***Instructions for Use:***
***Augment® Injectable Bone Graft***

Augment® Injectable Bone Graft is a synthetic bone graft substitute composed of beta-tricalcium phosphate granules/soluble bovine Type I collagen and recombinant human platelet-derived growth factor BB, packaged as two components.

- A matrix consisting of beta-tricalcium Phosphate (β-TCP) and bovine Type I collagen. β-TCP is a highly porous, resorbable and osteoconductive scaffold that provides a framework for bone cell ingrowth, aids in preventing soft tissue collapse and promotes stabilization of the blood clot. The particle size ranges from approximately 100 to 300 microns in diameter and a bovine Type I collagen added to enhance the handling characteristics and delivery of the product.
- 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 osteoblasts and mesenchymal stem cells, while also promoting revascularization through upregulation of vascular endothelial growth factor (VEGF). 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 Injectable Bone Graft are provided as two sterile tray configurations:
    - The matrix tray contains a 10 ml polypropylene syringe containing either 0.5 or 1.0 grams of a milled β-TCP/bovine Type I collagen (ratio=4:1) matrix. Also included are an empty polypropylene syringe, one 18 gauge blunt tip needle for administration of the combination product, one 14 gauge blunt tip needle and female/female luer connector for mixing of the two components. The tray is sterilized by gamma irradiation.
    - The vial tray contains one vial, dependent on the kit configuration, of aseptically filled with either 1.5 ml or 3.0 ml of rhPDGF-BB solution (0.3mg/ml). The vial tray is sterilized by ethylene oxide.

At time of use, the contents of the trays are placed in a sterile field and the two primary components are combined in entirety, mixed and applied to the surgical site.

**STORAGE CONDITIONS**

Augment Injectable Bone Graft is light and heat sensitive and should be stored at 2-8°C (36-46°F) and should not be frozen.

Do not use product after the expiration date. Augment Injectable Bone Graft is intended for single use only; once opened it must be used or discarded. This product cannot be resterilized.

**INDICATIONS FOR USE**

Augment Injectable Bone Graft is indicated for use as an alternative to autograft in foot and ankle fusion procedures that require supplemental graft material, including tibiotalar, talocalcaneal, talonavicular, calcaneocuboid, tarsometatarsal, naviculo-cuneiform, metatarsophalangeal and interphalangeal fusions.

**CONTRAINDICATIONS**

- Augment Injectable 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 Injectable Bone Graft should not be used in patients with cancer.
- Augment Injectable Bone Graft should not be used in the vicinity of a resected or active tumor.
- Augment Injectable 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 Injectable Bone Graft should not be used in pregnant women. The potential effects of rhPDGF-BB on the human fetus have not been evaluated.
- Augment Injectable Bone Graft should not be implanted in patients with an active infection at the operative site.
- Augment Injectable Bone Graft should not be used in situations where soft tissue coverage is not achievable.
- Augment Injectable 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 Injectable Bone Graft should not be used as a substitute for structural graft.

**WARNINGS**

- In a retrospective post-marketing study of extended daily use of Regranex (a topical gel containing rhPDGF-BB) in treating fully contacting diabetic foot ulcers, an increased rate of death secondary to malignancies was observed in cases where three or more tubes were used. There was no observed effect on cancer incidence.
- Women of childbearing potential should be advised that the influence of antibody formation to rhPDGF-BB on fetal development have not been assessed.
- In clinical studies to support the safety and effectiveness of Augment Injectable Bone Graft, 63 patients were evaluated for the presence of antibodies to rhPDGF-BB. Antibodies were detected in 9 out of 63 (14.2%) patients. In one of the patients the antibodies were found to be neutralizing but all antibody responses were found to be transient. The clinical significance of these anti-bodies is not known.
- The safety and effectiveness of Augment Injectable 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 Injectable Bone Graft.
- The safety and effectiveness of Augment Injectable 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 Injectable Bone Graft does not have any biomechanical strength and must be used in conjunction with standard orthopedic hardware to achieve rigid fixation.
- Augment Injectable Bone Graft should be implanted such that it does not prevent bony apposition of the articular surfaces intended for fusion. Over-packing may impair healing and prevent fusion.

