

GEN 215™ PRODUCT INSERT APPROVED FOR USE IN USA

GEN 215™ GROWTH-FACTOR ENHANCED MATRIX

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Caution: Federal Law restricts this device to sale by or on the order of a dentist or physician.

DEVICE DESCRIPTION: GEN 215™ is a completely synthetic, grafting system for bone and periodontal regeneration composed of a purified recombinant growth factor and a synthetic calcium phosphate matrix.

GEN 215™ is composed of two sterile components:
- synthetic beta-tricalcium phosphate (β-TCP, Ca3(PO4)2) is a highly porous, resorbable interconnectivity scaffold or matrix that provides a framework for bone ingrowth, aids in preventing the collapse of the soft tissues and promotes stabilization of the blood clot.
- highly purified, recombinant human platelet-derived growth factor-BB (rhPDGF-BB, PDGF) is an active protein constituent of blood platelets, it is a tissue growth factor that is released at sites of injury during blood clotting. In vitro and animal studies have demonstrated PDGF's potent mitogenic, angiogenic, angiopoietic and chemotactic (directed cell migration) effects on bone and periodontal ligament derived cells. PDGF is known to be one protein involved in the multi-factorial and complex process of bone and wound repair. Animal studies have shown PDGF to promote the regeneration of periodontal tissues including bone, cementum, and periodontal ligament (PDL).

The contents of the cap of 8-TCP are supplied sterile by gamma irradiation. Sterile rhPDGF-BB is aseptically processed and filled into the syringe in which it is supplied.

INDICATIONS:

GEN 215™ is indicated to treat the following periodontally related defects:
- Intra-bony periodontal defects;
- Furcation periodontal defects; and
- Gingival recession associated with periodontal defects.

CONTRAINDICATIONS:

As with any periodontal procedure where bone-grafting material is used, GEN 215™ is CONTRAINDICATED in the presence of one or more of the following clinical situations:
- Untreated acute infections at the surgical site;
- Untreated malignant neoplasm(s) at the surgical site;
- Patients with a known hypersensitivity to any product component (8-TCP or rhPDGF-BB);
- Incomplete soft tissue coverage is required for a given surgical procedure but such coverage is not possible; or
- Conditions in which general bone grafting is not advisable.

WARNINGS:

The exterior of the cap and syringe are NOT sterile. See directions for use. It is not known if GEN 215™ interacts with other medications. The use of GEN 215™ with other drugs has not been studied. Carcinogenesis and reproductive toxicity studies have not been conducted.

The safety and effectiveness of GEN 215™ has not been established:
- in patients with an active malignant neoplasm and should therefore not be used in such patients;
- in other non-periodontal bony locations, including other tissues of the oral and craniofacial regions such as bone graft sites, both extraction sites, bone cavities after cystectomy, and bone defects resulting from traumatic or pathological origin. GEN 215™ has also not been studied in situations where it would be supplanting autogenous bone and other bone grafting materials;
- in pregnant and nursing women. It is not known whether rhPDGF-BB is excreted in the milk of nursing women;
- in pediatric patients below the age of 18 years;
- in patients with teeth exhibiting mobility of greater than Grade 4 or a Class I furcation;
- in patients with frequent or excessive use of tobacco products.

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).

GEN 215™ grafting material is intended to be placed into periodontally related defects. It must not be injected systemically.

The radiopacity of GEN 215™ is comparable to that of bone and dimethacryl in GEN 215™ is resorbable. The radiopacity of GEN 215™ must be considered when evaluating radiographs as it may mask underlying pathological conditions.

PRECAUTIONS:

GEN 215™ contains beta-tricalcium phosphate, a recombinantly produced, human platelet-derived growth factor, homodimer BB (rhPDGF-BB), which is a protein that has been shown to stimulate the formation of a periodontal defect. rhPDGF-BB (PDGF) is also the active ingredient of another FDA approved product, REGENERAX® Gel, which is a topical gel formulation, indicated for the treatment of lower extremity diabetic neurologic ulcers.

An increased rate of mortality secondary to malignancy with use of high quantities (i.e., 3 or more tubes of REGENERAX® Gel) was demonstrated in a single study (14 use in treatment of diabetic neurologic ulcers). The subsequent studies did not demonstrate this increased rate. No relationship has been demonstrated regarding use of PDGF in periodontal defects and malignancy or mortality secondary to malignancy. Note the following information:

Post-Operative Studies regarding Cancer Risk in Patients Treated with REGENERAX® Gel and This Applicability to use of GEN 215™:

The product label of REGENERAX® Gel contains a warning identifying an increased rate of mortality secondary to malignancy in patients treated with three or more tubes of this product based on the results of the first of three post-operative studies of REGENERAX® Gel.

