DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

# Memorandum

Date SEP 30 1996

From Director, Office of Device Evaluation (HFZ-400)
Center for Devices and Radiological Health (CDRH)

Subject Premarket Approval of Biora AB
EMDOGAIN® - ACTION

To The Director, CDRH
ORA _____

ISSUE. Publication of a notice announcing approval of the subject PMA.

FACTS. Tab A contains a FEDERAL REGISTER notice announcing:

(1) a premarket approval order for the above referenced medical device (Tab B); and

(2) the availability of a summary of safety and effectiveness data for the device (Tab C).

RECOMMENDATION. I recommend that the notice be signed and published.

Susan Alpert, Ph.D., M.D.

Attachments
Tab A - Notice
Tab B - Order
Tab C - S & E Summary

DECISION

Approved _____ Disapproved _____ Date _____

Prepared by Pamela D. Scott, CDRH, HFZ-480, March 26, 1996, 443-8879

DRAFT

DEPARTMENT OF HEALTH AND HUMAN SERVICES

FOOD AND DRUG ADMINISTRATION

[DOCKET NO. _____]

Biora US, Inc.; PREMARKET APPROVAL OF EMDOGAIN®

AGENCY: Food and Drug Administration, HHS.

ACTION: Notice.

SUMMARY: The Food and Drug Administration (FDA) is announcing its approval of the application by Biora US, West Chester, OH, for premarket approval, under the Federal Food, Drug, and Cosmetic Act (the act), of EMDOGAIN®. After reviewing the recommendation of the Dental Products Panel, FDA's Center for Devices and Radiological Health (CDRH) notified the applicant, by letter on September 30, 1996, of the approval of the application.

DATES: Petitions for administrative review by (insert date 30 days after date of publication in the FEDERAL REGISTER).

ADDRESSES: Written requests for copies of the summary of safety and effectiveness data and petitions for administrative review, to the Dockets Management Branch (HFA-305), Food and Drug Administration, 12420 Parklawn Dr., rm. 1-23, Rockville, MD 20857.

FOR FURTHER INFORMATION CONTACT:

Ms. Pamela D. Scott,

Center for Devices and Radiological Health (HFZ-480),

Food and Drug Administration,

9200 Corporate Blvd.,

Rockville, MD 20850,

301-443-8879.

SUPPLEMENTARY INFORMATION: On July 19, 1993, Biora US, West Chester, OH, 45069, submitted to CDRH an application for premarket approval of EMDOGAIN®. The device is a bone filling and augmentation device and is indicated for use as an adjunct to periodontal surgery for topical application onto exposed root surfaces to treat intrabony defects without furcations resulting from loss of tooth support due to moderate or severe periodontitis. EMDOGAIN® is to be used with the supplied vehicle solution of propylene glycol alginate.

On February 27, 1996, the Dental Products Panel of the Medical Devices Advisory Committee, an FDA advisory committee, reviewed and recommended approval of the application.

On September 30, 1996, CDRH approved the application by a letter to the applicant from the Director of the Office of Device Evaluation, CDRH.

A summary of the safety and effectiveness data on which CDRH based its approval is on file in the Dockets Management Branch (address above) and is available from that office upon written request. Requests should be identified with the name of the device and the docket number found in brackets in the heading of this document.

## Opportunity for Administrative Review

Section 515(d)(3) of the act, (21 U.S.C. 360e(d)(3)) authorizes any interested person to petition, under section 515(g) of the act, for administrative review of CDRH's decision to approve this application. A petitioner may request either a formal hearing under part 12 (21 CFR part 12) of FDA's administrative practices and procedures regulations or a review of the application and CDRH's action by an independent advisory committee of experts. A petition is to be in the form of a petition for reconsideration under 10.33(b) (21 CFR 10.33(b)). A petitioner shall identify the form of review requested (hearing or independent advisory committee) and shall submit with the petition supporting

data and information showing that there is a genuine and substantial issue of material fact for resolution through administrative review. After reviewing the petition, FDA will decide whether to grant or deny the petition and will publish a notice of its decision in the FEDERAL REGISTER. If FDA grants the petition, the notice will state the issue to be reviewed, the form of the review to be used, the persons who may participate in the review, the time and place where the review will occur, and other details.

Petitioners may, at any time on or before (insert date 30 days after date of publication in the FEDERAL REGISTER), file with the Dockets Management Branch (address above) two copies of each petition and supporting data and information, identified with the name of the device and the docket number found in brackets in the heading of this document. Received petitions may be seen in the office above between 9 a.m. and 4 p.m., Monday through Friday.

This notice is issued under the Federal Food, Drug, and Cosmetic Act (secs. 515(d), 520(h) ((21 U.S.C. 360e(d), 360j(h))) and under authority delegated to the Commissioner of Food and Drugs (21 CFR 5.10) and redelegated to the Director, Center for Devices and Radiological Health (21 CFR 5.53).

Dated:_____.

_____

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
9200 Corporate Boulevard
Rockville MD 20850

Otis Bouwsma, Ph.D., D.M.D.
Medical Director
Biora US, Incorporated
6375 Wilderness Trail
West Chester, Ohio 45069

SEP 30 1996

Re: P930021
EMDOGAIN®
Filed: July 19, 1993
Amended: January 28 and February 17, 1994; June 5 and 26, 1995; August 4, 1995; January 17, June 14, June 27, August 9, August 28, August 30 and September 30, 1996

Dear Dr. Bouwsma:

The Center for Devices and Radiological Health (CDRH) of the Food and Drug Administration (FDA) has completed its review of your premarket approval application (PMA) for the EMDOGAIN®. This device is indicated for use as an adjunct to periodontal surgery for topical application onto exposed root surfaces to treat intrabony defects without furcations, resulting from loss of tooth support due to moderate or severe periodontitis. EMDOGAIN® is to be used with the supplied vehicle solution of propylene glycol alginate. We are pleased to inform you that the PMA is approved subject to the conditions described below and in the "Conditions of Approval" (enclosed). You may begin commercial distribution of the device upon receipt of this letter.

The sale, distribution and use of this device are restricted to prescription use in accordance with 21 CFR 801.109.

In addition to the postapproval requirements in the enclosure, the postapproval reports must include the following information:

1. Clinical follow-up data on 400 patients or for 3 years, which ever occurs first, and information as described in the approved protocol for the postapproval study to further evaluate the potential for sensitization to EMDOGAIN® in patients receiving repeated use of the device with two or more months between treatments and

2. One year clinical follow-up data and information as described in the approved protocol for the postapproval study to establish the long term effectiveness of

1

EMDOGAIN® for the treatment of intrabony periodontal defects without furcation lesions.

Expiration dating for this device has been established and approved at 3 years at room temperature or under refrigeration.

CDRH will publish a notice of its decision to approve your PMA in the FEDERAL REGISTER. The notice will state that a summary of the safety and effectiveness data upon which the approval is based is available to the public upon request. Within 30 days of publication of the notice of approval in the FEDERAL REGISTER, any interested person may seek review of this decision by requesting an opportunity for administrative review, either through a hearing or review by an independent advisory committee, under section 515(g) of the Federal Food, Drug, and Cosmetic Act (the act).

Failure to comply with the conditions of approval invalidates this approval order. Commercial distribution of a device that is not in compliance with these conditions is a violation of the act.

You are reminded that as soon as possible, and before commercial distribution of your device, that you must submit an amendment to this PMA submission with copies of all approved labeling in final printed form.

All required documents should be submitted in triplicate, unless otherwise specified, to the address below and should reference the above PMA number to facilitate processing.

