GEM 21S® PRODUCT INSERT APPROVED FOR USE IN THE USA AND AUSTRALIA

Geistlich GEM 21S®

Growth Factor Enhanced Matrix

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SPC0010.01
640222

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) [Ca_3 ($P0_4$)] 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. *In vitro* and animal studies have demonstrated PDGF's potent mitogenic (proliferative), angiogenic (neovascularization) and chemotactic (directed cell migration) effects on bone and periodontal ligament derived cells. PDGF is known to be one protein involved in the multi-factored 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 cup of β-TCP are 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:

- lntrabony periodontal defects;
- Furcation periodontal defects; and
- 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);
- lntraoperative 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.

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 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 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® contains becaplermin - a recombinantly produced, human platelet-derived growth factor, homodimer BB (rhPDGF-BB), which is a protein that has been shown to promote the formation of bone in periodontal defects. rhPDGF-BB ("PDGF") is also the active ingredient of another FDA approved product, REGRANEX® Gel, which is a topical gel formulation, indicated for the treatment of lower extremity diabetic neuropathic ulcers.[1]

An increased rate of mortality secondary to malignancy with use of high quantities (i.e., 3 or more tubes of REGRANEX® Gel) was demonstrated in a single study of its use in treatment of diabetic, neuropathic ulcers. Two 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-Approval Studies regarding Cancer Risk in Patients Treated with REGRANEX® Gel and Their Applicability to use of GEM 21S®

The product label of REGRANEX® 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-approval studies of REGRANEX® Gel.

Summary of the Three REGRANEX® Post-Approval Studies[1] Findings Regarding Cancer

First, in a retrospective study[2] of a medical claims database, cancer rates and overall cancer mortality were compared between 1622 patients who used REGRANEX® Gel and 2809 matched comparators. Estimates of the incidence rates reported below may be under-reported due to limited follow-up for each individual.

- The incidence rate for all cancers was 10.2 per 1000 years for patients treated with REGRANEX® Gel and 9.1 per 1000 years for the comparators. Adjusted for several possible confounders, the rate ratio was 1.2 (95% confidence interval 0.7-1.9). Types of cancers varied and were remote from the site of treatment.
- The incidence rate for mortality from all cancers was 1.6 per 1000 person years for those who received REGRANEX® Gel and 0.9 per 1000 person years for the comparators. The adjusted rate ratio was 1.8 (95% confidence interval 0.7-4.9).
- The incidence rate for mortality from all cancers among patients who received 3 or more tubes of REGRANEX® 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 none was 5.2 (95% confidence interval 1.6-17.6), 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 REGRANEX® Gel did not have a greater incidence of post-treatment cancer, but patients treated with 3 or more tubes of REGRANEX® Gel had a statistically significant increased rate of mortality, i.e., a 5.2 fold greater rate, secondary to malignancy, unadjusted for other confounders. The malignancies observed were distant from the site of application in becaplermin (PDGF) users evaluated in the postmarketing study.

Second, in the follow-up epidemiologic study of these same patient cohorts (post-treatment years 3 to 6), investigators found that the becaplermin treated group receiving 3 or more tubes of REGRANEX® 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 0.8-7.4) in the becaplermin treated group receiving 3 or more tubes of REGRANEX® Gel, the rate was not statistically different than the rate of cancer mortality of the control group during this observation period. The findings of the second study of patients in post-treatment years 4 to 6 are not considered to negate the findings of the first study of patients in post-treatment years 1 to 3, just as the findings of the first study are not considered to negate the findings of the second study.

Third, a study evaluating cancer risk associated with the use of Becaplermin (rhPDGF-BB) for the treatment of diabetic foot ulcers was conducted by the Veterans Administration. This study compared cancer rates and overall cancer mortality between 6429 patients who used REGRANEX® Gel and 6429 matched comparators followed over 11 years (1998 through 2009). The hazard ratio for cancer mortality among those who received 3 or more tubes of REGRANEX® Gel relative to those who received none was 1.04 (95% confidence interval 0.73-1.48). This study provided no evidence of a cancer risk among becaplermin users, and did not indicate an elevated risk of cancer mortality.

