

LABELING

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GEM 21S™

Growth-factor Enhanced Matrix

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

DEVICE DESCRIPTION:

GEM 21S™ is a completely synthetic grafting system for bone and periodontal regeneration composed of a purified recombinant growth factor and a synthetic calcium phosphate matrix.

GEM 21S™ is composed of two sterile components:

- synthetic beta-tricalcium phosphate (β -TCP) [$\text{Ca}_3(\text{PO}_4)$] is a highly porous, resorbable osteoconductive 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. Pore diameters of the scaffold are specifically designed for bone ingrowth and range from 1 to 500 μm . The particle size ranges from 0.25 to 1.0 mm and
- highly purified, recombinant human platelet-derived growth factor-BB (rhPDGF-BB). PDGF is a native protein constituent of blood platelets. It is a tissue growth factor that is released at sites of injury during blood clotting. Extensive *in vitro* and animal studies have demonstrated its potent mitogenic (proliferative) and chemotactic (directed cell migration) effects on bone and periodontal ligament derived cells. Animal studies have shown PDGF to promote the regeneration of periodontal tissues including bone, cementum, and periodontal ligament (PDL).

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

INDICATIONS:

GEM 21S™ is indicated to treat the following periodontally related defects:

- Intrabony periodontal defects;
- Furcation periodontal defects;
- Gingival recession associated with periodontal defects.

CONTRAINDICATIONS:

As with any periodontal procedure where bone grafting material is used, *GEM 21S™* 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 (β -TCP or rhPDGF-BB);
- Intraoperative 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 cup and syringe are **NOT** sterile. See directions for use.

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It is not known if *GEM 21S™* interacts with other medications. The use of *GEM 21S™* with other drugs has not been studied. Carcinogenesis and reproductive toxicity studies have not been conducted.

The safety and effectiveness of *GEM 21S™* has not been established:

- In other non-periodontal bony locations, including other tissues of the oral and craniofacial region such as bone graft sites, tooth extraction sites, bone cavities after cystectomy, and bone defects resulting from traumatic or pathological origin. *GEM 21S* has also not been studied in situations where it would be augmenting 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 II or a Class III 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*).

The *GEM 21S™* grafting material is intended to be placed into periodontally related defects. It must not be injected systemically.

The radiopacity of *GEM 21S™* is comparable to that of bone and diminishes as *GEM 21S™* is resorbed. The radiopacity of *GEM 21S™* must be considered when evaluating radiographs as it may mask underlying pathological conditions.

PRECAUTIONS:

GEM 21S™ is intended for use by clinicians familiar with periodontal surgical grafting techniques.

GEM 21S™ is supplied in a single use kit. Any unopened unused material must be discarded and components of this system should not be used separately.

HOW *GEM 21S™* IS SUPPLIED:

Each *GEM 21S™* kit consists of:

(1) one cup containing 0.5 cc of β -TCP particles (0.25 to 1.0 mm);

(2) one syringe containing a solution of 0.5 ml rhPDGF-BB (0.3 mg/ml);

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All of these components/accessories are **for single use only**.

CLINICAL STUDY:

A 180 patient, double-blinded, controlled, prospective, randomized, parallel designed multicenter clinical trial in subjects who required surgical intervention to treat intraosseous periodontal defects was completed.

The major inclusion criteria were:

- a. No localized aggressive periodontitis
- b. Treatment site with the following characteristics:
 - Probing pcket depth \geq 7mm at baseline,
 - After surgical debridement, \geq 4mm vertical bone defect with at least 1 bony wall,
 - Sufficient keratinized tissue to allow complete tissue coverage of defect, and
 - Radiographic base of defect \geq 3mm coronal to the apex of the 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): β -TCP and 0.3 mg/ml rhPDGF-BB (*GEM 21S™*)
- Group II (n=61): β -TCP and 1.0 mg/ml rhPDGF-BB
- Group III (n=59): β -TCP and buffer alone (active control)

The baseline characteristics among the subjects in each group were similar with the exception of “base of defect to root apex”. Group I had a mean defect which was significantly less than in Group III (6.5mm vs. 7.7mm, p=0.04).

Schedule of Patient Visits

Patients had 4 visits over the 6 months prior to surgery and device implantation. Scaling and root planning were performed if necessary within 3 months prior to the implant surgery date (Visit 5). Following implantation, subjects underwent 4 follow-up visits during the first 24 days to assess wound healing and pain assessment and then 4 further follow-up 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 1) for each group to a historically

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established level of effectiveness (mean change of 1.5 mm) and 2) between Group I and Group III. The pre-defined secondary endpoints included:

- Comparison of linear bone growth (LBG)
- Comparison of % bone defect fill (%BF) 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:

Group of Interest and Change	Control Group and Change	Difference	p-value
Group I 3.7 mm	Historical 1.5 mm	2.2 mm	<0.001
Group II 3.7 mm	Historical 1.5 mm	2.2 mm	<0.001
Group III 3.5 mm	Historical 1.5 mm	2.0 mm	<0.001
Group I 3.7 mm	Group III 3.5 mm	0.2 mm	0.20

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 GEM 21S ($p = 0.20$). However, at 3 months (not included in the Table above), the difference was 0.5 mm (3.8 mm vs 3.3 mm) which was statistically significant ($p = 0.04$) suggesting that the device may facilitate *earlier* resolution of periodontal intrabony lesions.

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.