PMA Document Mail Center (HFZ-401)
Center for Devices and Radiological Health
Food and Drug Administration
9200 Corporate Blvd.
Rockville, Maryland 20850

If you have any questions concerning this approval order, please contact Ms. Pamela D. Scott at (301) 443-8879.

Sincerely yours,

Susan Alpert, Ph.D., M.D.
Director
Office of Device Evaluation
Center for Devices and
Radiological Health

Enclosure

8

# Enamel Matrix Derivative: SUMMARY OF SAFETY AND EFFECTIVENESS DATA

## Table of Contents



9

## I GENERAL INFORMATION

| | |
|---|---|
| Device generic name: | Enamel Matrix Derivative ( EMD ) |
| Device trade name: | EMDOGAIN® |
| Name and address of applicant: | BIORA AB<br>IDEON-Malmö<br>S-205 12 Malmö<br>Sweden |
| United States Representative: | Biora US, Incorporated<br>6375 Wilderness Trail<br>West Chetser, OH 45069 |
| PMA number: | P930021 |
| Date of panel recommendation: | February 27, 1996 |
| Date of notice of approval to the applicant: | May 7, 1996 |

## II INDICATIONS FOR USE

EMDOGAIN® is intended as an adjunct to periodontal surgery for topical application onto exposed root surfaces to treat intrabony defects without furcations, resulting from loss of tooth support due to moderate or severe periodontitis.

## III DEVICE DESCRIPTION

EMDOGAIN® consists of hydrophobic enamel matrix proteins (amelogenins) of porcine origin. These proteins are referred to as Enamel Matrix Derivative or EMD. The device consists of 80 per cent (dry weight) freeze-dried amelogenin (protein); the remaining 20 per cent is residual water, salts and acetic acid. Propylene glycol alginate is used as a vehicle solution for the application of EMDOGAIN® onto the root surface. The product is supplied with one vial containing 30 mg of sterile lyophilized EMD and a second vial containing the sterile vehicle solution, Propylene Glycol Alginate (PGA). The vehicle solution is acidic (pH 3-4) in order to assist in the dissolution of EMD. It is also viscous ( 1.5-2.5 Pa with EMD added) to facilitate homogenous application onto surgically

exposed root surfaces. After application, the physiological conditions will decrease the acidity and viscosity, and allow reformation of the insoluble matrix on the root surfaces. The material provides the surface matrix for repair of the defect sites.

## IV CONTRAINDICATIONS

EMDOGAIN® should not be used in patients with disorders or conditions including, but not limited to the following: uncontrolled diabetes or other uncontrolled systemic disease, disorders or treatments that compromise wound healing, chronic high dose steriod therapy, bone metabolic diseases, radiation or other immuno-oppressive therapy and infections or vascular impairment at the implant site.

For warning and precautions, please refer to the attached labeling.

## V ALTERNATIVE PRACTICES AND PROCEDURES

In periodontal surgery, mucoperiosteal flaps to expose marginal alveolar bone are developed and pocket epithelium and granulation tissue are removed. In conventional flap surgery, debridement is performed to remove the collar of inflamed tissue around the teeth and the diseased root surfaces are scaled and root-planed to remove soft and hard bacterial deposits. Subsequently, the flaps are repositioned over the alveolar bone and sutured.

Physical barriers, such as membranes (biodegradable or non-biodegradable), have been used to retard or prevent apical migration of epithelium, as well as exclude gingival connective tissue from the periodontal wound. This allows for selective recolonization of the root surfaces exposed by means of flap surgery.

Autogenous and allogenic bone grafts have been used as an adjunct to conventional flap surgery and debridement to fill periodontal defects. Demineralized freeze dried bone is a common bone graft material used for this application. Other types of bone grafting materials include allogenic bone marrow or lyophilized, allogenic cartilage and demineralized bone or dentin. Alloplastic materials such as tricalcium phosphate and nonporous or porous hydroxyapatite are also used as bone grafting device to aid in the repair of periodontal defects. Hydroxylapatite has also been extracted from animal sources and sterilized for use as a bone grafting device for filling periodontal defects.

## VI MARKETING HISTORY

EMDOGAIN® was approved for marketing in Sweden, Denmark, Norway and Finland in December 1994. In June 1995, the device received simultaneous marketing approval in 14 additional countries of the European Economic Area (Austria, Belgium, France, Germany, Greece, Holland, Iceland, Ireland, Italy, Luxemburg, Portugal, Spain, Switzerland and UK) and Canada. EMDOGAIN® is CE-marked in these 18 European countries in accordance with the EC Medical Device Directive. The device has not been withdrawn from approved status or marketing for any reason relating to the safety and effectiveness of the device. More than 2000 EMDOGAIN® units were sold in 1995, mainly in Sweden and Germany.

## VII ADVERSE EFFECTS OF THE DEVICE ON HEALTH

The following adverse events were observed in clinical trials for EMDOGAIN®; however, a distinction of adverse events seen due to EMDOGAIN® alone could not be performed. EMDOGAIN® is labelled for use only in conjunction with periodontal surgery; hence, inherent in this procedure are the risks associated with conventional periodontal surgery. Complications and adverse events related to the surgical procedure include the following: post-operative hemorrhage, paraesthesia and hematoma, edema, sloughing of tissue, bleeding, swelling, increased tooth mobility, hypersensitive root surfaces (root sensitivity), pain, infection, wound dehiscence, other mucosal reactions and loosening of sutures. The adverse events observed in the clinical trials are listed below by the type of event and in the order of severity.

Local soft tissue reactions:

Local redness, inflammation, soreness, gingival irritation, hematoma/echynosis, oral candidiasis, tissue necrosis/cratering, angulitis, herpes-like blisters, hypoesthesia (burning and itching reaction on the tongue), oral mucosa reaction, fibrin layer, discoloration

Local tooth-related reactions:

Increased tooth mobility, hypersensitive root surfaces (root sensitivity), pain

General reactions:

Urticaria, itching skin reaction, gastrointestinal disturbances, urogenital disturbances

## VIII SUMMARY OF PRECLINICAL STUDIES

### A. MICROBIOLOGICAL STUDIES

All batches of EMDOGAIN® and vehicle solution are tested for sterility and pyrogens based on USP 23 procedures, including growth promotion of media. Media fills, personnel monitoring and environmental monitoring follow the ISO draft standard "Aseptic processing of health care products" (ISO/TC 198 WG9).

### B. PRECLINICAL ANIMAL STUDIES

The safety of EMDOGAIN® has been documented in mice, rats, rabbits, dogs, monkeys and *in vitro* systems.

### Kinetic Studies

EMDOGAIN® is a resorbable device and animal studies demonstrated that EMDOGAIN® remains within the site of application for at least one week and is gradually absorbed. In a study using Iodine-labelled EMD in different vehicle solutions, implanted at the periodontal site, the average total time until 99% of EMDOGAIN® was removed was calculated to be 15 days in 17 test rats studied and 8 to 11 days in two pigs. Virtually all EMDOGAIN® deposited in the periodontal environment is ultimately digested enzymatically, based on kinetic study 4, an *in vitro* showing that EMDOGAIN® is degraded by proteolytic enzymes and macrophages into peptide fragments or amino acids. Kinetic study 4 also demonstrated that only a small amount of EMDOGAIN® is degraded by human gingival tissue. Two studies using 10 rats in each study, revealed that EMDOGAIN® is primarily taken up by the liver, kidneys and thyroid gland. Tests also showed that Iodine-labeled EMDOGAIN® was removed from the circulation within 4 to 24 hours and is subsequently excreted via the kidneys. Theoretically, some undigested EMDOGAIN® may be transported away from the periodontal site. Should any EMDOGAIN® be swallowed, it is rapidly digested by proteases present in the gastrointestinal tract.