These three studies have limited relevance to the use of GEM 21S® in treatment of periodontal defects due to:
- higher doses of rhPDGF-BB with REGRANEX® Gel compared to GEM 21S®,
- their different intended uses,
- the locations where the products containing PDGF were placed,
- possible gender bias, and
- limited statistical power to detect small incident cancer death risks.

Non-clinical Toxicology Carcinogenesis, Mutagenesis, Impairment of Fertility Testing

Becaplermin was not genotoxic in a battery of *in vitro* assays (including those for bacterial and mammalian cell point mutation, chromosomal aberration, and DNA damage/repair) in reports identified for the REGRANEX® Gel product, nor was becaplermin found to be mutagenic in mutagenicity evaluations conducted for GEM 21S®. Becaplermin/REGRANEX® Gel was also not mutagenic in an *in vitro* assay for the induction of micronuclei in mouse bone marrow cells. Other non-clinical studies including long term implantation, acute and repeated dose toxicity, reproductive/development toxicity, and rodent pharmacokinetic studies were conducted to evaluate the safety of rhPDGF-BB at doses far in excess of the usual dental dose of a single administration in GEM 21S®. These studies have shown no adverse findings.

No Clinical Evidence of Increased Cancer Incidence or Mortality in GEM 21S® Patients

There is no information that suggests an increased cancer incidence or mortality associated with PDGF in data from human clinical trials of GEM 21S® 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 pharmacovigilance mechanism is a voluntary system in which patient outcomes are not actively researched.

This information is being supplied to permit the attending surgeon to evaluate all known aspects of the use of GEM 21S® 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 precautionary information in mind.

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); 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 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 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 base of defect ≥ 3 mm 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 (6.5 mm vs. 7.7 mm, p = 0.04).

Schedule of Patient Visits

Patients had 4 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 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 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 2.52 mm	Group III 0.89 mm	1.63 mm	< 0.001
	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 4.4 mm	Group III 4.2 mm	0.2 mm	0.38
	Group I 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 low-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.

Long-Term Follow-up

Throughout the 24 month observation period, study data demonstrated the continued long-term efficacy of GEM 21S® treatment.

Radiographic (x-ray) analysis of bone growth showed 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 GEM 21S® group demonstrated a statistically significant greater amount of bone formation compared to the β-TCP matrix alone. In addition, after 24 months, the β-TCP group failed to experience the level of radiographic bone fill that was achieved by the GEM 21S® group at the end of the first six months of this trial.

Long-Term Parameter	Primary Group and Mean Change	Control Group and Mean Change	Difference in Means	p-value
Linear Bone Growth (24 Months)	Group I 3.32 mm	Group III 1.81 mm	1.51 mm	< 0.001
	Group II 2.40 mm	Group III 1.81 mm	0.59 mm	0.074
% Bone Fill (24 Months)	Group I 68.3%	Group III 41.5%	26.8%	< 0.001
	Group II 57.3%	Group III 41.5%	15.8%	0.022
CAL Gain (24 Months)	Group I 4.07 mm	Group III 3.28 mm	0.79 mm	0.117
	Group III 3.47 mm	Group III 3.28 mm	0.19 mm	0.711
PDR (24 Months)	Group I 4.48 mm	Group III 3.79 mm	0.69 mm	0.121
	Group II 4.03 mm	Group III 3.79 mm	0.24 mm	0.597
Change in GR (24 Months)	Group I 0.41 mm	Group III 0.52 mm	0.11 mm	0.726
	Group II 0.57 mm	Group III 0.52 mm	-0.05 mm	0.850

Comparison of Emdogain® and GEM 21S® Pivotal Clinical Trial Results

The table below compares the results obtained in the GEM 21S® pivotal clinical trial to two safety and efficacy studies submitted as part of the Emdogain® PMA application. Improvements in clinical and radiographic parameters in the GEM 21S® trial compare favorably with, or exceed, documented outcomes for other regenerative therapies in studies examining defects with similar baseline characteristics.

