%)	2 (1.4%)
Endocrine disorders	0 (0.0%)	2 (0.70%)	0 (0.0%)
Eye disorders	0 (0.0%)	2 (0.70%)	3 (2.0%)
Gastrointestinal disorders	3 (5.0%)	35 (12%)	17 (11%)
General disorders and administration site condition	51 (85%)	49 (17%)	23 (16%)
Hepatobiliary disorders	0 (0.0%)	1 (0.35%)	0 (0.0%)
Immune System Disorders	0 (0.0%)	11 (3.8%)	2 (1.4%)
Infections and Infestations	12 (20%)	61 (21%)	28 (19%)
Injury, poisoning and procedural complications	33 (55%)	73 (25%)	37 (25%)
Investigations	1 (1.7%)	6 (2.1%)	3 (2.0%)
Metabolism and nutrition disorders	0 (0.0%)	4 (1.4%)	4 (2.7%)
Musculoskeletal and connective tissue disorders	14 (23%)	119 (42%)	51 (34%)
Neoplasms, benign	0 (0.0%)	2 (0.70%)	0 (0.0%)
Neoplasms, malignant and unspecified	1 (1.7%)	3 (1.0%)	2 (1.4%)
Nervous system disorders	8 (13%)	45 (16%)	17 (11%)
Psychiatric disorders	1 (1.7%)	11 (3.8%)	5 (3.4%)
Renal and urinary disorders	2 (3.3%)	18 (6.3%)	11 (7.4%)
Reproductive system and breast disorders	1 (1.7%)	1 (0.35%)	2 (1.4%)
Respiratory, thoracic and mediastinal disorders	2 (3.3%)	14 (4.9%)	11 (7.4%)
Skin and subcutaneous tissue disorders	2 (3.3%)	43 (15%)	22 (15%)
Surgical and medical procedures	2 (3.3%)	9 (3.1%)	5 (3.4%)
Vascular disorders	1 (1.7%)	20 (7.0%)	9 (6.1%)

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) and transfer the fluid to the surgical bowl containing the β-TCP granules. If multiple vials 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 of the β-TCP particles.
6) The product should be implanted within one (1) hour after mixing the two components.
7) Any excess 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 Canada, 60 patients requiring ankle, hindfoot or midfoot fusion surgery were treated with AUGMENT® Bone Graft to facilitate bony healing and union. Success rates for clinical and radiographic endpoints are shown in Table 2 below. Radiographic success, at 9 months, was defined as bridging on at least 2 of 4 radiologic aspects from plain film radiographs. Clinical success indicates that patients did not require and were not recommended for revision surgery within 12 months of the index surgery.

Table 2 – Summary Foot/Ankle Fusion Study Results Canada

Success criterion	Augment™ N=60
Radiographic union	52 (87%)
Clinical healing	54 (90%)

In the United States, a similar trial was conducted with an autograft control group. In this study, 397 patients requiring hindfoot or ankle fusion surgery were treated per the protocol with either AUGMENT® Bone Graft or autograft in a 2:1 ratio. Success rates for clinical and rigorous CT-based endpoints are shown in Table 3 below. CT fusion was defined as at least 50% osseous bridging on all joints being treated. Clinical healing indicates that the surgeon declared the patient to possess clinical union. Non-union indicates that the surgeon declared the patient to be not fused or had previously prescribed secondary treatment to facilitate fusion.

Table 3 – Summary Foot/Ankle Fusion Study Results United States and Canada

Success criterion	Augment™ N=260	Autograft N=137
CT fusion (24 weeks)	159 (61.2%)	86 (62.0%)
Clinical healing (52 weeks)	228 (87.7%)	121 (88.3%)
Non-union (52 weeks)	19 (7.3%)	11 (8.0%)

SYMBOLS:

	Attention, See Instructions for Use
	Single Use Only
	Expiration Date
	Prescription Only
	Store at Refrigerated Temperature
	Manufacturer
	Do Not Use If Package Is Open Or Damaged
	Reorder Number
	Lot Number
	Sterilized by Irradiation
	Sterilized by Ethylene Oxide
	Sterilized by Aseptic Techniques
	Peel Here

Catalog (REF) Numbers

REF	Product
K200-015-30	Augment Bone Graft 1.5 cc Kit
K200-030-30	Augment Bone Graft 3.0 cc Kit
K200-060-30	Augment Bone Graft 6.0 cc Kit
K200-090-30	Augment Bone Graft 9.0 cc Kit

This product is covered by one or more of the following Australian patents: 2005295919 and 2009202532. Other patents pending.

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Regranex® Gel is a topical ointment indicated for the treatment of diabetic foot ulcers. Regranex® is a registered trademark of Smith and Nephew plc.

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