No uptake was detected in fetal kidneys when EMDOGAIN® was injected to pregnant rats, suggesting that no EMDOGAIN® crossed the placenta. Although radioactivity was detected in the fetal tissues, the distribution was even except for the thyroid and gastric content, suggesting that the radioactivity represented free iodine.

## Toxicological Studies

The following toxicological studies were performed: irritation, acute toxicity, mutagenicity, chronic toxicity and reproductive toxicity. The immunological studies included sensitization assays and circulating antibody studies.

The toxicological studies showed that EMDOGAIN® does not illicit a general toxicological response. In toxicological study 5, three groups of rats, each with 10 females and 10 males, were injected with saline, the PGA vehicle or EMD in PGA. Transient local swelling was seen at the injection sites after multiple subcutaneous applications in the test group and PGA vehicle control group. The results of the Guinea Pig Maximization Test showed no indication of delayed contact hypersensitivity by EMDOGAIN®.

The acute toxicity of EMDOGAIN® was evaluated in 10 rats and 10 mice after intravenous administration. At the highest levels that could practically be given in these species, there were no signs of acute toxicity, no deaths or gross pathological changes and no serious clinical effects observed. In the acute toxicity studies performed in mice, the animals were injected with 200 mg of EMDOGAIN® per kilogram of body weight. The mice demonstrated decreased motor activity and decreased respiratory frequency for the first one half hour after the injection; however, no mice died after the treatment. It was concluded that the minimum lethal dose exceeds 200 mg of protein/kg of body weight. This dose is about 400 to 1000 times greater than the amount to be used for topical application to tooth roots in human patients. Slight behavioral and neurological signs were reported in the chronic toxicity study in 18 dogs. The dogs were divided into three dose groups and one control group; they were administered EMD once a week for 3 months. The behavioral and neurological signs were mostly transient. However, there were no adverse effects related to EMDOGAIN® in any of the dose groups in three month intravenous studies in rats at elevated doses.

In three of the reproductive studies performed, a slightly higher incidence of embryonic loss around the time of implantation in the highest dose group. In these studies, severe fetal developmental abnormalities were also reported for both EMD-treated and control groups, although it appeared to more predominant in the medium and high dose groups. In one of the studies, 15 rabbits were studied using one dose and in the other two studies, 15 rabbits were used in each of the low, medium and high dose groups. The incidence of increased embryonic loss and severe fetal devlopmental abnormalities, however, was attributed to a problem with genetic drift in the breed of rabbit used. Data was provided for both control and test animals in various studies, including studies using other test substances, that documented a high incidence of severe fetal abnormalities occurring in both test and control animals within the particular strain of rabbits used (Froxfield rabbits).

Another reproductive study was performed in 45 rabbits of a different breed (15 rabbits in each dose group), in which a higher incidence of early embryonic loss was reported after implantation of EMDOGAIN® in the higher dose group and to a lesser extent in the medium dose group. However, the difference in the incidence of early embryonic loss between the highest dose group and the medium and low dose groups was not significant. In addition, the dose given to the medium and high dose groups was several orders of magnitude higher than the dose that a human patient would be expected to receive. The reproductive study performed in rats did not indicate a teratogenic potential of EMDOGAIN® based on comparative results for other materials and control animals.

The test results demonstrated that EMDOGAIN® can be safely used in animals and humans.

**Immunological Studies**

When challenged through three months with multiple exposures of high concentrations of EMDOGAIN®, no clinical signs of hypersensitivity were seen in any animal species and as stated above, and there were no sensitization reactions in the Guinea Pig Maximization Test.

**Device validation**

Ten studies totaling 300 periodontal sites in 53 monkeys were performed to validate the effectiveness of the device. Effectiveness of the device was evaluated using the monkey dehiscence model from development of the crude enamel matrix to the final formulation of the device. In 9 of these studies, a dehiscence model with histological evaluation two months after treatment was used and in the other study, monkeys with naturally occurring periodontitis were used and the histological evaluation was performed six months after treatment. These studies showed that cementum forming cells may recolonize on the EMD matrix material covering the root. The histological results have shown that application of EMDOGAIN® onto cleaned root surfaces in monkeys yielded adhering cementum with extrinsic collagen fibers and associated periodontal tissues (functional periodontium) covering 60 to 90% of the root. Alveolar bone associated with the periodontal tissue forms to almost the same extent. By contrast, unconditioned root surfaces or root surfaces treated with various vehicle solutions healed with minimal formation of cementum and no alveolar bone formation. The regeneration of cementum and a periodontal attachment apparatus, however, have not been confirmed in humans.

## IX SUMMARY OF CLINICAL STUDIES

### CLINICAL EVALUATION

The objective of the clinical studies of EMDOGAIN® were to demonstrate that applicaation of EMDOGAIN® during surgery would provide for regrowth of alveolar bone which is associated with clinical attachment gain. Normally, periodontal tissues do not regenerate after conventional treatment of adult periodontitis using nonsurgical or surgical procedures such as debridment. Osseous defects, especially narrow 3-wall defects, may remodel through osseous regrowth after surgical debridement followed by optimal plaque control, however, this is generally not the case. A long junctional epithelium generally forms between the root surface and soft tissue interface, with no evidence of periodontal tissue or bone regeneration.

Two pilot and four pivotal studies involving over 250 patients undergoing periodontal surgery were conducted to evaluate the safety and effectiveness of EMDOGAIN®. The selection criteria for these studies were chosen to allow inclusion of a representative sample of adult patients with periodontal defects eligible for surgery in standard clinical practice. The defects treated were required to have a probing pocket depth of at least 6 mm and 1- or 2-wall intrabony lesions with a depth of at least 3 mm and a width of 2 mm or greater, as measured on by radiography. Occasionally, patients who did not meet the inclusion criteria of having a probing pocket depth of at least 6 mm were included. In one study, 3-wall defects were also allowed. Sites with furcation involvement were excluded in all of the studies except for clinical study number 4 in which mandibular Class II furcations with horizontal probing defects of 3 mm or greater were specifically studied.

The results obtained in the EMDOGAIN® treated and control sites for the two primary efficacy parameters, clinical attachment level and radiographic bone gain, from the four pivotal studies are summarized in Tables 1 and 2. The data are reported as the difference between the clinical measurments taken at baseline during the initial operation and the clinical measurments taken at the designated follow-up periods. For the clinical parameters of pocket depth reduction and clinical attachment gain, the data is also expressed as the percent difference between the results of the surgical procedure alone and treatment with EMODGAIN®. Radiographic bone gain is reported as the linear measurment and as the percentage of the inital bone loss that was regained.

The mean age of all patients was 48 years (range 30 - 73 years) and 51% of the patients were women. No precautions were taken to control tobacco smoking or concomitant medication (other than antibiotics) prescribed for any acute or chronic disease. More than half of the patients were smokers (an average 64% smokers in studies where smoking was recorded), and about one third were on regular prescription

medicines, which is typical for an adult population with chronic periodontitis. However, the results of statistical analyses showed that the outcome of the clinical trials was not significantly confounded by these factors or by gender or age.