	Baseline Measures			Treatment Outcomes		
	Probing Pocket Depth (mm)	Clinical Attachment Level (mm)	Defect Depth (mm)	Clinical Attachment Level Gain (mm)	Radiographic Linear Fill (mm)	Radiographic % Defect Fill
GEM 21S® N=60	8.6 ± 1.6	9.1 ± 1.6	6.0 ± 1.6	3.7 ± 1.6	2.5 ± 1.6	56
Emdogain®* N:34	7.8 ± 1.1	9.4 ± 1.5	7.1 ± 2.2	2.1 ± 1.5	0.9 ± 0.6	13
Emdogain® N:104**	7.4 ± 1.2	8.7 ± 1.7	N/A	3.1 ± 1.4	1.2 ± 1.1	15

Emdogain is a registered trademark of Bioventures BV Corporation (PMA# P930021).

*Heijl L, Heden G, Svardstrom G, Ostgren A. Enamel matrix derivative (EMDOGAIN) in the treatment of intrabony periodontal defects. *J Clin Periodontal.* 1997;24:705-714.

**Zetterstrom 0, Andersson C, Eriksson L et al. Clinical safety of enamel matrix derivative (EMDOGAIN) in the treatment of periodontal defects. *J Clin Periodontal.* 1997;24:697-704.

Safety
During the initial 6 month observation period, 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.

No safety measurements were collected during the long term follow-up observation period (month 7 through 24).

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. The therapeutic effects of GEM 21S® compare favorably with, or exceed, documented outcomes with enamel matrix derivative. 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. The long-term follow up data demonstrates that the effectiveness of GEM 21S® is sustained for at least 2 years and remains statistically significantly superior to the control group in terms of radiographic percent bone fill and linear bone gain.

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 are 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.

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° 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 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."

[1]Comparison of GEM 21S® and REGRANEX® Gel
The clinical evaluation of REGRANEX® Gel included a treatment regimen of applying the gel daily to skin ulcers 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 secondarily to cancer would have received 450 mg, or more, of PDGF. Each tube of REGRANEX® Gel contains 15 g of a 0.01% formulation of PDGF.

Patients treated with GEM 21S®, on a one-time basis could receive 150 µg of PDGF since each GEM 21S® kit contains 0.5 mL of a 0.3 mg PDGF formulation. Patients who have periodontal defects may have periodontal disease and could require multiple defect repairs and therefore, per the treating physician's opinion for the use of GEM 21S®, patients may be treated with more than the one-time amount of 150 µg PDGF.

The amount of PDGF in GEM 21S® used in repair of 1 periodontal defect is 3000 fold less than the amount of PDGF in three tubes of REGRANEX® Gel. There are many variables specific to the REGRANEX® 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 REGRANEX® Gel whereas physicians are instructed not to treat patients with GEM 21S® who have active neoplasms.

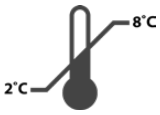
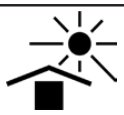
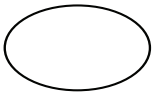
[2]Bench and Clinical Data Regarding GEM 21S® Do Not Indicate an Increased Cancer Incidence or Mortality.