**PRECAUTIONS**

- Augment Injectable Bone Graft should only be used by surgeons who are familiar with bone grafting techniques used in foot and ankle surgery.
- When evaluating radiographs, it must be remembered that the β-TCP component has a radiographic density similar to that of bone. As such, it has the potential to mask underlying pathological conditions.
- In order to enhance the formation of new bone, Augment Injectable 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 Injectable Bone Graft should be implanted such that it does not prevent bony apposition of the articular surfaces intended for fusion. The safety and effectiveness of repeat applications of Augment Injectable Bone Graft has not been established.
- The safety and effectiveness of Augment Injectable Bone Graft has not been established outside of the foot and ankle indications.
- Careful consideration should be given to alternative therapies prior to performing bone grafting in patients who have severe endocrine-induced bone diseases (e.g. hyper-parathyroidism); 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 Injectable Bone Graft in pediatric patients below the age of 18 years has not been established.
- Augment Injectable 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.
- Do not use after expiration date located on the product carton. The product expires on the last date of the month indicated on the carton.
- 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, LLC.
- The β-TCP/Collagen Matrix is non-pyrogenic and nontoxic. Sterility of the matrix is maintained unless the package is opened or damaged. If the package is open, the matrix must be discarded.

**IMMUNOGENICITY**

With regard to anti-rhPDGF antibodies, 9 out of 63 patients (14.2%) receiving Augment® Injectable in the Canadian Clinical trial were reported to have a positive antibody response, compared to 3 out of 154 patients (1.9%) receiving autograft (control). One sample tested positive for the presence of neutralizing anti-rhPDGF-BB antibodies (NAbs). Samples from the same subject did not show NAbs at subsequent visits. There were no observed adverse events and no apparent clinical significance related to these antibody results.

**ADVERSE EVENTS**

No serious adverse events (SAE's) attributed to Augment Injectable Bone Graft were reported in a clinical study with the product. However patients may experience any of the following adverse events reported in the literature with regard to bone graft substitutes or autograft including injection of material into a blood vessel, rash, infection, pressure due to swelling of graft material, bleeding, superficial or deep wound infection, cellulitis, wound dehiscence, non-union, pain, rapid resorption leading to treatment failure, vasodilatation, neuralgia loss of sensation locally and peripherally and depression and anaphylaxis. The 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) summarizes the adverse events reported in the Augment Injectable clinical study.

**Table 1 - Summary of Adverse Events for All Patients in the Foot and Ankle Clinical Study**

| System Organic Class | Augment® Injectable (N=63) | Autograft* (N=154) |
|---|---|---|
| Total | 51(81%) | 115(74.7%) |
| Blood and lymphatic system disorders | 1(1.6%) | 2(1.3%) |
| Cardiac disorders | 6(9.5%) | 6(3.9%) |
| Congenital, familial and genetic disorders | 0(0%) | 2(1.3%) |
| Ear and labyrinth disorders | 3(4.8%) | 2(1.3%) |
| Endocrine disorders | 2(3.2%) | 0(0%) |
| Eye disorders | 1(1.6%) | 3(1.9%) |
| Gastrointestinal disorders | 21(33.3%) | 20(13%) |
| General disorders and administration site conditions | 15(23.8%) | 20(13%) |
| Immune system disorders | 1(1.6%) | 2(1.3%) |
| Infections and infestations | 10(15.9%) | 33(21.4%) |
| Injury, poisoning and procedural complications | 13(20.6%) | 42(27.3%) |
| Investigations | 2(3.2%) | 4(2.6%) |
| Metabolism and nutrition disorders | 3(4.8%) | 4(2.6%) |
| Musculoskeletal and connective tissue disorders | 26(41.3%) | 56(36.4%) |
| Neoplasms benign, malignant and unspecified (incl cysts and polyps) | 1(1.6%) | 2(1.3%) |
| Nervous system disorders | 17(27%) | 17(11%) |
| Psychiatric disorders | 3(4.8%) | 5(3.2%) |
| Renal and urinary disorders | 6(9.5%) | 11(7.1%) |
| Reproductive system and breast disorders | 2(3.2%) | 2(1.3%) |
| Respiratory, thoracic and mediastinal disorders | 6(9.5%) | 12(7.8%) |
| Skin and subcutaneous tissue disorders | 14(22.2%) | 21(13.6%) |
| Surgical and medical procedures | 1(1.6%) | 5(3.2%) |
| Vascular disorders | 3(4.8%) | 12(7.8%) |

*The control group (autograft) includes patients from a separate study (N=142) who received autograft using the same surgical protocol.

There were no unusual trends noted in the safety results (Table 2). Augment Injectable resulted in similar rates compared to autograft in Treatment Emergent Adverse Events (81.0% vs. 74.7%), serious TEAEs (14.3% vs. 14.9%), TEAEs (3.2% vs. 3.9%) considered to be "likely" related to the investigational product, and serious surgical complications (6.3% vs. 7.1%). The rates and types of adverse events were consistent with those expected for patients who undergo fusion procedures. The serious adverse events reported in this study were unrelated to study treatment. The only notable difference in the safety profile of the two investigational treatments that can reasonably be attributed to the treatment administered are that 9% of autograft subjects experienced chronic and significant pain associated with the autograft harvest procedure, whereas the Augment Injectable subjects were spared the additional pain and morbidity associated with autograft harvest.