In the first pilot study, 18 patients were treated with EMDOGAIN® and followed for six months. Comparisons were made to historical controls. The second was an experimental study in a created defect in one volunteer with histological evaluation confirming the regeneration of new cementum and periodontal tissue. However, it must be noted that this study was performed using a created defect in a healthy site rather than a diseased defect resulting from periodontitis, in which the healing process would be much different. A created defect in a healthy site might be expected to regenerate spontaneously or may respond to the device more effectively. Hence, the results of this study and the results of the histology from the animal studies can not be extrapolated to the response of defects in patients with periodontitis. Clinical studies 3, 5 and 6 were controlled investigations studying the use of EMDOGAIN® in interproximal, intrabony defects and clinical study 4 was a controlled investigation of treatment with EMDOGAIN® in Class II furcations. The control treatment in all of the studies, except for clinical study 6, was conventional treatment including the Modified Widman Flap procedure with surgical debridement. In clinical study 6, the control treatment included conventional periodontal surgery in addition to the application of propylene glycol alginate which is the vehicle solution for EMDOGAIN®.

All of the studies had up to eight months of follow-up; studies 3 and 6 also included a three year evaluation of patients. The clinical studies showed that after treatment with EMDOGAIN® as an adjunct to periodontal surgery, there was moderate gain in clinical attachment and a reduction in probing pocket depths. However, compared to the control treatments, the difference was not always statistically significant, but was always higher for the treatment group. The most notable difference between treatment with EMDOGAIN® and the control treatment of periodontal surgery alone was the bone regeneration that was measured radiographically in treated sites. Radiographic examiners were masked as to the treatment received. There was little or no bone gain in defect sites receiving the control treatment compared to sites treated with EMDOGAIN® in which there was bone gain in the defect area.

Radiographic evaluation is a noninvasive method which allows assessment of the bone regeneration process. Bone level measurements were therefore regarded as an important additional criteria of the effectiveness of EMDOGAIN® treatment and a further corroboration of its clinical relevance. Differences between the EMDOGAIN® treated and control sites measured by radiographic bone gain were statistically significant in all studies where this was measured. However, neither clinical probing nor radiographic measurements give any information on the quality of the tissues which mediate the root surface to soft tissue interface. Only histological data can differentiate between the types of periodontal healing that occur as a result of treatment. For ethical reasons, this type of investigation was not performed.

## TABLE 1: Attachment Gain and Radiographic Bone Gain at 8 and 16 months Post-surgery for EMDOGAIN® Pivotal Clinical Trials

| Sty. No. | Design | No. of pts. | Radiographic Bone Gain (mm) {range [min., max.]} | | | | | Clinical Attachment Gain (mm) {range [min., max.]} {For Study 4, furcation reduction} | | | | Pocket Depth Reduction (mm) {range [min., max.]} | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | **EMD-OGAIN®** | Control | Diff. | **% of initial bone loss regained** | | EMD-OGAIN® | Control | Diff. | % diff. of control | EMD-OGAIN® | Control | Diff. | % diff. of control |
| | | | | | | **EMD** | Contr. | | | | | | | | |
| 3 | Parallel groups 1-, 2-, and 3-wall Control: surgery | 107T 33C | **1.2 [-2.1, +4.8]** | 0.3 [-1.1, +3.1] | **0.9*** | **15%** | 4% | 3.1 [-1.0, +11.0] | 2.6 [0, + 5.0] | 0.5 | 19% | 4.3 [+0.5, +12.5] | 3.7 [+1.0, +7.0] | 0.6* | 16% |
| 4 | Split-mouth‡ Class II furcations Control: surgery | 10 | NA† | NA | NA | NA | NA | 2.1 [0, +4.0] | 1.2 [0, +2.0] | 0.9* | 75% | 1.8 [0, +3.0] | 1.2 [-1.0, +3.0] | 0.6 | 50% |
| 5 | Split-mouth 1- or 2-wall Control: surgery | 26 | **0.7 [-0.6, +1.8]** | 0.1 [-1.3, +2.1] | **0.6*** | **12%** | 0% | 2.1 [-1.0, +5.5] | 1.8 [-1.0, +4.0] | 0.3 | 16% | 3.3 [-0.5, +7.0] | 3.1 [0, +6.0] | 0.2 | 6% |
| | | 10# | **0.8 [0, +1.5]** | 0 [-0.9, +1.9] | **0.8**** | **8%** | 0% | 3.5 [+1.5, +5.5] | 2.2 [0, +4.0] | 1.3* | 59% | 3.6 [+1.5, +5.5] | 3.6 [0, +7.0] | 0 | 0% |
| 6 | Split-mouth, 1- or 2-wall Control: placebo | 34 | **0.9 [-0.3, +2.1]** | -0.1 [-1.0, + 0.9] | **1.0 **** | **13%** | -2% | 2.1 [-0.5, +5.5] | 1.5 [-1.0, +3.5] | 0.6** | 40% | 3.3 [+0.5, +6.5] | 2.6 [0, +5.0] | 0.7** | 27% |
| | 16 month follow-up | 31 | **2.2 [-0.4, +6.0]** | -0.2 [-1.2, +1.4] | **2.4***** | **31%** | -4% | 2.3 [-1.0, +5.0] | 1.7 [-1.0, +4.5] | 0.6** | 35% | 3.3 [+0.5, +6.5] | 2.6 [-1.0, +4.5] | 0.7** | 27% |

T, C test and control patients, respectively
‡ The split mouth design indicates that the patient serves as his/her own control
# Patients with deepest baseline pocket exceeding 8 mm
*,**,*** $p < 0.05$, $p < 0.01$, and $p < 0.001$, respectively
¤ $p = 0.01$
† Radiographic bone gain can not be measured for furcation defects

The magnitude of the difference in clinical attachment gain between test and control sites at 8 months of follow-up was 0.3 mm to 0.6 mm in intrabony defects without furcation involvement and 0.9 mm in Class II furcations. These levels of improvement were maintained over 16 months. Gain in clinical attachment levels was also calculated as the percentage of the effect of the surgical procedure alone. This varied from 16% to 40% in intrabony defects and 75% in Class II furcations at the 8 month assessment and was 35% in intrabony defects after the 16 month evaluation in clinical study 6.

At the 8 month assessment, radiographic bone gain for intrabony defects was 0.7 - 1.2mm or 12 - 15% when expressed as a percentage of the initial bone loss. The corresponding values for intrabony defects after 16 months were 2.2 mm gain or 31% of the initial bone loss. Surgery alone did not significantly influence radiographic bone gain, as shown by the negative or near zero values for the control sites in TABLE 1; hence, the effect of the EMDOGAIN® treatment on bone gain could not be expressed as a percentage of the effect of the control procedure as was possible for clinical attachment gain.

To illustrate the results on the individual patient level, 16 month follow-up data from clinical study 6 are given in Figure 1 (Radiographic Bone Gain) and in Figure 2 (Clinical Attachment Gain). Twenty-three test (74%) but no control sites had a bone gain of more than 20% of the initial defect and 18 test and 8 control sites (58% and 26%, respectively) had gained more than 2 mm of clinical attachment.

FIG 1: Individual data for Radiographic Bone Gain 16 months postsurgery for test and control sites in study 6 (n=31). Data points where there is no bar are zero or near zero values.