LYNCH BIOLOGICS LLC

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800-874-2334

July 2025
MG # 26792

This product is sold and distributed under US patents:
4,845,075; 5,045,633; 5,124,316; 7,473,678

Symbol	Symbol description
	**Manufacturer**
	**Sterilized using aseptic processing techniques**
	**Sterilized using irradiation**
	**Caution**
	**Batch Code**
	**Do not use if package is damaged and consult instructions for use**
	**Consult *instructions for use* or consult electronic *instructions for use***
	**Temperature limit (2-8°C)**
	**Do not re-use (single use only)**
	**Catalogue Number**
	**Use-by date**
	**Keep away from sunlight**
	**Single sterile barrier system**
Rx	**Caution: Federal law restricts this device to sale by or on the order of a dentist or physician.**

GEM 21S® PRODUCT INSERT APPROVED FOR USE IN CANADA

Geistlich GEM 21S®

Growth Factor Enhanced Matrix

ENGLISH

A. DESCRIPTION:

GEM 21S® Growth Factor Enhanced Matrix is a sterile, biocompatible, resorbable device composed of porous mineral granules that are packed into a bone void, physically filling the bone defect and providing an osteoconductive lattice or framework upon which bone grows. The granules are provided dry in one container, which is packaged with a separate container containing a sterile physiologic buffer solution of synthetic platelet-derived growth factor (PDGF) that is used to hydrate the granules. Prior to packing into the bone void, the bone mineral granules are wetted with the solution which improves the handling of the graft particles, and the hydrated bone graft is then used to fill bone voids in dental, periodontal, oral and maxillofacial surgery.

The osteoconductive bone mineral granules provide a physical lattice or scaffold for bone growth and the solution of rhPDGF is used to hydrate the granules. The bone mineral substitute is terminally sterilized by gamma irradiation and the sterile solution of synthetic PDGF is aseptically filled into a syringe to facilitate delivery of the solution onto the bone granules during mixing prior to implantation.

The bone substitute in GEM 21S is composed of synthetic tricalcium phosphate (TCP) scaffold which has chemical, physical and mechanical properties similar to human bone. The rhPDGF facilitates the handling and incorporation of the graft particles. The consistency of this material readily allows it to take the shape of the defect. The graft is resorbed and replaced with new bone.

The mineral matrix physically fills bone voids, providing a matrix or scaffolding for bone formation. By filling the defect, it also prevents the collapse of the soft tissues into the bone defect and, due to its porous nature, facilitates stabilization of the blood clot. The mineral matrix provides an osteoconductive framework for the formation of new bone. PDGF-BB is a well characterized endogenous protein with a scientifically established localized mode of action that is known to enhance tissue healing responses and angiogenesis. Combining rhPDGF-BB solution with osteoconductive bone mineral improves the handling of the graft particles and enhances the bone mineral's physical and mechanical actions, similar to how collagen added to bone mineral substitutes facilitates the handling and action of bone mineral (e.g., see CE Marked products GEM Bone Graft Putty, Bio-Oss Collagen™, and Osteobiol™)

GEM 21S is a kit of two sterile components:

1. one cup containing 0.5 cc of scaffold (synthetic beta-tricalcium phosphate (β-TCP) [Ca_3 (PO_4)] particles)
2. 0.5ml syringe of 0.3mg/mL rhPDGF-BB in 20 mmol sodium acetate buffer pH 6, a highly purified, recombinant human platelet-derived growth factor)

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

B. INDICATIONS:

GEM 21S is intended for use as a grafting device in periodontal regenerative procedures and is indicated for:

- Augmentation or reconstructive treatment of the alveolar ridge
- Filling of periodontal defects
- Filling of extraction sockets to enhance preservation of the alveolar ridge
- Elevation of the maxillary sinus floor
- Filling of bone defects in conjunction with Guided Tissue Regeneration (GTR) and Guided Bone Regeneration (GBR)
- Filling of peri-implant defects in conjunction with products intended for GBR, and
- Gingival recession associated with periodontal disease.

C. CONTRAINDICATIONS:

GEM 21S is contraindicated for use in the presence of one or more of the following clinical situations:

- Untreated acute infections at the surgical site;
- Patients with cancer, including those being treated for cancer;
- Patients with a known hypersensitivity to any product component (β-TCP (GEM 21S) 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.

GEM 21S should not be used in patients who are skeletally immature (<18 years of age or no radiographic evidence of closure of epiphyses).

