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APPROVAL ORDER

00M-0810

AAV1



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
9200 Corporate Boulevard
Rockville MD 20850

FEB 22 2000

Mr. John P. Ryaby
Chairman of the Board
Exogen, Inc.
10 Constitution Avenue
Piscataway, New Jersey 08855

Re: P900009/S6
Exogen 2000® or Sonic Accelerated Fracture Healing System (SAFHS®)
Filed: August 11, 1998
Amended: December 7, 1998; January 8, 1999 and August 23, 1999

Dear Mr. Ryaby:

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) supplement for the Exogen 2000® or Sonic Accelerated Fracture Healing System (SAFHS®). This device is indicated for the non-invasive treatment of established nonunions excluding skull and vertebra, and for accelerating the time to a healed fracture for fresh, closed, posteriorly displaced distal radius fractures and fresh, closed or Grade I open tibial diaphysis fractures in skeletally mature individuals when these fractures are orthopedically managed by closed reduction and cast immobilization. A nonunion is considered to be established when the fracture site shows no visibly progressive signs of healing.

The PMA supplement is approved subject to the conditions described below and in the "Conditions of Approval" (enclosed). You may begin commercial distribution of the device as modified 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

CDRH will notify the public of its decision to approve your PMA by making available a summary of the safety and effectiveness data upon which the approval is based. The information can be found on the FDA CDRH Internet homepage located at <http://www.fda.gov/cdrh/pmapage.html>. Written requests for this information can also be made to the Dockets Management Branch (HFA-305), Food and Drug Administration, 5630 Fishers Lane, rm. 1061, Rockville, MD 20852. The written request should include the PMA number or docket number. Within 30 days from the date that this information is placed on the Internet, 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).

Page 2 - Mr. John P. Ryaby

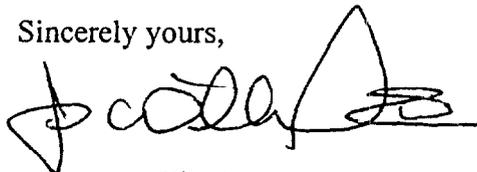
Failure to comply with the conditions of approval invalidates this approval order. Commercial distribution of a device that is not in compliance with these conditions is a violation of the act. You are reminded that, as soon as possible and before commercial distribution of your device, you must submit an amendment to this PMA submission with copies of all approved labeling affected by this supplement in final printed form. As part of our reengineering effort, the Office of Device Evaluation is piloting a new process for review of final printed labeling. The labeling will not routinely be reviewed by FDA staff when PMA supplement applicants include with their submission of the final printed labeling a cover letter stating that the final printed labeling is identical to the labeling approved in draft form. If the final printed labeling is not identical, any changes from the final draft labeling should be highlighted and explained in the amendment. Please see the CDRH Pilot for Review of Final Printed Labeling document at <http://www.fda.gov/cdrh/pma/pilotpma.htm> for further details.

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 Mr. Theodore R. Stevens at (301) 594-2036, ext. 166.

Sincerely yours,



James E. Dillard III
Acting Director
Division of General and
Restorative Devices
Office of Device Evaluation
Center for Devices and
Radiological Health

Enclosure

Issued: 3-4-98

CONDITIONS OF APPROVAL

APPROVED LABELING. As soon as possible, and before commercial distribution of your device, submit three copies of an amendment to this PMA submission with copies of all approved labeling in final printed form to the PMA Document Mail Center (HFZ-401), Center for Devices and Radiological Health, Food and Drug Administration (FDA), 9200 Corporate Blvd., Rockville, Maryland 20850.

ADVERTISEMENT. No advertisement or other descriptive printed material issued by the applicant or private label distributor with respect to this device shall recommend or imply that the device may be used for any use that is not included in the FDA approved labeling for the device. If the FDA approval order has restricted the sale, distribution and use of the device to prescription use in accordance with 21 CFR 801.109 and specified that this restriction is being imposed in accordance with the provisions of section 520(e) of the act under the authority of section 515(d) (1) (B) (ii) of the act, all advertisements and other descriptive printed material issued by the applicant or distributor with respect to the device shall include a brief statement of the intended uses of the device and relevant warnings, precautions, side effects and contraindications.

PREMARKET APPROVAL APPLICATION (PMA) SUPPLEMENT. Before making any change affecting the safety or effectiveness of the device, submit a PMA supplement for review and approval by FDA unless the change is of a type for which a "Special PMA Supplement-Changes Being Effected" is permitted under 21 CFR 814.39(d) or an alternate submission is permitted in accordance with 21 CFR 814.39(e). A PMA supplement or alternate submission shall comply with applicable requirements under 21 CFR 814.39 of the final rule for Premarket Approval of Medical Devices.

All situations which require a PMA supplement cannot be briefly summarized, please consult the PMA regulation for further guidance. The guidance provided below is only for several key instances.

A PMA supplement must be submitted when unanticipated adverse effects, increases in the incidence of anticipated adverse effects, or device failures necessitate a labeling, manufacturing, or device modification.

A PMA supplement must be submitted if the device is to be modified and the modified device should be subjected to animal or laboratory or clinical testing designed to determine if the modified device remains safe and effective.

A "Special PMA Supplement - Changes Being Effected" is limited to the labeling, quality control and manufacturing process changes specified under 21 CFR 814.39(d)(2). It allows for the addition of, but not the replacement of previously approved, quality control specifications and test methods. These changes may be implemented before FDA approval upon acknowledgment by FDA that the submission is being processed as a "Special PMA Supplement - Changes Being Effected." This acknowledgment is in addition to that issued by the PMA Document Mail Center for all PMA supplements submitted. This procedure is not applicable to changes in device design, composition, specifications, circuitry, software or energy source.