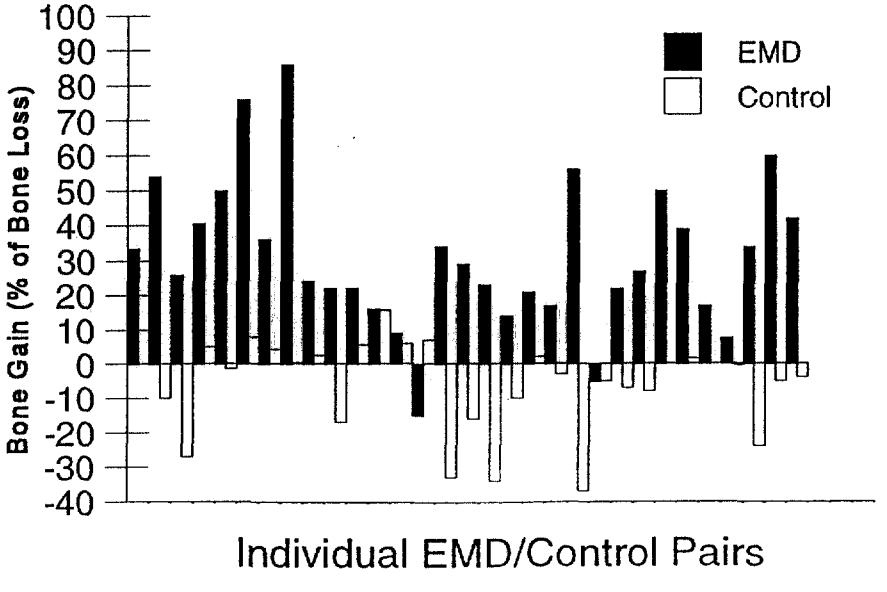
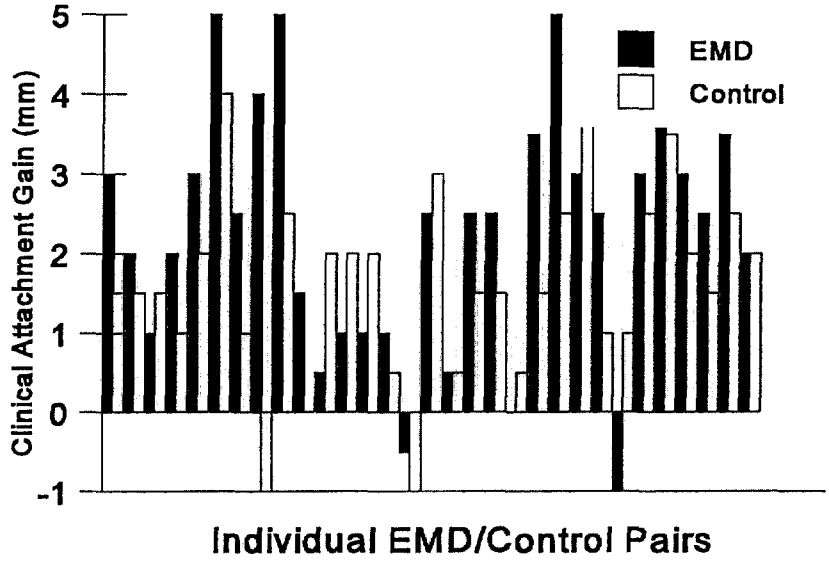


FIG 2: Individual data for Clinical Attachment Gain 16 months postsurgery for test and control sites in study 6 (n=31). Data points where there is no bar are zero or near zero values.




## Long-term follow-up

Long-term clinical data (3 years postsurgery) exist for 92 patients from clinical studies 3 and 6 and are summarized in Table 2.

**TABLE 2: Pocket Depth Reduction, Clinical Attachment and Radiographic Bone Gain 3 years Post-surgery**

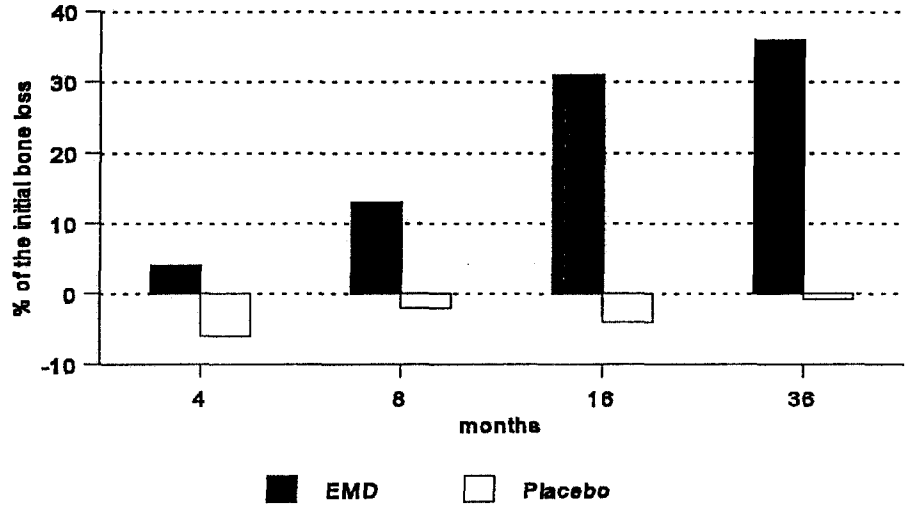
| Study No. | **Radiographic Bone Gain** (mm) [range] | | | | | Clinical Attachment Gain (mm) [range] | | | | Pocket Depth Reduction (mm) [range] | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | **EMD-OGAIN®** | Control | *Diff.* | **% of initial bone loss regained** | | EMD-OGAIN® | Control | *Diff.* | % diff. of contr. | EMD-OGAIN® | Control | *Diff.* | % diff. of contr |
| | | | | EMD | Contr | | | | | | | | |
| 3 (n=45 T +21C) | **2.5 [-0.6, +5.4]** | 0 [-1.4, 2.5] | ***2.5**** | **31%** | 0% | 2.9 [+0.5, +7.5] | 2.2 [0, +4.5] | *0.7¤* | 32% | 3.8 [+0.5, +8.5] | 3.2 [0, +8.0] | *0.6* | *19%* |
| 6 (n=27) | **2.6 [+0.08, +7.1]** | 0 [-1.1, +1.54] | ***2.6**** | **36%** | 0% | 2.2 [0, +4.5] | 1.7 [-1.0, +3.5] | *0.5*** | 30% | 3.1 [+1.0, +6.0] | 2.3 [-0.5, +4.5] | *0.8**** | *35%* |

T,C test and control patients, respectively

¤,*,**,*** p=0.08, p< 0.05, p< 0.01, and p< 0.001, respectively

The EMDOGAIN® treated sites achieved a sustained level of pocket depth reduction and clinical attachment gain, both in absolute terms and expressed as the percent difference of the values obtained by the surgical procedure alone. These results are supported by the radiographic bone gain measurements, which reveal a gradual regrowth of alveolar bone over the 3 year period, amounting to over 30% of the initial bone loss in EMDOGAIN® treated sites. The radiographic bone gain in clinical study 6 over time is illustrated in Figure 3.

**FIG 3:** Radiographic Bone Gain as a function of time, Study No. 6




## SAFETY EVALUATION IN CLINICAL TRIALS

Over 250 patients have been treated with EMDOGAIN® in the clinical trial program. Results from six clinical studies were provided. Several patients were reported to experience urticaria in various sites on the body, itching skin reactions, oral mucosa reactions and hematoma. One patient noted a burning and itching sensation on the tongue, combined with inflammation of the angle of the mouth (anguilitis). During the following two months postsurgery, herpes-like blisters appeared in an intermittent fashion for the same patient. One patient experienced urticaria at several sites including the arms, chest, back, thighs, soles of the feet and palms of the hands. These patients underwent immunoassays and skin tests; blood samples from these patients were analyzed, but there was no EMD reactive IgG or IgE antibody formation. There may be a correlation to the postsurgical antibiotic regimen. However, the possibility that these reactions were caused by treatment with EMDOGAIN® can not be ruled out at this time.