D. WARNINGS:

- GEM 21S is for single use only. GEM 21S is supplied in a single use kit. Any unopened or unused material must be discarded
- Components of this system should not be used separately
- The exterior of the cup and syringe are NOT sterile.
- GEM 21S is intended to be placed into periodontally related defects only and must not be injected systemically.

E. PRECAUTIONS:

- 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 pregnant and nursing women. It is not known whether rhPDGF-BB is excreted in the milk of nursing women or pediatric patients below the age of 18 years.
- 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 radiopacity of GEM 21S is comparable to that of bone and diminishes as it is resorbed. The radiopacity of GEM 21S must be considered when evaluating radiographs as it may mask underlying pathological conditions.
- GEM 21S is intended for use by clinicians familiar with periodontal surgical grafting techniques
- The effectiveness of GEM 21S has not been established for the treatment of Class III furcation periodontal defects or teeth exhibiting greater than Class II mobility

F. 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.

G. STORAGE CONDITIONS:

GEM 21S kit must be refrigerated at 2° to 8° C (36° to 46° F) in a dry place. Do not freeze.
The individual rhPDGF-BB component must be refrigerated at 2° to 8° C (36° to 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 tray until use. Do not use after the expiration date.

H. DIRECTIONS FOR USE:

1) PREPARATION OF GEM 21S

Appropriate sterile transfer techniques must be used to prevent contamination of the contents of the cup and syringe. While the contents of the cup containing scaffold (β-TCP) are supplied sterile by gamma radiation and rhPDGF-BB is aseptically processed and filled into the syringe, the exterior of the cup containing scaffold and the exterior surface of the syringe are non-sterile. Because of this, it is recommended that scaffold particles be transferred into a sterile container in the sterile operating field in an aseptic manner prior to adding the rhPDGF-BB solution. Care must also be taken to minimize crushing the scaffold particles.

Inspect each individual sterile component of the kit to assure the product has not been breached 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.

The clinician prepares GEM 21S by fully saturating the scaffold 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. It is best to prepare GEM 21S after the surgical wound is properly prepared (see Surgical Technique).

(2) SURGICAL TECHNIQUE

Familiarity 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. 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 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.

LYNCH BIOLOGICS LLC

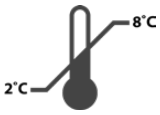
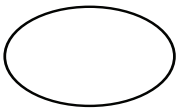
393 Nichol Mill Lane, Suite 280
Franklin, TN 37067 USA
800-874-2334

This product is sold and distributed under US patents: 4,845,075; 5,045,633; 5,124,316; 7,473,678

July 2025

MG # 26792

Symbol	Symbol description	Descrition du symbole
	**Manufacturer**	**Fabricant**
STERILE A	**Sterilized using aseptic processing techniques**	**Stérilisé à l'aide de techniques de traitement aseptique**
STERILE R	**Sterilized using irradiation**	**Stérilisé par irradiation**
	**Caution**	**prudence**

LOT	**Batch Code**	**code de lot**
	**Do not use if package is damaged and consult instructions for use**	**Ne pas utiliser si l'emballage est endommagé et consulter le mode d'emploi**
	**Consult *instructions for use* or consult electronic *instructions for use***	**Consultez le mode d'emploi ou consultez le mode d'emploi électronique**
	**Temperature limit (2-8°C)**	**Limite de température (2-8°C)**
	**Do not re-use (single use only)**	**Ne pas réutiliser (à usage unique seulement)**
REF	**Catalogue Number**	**N° de catalogue**
	**Use-by date**	**Date limite de consommation**
	**Keep away from sunlight**	**Tenir à l'abri de la lumière du soleil**
	**Single sterile barrier system**	**Système de barrière stérile unique**
Rx	**Caution: Federal law restricts this device to sale by or on the order of a dentist or physician.**	**sans objet**