Alternate submissions permitted under 21 CFR 814.39(e) apply to changes that otherwise require approval of a PMA supplement before implementation of the change and include the use of a 30-day PMA supplement or annual postapproval report. FDA must have previously indicated in an advisory opinion to the affected industry or in correspondence with the applicant that the alternate submission is permitted for the change. Before such can occur, FDA and the PMA applicant(s) involved must agree upon any needed testing protocol, test results, reporting format, information to be reported, and the alternate submission to be used.

POSTAPPROVAL REPORTS. Continued approval of this PMA is contingent upon the submission of postapproval reports required under 21 CFR 814.84 at intervals of 1 year from the date of approval of the original PMA. Postapproval reports for supplements approved under the original PMA, if applicable, are to be included in the next and subsequent annual reports for the original PMA unless specified otherwise in the approval order for the PMA supplement. Two copies identified as "Annual Report" and bearing the applicable PMA reference number are to be submitted to the PMA Document Mail Center (HFZ-401), Center for Devices and Radiological Health, Food and Drug Administration, 9200 Corporate Blvd., Rockville, Maryland 20850. The postapproval report shall indicate the beginning and ending date of the period covered by the report and shall include the following information required by 21 CFR 814.84:

- (1) Identification of changes described in 21 CFR 814.39(a) and changes required to be reported to FDA under 21 CFR 814.39(b).
- (2) Bibliography and summary of the following information not previously submitted as part of the PMA and that is known to or reasonably should be known to the applicant:
 - (a) unpublished reports of data from any clinical investigations or nonclinical laboratory studies involving the device or related devices ("related" devices include devices which are the same or substantially similar to the applicant's device); and

- (b) reports in the scientific literature concerning the device.

If, after reviewing the bibliography and summary, FDA concludes that agency review of one or more of the above reports is required, the applicant shall submit two copies of each identified report when so notified by FDA.

ADVERSE REACTION AND DEVICE DEFECT REPORTING. As provided by 21 CFR 814.82(a)(9), FDA has determined that in order to provide continued reasonable assurance of the safety and effectiveness of the device, the applicant shall submit 3 copies of a written report identified, as applicable, as an "Adverse Reaction Report" or "Device Defect Report" to the PMA Document Mail Center (HFZ-401), Center for Devices and Radiological Health, Food and Drug Administration, 9200 Corporate Blvd., Rockville, Maryland 20850 within 10 days after the applicant receives or has knowledge of information concerning:

- (1) A mix-up of the device or its labeling with another article.
- (2) Any adverse reaction, side effect, injury, toxicity, or sensitivity reaction that is attributable to the device and
 - (a) has not been addressed by the device's labeling or
 - (b) has been addressed by the device's labeling, but is occurring with unexpected severity or frequency.
- (3) Any significant chemical, physical or other change or deterioration in the device or any failure of the device to meet the specifications established in the approved PMA that could not cause or contribute to death or serious injury but are not correctable by adjustments or other maintenance procedures described in the approved labeling. The report shall include a discussion of the applicant's assessment of the change, deterioration or failure and any proposed or implemented corrective action by the applicant. When such events are correctable by adjustments or other maintenance procedures described in the approved labeling, all such events known to the applicant shall be included in the Annual Report described under "Postapproval Reports" above unless specified otherwise in the conditions of approval to this PMA. This postapproval report shall appropriately categorize these events and include the number of reported and otherwise known instances of each category during the reporting period. Additional information regarding the events discussed above shall be submitted by the applicant when determined by FDA to be necessary to provide continued reasonable assurance of the safety and effectiveness of the device for its intended use.

REPORTING UNDER THE MEDICAL DEVICE REPORTING (MDR) REGULATION.

The Medical Device Reporting (MDR) Regulation became effective on December 13, 1984. This regulation was replaced by the reporting requirements of the Safe Medical Devices Act of 1990 which became effective July 31, 1996 and requires that all manufacturers and importers of medical devices, including in vitro diagnostic devices, report to the FDA whenever they receive or otherwise become aware of information, from any source, that reasonably suggests that a device marketed by the manufacturer or importer:

- (1) May have caused or contributed to a death or serious injury; or
- (2) Has malfunctioned and such device or similar device marketed by the manufacturer or importer would be likely to cause or contribute to a death or serious injury if the malfunction were to recur.

The same events subject to reporting under the MDR Regulation may also be subject to the above "Adverse Reaction and Device Defect Reporting" requirements in the "Conditions of Approval" for this PMA. FDA has determined that such duplicative reporting is unnecessary. Whenever an event involving a device is subject to reporting under both the MDR Regulation and the "Conditions of Approval" for a PMA, the manufacturer shall submit the appropriate reports required by the MDR Regulation within the time frames as identified in 21 CFR 803.10(c) using FDA Form 3500A, i.e., 30 days after becoming aware of a reportable death, serious injury, or malfunction as described in 21 CFR 803.50 and 21 CFR 803.52 and 5 days after becoming aware that a reportable MDR event requires remedial action to prevent an unreasonable risk of substantial harm to the public health. The manufacturer is responsible for submitting a baseline report on FDA Form 3417 for a device when the device model is first reported under 21 CFR 803.50. This baseline report is to include the PMA reference number. Any written report and its envelope is to be specifically identified, e.g., "Manufacturer Report," "5-Day Report," "Baseline Report," etc. Any written report is to be submitted to:

Food and Drug Administration
Center for Devices and Radiological Health
Medical Device Reporting
PO Box 3002
Rockville, Maryland 20847-3002

Copies of the MDR Regulation (FOD # 336&1336) and FDA publications entitled "An Overview of the Medical Device Reporting Regulation" (FOD # 509) and "Medical Device Reporting for Manufacturers" (FOD #987) are available on the CDRH WWW Home Page. They are also available through CDRH's Fact-On-Demand (F-O-D) at 800-899-0381. Written requests for information can be made by sending a facsimile to CDRH's Division of Small Manufacturers Assistance (DSMA) at 301-443-8818.