Summary of the Three REGENERAX® Post-Operative Studies Findings Regarding Cancer:

First, in a retrospective study of a medical claims database, cancer rates and overall cancer mortality were compared between 9122 patients who used REGENERAX® Gel and 2693 matched comparators. Estimates of the incidence rates reported may be under-reported due to limited follow-up for individuals.
- The incidence rate for all cancers was 30.3 per 1000 person years for patients treated with REGENERAX® Gel and 5.9 per 1000 years for the comparator. Adjusted for several possible confounders, the rate ratio was 1.2 (95% confidence interval 0.7-1.9). Types of cancers varied and were more remote from the site of treatment.
- The incidence rates for mortality from all cancers was 1.6 per 1000 person years for those who received REGENERAX® Gel and 0.9 per 1000 person years for the comparator. The adjusted rate ratio was 1.8 (95% confidence interval 0.2-10.5).
- The incidence rate for mortality from all cancers among patients who received 3 or more tubes of REGENERAX® Gel was 3.9 per 1000 years and 0.9 per 1000 person years for the comparators. The rate ratio for cancer mortality among those who received 3 or more tubes relative to those who received one was 5.2 (95% confidence interval 0.6-16.0), although this estimate ignored confounders in the incidence model due to the small number of events in this group.

These results are based on follow-up information, post-treatment out to 3 years. The information indicates that patients treated with REGENERAX® Gel did not have a greater incidence of post-treatment cancer, but patients treated with 3 or more tubes of REGENERAX® Gel had a statistically significantly increased rate of mortality, i.e., a 2-fold greater rate, secondary to malignancy, unadjusted for other confounders. The malignancies were not distant from the site of application in bicuspid (PDGF) users evaluated in the postmarketing study.

Second, in the follow-up retrospective study of the same patient cohorts (total treatment 29134), investigators found that the bicuspid treatment group received 3 or more tubes of REGENERAX® Gel did not have an increased incidence of cancer as compared to the control group. While the cancer mortality rate remained higher (the adjusted rate ratio was 2.4 with 95% confidence interval 0.3-14.6) in the bicuspid treatment group receiving 3 or more tubes of REGENERAX® Gel, the rate was not statistically different from the rate of cancer mortality of the control group during this observation period. The findings of the second study of this post-treatment group 4 to 6 years are not considered to negate the findings of the first study of patients in post-treatment of this group (1 to 3 years) as the findings of the second study were not considered to negate the findings of the first study.

Third, a study evaluating cancer risk associated with the use of Becaplermin (rhPDGF-BB) for the treatment of diabetic foot ulcers were conducted by the Veterans Administration. This study compared cancer rates and overall cancer mortality between 6429 patients who used REGENERAX® Gel and 6425 matched comparators followed over 11 years (1998 through 2009). The hazard ratio for cancer mortality among those who received 3 or more tubes of REGENERAX® Gel relative to those who received one was 1.04 (95% confidence interval 0.73-1.48). This study provided no evidence of a cancer risk among bicuspid users, and did not indicate an elevated risk of cancer mortality.

These three studies have limited relevance to the use of GEN 215™ in treatment of periodontal defects due to:

- higher doses of rhPDGF-BB than REGENERAX® Gel or GEN 215™;
- their different intended uses;
- the locations where the products containing PDGF were placed;
- possible gender bias; and
- limited statistical power to detect small increase cancer death risks.

Non-clinical Safety/Carcinogenesis, Mutagenesis, Impairment of Fertility Testing

Becaplermin was tested in a battery of *in vitro* assays including those for bacterial and mammalian cell transformation, chromosomal aberrations, and DNA damage; *in vivo* assays reported identified for the REGENERAX® Gel production, cell population tested to be mutagenic or mutagenicity evaluation conducted for GEN 215™. Becaplermin/REGENERAX® Gel was also not mutagenic as *in vivo* assays for the induction of micronuclei in mouse bone marrow cells. Other non-clinical studies including long term implantation, acute and repeated dose toxicity, reproductive/developmental toxicity, and related pharmacokinetic studies were conducted to evaluate the safety of rhPDGF-BB doses for use in excess of the usual dental use of a single administration in GEN 215™. These studies have shown no adverse findings.