FRANÇAIS

A. DESCRIPTION:

GEM 21S® Growth Factor Enhanced Matrix est un dispositif stérile, biocompatible et résorbable composé de granules minéraux poreux qui sont comprimés dans un vide osseux, remplissant physiquement le défaut osseux et fournissant un réseau ou un cadre ostéoconducteur sur lequel l'os se développe. Les granules sont fournis secs dans un récipient, qui est emballé avec un récipient séparé contenant une solution tampon physiologique stérile de facteur de croissance synthétique dérivé des plaquettes (PDGF) qui est utilisée pour hydrater les granules. Avant d'être comprimés dans le vide osseux, les granules minéraux osseux sont humidifiés avec la solution, ce qui améliore la manipulation des particules de greffe, et la greffe osseuse hydratée est ensuite utilisée pour combler les vides osseux en chirurgie dentaire, parodontale, buccale et maxillo-faciale.

Les granules minéraux osseux ostéoconducteurs fournissent un réseau physique ou un échafaudage pour la croissance osseuse et la solution de rhPDGF est utilisée pour hydrater les granules. Le substitut minéral osseux est stérilisé au stade terminal par irradiation gamma et la solution stérile de PDGF synthétique est introduite de manière aseptique dans une seringue pour faciliter l'administration de la solution sur les granules osseux pendant le mélange avant l'implantation.

Le substitut osseux dans GEM 21S est composé d'un échafaudage synthétique de phosphate tricalcique (TCP) qui possède des propriétés chimiques, physiques et mécaniques similaires à celles de l'os humain. Le rhPDGF facilite la manipulation et l'incorporation des particules greffées. La consistance de ce matériau lui permet aisément de prendre la forme du défaut. La greffe est résorbée et remplacée par du nouvel os.

La matrice minérale remplit physiquement les vides osseux, fournissant une matrice ou un échafaudage pour la formation osseuse. En comblant le défaut, il empêche également l'affaissement des tissus mous dans le défaut osseux et, en raison de sa nature poreuse, facilite la stabilisation du caillot sanguin. La matrice minérale fournit un cadre ostéoconducteur pour la formation d'un nouvel os. Le PDGF-BB est une protéine endogène bien caractérisée dont le mode d'action localisé est scientifiquement établi et connu pour améliorer les réponses de guérison des tissus et l'angiogenèse. La combinaison de la solution rhPDGF-BB avec un minéral osseux ostéoconducteur améliore la manipulation des particules de greffe et améliore les actions physiques et mécaniques du minéral osseux, de la même manière que le collagène ajouté aux substituts minéraux osseux facilite la manipulation et l'action du minéral osseux (par ex., voir les produits marqués CE GEM Bone Graft Putty, Bio-Oss Collagen™ et Osteobiol™)

GEM 21S est une trousse composée de deux composants stériles:

1. une coupelle contenant 0,5 cc d'échafaudage (particules de phosphate bêta-tricalcique synthétique (β-TCP) [particules de $Ca_3 (PO_4)$]
2. une seringue de 0.5 ml de 0.3 mg/ml de rhPDGF-BB dans 20 mmol de tampon d'acétate de sodium à pH 6, un facteur de croissance humain recombinant dérivé des plaquettes hautement purifié)

La biocompatibilité a été démontrée conformément à la norme internationale ISO 10993-1 « Évaluation biologique des dispositifs médicaux - Partie 1: Évaluation et essais ».

B. INDICATIONS:

GEM 21S est destiné à être utilisé comme dispositif de greffe dans les procédures régénératives de chirurgie parodontale et est indiqué pour:

- L'augmentation ou traitement reconstructif de la crête alvéolaire
- Le comblement des défauts parodontaux
- Le comblement des alvéoles d'extraction pour améliorer la préservation de la crête alvéolaire
- L'élévation du plancher sinusal maxillaire
- Le comblement des défauts osseux en association avec la régénération tissulaire guidée (GTR) et la régénération osseuse guidée (GBR)
- Le comblement des défauts péri-implantaires en association avec des produits destinés à la GBR, et
- La récession gingivale associée à une maladie parodontale.