SUMMARY OF SAFETY AND
EFFECTIVENESS DATA (SSED)

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Exogen 2000® SUMMARY OF SAFETY AND EFFECTIVENESS

I. General Information

Device Generic Name: Low-Intensity Pulsed Ultrasound Device for the Noninvasive Treatment of Nonunions

Device Trade Name: Exogen 2000® or Sonic Accelerated Fracture Healing System (SAFHS®)

Applicant's Name and Address: EXOGEN®, a Smith and Nephew Company
10 Constitution Avenue
P. O. Box 6860
Piscataway, NJ 08855
(732) 981-0990

Date of Panel Recommendation: None

Premarket Approval Application (PMA): P900009
Supplement Number: S006

Date of Notice of Approval to Applicant: FEB 22 2000

II. Indications for Use

The Exogen 2000® or Sonic Accelerated Fracture Healing System (SAFHS®) is indicated for the non-invasive treatment of established nonunions* excluding skull and vertebra, and for accelerating the time to a healed fracture for fresh, closed, posteriorly displaced distal radius fractures and fresh, closed or Grade I open tibial diaphysis fractures in skeletally mature individuals when these fractures are orthopedically managed by closed reduction and cast immobilization.

*A nonunion is considered to be established when the fracture site shows no visibly progressive signs of healing.

III. Contraindications

There are no known contraindications for the SAFHS® device.

IV. Warnings and Precautions

Warnings

- The safety and effectiveness of the use of this device has not been established in nonunions for the following:
 - nonunions of the vertebra and the skull.
 - individuals lacking skeletal maturity

Precautions

- The safety and effectiveness of the use of this device in pregnant/nursing women has not been established.
- Careful consideration of the use of this device must be decided on an individual basis in the presence of malaligned nonunion since the device will not correct or alter displacement, angulation or other malalignment.
- With active, implantable devices, such as cardiac pacemakers, operation may be adversely affected by close exposure to the SAFHS® device; therefore, evaluation during SAFHS® treatment by the attending cardiologist or physician is recommended.
- Patients in the clinical study were instructed to apply the device for one treatment period of twenty-minutes each day. The safety and effectiveness of the SAFHS® device when used for other than one daily twenty-minute treatment is unknown.
- The age range of the patients in this PMA nonunion study was 17- 86. The effect of SAFHS® therapy on patients outside this age range is unknown.

V. Device Description

The SAFHS® is a portable, battery powered, non-invasive ultrasonic bone growth stimulator. It incorporates the same technological features as the original SAFHS® device approved for treatment of fresh fractures (P900009, approved October 5, 1994).

The SAFHS® system provides a specifically-programmed low-level micromechanical force via ultrasonic acoustic pressure waves with an intensity of 30 milliwatts per square centimeter (mW/cm^2) [S.A.T.A. (Spatial Average-Temporal Average)]. The SAFHS® system low-intensity ultrasound level is comparable to diagnostic ultrasound intensity levels used in sonogram (fetal monitoring) procedures and is 1% to 5% of the intensities used for conventional therapeutic

ultrasound. Neither the physician nor the patient can select or change any of the low-intensity ultrasound signal specifications.

VI. Alternative Practices and Procedures

Alternative methods for treating nonunion are: 1) use of other approved bone growth stimulating devices; 2) surgical procedures which may involve internal fixation with a device and/or bone grafting; 3) procedures which may involve external fixation; or 4) conservative procedures.

VII. Marketing History

The SAFHS® device was initially approved for commercial marketing on October 5, 1994 with the indications of accelerating the time to a healed fracture for fresh, closed, posteriorly displaced distal radius fractures and fresh, closed or Grade I open tibial diaphysis fractures in skeletally mature individuals when these fractures are orthopedically managed by closed reduction and cast immobilization. SAFHS® devices have been marketed for the approved indications in the United States (originally as Model 2A and since PMA Supplement Approval for Model 2000 in March of 1997 as either Model 2A or 2000) since October 17, 1994. The SAFHS® device has also been marketed in Germany, The Netherlands, France, Denmark, Sweden, Norway, Italy, United Kingdom, Israel, Spain, Belgium, Japan, Australia, Austria, Switzerland, Finland, and Luxembourg and has not been removed from the market in any of these countries.

VIII. Potential Adverse Effects of the Device on Health

No device-related adverse reactions or medical complications related to the use of this device were reported during the clinical studies. Two patients in a post-market registry reported mild skin irritation caused by skin sensitivity to the coupling gel. Both were resolved by a change of coupling medium to mineral oil or glycerine.

IX. Summary of Nonclinical Studies

Studies Previously Reported in PMA P900009¹- Several studies were conducted for the initial fresh fracture PMA Application P900009 to assess the safety and effectiveness of the SAFHS® device. The *in vitro* and *in vivo* animal studies showed no harmful thermal or genetic effects of low intensity pulsed ultrasound and suggested that the use of low intensity pulsed ultrasound would stimulate normal bone healing and other related biological responses.

Studies Reported in this PMA Supplement

Many fracture nonunions have metallic internal fixation devices present as the result of previous treatment. This PMA Supplement presents several reports of preclinical testing using internal-fixation animal models.

Two studies^{2,3} reported on ultrasound fracture treatment in a model of bilateral closed femoral shaft fractures made in skeletally male Long-Evans rats and stabilized by a 1.14 x 26 mm Kirschner wire, serving as an intramedullary rod. Fracture repair was evaluated on postoperative day 21, and treated fractures were shown to be significantly stronger and stiffer than the controls, showing that the stimulatory effect of ultrasound on fracture repair was not inhibited by the presence of a metallic internal fixation device.

In another case, the *in vivo* temperature changes in bone and surrounding soft tissues generated by pulse mode ultrasound beam were evaluated in the tibiae of the turkey and in the femora of the dog, with and without an intramedullary rod in place. The results indicate that ultrasound has a minimal influence of temperature, and that internal fixation devices do not affect the thermal field.