No Clinical Evidence of Increased Cancer Incidence or Mortality in GEN 215™ Patients: There is no information that suggests an increased cancer incidence or mortality associated with PDGF in data from human clinical trials of GEN 215™ or in preclinical studies of PDGF. Additionally, no potential safety concerns related to cancer or cancer mortality have been identified through routine postmarketing pharmacovigilance; however, it is important to recognize that the pharmacologic mechanism is a regulatory system in which patient outcomes are not actively checked.

This information is being supplied to permit the attending surgeon to evaluate all pharmacologic aspects of the use of GEN 215™ in his/her intended patients. Interpretation of the results of these and all studies should be made with caution. Use of the product should be evaluated with this pre-cautionary information in mind.

GEN 215™ is intended for use by clinicians familiar with periodontal surgical grafting techniques.

GEN 215™ is supplied in a single unit only. Any unopened unused material must be discarded and component of this system should not be used separately.

HOW GEN 215™ IS SUPPLIED:

Each GEN 215™ kit consists of:
(1) one cap containing 0.5 cc of 8-TCP particles (0.25 to 1.0 mm); and
(2) one syringe containing a solution of 0.5 mL rhPDGF-BB (0.3 mg/mL).
All of these components are for single use only.

CLINICAL STUDY:

A 100 patient, double-blinded, controlled, prospective, randomized, parallel designed multicenter clinical trial in subjects who required surgical interventions to treat intrabony periodontal defects was completed.

The major inclusion criteria were:
a. No local or systemic aggressive periodontitis
b. Treatment site with the following characteristics:
- Probing pocket depth > 7 mm at baseline,
- After surgical debridement, > 4 mm vertical bone defect with at least 1 bony wall,
- Sufficient keratinized tissue to allow complete tissue coverage of defect, and
- Radiographic bone of defect > 2 mm coronal to the apex of tooth.

The major exclusion criteria were:
a. No periodontal surgery on the subject tooth within the last year;
b. No significant recent tobacco use;
c. Allergy to yeast-derived products;
d. Using an investigational therapy within the past 30 days.

The duration of the study was six (6) months following implantation of the product. Patients were randomized into three patient treatment groups:
- Group I (n=60): 8-TCP and 0.3 mg/mL rhPDGF-BB (GEN 215™)
- Group II (n=6): 8-TCP and 1.0 mg/mL rhPDGF-BB
- Group III (n=35): 8-TCP and buffer alone (active control)

The baseline characteristics among the subjects in each group were similar with the exception of "none of defect to root apex." Group I had a mean defect which was significantly less than in Group II (0.5 mm vs. 1.7 mm, p < 0.04).

Schedule of Patient Visits:

Patients had 6 visits over the 6 months prior to surgery and device implantation. Scaling and root planing were performed if necessary within 3 months prior to the implant surgery (Visit 1). Following randomization, subjects underwent 6 follow-up visits during the first 24 days to assess wound healing and pain assessment and then 4 further visits every 6 weeks through 6 months. At these latter visits, clinical measurements and radiographs were performed.

Endpoints:

The pre-defined primary effectiveness endpoint was the mean change in CAL between baseline and 6 months. Results were to be compared for each group to a historically established level of effectiveness (mean change of 1.5 mm) and to between Group I and Group II. The pre-defined secondary endpoints included:
- Comparison of linear bone growth (LBG)
- Comparison of % bone defect fill (BDF) based on radiographs
- Area under the curve for change in CAL
- Change in CAL between baseline and 6 months
- Pocket depth reduction (PDR) change between baseline and 6 months
- Gingival recession (GR) change between baseline and 6 months
- Wound healing during first 3 weeks post-operatively

Primary Endpoint Results:

The primary effectiveness endpoint was evaluated using the mean change in CAL gain [mm] from baseline to 6 months for each of the three groups. Mean changes at 6 months are presented in the table below:

Table with 5 columns: Group of Interest and Change, Control Group and Mean Change, Difference, p-value. Rows include Linear Bone Growth, % Bone Fill, AUC for CAL Gain, PDR, GR, and Wound Healing.

As seen in the table above, all three groups, including the control group, had statistically and clinically meaningful mean CAL gains when compared to the historically established 1.5 mm level (p < 0.001). At 6 months, there was no statistically or clinically significant difference in CAL gain for the low concentration group (Group I) when compared to the active control without GEN 215™ (p > 0.20). However, at 3 months post-implant (see Table above), the difference was 0.5 mm (3 mm vs. 3.3 mm) which was statistically significant (p < 0.04) suggesting that the device may facilitate earlier restorative treatment.