C. CONTRE-INDICATIONS:

L'utilisation du GEM 21S est contre-indiquée en présence d'une ou plusieurs des situations cliniques suivantes:

- Infections aiguës non traitées sur le site chirurgical;
- Patients attients de cancer, y compris ceux qui sont traités pour un cancer;
- Patients présentant une hypersensibilité connue à l'un des composants du produit (β-TCP (GEM 21S) ou rhPDGF-BB);
- Une couverture peropératoire des tissus mous est nécessaire pour une intervention chirurgicale donnée, mais une telle couverture n'est pas possible; ou alors
- Conditions dans lesquelles la greffe osseuse générale n'est pas recommandée.

GEM 21S ne doit pas être utilisé chez les patients dont le squelette est immature (< 18 ans ou aucun signe radiographique de fermeture des épiphyses).

D. AVERTISSEMENTS:

- GEM 21S est à usage unique. GEM 21S est fourni dans une trousse à usage unique. Tout matériel non ouvert ou non utilisé doit être jeté
- Les composants de ce système ne doivent pas être utilisés séparément.
- L'extérieur du gobelet et de la seringue n'est PAS stérile.
- GEM 21S est destiné à être placé dans des défauts parodontaux uniquement et ne doit pas être injecté de manière systémique.

E. PRÉCAUTIONS:

- On ne sait pas si GEM 21S interagit avec d'autres médicaments. L'utilisation de GEM 21S avec d'autres médicaments n'a pas été étudiée.
- Aucune étude de carcinogenèse et de toxicité pour la reproduction n'a été menée. La sécurité et l'efficacité de GEM 21S n'ont pas été établies chez les femmes enceintes et celles qui allaitent. On ne sait pas si le rhPDGF-BB est excrété dans le lait des femmes qui allaitent ou des patientes pédiatriques de moins de 18 ans.
- Une attention particulière doit être accordée aux alternatives de traitement avant d'effectuer une greffe osseuse chez les patients:
    - Qui ont des maladies osseuses sévères secondaires à un trouble endocrinien (par ex. une hyperparathyroïdie);
    - qui reçoivent un traitement immunosuppresseur; ou alors
    - qui ont des conditions connues pouvant entraîner des complications hémorragiques (p. ex. hémophilie).
- La radio-opacité du GEM 21S est comparable à celle de l'os et diminue au fur et à mesure de sa résorption. La radio-opacité du GEM 21S doit être prise en compte lors de l'évaluation des radiographies car elle peut masquer des conditions pathologiques sous-jacentes.
- GEM 21S est destiné à être utilisé par des cliniciens familiers avec les techniques de greffe chirurgicale parodontale
- L'efficacité de GEM 21S n'a pas été établie pour le traitement des défauts parodontaux de furcation de classe III ou des dents présentant une mobilité supérieure à la classe II.

F. ÉVÉNEMENTS INDÉSIRABLES:

Bien qu'aucun effet indésirable grave attribuable au GEM 21S n'ait été rapporté dans un essai clinique mené auprès de 180 patients, les patients traités par GEM 21S peuvent présenter l'un des événements indésirables suivants qui ont été rapportés dans la littérature concernant les procédures de greffe chirurgicale parodontale : enflure; douleur; saignement; hématome; étourdissement; évanouissement; difficulté à respirer, à manger ou à parler; sinusite; maux de tête; augmentation de la mobilité dentaire; infection de la plaie superficielle ou profonde; cellulite; déhiscence de la plaie; névralgie et perte de sensation locale et périphérique; et anaphylaxie.

L'apparition d'une ou plusieurs de ces conditions peut nécessiter une intervention chirurgicale supplémentaire et peut également nécessiter le retrait du matériel de greffe.