Several reference articles have focused on conventional therapeutic ultrasound's effect on surgical metallic implants. Lehman et al.⁴ reported that, based on histological studies, ultrasound applied in the presence of metal implants did not produce any untoward effects. Gersten⁵ reported that temperature rises in the region of maximal ultrasound field were smaller with metal than with bone at the same depth; the presence of metal was not a contraindication to the use of ultrasound. Lotsova⁶ reported that investigations carried out with Kirschner needles used as fixation in ultrasound-treated patients did not affect migration of the pins or affect the structural integrity of the pins as determined by metallographic analysis. A canine study of the effect of ultrasound on internal fixation screws by Skoubo-Kristiansen and Sommer⁷ concluded that no untoward effect of ultrasound was observed on the fixation screws and the torques used for loosening the screws could not be related to treatment with ultrasound.

The above studies on metal implants utilized ultrasound intensity levels ranging from 0.5 W/cm² to 2 W/cm² and no untoward effects were noted. These intensities are 16 to 60 times higher than the intensity used in the SAFHS® clinical and associated animal studies reported herein. Therefore, it is reasonable to conclude that metal implants such as plates, screws, and intramedullary (IM) rods present at or near a fracture would not affect the safety and effectiveness of SAFHS®.

This PMA Supplement reported on a study of whether SAFHS ultrasound at 3 times the intensity of the clinical signal for 30 hours would affect the composition of AISI 316-L stainless steel orthopedic fixation plates in a physiological medium. Metallographic analysis followed the routine procedures of electropolishing, chemical treatment, and optical microscope and photography with magnifications at 55, 110, 220 and 440X. No changes or effects were observed in the ultrasound-stimulated plate versus the non-stimulated plate.

Based on these references and this study, low-intensity ultrasound does not compromise the integrity of this commonly used orthopedic implant material even after 30 hours of continuous exposure.

X. Summary of Clinical Studies

A. Objectives

The objectives of the clinical studies were to assess the safety and effectiveness of SAFHS® in the treatment of nonunions.

Study Design

This PMA Supplement reports the retrospective analysis of a group of patients in Germany and Austria treated with SAFHS® for nonunions. The study had a self-paired control design with each nonunion case serving as its own control, and with the prior treatment result of failed orthopedic care as the control compared to ultrasound as the only new treatment.

The study includes nonunion cases treated with the SAFHS® device from the initial device introduction date. Each prescribing physician (investigator) provided initial fracture and nonunion data for their own cases, followed them, and provided clinical and radiographic assessment data including any adverse reactions, complications or complaints. Three principal investigators (PIs) determined whether cases met the study inclusion and exclusion criteria, and determined radiographic outcome.

B. Inclusion/Exclusion Criteria

For this PMA supplement, the primary criterion for the definition of nonunion cases was the minimum time from fracture of nine (9) months. Nonunion cases meeting the minimum 9 month criterion were then classified into two mutually exclusive categories descriptively characterized as “core group” and “non-core group”. The core group category required nonunion cases to have established nonunions, to have completed treatment and to have no surgical intervention within the three months prior to SAFHS® treatment in addition to the 9 month minimum time from initial injury. The non-core group category included those completed cases that could not be validated as established nonunions by the PIs, those completed cases with surgical procedures within the three months prior to SAFHS® treatment, cases with incomplete data, and all incomplete cases (1 deceased, 2 non-compliant, and 2 withdrawals) in addition to the 9 month minimum time from initial injury. Exclusions for either group were pregnant females, nonunions of spine or skull, or tumor-related nonunions, and patients who could not comply with the required treatment regimen.

C. Criteria for Measuring Safety

The safety information provided in the approved PMA-P900009 for SAFHS® for the fresh fracture indication provided assurance that the pulsed, low-intensity ultrasound intensities transmitted to bone and surrounding tissue posed no observed or known risks. Additional preclinical studies reported in this PMA Supplement support this conclusion. Furthermore, adverse effects, complications, and complaints were monitored and no device related incidents were reported.

D. Criteria for Measuring Effectiveness

The clinical records and the radiographic series of all of the cases were reviewed by one or more of the PIs to insure adherence to the inclusion and exclusion criteria. The period between the initial injury and the time of the start of low-intensity ultrasound treatment was verified from the records. The radiographic series for each case was reviewed to determine that the healing process had stopped and that the nonunion line was visible in two views. The investigator provided the sponsor with the signed prescription form, demographic data, prior orthopedic and surgical history data, and orthopedic care data received by the patient prior to and at the time of the start of SAFHS® treatment. Investigators followed the standard orthopedic practice of taking anterior/posterior and lateral radiographs, with oblique views taken if the nonunion gap was more clearly seen on these views. Standard clinical examinations for pain upon gentle stress and upon weight bearing were performed at each follow-up visit to determine the extent of clinical healing. Investigators followed standard orthopedic management practice and scheduled clinical and radiographic follow-ups at 1 to 2 month intervals. A long-term follow-up of the healed cases was conducted approximately one year after the patient was judged to be healed.

Upon completion of SAFHS® therapy, the outcome of “healed” or “failed” was determined. Those cases with healed or failed outcome were designated as “completed cases” and cases that did not complete SAFHS® therapy were designated as “incomplete cases”. A nonunion was determined as healed when it was both clinically healed [no pain upon gentle stress and weightbearing (for long bones only)] and radiographically healed [for long bones, at least three (3) of four (4) bridged cortices] and, for other bones, callus bridging the nonunion site. Failed outcome was defined as not meeting the criteria to be determined as healed, for cases with completed SAFHS® therapy. The three “incomplete cases” categories were deceased (died during the study), non-compliant (non-compliance with SAFHS® device use or prescribed treatment regimen), and withdrawal (withdrawal from the study prior to outcome determination, based on a decision by the investigator or the patient).