**Table 2 - Trends in Safety Results**

| | Augment Injectable (N=63) | Autograft (N=154) |
|---|---|---|
| Treatment Emergent Adverse Events (TEAEs) | 81.0% | 74.7% |
| Serious TEAEs | 14.3% | 14.9% |
| TEAEs considered to be "likely" related | 3.2% | 3.9% |
| Complications associated with surgical procedure | 42.9% | 31.8% |
| Serious surgical complications | 7.9% | 7.1% |

Subjects treated with Augment® Injectable Bone Graft had fewer serious TEAEs, fewer related TEAEs, and fewer serious complications associated with the surgical procedure than subjects treated with autograft. There was a higher incidence of non-serious complications associated with the Augment Injectable treatment group procedure, although this difference was not significant. There was one serious adverse event attributable to the autograft harvest procedure (infection; proximal tibia).

These safety data, in concert with the existing safety data for rhPDGF-BB in other bone applications, demonstrate that Augment® Injectable is a safe alternative to autograft for hindfoot and ankle fusion applications.

**DIRECTIONS FOR USE**

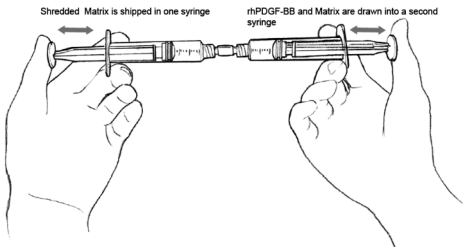
At time of use, the two primary components are combined in entirety, mixed and applied to the surgical site.

Following exposure of the surgical site, the joint(s) should be adequately debrided and prepared according to standard surgical technique. All remaining cartilage should be removed and the opposing bony surfaces adequately prepared to optimize apposition of healthy, vascularized bone. This should be done by feathering and/or perforating the remaining subchondral plate with standard use of curettes, burrs, drill bits or osteotomes as a means of maximizing the surface area of exposed bleeding bone prior to insertion of the graft.

1. Completely withdraw the contents of the vial containing the rhPDGF-BB solution using the empty syringe and the 18 gauge needle. After all of the fluid has been extracted from the vial, remove the needle and displace any air remaining in the syringe.
2. Remove the cap from the syringe containing the β-TCP/collagen matrix. Pull the plunger to the 10ml mark and tap the syringe to loosen the matrix.
3. Connect the syringe containing the rhPDGF-BB solution with the syringe containing the matrix using the female-to-female luer-lock connector.
4. Transfer the rhPDGF-BB solution into the syringe containing the matrix. After transferring all of the rhPDGF-BB solution, pull the plunger on the syringe containing the hydrated matrix past the 10ml mark.

   Note: For the 1.5 g kit, pull the plunger to the 5.5 ml mark.
5. Release the plunger of the syringe containing the hydrated matrix. Let the syringes sit undisturbed for a minimum of 90 seconds.

6. Augment Injectable Bone Graft is then prepared by completely saturating the β-TCP/collagen matrix with the rhPDGF-BB solution, as shown in the following diagram:




7. After hydrating the matrix, transfer the contents back and forth between the two syringes for no less than (20) twenty cycles. Note: A cycle is defined as passing the matrix to the empty syringe and back. Upon completion, the matrix should form a homogenous paste.
8. Transfer all of the paste to one of the syringes, and relieve any pressure built up during the mixing process by gently pulling the plunger containing the matrix.
9. Disconnect the empty syringe and female-to-female luer-lock connector from the syringe that contains the paste. Displace any air remaining in the syringe by holding the barrel of the syringe and gently tapping (vertically) onto the plunger end to shift the paste toward the plunger seal.
10. Connect the14 gauge needle and dispense the hydrated matrix into the surgical site. Note: It may require an initial force to get the paste to flow through the 14 gauge needle. However, once the paste starts to flow the force required to maintain a flow will be reduced.
11. Carefully apply the hydrated matrix to the surgical site (i.e. the subchondral voids, and surface irregularities visualized throughout the entire joint) such that the graft material is in contact with the entire osseous surfaces to be fused/repaired while allowing rigid fixation and primary bone contact to occur between the osseous surfaces. Immediately after joint reduction and screw fixation of the fusion site, any remaining (unused) Augment Injectable bone graft *should* be packed around the external perimeter of the fusion construct (Please refer to the Surgical Manual).
12. In order to enhance the formation of new bone, Augment Injectable Bone Graft should be placed in direct contact with well-vascularized bone. Cortical bone may be perforated prior to placement of the Augment Injectable Bone Graft material.
13. Once Augment Injectable Bone Graft has been packed into the defect site, carefully layer periosteal and overlying soft tissue to enclose and contain the graft material. This will minimize washout, subperiosteal resorption, exostosis, and ulceration at the surgical site. Care should be taken not to irrigate the graft site following implantation of Augment Injectable Bone Graft.
14. The Augment Injectable product does not harden or "set". Standard hardware implantation to ensure rigid fixation is necessary.
15. Employ standard surgical technique to complete the procedure.
16. Any remaining graft material should be discarded.