Several of the immunological antibody studies showed a trend in increased EMD reactive IgE levels outside of the normal range. In the final analysis of 119 patients in immunological study number 8, eleven patients were just outside the control range. There is concern that a small number of patients may respond to the device by exhibiting signs of hypersensitivity after repeated use. It must be taken into consideration that this product is a foreign protein and although allergic reaction as a result of using the device has not been confirmed, there could be potential for the device to be immunogenic or allergenic.

Based on the immunological studies, the frequencies of antibody levels outside the normal ranges were generally not different from those of comparable control groups; however, there were a small number of EMDOGAIN® treated patients that had an increase in EMD specific IgE. Although the number of patients was small, the results indicate that there may be a potential for a small percentage of patients to experience an immunological response, such as hypersensitivity of either the immediate or delayed type. In particular, patients receiving repeated application of EMDOGAIN® in conjunction with periodontal surgery must be monitored carefully. The skin prick test to EMD both in nonexposed and pre-exposed individuals, and the intracutaneous challenge in occupationally-exposed individuals revealed that EMD sensitivity does not pre-exist. A DermaPik skin prick test for sensitivity to EMDOGAIN® was performed and one patient experienced slight itching on the arm at a site distant (8 inches) from the site of the skin test. The clinician assessed this response as incidental and the patient later received treatment with EMDOGAIN® in conjunction with periodontal surgery without demonstrating any adverse reactions to the device.

## ANCILLARY CLINICAL DATA

Postmarket surveillance is being performed by BIORA AB in Sweden. BIORA has initiated a systematic collection of complaints and adverse experiences by sending a questionnaire with every unit sold in Sweden, requesting clinicians to report subjective complaints from the patients as well as their own objective assessments. As of November 1995, 330 of 750 forms were returned with 1-6 month follow up data from EMDOGAIN® treated patients. Ten patients of these 330 (3%) had transient swelling without any inflammation (including two patients where the surgical procedure was delayed because of photographs that were taken during surgery), and 8 patients (2%) experienced a sensitive root during the first days postsurgery (typically found after intensive instrumentation; several of these patients were treated by the same dentist). No actions or interventions were needed. A total of 6 patients (<2%) complained about pain after surgery, and two patients received antibiotics for a suspected postsurgical infection one week after EMDOGAIN® treatment (no antibiotic regimen had been given at the time of surgery).

Reports have been received from twelve of the patients (4%) who were treated twice with EMD in different quadrants 2-4 weeks apart and from one patient who was treated 3 times in a seven week period. None of the patients with multiple EMD treatment reported any complaints; nor did the clinicians report any adverse experiences for any of these patients. In addition, no increased EMD-reactive IgG or IgE values were found in a serum sample from the triple-treated patient. In summary, the current post marketing surveillance in Sweden indicates a very low incidence of complaints of the type often encountered after flap surgery, and no adverse experiences have been spontaneously reported.

## X CONCLUSIONS DRAWN FROM THE STUDIES

As discussed in section VIIIB, the device validation studies in monkeys, with histological evaluation, have demonstrated the capacity of EMDOGAIN® to support regeneration of periodontal attachment, involving formation of an acellular extrinsic fiber cementum firmly attached to the underlying root surface with an associated periodontal ligament and alveolar bone. These results are not achieved by periodontal surgery alone. However, the histological results could not necessarily be extrapolated to the treatment of diseased periodontal defects in human patients and further studies were needed.

The controlled clinical trials have demonstrated marginal effectiveness and clinical utility of EMDOGAIN®. The effect of adjunctive periodontal treatment using EMDOGAIN®, assessed by means of clinical probing parameters and radiographic measurements, were within the same magnitude in all studies. When the adjunctive effect of EMDOGAIN® was compared to that of the surgical procedure alone, all studies showed statistically significant improvement in radiographic measurements, when the baseline defects were comparable. When the probing difference between test and control is expressed as a percentage of that for the Modified Widman Flap procedure with surgical debridement (the control treatment) alone, the results suggest favorable clinical effectiveness. However, when comparing the mean differences in millimeters between treatment with EMDOGAIN® and the control treatment, the results demonstate marginal clinical effectiveness, with the most significant finding being that for bone level gained in the defect area. Consistent radiographic bone level results were found for all studies where radiography was performed, demonstrating a difference between EMDOGAIN® treated sites in which there was bone level gain and control sites with unchanged bone levels. Radiographic bone gain levels at the 8 month follow-up in clinical studies 3 and 6 were 1.2 mm and 0.9 mm, and increased to 2.5 mm and 2.6 mm 3 years after surgery.

Although it was difficult to assess the clinical significance of the use of EMDOGAIN® for the treatment of periodontal defects as compared to the control treatment based on

the various studies, the data do show that the device is effective in providing the intended clinical outcome of increased gain in clinical attachment, reduction in pocket depth and demonstrable bone gain. In general, use of EMDOGAIN® resulted in mean clinical attachment gain ranging from 2.1 mm to 2.9 mm and pocket depth reduction ranging from 1.8 mm to 4.3 mm. Gain in bone within the defect as assess radiographically ranged from 0.9 mm at 8 months postoperatively to 2.6 mm 3 years postoperatively. Compared with baseline measurements, these gains can be considered clinically relevant.

### Risk/Benefit Statement

Safety testing of EMDOGAIN®, with single and repeated exposure in multiple species and at elevated doses, has revealed minimal adverse findings. Other short- and long-term nonclinical studies, by various routes of administration, support these findings. Because EMDOGAIN® is a foreign protein, it may have a potential for immunotoxicity, local irritation or sensitization. Based on animal studies, it does not pose a mutagenic or teratogenic risk.

The use of EMDOGAIN® as an adjunct to periodontal surgery presents minimal risks; however, the benefits of this device as evaluated by conventional standards is modest. The clinical trial program has shown that most of the EMDOGAIN® treated defects regained attachment lost to the disease as assessed by gain in clinical attachment and even more predominantly by increase in radiographic bone gain. Therefore, it is reasonable to conclude that the benefits of use of thedevice for the target population outweigh the risk of illness or injury when used as indicated in accordance with the directions for use.

## XI PANEL RECOMMENDATIONS

The Dental Products Panel met on February 27, 1996 to discuss this premarket approval application. The Panel expressed concern regarding the potential for sensitization to the device as a result of repeated use. The Panel concluded, however, that this risk was low and the concern could be addressed through labeling and a postapproval study. Therefore, as a condition of approval, the Panel recommended that a postapproval study be performed to assess the potential for sensitization from the use of EMDOGAIN®.

There was concern by some Panel members that the results did not adequately demonstrate the clinical significance of treatment with this device. However, the majority of the Panel concluded that the results for bone level gain as documented by radiographs was sufficient to establish the clinical significance of using the device.

There was consensus that a claim of superiority of treatment with EMDOGAIN® when compared to conventional surgery could not be made because the type of regeneration obtained with EMDOGAIN® was not well documented. In addition, it has not been established that regeneration of periodontal tissue yields better long term results than conventional surgery which results in epithelial growth along the root surface. There were some Panel members who questioned the clinical relevance of treatment with this device; however, most Panel members agreed that the device poses low risks.

The Panel voted 5 to 4 in favor of the approval of this PMA with conditions. These conditions included the following:

1. Revised labeling with a limited claim for the use of the device as an adjunct to periodontal surgery in patients with moderate to severe periodontitis with intrabony pockets without furcation lesions;

2. A statement in the labeling warning that the product has potential for sensitization and

3. A postapproval study to further assess the potential of EMDOGAIN® to cause sensitization in a small number of patients.