The primary efficacy parameter was outcome of “healed” due to SAFHS® treatment. The secondary efficacy parameter was heal time, defined as days from SAFHS® start to the healed outcome determination date. A descriptive parameter, reported for purposes of description or characterization and not for purposes of determining safety and effectiveness, was fracture age defined as days from initial injury to the start of SAFHS® therapy (Table 1 for completed cases). Table 2 provides an efficacy summary for a comparison of completed cases and its subsets of core and non-core groups and the intention-to-treat analysis. Table 3

presents the stratification analyses for categorical variables at the start of SAFHS® treatment with the percent healed compared for homogeneity across strata for the clinically relevant variables.

Statistical analyses were based on each specific nonunion case. All times to a specific response or event were calculated (number of days). Statistics were presented relating to average or central tendency, e.g., mean or median, and percentage of cases and the numerator/denominator (in parenthesis) that were the basis for the percentage of cases. Standard error of the mean (S.E.M.) was the measure of variability presented. The Kruskal-Wallis test was utilized for each non-categorical variable and Fisher's exact test was utilized for each categorical variable. All hypothesis tests were performed with alpha equal 0.05; therefore, a p-value of less than or equal to 0.05 was the basis for declaring a result statistically significant. For comparisons between groups, the null hypothesis was that the distribution of the variable was the same (i.e., homogeneous) across the comparator groups. The alternative hypothesis was that the distribution of the variable was not the same across the comparator groups.

The outcome of SAFHS® treatment was the primary efficacy parameter for this paired design clinical investigation where each case served as its own control. Nonunion cases have essentially a zero probability of achieving a healed state without intervention; however, the sponsor conservatively assumed that the healed rate without SAFHS® therapy during the time period of this study would be 5% rather than 0%. Therefore, the null hypothesis was that the healed rate was less than or equal to 5%, and the alternative hypothesis was that the healed rate was greater than 5%.

Comparability analyses were performed for 75 non-categorical and categorical variables.

E. Study Population

1. **General** - All cases with SAFHS® low-intensity ultrasound therapy started during the period of July, 1995 (the initial device introduction month) to April, 1997 were reviewed by the PIs to determine whether they met the study inclusion and exclusion criteria.

There was one patient in the study with more than one nonunion. To avoid the complications of patient and fracture number differences, each nonunion is considered a separate case. All comparability and effectiveness analyses refer to nonunion cases and not patients.

The study consisted of 79 patients with 80 nonunion cases from 54 investigators. Five cases were without a final healing status and were incomplete cases: 2 non-compliant, 2 withdrawn and 1 deceased.

Patient demographics for the eighty cases were summarized for age, sex, and weight. Females constituted 42% (33/79) and males were 58% (56/79) of the total number of patients. The average patient age was 46 years with a range of 17-86 years. The mean fracture age (days from initial injury to the start of SAFHS treatment) was 1136 days (3.1 years) with a range of 257 to 6011 days. The mean number of prior surgical procedures was 2.4. The mean number of days without surgery (days from last surgical procedure to SAFHS start) was 665 days (1.8 years).

2. Comparisons across investigators and comparability of groups - Comparisons were assessed for the non-categorical variables of patient age, weight (kg.), days without surgery, fracture age, total number of surgical procedures combining initial and all subsequent interventions and surgical and other procedures by type combining initial and all subsequent interventions. Comparisons were also assessed for the categorical variables of gender, age, weight, fracture age, total number of surgical procedures combining initial and all subsequent interventions, surgical and other procedures by type combining initial and all subsequent procedures, days without surgery, bone, long bones versus other bones, displaced at initial injury, long bone type, initial fracture type, fixation present at the start of and during SAFHS® treatment, medication, disease, concomitant clinical condition, smoking status, compliance with device use during SAFHS® treatment, and nonunion type.

a. Justification for combining the data across investigators for all cases - Since the data from many investigators were pooled for the effectiveness results, comparability across investigators was evaluated, in particular, for the categorical variable at the completion of SAFHS® treatment of both the outcome of healed or failed. A comparison across investigators was also performed for all categorical and non-categorical variables to assess the validity of combining the data from all investigators within each study, with a non-significant result for 95% (71/75) of the comparisons.

b. Primary core group versus non-core group comparison - As the primary comparison between groups, the core group was compared to the non-core group for the non-categorical variables and the categorical variables to assess for the potential introduction of bias by the classification of cases as core group or non-core group. For this study, 95% (71/75) of the total comparisons were non-significant.

3. Summary of Results of Comparability Analyses - The comparability across investigators showed that combining the data from all investigators for the evaluation of safety and efficacy was justified based on the results of the comparability analyses which did not identify systematic differences across investigators; it was also justified because of the common inclusion/exclusion criteria and evaluation definitions that were utilized across all investigators. Most importantly, the comparisons were non-significant for outcome of SAFHS® treatment across investigators.

There were no systematic clinically relevant differences for the primary comparability

analyses for the core group cases compared to the non-core group cases. This demonstrates that there was no introduction of bias by the classification of cases as core group and non-core group. The comparisons also established that there were similar characteristics in both groups.

F. Results

1. **Safety** - No device-related adverse reactions or medical complications related to the use of this device were reported during the clinical study.

2. **Effectiveness** - Outcome analyses were completed using the healed or failed outcome of the SAFHS® treated nonunion and the associated date as determined by the principal investigators. For the purposes of this summary, results are reported for completed cases, the core and non-core group subsets of completed cases, and for all cases in an intention-to-treat analysis. One case involving a failed cementless knee arthroplasty (tibial component) was included in the safety and intention-to-treat analyses but not the efficacy analysis.

a. Primary and secondary efficacy parameters, and descriptive parameter.

Of the 74 completed cases, 86% (64/74) healed and 14% (10/74) were failures of SAFHS® treatment. When this healed rate was compared with the paired control of prior failed treatment, the result was significant at $p=0.00001$ (Table 1.). The mean time to a healed fracture was 163 ± 9.4 days. The median heal time was 142 days with a range of 53 to 375 days. The mean fracture age for the healed cases in the core group was 934 ± 151.6 days or nearly 3 years and the median fracture age was 494 days with a range of 257-6011 days (Table 1).