Parameter	Primary Group and Mean Change	Control Group and Mean Change	Difference in Means	p-value
Linear Bone Growth	Group I	Group III	1.63 mm	<0.001

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	2.52 mm	0.89 mm		
	Group II 1.53 mm	Group III 0.89 mm	0.64 mm	0.02
% Bone Fill	Group I 56.0%	Group III 17.9%	38.1%	<0.001
	Group II 33.9%	Group III 17.9%	16.0%	0.02
AUC for CAL Gain (mm-weeks)	Group I 67.5	Group III 60.1	7.4	0.05
	Group II 61.8	Group III 60.1	1.7	0.35
CAL Gain	Group II 3.7 mm	Group III 3.5 mm	0.2 mm	0.29
PDR	Group I 4.4mm	Group III 4.2 mm	0.2 mm	0.38
	Group II 4.3 mm	Group III 4.2 mm	0.1 mm	0.66
PDR – 3 Months*	Group I 4.2 mm	Group III 4.2 mm	0.0 mm	0.80
	Group II 4.1 mm	Group III 4.2 mm	0.1 mm	0.67
GR	Group I 0.7 mm	Group III 0.7 mm	0.0 mm	0.95
	Group II 0.6 mm	Group III 0.7 mm	0.1 mm	0.81
GR – 3 Months*	Group I 0.5 mm	Group III 0.9 mm	0.4 mm	0.04
	Group II 0.7 mm	Group III 0.9 mm	0.2 mm	0.46

* 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 high-dose group, these benefits were not maintained over control at 6 months. Again, several of these results suggest that the device facilitates *earlier* resolution of periodontal intrabony lesions.

Safety

There were 18 patients (7 Group I, 6 Group II, 5 Group III) with adverse events reported as related to the device. None of these were serious. They were all classified as surgical site reactions. There were no significant differences in the incidence of adverse events across the three treatment groups.

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Conclusion

GEM 21S™ was shown, by both clinical and radiographic measures, to be effective in treating moderate to severe periodontally related defects within six months of implantation. When implanted into bony defects of the periodontium, *GEM 21S™* has been shown to speed clinical attachment level (CAL) gain, reduce gingival recession, and improve bone growth resulting in increased bone fill of the osseous defect.

ADVERSE EVENTS:

Although no serious adverse reactions attributable to *GEM 21S™* were reported in a 180 patient clinical trial, patients being treated with *GEM 21S™* may experience any of the following adverse events that have been reported in the literature with regard to periodontal surgical grafting procedures: swelling; pain; bleeding; hematoma; dizziness; fainting; difficulty breathing, eating, or speaking; sinusitis; headaches; increased tooth mobility; superficial or deep wound infection; cellulitis; wound dehiscence; 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.

DIRECTIONS FOR USE:

ASEPTIC TECHNIQUE

- The contents of the cup of β -TCP is supplied sterile by gamma radiation.
- Sterile rhPDGF-BB is aseptically processed and filled into the syringe in which it is supplied.

The exterior portion of the cup of β -TCP and the exterior surface of the syringe are non-sterile. Because of this, it is recommended that transfer of the β -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 crushing the β -TCP particles. Appropriate sterile transfer techniques must be used to prevent contamination of the contents of the cup and syringe.

SURGICAL TECHNIQUE

Familiarization with the device and following proper surgical grafting techniques are extremely important when using *GEM 21S™*. Radiographic evaluation of the defect site 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, if left in the defect, could be stimulated by the rhPDGF-BB component, diminishing the desired regenerative response. Exposed tooth root surfaces should also be thoroughly planed.

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Following thorough debridement of the osseous defect, the clinician, based on his or her experience, estimates the amount of *GEM 21S™* needed to fill the defect. For best results, *GEM 21S™* must completely fill the defect to the level of the surrounding bony walls. Overfilling should be avoided. The clinician prepares the *GEM 21S™* graft by fully saturating the β -TCP particles with the rhPDGF-BB solution and letting the product sit for approximately ten (10) minutes. Proper aseptic technique must be employed in preparing and applying *GEM 21S™*.

The saturated *GEM 21S™* should be placed into the defect using moderate pressure, taking care not to crush the particles. In order to enhance the formation of new bone, *GEM 21S™* should be placed in direct contact with well-vascularized bone. Excessive bleeding should be controlled prior to placing grafting materials. Following placement of the *GEM 21S™* and completion of any additional surgical steps, the mucoperiosteal flaps should be sutured to achieve primary closure wherever possible.

Postoperative patient management should follow the same regimen as similar cases utilizing autogenous bone grafting. Pre-requisites for all regenerative procedures include prevention of wound dehiscence, a stable clot and minimal bacterial contamination.

The *GEM 21S™* 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 inner or outer 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 *GEM 21S™* kit must be refrigerated at 2°-8° C (36°-46° F). Do not freeze. The individual rhPDGF-BB component must be refrigerated at 2°-8° C (36°-46° F). The β -TCP cup 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:

GEM 21S™ biocompatibility has been demonstrated in accordance with the International Standard ISO 10993-1:1997 "Biological Evaluation of Medical Devices – Part 1: Evaluation and Testing".

Manufactured By:

BioMimetic Pharmaceuticals, Inc.
330 Mallory Station No. A1

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Franklin, TN 37067

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This product is sold and distributed under US patents:

4,766,073
4,769,328
4,801,542
4,845,075
5,045,633
5,124,316
5,187,263