Secondary Endpoint Results:

As noted above, numerous secondary endpoints were pre-defined in the clinical protocol. The results for these are presented in the Table below. The results represent changes from baseline to 6 months unless otherwise noted.

Table with 5 columns: Parameter, Primary Group and Mean Change, Control Group and Mean Change, Difference in Means, p-value. Rows include Linear Bone Growth, % Bone Fill, AUC for CAL Gain, CAL Gain, PDR, GR, and Wound Healing.

*Not a pre-defined secondary or primary endpoint.

The table illustrates that both the low- and high-dose device achieved significant improvement over the control device (no rhPDGF-BB) at 6 months for linear bone growth and percent bone fill. Although other parameters CAL gain and gingival recession showed significant changes at 3 months for the low concentration group (Group I) when compared to the active control without GEN 215™ (p < 0.20). Again, several of these results suggest that the device facilitates earlier resolution of periodontal bony lesions.

Long Term Follow-up:

Following the 24-month observation period, study data demonstrated the continued long term efficacy of GEN 215™ treatment.

Statistical analysis of the long term follow-up data demonstrated that over the 24-month observation period, all treatment groups demonstrated an increase in bone fill. At the end of the 24-month observation period, the GEN 215™ group demonstrated a statistically significant greater amount of bone formation compared to the 8-TCP matrix alone. In addition, after 24 months, the 8-TCP group failed to experience the level of radiographic bone fill that was achieved by the GEN 215™ group at the end of the first six months of this trial.

Table with 5 columns: Long Term Parameter, Primary Group and Mean Change, Control Group and Mean Change, Difference in Means, p-value. Rows include Linear Bone Growth, % Bone Fill, CAL Gain, PDR, and Change in GR.

Comparison of Endosseous™ and GEN 215™ Pretrial Clinical Trial Results:

The table below compares the results obtained in the GEN 215™ pretrial clinical trial to two safety and efficacy studies submitted as part of the Endosseous™ device. When implanted into bony defects of the maxilla and mandible, the GEN 215™ clinical and radiographic parameters in the GEN 215™ clinical trial were similar to those reported for other regenerative therapies in studies examining defects with similar bony characteristics.

Table with 2 columns: Measure/Parameter and Treatment Outcomes. Rows include Healing Period, Clinical Attachment Level, Defect Depth, Clinical Attachment Level Gain, Radiographic Linear Fill, and Radiographic % Defect Fill.

Endosseous is a registered trademark of Biomet/Biomet 3C Corporation (PMP# P30001).
*Hugli, L., Hilde, S., Swendson, G., Ostgren A. Enamel matrix derivative (EMDOGAIN) in the treatment of intra-bony periodontal defects. / Clin Periodontol. 1992;19:242-250.
†Asterholm D., Anderson, J., Eriksson J. Clinical safety of enamel matrix derivative (EMDOGAIN) in the treatment of periodontal defects. / Clin Anesthet. 1999;124:659-704.

Safety:

During the initial 6-month observation period, there were 3 patients (0 Group 1, 6 Group 5, 5 Group 6) with adverse events reported as incidence of adverse events across the three treatment groups.

No safety measurements were collected during the long term follow-up observation period (month 3 through 24).

Conclusion:

GEN 215™ was shown, by both clinical and radiographic measures, to be effective in treating moderate to severe periodontally related defects within 6 months of implantation. The therapeutic effects of GEN 215™ require bony growth, or exceed, documented outcomes with control matrix derivatives. When implanted into bony defects of the maxilla and mandible, GEN 215™ has been shown to speed clinical attachment level (CAL) gains, reduce gingival recession, and improve bone growth resulting in increased bone fill of the osseous defect. The long term follow-up data demonstrate that the effectiveness of GEN 215™ is sustained for at least 2 years and remains statistically significantly superior to the control device in terms of radiographic percent bone fill and linear bone gain.

ADVERSE EVENTS:

Although serious adverse reactions attributable to GEN 215™ were reported in a 180 patient clinical trial, patients being treated with GEN 215™ may experience any of the following adverse events that have been reported in the literature with regard to periodontally surgical grafting procedures: swelling, pain, bleeding, hematoma, dizziness, lightheadedness, nausea, vomiting, or weakness; increased tooth mobility; suppuration or deep wound infection; cellular, wound dehiscence; emergence and loss of restorative healthily and esthetically 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.