In Table 2, a comparison summary provides the efficacy results for the core and non-core group subsets of completed cases. Of the 41 core group cases, 88% (36/41) healed and 12% (5/41) were failures of SAFHS® treatment. The healed rate for the non-core group was 85% (29/34). Both core and non-core group results were significant at $p=0.00001$ when compared to the paired control of prior failed treatment.

The intention-to-treat analysis evaluated all 80 cases and showed 81% (65/80) healed and 19% (15/80) as not healed (10 failed and 5 incomplete cases designated as not healed). A comparison with the paired control of prior failed treatment was significant at $p=0.00001$.

b. Completed Cases Stratified by Variable (Table 3)

Healing rates were stratified by a number of variables, and were consistently similar across most variables including gender and age, . Statistically significant differences

in healing were seen in stratifications by bone, long bones versus other bones, and the fracture age stratum of over 5 years (≥ 1827 days). All three of these differences were attributable to the four scaphoid nonunion failures that were all more than 10 years in fracture age and, therefore, were very difficult and challenging cases.

3. **Long-term Follow-up** - A long-term follow-up was performed for all 80 cases by telephone to determine whether healed cases were still healed. This follow up documented 92% (60/65) as still healed with 8% (5/65) of cases that could not be located with an average long-term follow-up time of 407 ± 7.4 days and median time of 386 days with a range of 188-778 days.

4. **Compliance with device usage** - Patients were instructed to use their SAFHS® device at home for one continuous twenty-minute treatment per day until advised to stop treatment by their physician. The SAFHS® device recorded the actual usage time of the device. The patient compliance monitor (PCM) microprocessor storing the usage time was downloaded when the devices were returned to Exogen upon completion of treatment. For all 80 cases, twenty-two had missing PCM usage data either because the device was not returned or the battery powering the PCM circuit was discharged (low battery). The cases that had PCM data numbered 58 and an additional three cases without PCM data were termed “good” in compliance by the investigator’s assessment. Of the 58 cases with PCM data, 43 used their devices over 2,000 minutes (100 days if used once a day), 12 used their devices for between 1000 and 2000 minutes, and 3 used their devices for less than 1000 minutes.

For the 47 healed cases with PCM data, the mean PCM device usage was 2661 ± 192.6 minutes with a median of 2254 minutes and a range of 490 to 6865 minutes.

5. **Summary of Efficacy Results** - The comparability of core and non-core group cases was established and the comparability across investigators did not identify any systematic differences that would preclude the combining or pooling of data from all investigators. Given the percent healed rate, number of cases (N) and alpha equal .05, the power of the analyses was at least 99.9%.

All healed analyses consistently demonstrated efficacy with the completed cases having a healed rate of 86% (64/74) while the core group subset of completed cases had a healed rate of 88% (36/41). The core group subset healed rate was similar to the completed cases non-core subset healed rate of 85% (28/33). The intention-to-treat analysis of all cases was 81% (65/80). The healed rate results were also consistently similar across stratification variables including gender and age; except for the decreased healing response rate for scaphoid nonunions which affected stratifications by bone, long bones versus other bones, and the fracture age stratum of over 5 years (≥ 1827 days). The scaphoid nonunion healed rate of 33% (2/6) was attributable to the four scaphoid nonunion failures that were all more than 10 years in fracture age and, therefore, were

Table 1: Efficacy Results for SAFHS® Treated Completed Cases*

* Excludes five (5) cases with outcomes of non-compliant (2), withdrawal (2), and deceased (1).

**Binomial test of the null hypothesis that the ultrasound treatment period heal rate was less than or equal to 5%.

A. Primary Efficacy Parameter - Outcome, Number (and %) of Cases: N= 74			
Outcome	Prior Orthopedic Treatment Period	Ultrasound Treatment Period	Exact (one-sided) P-Value**
Healed	0 (0%)	64 (86%)	0.00001
Failed	74 (100%)	10 (14%)	
Total	74 (100%)	74 (100%)	
B. Secondary Efficacy Parameter-Heal Time and Descriptive Parameter of Fracture Age			
1. Healed Cases: N= 64			
a. Heal Time (days) Mean ± S.E.M.: 163 ± 9.4 Median: 142 days Range: 53 to 375 days Percentile Heal Time: 25% ≤ 104 days 50% ≤ 142 days 75% ≤ 211 days 90% ≤ 270 days		b. Fracture Age (days) Mean ± S.E.M.: 934 ± 151.6 Median: 494 days Range: 257 to 6011 days Percentile Fracture Age: 25% ≤ 348 days 50% ≤ 494 days 75% ≤ 991 days 90% ≤ 1458 days	
2. Failed Cases: N= 10			
a. Fail Time (days) Mean ± S.E.M.: 241 ± 42.7 Median: 218 days Range: 118 to 572 days Percentile Outcome Time: 25% ≤ 141 days 50% ≤ 218 days 75% ≤ 280 days 90% ≤ 453 days		b. Fracture Age (days) Mean ± S.E.M.: 2570 ± 674 Median: 2387 days Range: 272 to 5893 days Percentile Fracture Age: 25% ≤ 485 days 50% ≤ 2387 days 75% ≤ 4740 days 90% ≤ 5351 days	

Table 2: Effectiveness Summary for Completed Cases and Its Subsets of Core and Non-core Groups and the Intention-to-Treat Analysis

	Total	Healed	Failed	% Healed	p-value*
Completed Cases:	74	64	10	86%	0.00001
<i>Core Group:</i>	<i>41</i>	<i>36</i>	<i>5</i>	<i>88%</i>	<i>0.00001</i>
<i>Non-Core group:</i>	<i>33</i>	<i>28</i>	<i>5</i>	<i>85%</i>	<i>0.00001</i>
Intention-to-Treat Analysis (all cases):	80	65	15	81%	0.00001

*p-value for comparison against prior orthopedic treatment results of 100% failed cases.