G. CONDITIONS DE STOCKAGE:

La trousse GEM 21S doit être réfrigérée entre 2° et 8 °C (36° à 46 °F) dans un endroit sec. Ne congelez pas. Le composant individuel du rhPDGF-BB doit être réfrigéré entre 2° et 8 °C (36° à 46 °F). Le gobelet β-TCP peut être conservé à température ambiante, jusqu'à 30 °C (86 °F). Le composant rhPDGF-BB doit être protégé de la lumière avant utilisation. Ne pas retirer du plateau extérieur avant utilisation. Ne pas utiliser après la date d'expiration.

H. MODE D'EMPLOI:

(1) PRÉPARATION DU GEM 21S

Des techniques de transfert stérile appropriées doivent être utilisées pour éviter la contamination du contenu du gobelet et de la seringue. Alors que le contenu du gobelet contenant l'échafaudage (β-TCP) est fourni stérile par rayonnement gamma et que le rhPDGF-BB est traité de manière aseptique et versé dans la seringue, l'extérieur du gobelet contenant l'échafaudage et la surface extérieure de la seringue ne sont pas stériles.
Pour cette raison, il est recommandé que les particules d'échafaudage soient transférées dans un récipient stérile dans le champ opératoire stérile de manière aseptique avant d'ajouter la solution de rhPDGF-BB. Des précautions doivent également être prises pour minimiser l'écrasement des particules d'échafaudage.

Inspectez chaque composant stérile individuel de la trousse pour vous assurer que le produit n'a pas été contaminé avant l'utilisation. Si le sceau d'un contenant intérieur ou extérieur est ouvert, brisé ou autrement endommagé, le produit doit être considéré comme non stérile et, par conséquent, ne doit pas être utilisé.

Tout matériel non utilisé ouvert doit être jeté et les composants de ce système ne doivent pas être utilisés séparément.

Le clinicien prépare le GEM 21S en saturant complètement les particules d'échafaudage avec la solution de rhPDGF-BB et en laissant le produit reposer pendant environ dix (10) minutes. Une technique aseptique appropriée doit être employée pour préparer et appliquer GEM 21S. Il est préférable de préparer GEM 21S une fois la plaie chirurgicale correctement préparée (voir Technique chirurgicale).

(2) TECHNIQUE CHIRURGICALE

Il est extrêmement important de se familiariser avec le dispositif et de suivre les techniques chirurgicales de greffe appropriées lors de l'utilisation de GEM 21S. Une évaluation radiographique du site du défaut avant l'utilisation est essentielle pour évaluer avec précision l'étendue du défaut et pour faciliter la mise en place du matériau de greffe.

Après exposition du défaut avec un lambeau mucopériosté de pleine épaisseur, tout le tissu de granulation doit être soigneusement retiré. Un débridement complet des tissus mous du défaut est essentiel à une régénération réussie. Le tissu de granulation, s'il est laissé dans le défaut, pourrait être stimulé par le composant rhPDGF-BB, diminuant la réponse régénérative souhaitée. Les surfaces radiculaires exposées doivent également être soigneusement rabotées. Suite à un débridement complet du défaut osseux, le clinicien, sur la base de son expérience, estime la quantité de GEM 21S nécessaire pour combler le défaut. Pour de meilleurs résultats, GEM 21S doit combler complètement le défaut au niveau des parois osseuses environnantes. Un remplissage excessif doit être évité.

Le GEM 21S saturé doit être placé dans le défaut en utilisant une pression modérée, en prenant soin de ne pas écraser les particules. Afin d'améliorer la formation d'os nouveau, GEM 21S doit être placé en contact direct avec un os bien vascularisé. Les saignements excessifs doivent être contrôlés avant de placer les matériaux de greffe. Après la mise en place du GEM 21S et l'achèvement des étapes chirurgicales supplémentaires, les lambeaux mucopériostés doivent être suturés pour obtenir une fermeture primaire dans la mesure du possible.

La prise en charge postopératoire des patients doit suivre le même schéma que les cas similaires utilisant une greffe osseuse autogène. Les conditions préalables à toutes les procédures de régénération comprennent la prévention de la déhiscence de la plaie, un caillot stable et une contamination bactérienne minimale.