The Panel also recommended in addition to the studies already performed in animals, that the applicant conduct new studies in an animal model with naturally occuring perdiodontal defects of infectious etiology, along with subsequent histological analysis. This information would provide additional support for the claim that the product promotes periodontal regeneration.

## XII FDA DECISION

CDRH concluded that there was sufficient data to support the indication for use of EMDOGAIN® as an adjunct to periodontal surgery for topical application to the root surface to treat intrabony defects, not affected with furcation lesions, that are a result of tooth support that has been lost because of moderate or severe periodontitis. CDRH also agreed with the Panel that a warning stating the potential for sensitization to EMDOGAIN® be included in the labeling and that a postapproval study be conducted in order to further asess the potential for sensitization to the product in a selected population of patients. In addition, the FDA has concluded that an additional postapproval study be performed in order to further document the long-term effectiveness of the device. Evaluation of long-term effectiveness and possible sensitization may be combined within one study. The data from this study and the postapproval study evaluating the potential for sensitization by repeat use of the device should be submitted to the FDA for evaluation upon completion.

CDRH concurred with the Dental Device Panel's recommendation of February 27, 1996 and issued an approvable letter to the U.S. Representative for Biora AB, on May 7, 1996, advising that its PMA was approvable subject to the conditions of approval listed below as recommended by the Panel and required by FDA.

1. Limit the indications for use of EMDOGAIN® to use as an adjunct to periodontal srugery for topical application to the root surface to treat infabony defects, not affected with furcation lesions; remove the indication for the treatment of defects affected with furcation lesions and remove all claims of regeneration;

2. Conduct and submit the results of a postapproval study to further evaluate the potential for sensitization to EMDOGAIN® in patients receiving repeated use of the device with two or more months between treatments and

3. Conduct and submit the results of a postapproval study to confirm the long term effectiveness of EMDOGAIN® for the treatment of intrabony periodontal defects without furcation lesions.

CDRH also required that the applicant modify their labeling to include a warning regarding the potential for sensitization to EMDOGAIN®.

## XIII APPROVAL SPECIFICATIONS

| | |
|---|---|
| Directions for use: | See the labeling (Attachment 2) |
| Warnings, hazards to health from use of the device: | See Indications, Contraindications, Warnings, Precautions and Adverse Events sections in the lableing (Attachment 2) |
| Postapproval requirements and restrictions: | See the Approval order (Attachment 1) |

## PACKAGE INSERT - EMDOGAIN®

EMDOGAIN® is a resorbable, implantable material. It consists of hydrophobic enamel matrix proteins extracted from developing embryonal enamel of porcine origin. It is supplied in sterile, lyophilized form. The vehicle supplied is a sterile aqueous solution of Propylene Glycol Alginate, with a suitable viscosity to facilitate application of EMDOGAIN® onto root surfaces exposed during periodontal surgery.

## INDICATIONS FOR USE

EMDOGAIN® is intended as an adjunct to periodontal surgery for topical application onto exposed root surfaces to treat intrabony defects without furcations resulting from loss of tooth support due to moderate or severe periodontitis.

## CONTRAINDICATIONS

EMDOGAIN® should not be used in patients with disorders or conditions including, but not limited to the following: uncontrolled diabetes or other uncontrolled systemic disease, disorders or treatments that compromise wound healing, chronic high dose steroid therapy, bone metabolic diseases, radiation or other immuno-oppressive therapy and infections or vascular impairment at the surgical site.

## WARNINGS

- Immunological studies suggest that a small number of patients may become sensitized to EMDOGAIN® as a result of repeated use. Please use caution in patients predisposed to allergic reaction and follow patients receiving repeated use closely.

- The safety and effectiveness of EMDOGAIN® has not been established in patients undergoing anticoagulant therapy. Careful consideration should be given before using EMDOGAIN® for these patients.

- EMDOGAIN® is intended for application around teeth only. Gain of tooth support occurs only to the level on the root surface covered by repositioned oral soft tissue. Therefore, EMDOGAIN® should be used only in areas where there is adequate tissue for root coverage. EMDOGAIN® should be used only after plaque and calculus has been removed from the diseased site.

## PRECAUTIONS

- Appropriate oral hygiene is necessary for proper healing to take place. Please refer to the "Clinical Considerations" section for additional information.
- Preclinical and radiographic evaluation should be performed before treatment.
- It is important to maintain asepsis during surgery.

## ADVERSE REACTIONS/COMPLICATIONS

**The following adverse events were observed in clinical trials for EMDOGAIN®. A distinction of adverse events seen due to EMDOGAIN® alone could not be performed because EMDOGAIN® is labeled for use in conjunction with conventional periodontal surgery for which there are associated risks. The adverse events observed in the clinical trials are listed below by the type of event and in the order of severity.**

Local soft tissue reactions:

Local redness, inflammation, soreness, gingival irritation, hematoma/ecchymosis, oral candidiasis, tissue necrosis/cratering, angulitis, herpes-like blisters, hypoesthesia (burning and itching reaction on the tongue), oral mucosa reaction, fibrin layer, discoloration

Local tooth-related reactions:

Increased tooth mobility, hypersensitive root surfaces (root sensitivity), pain

General reactions:

Urticaria, itching skin reaction, gastrointestinal disturbances, urogenital disturbances

The following additional adverse events and surgical complications, although not observed in the studies, may be related to this type of surgical procedure and have the potential to occur: postoperative hemorrhage, infection, wound dehiscence, sloughing of tissue, paresthesia, bleeding, loosening of sutures.

## DIRECTIONS FOR USE

Each set of vials (EMDOGAIN® and vehicle solution) is intended for use in one patient only. EMDOGAIN® from one set of vials is sufficient for the treatment of up to three periodontally involved teeth.

## PREPARATION OF EMDOGAIN®

**Preparation should be initiated approximately 15 minutes before application. Until then the vials should be stored in a refrigerator (36 - 46°F).**

1. Remove the center of the cap of the vial containing the vehicle solution. Use a sterile syringe (3-5ml) with sterile cannula (18Gx2") and slowly withdraw about 1 ml of vehicle solution through the rubber stopper.

2. Remove the center of the cap of the vial containing EMDOGAIN® and add the vehicle solution through the rubber stopper. Rotate the vial a few times to distribute the solution.

3. Wait until EMDOGAIN® powder is dissolved by the vehicle solution. Do not heat!

4. Withdraw the gel slowly to reduce air entrapment. Change to a short needle with a blunt end.

5. Use the EMDOGAIN® within 2 hours of mixing and discard any remaining gel.

## CLINICAL PROCEDURE

**The EMDOGAIN gel is intended for use in conjunction with periodontal surgery:**

1. Anesthetize the area selected for surgery by block and/or infiltration anesthesia. Avoid injection of local anesthetic with a vasoconstrictor into the interdental papilla or marginal gingiva.

2. Make intra-crevicular incisions. Then, if judged appropriate, make one or two vertical releasing incisions extending out into the alveolar mucosa. Raise full-thickness (mucoperiosteal) flaps on the buccal and palatal/lingual surfaces of the teeth. Preserve as much of the gingival connective tissue in the flap as possible. Maintain viability of periodontal cells by hydration of the soft tissue with saline.

3. Only remove the granulation tissue adherent to the alveolar bone and any associated osseous defects necessary to provide full access and visibility to the root surfaces. Remove subgingival plaque and calculus. Remove remaining smear layer by a quick surface cleaning (e.g. 15 s with citric or phosphoric acid). Rinse thoroughly with sterile saline. Avoid contamination of the cleaned root surfaces with saliva or blood after the final rinse.