The rhPDGF-BB solution is non-pyrogenic and nontoxic. Sterility is maintained unless the vial cap has been breached or damaged. If the vial has been breached, the rhPDGF-BB solution must be discarded.

There are potential risks associated with the use of Augment Injectable Bone Graft if used outside of the recommended storage conditions. The potency of rhPDGF-BB may be diminished if the product is exposed to storage conditions other than those recommended, including:

- Extended exposure to room temperature (*i.e.* > 10 hours) or freezing temperatures
- Improper mixing and/or implantation
- Delayed implantation (i.e. > 60 minutes following mixing)
- Direct exposure to sunlight prior to use
- Implantation of expired product kits

Once the components of the kit have been mixed, Augment Injectable Bone Graft must be used completely, if not the remainder must be discarded.

**SUMMARY OF CLINICAL EXPERIENCE**

In a multicenter clinical study conducted in Canada, 63 patients requiring ankle or hindfoot arthrodesis were treated with Augment Injectable Bone Graft to facilitate healing and union. These patients were then compared to an autograft control group that had the same surgical protocol. CT scan results may be found in Table 3.

**Table 3 - Summary of Foot and Ankle Fusion Study Results at 6 Months**

| | Augment® Injectable | Autograft* |
|---|---|---|
| Subjects (N=217) | (N=63) | (N=154) |
| Individual Joints [All Joints] (N=311) | (N=81) | (N=230) |
| CT Fusion Rates (≥50% osseous bridging) | | |
| Full Complement | 84.13% | 64.94% |
| All Joints* | 86.42% | 66.96% |
| Ankle | 80.65% | 76.27% |
| Talonavicular | 93.75% | 63.46% |
| Subtalar | 89.66% | 66.27% |
| Calcaneocuboid | 80.00% | 58.33% |

*The control group (autograft) includes patients from a separate study (N=142) who received autograft using the same surgical protocol.

The following secondary effectiveness results were reported in the same study.

**Table 4 - Effectiveness Results at 13 months – Treated Population**

| | Augment® Injectable | Combined Autograft |
|---|---|---|
| Subjects (N=217) | (N=63) | (N=154) |
| Individual Joints [All Joints] (N=311) | (N=81) | (N=230) |
| Plain Film Radiograph 3 aspects | | |
| Full Complement of Joints | 46.0% | 37.0% |
| All Joints | 54.3% | 45.7% |
| Plain Film Radiograph 2 aspects | | |
| Full Complement of Joints | 84.1% | 76.6% |
| All Joints | 84.0% | 79.6% |
| Clinical Healing Status at the subject level | 87.3% | 88.3% |
| Clinical Healing Status by Joint | | |
| Full Complement of Joints | 87.3% | 87.7% |
| All Joints | 86.4% | 87.8% |
| Clinical Success* | 90.5% | 77.9% |
| Therapeutic Failure | 11.1% | 8.4% |
| SF-12 Mean PCS Score | 44.6% | 45.0% |
| FFI Mean Total Score | 15.0% | 17.4% |
| AOFAS Mean Total Score | 80.0% | 78.5% |
| Mean Fusion Site Pain | 12.2% | 13.0% |
| Mean Weight Bearing Pain | 13.0% | 15.6% |
| CS Graft Harvest Site Pain | n/a | 9% |

*Clinical success was defined as improved pain while weight bearing and lack of need for revision surgery.

The results from the above noted clinical study indicate that Augment Injectable Bone Graft is associated with similar outcomes as the use of autograft in foot and ankle fusion surgery, while eliminating the pain, morbidity, costs, and increased surgical time and resources associated with harvesting autograft from another remote surgical site.

**SYMBOLS**

| | |
|---|---|
|  | Attention, See Instructions for Use |
|  | Prescription Only |
|  | Single Use Only |
|  | Do not Use if Damaged |
|  | Expiration Date |
|   | Store at Refrigerated Temperature |
|   | Reorder Number |
|   | Lot Number |
|   | Sterile using Aseptic Processing Techniques |
|   | Sterilized by Irradiation |
|   | Sterilized by Ethylene Oxide |
|  | Manufactured By |

This product is covered by the following U.S. patent: 7,473,678 and various foreign counterparts. Other patents pending.

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*REF*
*K300-015-00 1.5cc Kit*
*K300-030-00 3.0cc Kit*

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