Table 3: Completed Cases - Stratification by Categorical Variables

*Two-sided exact p-value, Fisher's exact test, testing homogeneity of strata.

Row	Categorical Variable Prior to Start of SAFHS® Treatment	Completed Cases Fishers Exact Probability*				
		Total	Healed	Failed	% Healed	p-value
1	Gender: Female Male	30 44	28 36	2 8	93% 82%	0.19
2	Age: ≤17 18-29 30-49 50-64 ≥65	1 12 32 21 8	1 9 27 19 8	0 3 5 2 0	100% 75% 84% 91% 100%	0.52
3	Weight (kg.): <65 kg. 65-80 kg. >80 kg.	12 35 27	11 31 22	1 4 5	92% 89% 81%	0.65
4	Fracture Age: 256-365 days 366-730 days 731-1826 days ≥ 1827 days	20 27 17 10	19 24 16 5	1 3 1 5	95% 89% 94% 50%	0.001
5	Total No. Surgical Procedures Combining Initial and All Subsequent Interventions: 0 1 2 3 or more	20 15 24 15	15 12 23 14	5 3 1 1	75% 80% 96% 93%	0.16
6	Prior Days Without Surgery (Days from Last Surgical Procedure to SAFHS® Start): ≤ 82 83-365 366-730 ≥ 731	9 39 12 14	9 34 12 9	0 5 0 5	100% 87% 100% 64%	0.03
7	Bone: Tibia/Tibia-Fibula/Fibula Femur Radius/Radius-Ulna/Ulna Humerus Metatarsal Other Foot Bones (calcaneus) Ankle* Scaphoid Other Hand Bones (metacarpal) Other (4-clavicle, 1-pelvis, 1-rib) *Tibio-talar arthrodesis	28 13 7 6 4 1 2 6 1 6	26 12 6 5 4 1 1 2 1 6	2 1 1 1 0 0 1 4 0 0	93% 92% 86% 83% 100% 100% 50% 33% 100% 100%	0.03

Row	Categorical Variable Prior to Start of SAFHS® Treatment	Completed Cases Fishers Exact Probability*				
		Total	Healed	Failed	% Healed	p-value
8	Long Bone vs. Other Bones: Long Bones - 28 tibia - 13 femur - 7 radius - 6 humerus - 4 metatarsal - 1 metacarpal Other Bones - 1 calcaneus - 4 clavicle - 1 pelvis - 1 rib - 6 scaphoid - 2 ankle	59	54	5	92%	0.02
		15	10	5	67%	
9	Displaced at the Start of SAFHS Therapy: Missing No Yes	(5) 56 13	(2) 50 12	(3) 6 1	 89% 92%	1.00
10	Long Bone Type: Only for Long Bone Cases: Missing Metaphyseal Diaphyseal	(5) 8 46	(3) 6 45	(2) 2 1	 75% 98%	0.05
11	Initial Fracture Type: Missing Closed Open Arthrodesis Osteotomy	(4) 40 22 2 6	(2) 34 21 1 6	(2) 6 1 1 0	 85% 95% 50% 100%	0.16
12	Fixation Present at Start of and During SAFHS® Treatment: IM Rod; Only for Long Bone Cases (N=59) No Yes Open Reduction, Internal Fixation (ORIF) No Yes External Fixation; Only for Long Bone Cases (N=59) No Yes	43 16 51 24 50 9	38 16 44 21 46 8	5 0 7 3 4 1	88% 100% 86% 88% 92% 89%	0.31 1.00 0.58

R o w	Categorical Variable Prior to Start of SAFHS® Treatment		Completed Cases Fishers Exact Probability*				
			Total	Healed	Failed	% Healed	p-value
	Conservative (Cast, Splint, Brace)	No Yes	59 16	52 13	7 3	88% 81%	0.44
	IM Rod, or ORIF, or External Fixation, or Conservative	No Yes	11 64	8 57	3 7	73% 89%	0.16
13	Prior Failed Lithotripsy Therapy:						
		No Yes	73 2	63 2	10 0	86% 100%	1.00
14	Smoking Status:						
		Missing	(2)	(2)	(0)		
	Never Smoked		34	31	3	91%	0.47
	Stopped Smoking Prior to SAFHS® Start		10	8	2	80%	
	Smoker at SAFHS® Start		28	23	5	82%	
15	Nonunion Type:						
		Missing	(22)	(17)	(5)		0.57
	Atrophic		41	36	5	88%	
	Hypertrophic		11	11	0	100%	

XI. Other Clinical Studies

There were two additional clinical studies reported on in this PMA as supportive data to the German study. These studies took place in the United States and in The Netherlands. In the United States, a registry of prescription use was maintained and data was reviewed for nonunion cases. In The Netherlands, a study identical to the German study was conducted.

The protocol details were similar for the inclusion/exclusion criteria, study design, and effectiveness measures in the United States study. Instead of independent evaluations by PIs, this study utilized the investigator determination of an established nonunion at the start of the study and a healed or failed outcome at the end of treatment. For the United States study, the completed cases group had an 82% (352/429) healed rate. When this healed rate is compared with the paired prior failed treatment control, the result is statistically significant at $p=0.00001$ in favor of the SAFHS® treated results. The core group healed rate of 80% (249/313) was similar to the non-core group healed rate of 88% (103/116). The intention-to-treat analysis resulted in a 64% (351/551) healed rate. The healed rate results were consistently similar across stratification variables including gender and age.

For the Netherlands study, the completed cases healed rate result was 90% (27/30). This healed rate when compared with the paired prior failed treatment was statistically significant at $p=0.00001$. The core group subset had a healed rate of 87.5% (21/24) which was similar to the non-core subset healed rate of 100% (6/6). The intention-to-treat analysis of all 33 cases was 82% (27/33). The healed rate results were consistently similar across stratification variables including gender and age.