4. Immediately apply EMDOGAIN gel onto the exposed root surfaces, starting at the most apical bone level. Apply EMDOGAIN to fully cover the exposed root surface areas. Overflow of surplus material during suturing should occur.

5. Complete coverage of the interproximal area and optimal soft tissue adaptation are essential. If deemed appropriate, a periosteal fenestration at the base of the flap may be used to facilitate coronal repositioning of the soft tissue. Suture materials appropriate for extended stable closure is preferred.

6. The patient should be advised to rinse daily with an antiseptic mouth rinse (e.g. 0.1-0.2% chlorhexidine solution) until 3-6 weeks post-surgery. Antibiotics may also be used if deemed appropriate based on the clinician's judgement.

7. Sutures may be removed when clinical healing of flaps and the root/soft tissue interface are stable or when they no longer add to the stability of the healing wound.

8. The patient should be instructed not to brush in the area where surgery has been performed until 6 weeks post-operatively. However, "professional tooth-cleaning" should be performed as needed. At 6 weeks post surgery the patient is reinstructed in appropriate tooth cleaning measures, including methods for interproximal cleaning. Recommendations for oral hygiene should be based on the need to maintain extended wound stability.

## CLINICAL CONSIDERATIONS

Use of periodontal devices in bony defects should only be performed by individuals who are clinically familiar with current periodontal therapy. Improper technique may yield suboptimal results. Preclinical and radiographic surgical evaluation is imperative. Special effort to maintain asepsis during surgery is most important. To prevent postoperative infection and to optimize healing, the use of an antiseptic mouth rinse is recommended for a period of 3 to 6 weeks post-surgery. Antibiotics may be used if deemed appropriate based on the nature of the severity of the disease/defect and the clinicians judgement.

Since maintenance of a stable wound is a critical factor for success, the patient should be instructed not to brush in the area where surgery has been performed until 6 weeks postoperatively. However, consistent with conventional post-surgical care the patients should be subjected to "professional tooth-cleaning" as needed. Recommendations for appropriate oral hygiene measures, including methods for interproximal cleaning, should be based on the clinician's judgement, the need for extended wound stability, and the awareness that regain of clinical attachment and alveolar bone has been shown to continue for more than a year following treatment with EMDOGAIN®.

Clinical studies with EMDOGAIN® demonstrated clinical attachment gain and interproximal alveolar bone gain in patients with moderate to severe periodontitis and infrabony pockets not affected with furcation lesions. The predominate support for use of EMDOGAIN® for this indication was based on the data for bone gain determined radiographically. The device is continuing to be evaluated for long-term effectiveness.

The following table presents results from three clinical trials to evaluate the use of EMDOGAIN®. The data are reported as the difference between the clinical measurements taken at baseline before the initial operation and the clinical measurements taken at the designated follow-up periods. For the clinical parameters of pocket depth reduction and clinical attachment gain, the data are also expressed as the percent difference between the results of the surgical procedure alone and treatment with EMODGAIN®. Radiographic bone gain is reported as the linear measurement and as the percentage of the initial bone loss that was regained.

| Design | Eval. Period (mon.) | No. of pts. | Radiographic Bone Gain (mm) {range [min., max.]} | | | | | Clinical Attachment Gain (mm) {range [min., max]} {For Study 4, furcation reduction} | | | | Pocket Depth Reduction (mm) {range [min., max.]} | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | **EMD-OGAIN®** | Control | Diff. | **% of initial bone loss regained** | | EMD-OGAIN® | Control | Diff. | % diff.. of control | EMD-OGAIN ® | Control | Diff. | % diff. of control |
| | | | | | | **EMD** | Contr. | | | | | | | | |
| Parallel groups 1-, 2-, and 3-wall Control: surgery | 8 | 107T 33C | **1.2 [-2.1, +4.8]** | 0.3 | **0.9*** | **15%** | 4% | 3.1 [-1.0, +11.0] | 2.6 [0, +5.0] | 0.5 | 19% | 4.3 [+0.5, +12.5] | 3.7 [+1.0, +7.0] | 0.6* | 16% |
| | 36 | 45T 21C | **2.5 [-0.6, +5.4]** | 0 [-1.4, + 2.5] | **2.5***** | **31%** | 0% | 2.9 [+0.5, +7.5] | 2.2 [0, +4.5] | 0.7¤ | 32% | 3.8 [+0.5, +8.5] | 3.2 [0, +8.0] | 0.6 | 19% |
| Split-mouth 1- or 2-wall Control: surgery | 8 | 26 | **0.7 [-0.6, +1.8]** | 0.1 [-1.3, +2.1] | **0.6*** | **12%** | 0% | 2.1 [-1.0, +5.5] | 1.8 [-1.0, +4.0] | 0.3 | 16% | 3.3 [-0.5, +7.0] | 3.1 [0, +6.0] | 0.2 | 6% |
| | | 10# | **0.8 [0, +1.5]** | 0 [-0.9, +1.9] | **0.8**** | **8%** | 0% | 3.5 [+1.5, +5.5] | 2.2 [0, +4.0] | 1.3* | 59% | 3.6 [+1.5, +5.5] | 3.6 [0, +7.0] | 0 | 0% |
| Split-mouth, 1- or 2-wall Control: placebo | 8 | 34 | **0.9 [-0.3, + 2.1]** | -0.1 [-1.0, +0.9] | **1.0 **** | **13%** | -2% | 2.1 [-0.5, +5.5] | 1.5 [-1.0, +3.5] | 0.6** | 40% | 3.3 [+0.5, +6.5] | 2.6 [0, +5.0] | 0.7** | 27% |
| | 16 | 31 | **2.2 [-0.4 , +6.0]** | -0.2 [-1.2, +1.4] | **2.4***** | **31%** | -4% | 2.3 [-1.0, +5.0] | 1.7 [-1.0, +4.5] | 0.6** | 35% | 3.3 [+0.5, +6.5] | 2.6 [-1.0 , +4.5] | 0.7** | 27% |
| | 36 | 27 | **2.6 [0.08 , +7.1]** | 0 [-1.1, +1.5] | **2.6***** | **36%** | 0% | 2.2 [0, +4.5] | 1.7 [-1.0, +3.5] | 0.5** | 30% | 3.1 [+1.0, +6.0] | 2.3 [-0.5, + 4.5] | 0.8*** | 35% |

T, C test and control patients, respectively

‡ The split mouth design indicates that the patient serves as his/her own control

# Patients with deepest baseline pocket exceeding 8 mm

*, **, ***, ¤ $p < 0.05$, $p < 0.01$, and $p < 0.001$, $p = 0.08$ respectively

# IMMEDIATE CONTAINER LABELS FOR VIALS

**EMD**

**E M D**

(Enamel Matrix Derivative, 30 mg/vial, Sterile)

Caution: Federal law restricts this device to sale, distribution and use by or order of a dentist.
Manufactured by: BIORA AB, Malmö, Sweden.
Storage conditions: Keep refrigerated.
Batch No. XXXOOO, Exp date 00/00.

**Vehicle Solution**

**VEHICLE SOLUTION**

(Propylene Glycol Alginate, 1.5 ml/vial, Sterile)

Caution: Federal law restricts this device to sale, distribution and use by or order of a dentist.
Manufactured by: BIORA AB, Malmö, Sweden.
Storage conditions: Keep refrigerated.
Batch No. XXXOOO, Exp date 00/00