DISPOSING FOR USE:

ASEPTIC TECHNIQUE:
- The contents of the cap of 8-TCP are supplied sterile by gamma irradiation.

- Once rhPDGF-BB is aseptically processed and filled into the syringe in which it is supplied.

The exterior of the cap of 8-TCP and the exterior surface of the syringe are non-sterile. Because of this, it is recommended that transfer of the 8-TCP particles to a sterile container in the sterile operating field be performed in a sterile manner prior to adding the PDGF from the syringe. Care must also be taken to minimize cooling the 8-TCP particles. Appropriate sterile transfer techniques must be used to prevent contamination of the contents of the cap and syringe.

SURGICAL TECHNIQUE:

Familiarization with the device and following proper surgical grafting techniques are extremely important when using GEN 215™. Radiographic evaluation of the defect prior to use is essential to accurately assess the extent of the defect and to aid in the placement of the grafting material. Following exposure of the defect with a full thickness mucoperiosteal flap, all granulation tissue must be carefully removed. Thorough soft tissue debridement of the defect is critical to successful regeneration. Granulation tissue, both in the defect, could be stimulated by the rhPDGF-BB component, diminishing the desired regenerative response. Exposed root surfaces should also be thoroughly planed.

Following thorough debridement of the osseous defect, the clinician, based on his or her experience, estimates the amount of GEN 215™ needed to fill the defect. For best results, GEN 215™ must completely fill the defect to the level of the surrounding bony walls. Overflowing should be avoided. The clinician requires the GEN 215™ to be placed in direct contact with the root surface. Careless handling should be controlled prior to placing grafting materials. Following placement of the GEN 215™ and completion of any additional surgical steps, the mucoperiosteal flap should be sutured to active primary closure whenever possible.

Postoperative patient management should follow the same regimen as similar cases utilizing autogenous bone grafts. Pre-requisites for all regenerative procedures include prevention of wound dehiscence, a stable diet and optimal buccal care.

The GEN 215™ kit and its components must not be re-sterilized by any method or reused. Inspect each individual sterile component of the kit for structural integrity prior to use. If the seal of any syringe or container is open, broken or otherwise damaged, the product must be assumed to be non-sterile and, consequently, must not be used.

Any opened unused material must be discarded and components of this system should not be used separately.

STORAGE CONDITIONS:

The GEN 215™ kit must be refrigerated at 2° to 8° C (36° to 46° F). Do not freeze. The individual rhPDGF-BB component must be refrigerated at 2° to 8° C (36° to 46° F). The 8-TCP cap can be stored at room temperature, up to 30° C (86° F). The rhPDGF-BB component must be protected from light prior to use; do not remove from outer covering prior to use.

Do not use after the expiration date.

BIOCOMPATIBILITY:

GEN 215™ biocompatibility has been demonstrated in accordance with the International Standard ISO 10993-1:1993 "Biological Evaluation of Medical Devices - Part 1: Evaluation and Testing."

Comparison of GEN 215™ and REGENERAX® Gel: The clinical evaluation of REGENERAX® Gel included a treatment regimen of applying the gel daily to sites after care for up to 20 weeks. Patients who were observed in the first study to have the unadjusted 5.2 fold greater rate of mortality due to cancer would have received 450 mg, or more, of PDGF. Each tube of REGENERAX® Gel contains 75 mg of PDGF. Thus, a 6 tube regimen would result in 450 mg of PDGF.

Patients treated with GEN 215™ in a one-time dose could receive 150 µg of PDGF since each GEN 215™ kit contains 0.5 mL of 0.3 mg PDGF. Patients who have periodontal defects may have periodontitis disease and could require multiple defect repairs and therefore, per the treating physician's opinion for the use of GEN 215™, patients may be treated with more than the one-time amount of 150 µg PDGF.

The amount of PDGF in GEN 215™ used in a periodontal defect is 3000 fold less than the amount of PDGF in the three tubes of REGENERAX® Gel. There are many variables specific to the REGENERAX® Gel patient population which might influence the apparent PDGF mortality rate association. Not least among these variables is the fact that patients with known malignancies were allowed to be treated with REGENERAX® Gel whereas patients are instructed to treat patients with GEN 215™ who are cancer-free.

*Reich and Child Reporting GEN 215™ Do Not Indicate an Increased Cancer Incidence or Mortality.

Manufactured by:

LYNCH BIOLOGICS LLC
Lynch Biologics, LLC
First Floor
800 974-2334
This product is sold and distributed under US patents: 4,846, 075; 5,045,633; 5,104,396; 7,473,078.

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