The results of these two additional studies also support the safety and efficacy conclusion for the SAFHS® device in treating nonunions.

XII. Conclusions Drawn From the Studies

The information provided in the previous sections describing the nonclinical and clinical studies provides reasonable assurance of the safety and effectiveness of the Exogen 2000® or Sonic Accelerated Fracture Healing System (SAFHS®) for the non-invasive treatment of established nonunions excluding skull and vertebra.

XIII. Panel Recommendation

This is a PMA supplement which did not require panel review

XIV. CDRH Decision

CDRH recommends approval for the Exogen 2000® or Sonic Accelerated Fracture Healing System (SAFHS®) for the non-invasive treatment of established nonunions, excluding skull and vertebra.

XV. Approval Specifications

A Post-market Study will not be required for this device. No significant clinical issues of safety and effectiveness remain to be collected which would yield clinically significant information which would necessitate modifications to device indications, adverse events, contra-indications, precautions or warnings.

XVI. References

- ¹ SAFHS® Pre-Market Approval (PMA-900009) - Summary of Safety and Effectiveness, October 5, 1994.
- ² Wang, S.J., Lewallen, D.G., Bolander, M.E., Chao, E.Y.S., Ilstrup, D.M., Greenleaf, J.F.: Low-intensity ultrasound treatment increases strength in a rat femoral fracture model. *J. of Orthop. Res.*, 12:40-47, 1994.
- ³ Yang, K.H., Parvizi, J., Wang, S.J., Lewallen, D.G., Kinnick, R., Greenleaf, J.F., Bolander, M.E.: Exposure to low-intensity ultrasound stimulates aggrecan gene expression in a rat femur fracture model. *J. of Orthop. Res.*, 14(5):802-809, 1996.
- ⁴ Lehman, J., et al.: Ultrasonic effects as demonstrated in live pigs with surgical metallic implants. *Arch. Phys. Med. And Rehabil.*, 483-488, 1979.
- ⁵ Gersten, J.W.: Effect of metallic objects on temperature rises produced in tissue by ultrasound. *Amer. J. Phys. Med.*, 37:75-82, 1988.
- ⁶ Lotsova, E.I.: Effect of ultrasound on the strength of metal fixing pins for fractures and joint injuries. *Mekh. Kompoz. Mat.*, 3: 548-549, 1979
- ⁷ Skoubo-Kristensen, E., Sommer, J.: Ultrasound influence on internal fixation with a rigid plate in dogs. *Arch. Phys. Med. Rehabil.*, 63, 371-373, 1982.

LABELING

SAFHS 2000[®]

SONIC ACCELERATED HEALING SYSTEM
FOR THE TREATMENT OF NONUNION

Physician's
Instructions
For Use

Caution: Federal law restricts this device to sale, distribution or use by or on the order of a physician. Use is restricted to the individual for whom it is prescribed.

EXOGEN[®] Inc.

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Replacement
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for Physician
Labeling

A. Indications for Use

The Exogen 2000® or Sonic Accelerated Fracture Healing System (SAFHS®) is an invasive treatment of established nonunions* excluding skull and vertebra, and for accelerating the time to a healed fracture for fresh, closed, posteriorly displaced distal radius fractures and fresh, closed or Grade I open tibial diaphysis fractures in skeletally mature individuals when these fractures are orthopedically managed by closed reduction and cast immobilization.

*A nonunion is considered to be established when the fracture site shows no visibly progressive signs of healing.

B. Contraindications

There are no known contraindications for the SAFHS® device.

C. Warnings and Precautions

Warnings:

- The safety and effectiveness of the use of this device has not been established in nonunions for the following:
 - nonunions of the vertebra and the skull.
 - individuals lacking skeletal maturity

Precautions:

- The safety and effectiveness of the use of this device in pregnant/nursing women has not been established.
- Careful consideration of the use of this device must be decided on an individual basis in the presence of malaligned nonunion since the device will not correct or alter displacement, angulation or other malalignment.
- With active, implantable devices, such as cardiac pacemakers, operation may be adversely affected by close exposure to the SAFHS® device; therefore, evaluation during SAFHS® treatment by the attending cardiologist or physician is recommended.
- Patients in the clinical study were instructed to apply the device for one treatment period of twenty-minutes each day. The safety and effectiveness of the SAFHS® device when used for other than one daily twenty-minute treatment is unknown.
- The age range of the patients in this PMA nonunion study was 17- 86. The effect of SAFHS® therapy on patients outside this age range is unknown.

C. DEVICE DESCRIPTION

The SAFHS® Device

The SAFHS® is a non-invasive device that the patient administers at home with one daily 20-minute treatment periods. The device transmits a low-intensity specific ultrasound signal to the nonunion site which stimulates the nonunion gap tissue to develop into a healed bone. Little or no sensation is felt by the patient during the treatment and a design feature alerts the patient in case of improper application or performance of the device. The SAFHS® devices have been designed both for use in a cast and for use with a Velcro® strap assembly when no cast is present.

Technical Specifications of the SAFHS® Ultrasound Signal

Operating frequency.....	1.5 ±5% megahertz
Modulating signal burst width	200 ±10% microseconds
Repetition rate	1 ±10% kilohertz
Effective radiating area	3.88 ±1% square centimeters (cm ²)
Temporal average power	117 ±30% milliwatts (mW)
Temporal maximum power	625 ±30% milliwatts (mW)
Peak power	1.25 ±30% watts
Spatial average-temporal average (SATA)	30 ±30% mW/cm ²
Spatial average-temporal maximum (SATM)	161 ±30% mW/cm ²
Beam nonuniformity ratio (BNR)	2.16

Device Components

The SAFHS 2000® device consists of two electronic sub-units which are interconnected by an electrical cable:

- The battery-powered Main Operating Unit (MOU) provides for the control of the 20-minute treatment duration and also monitors the proper attachment and operation of the Treatment Head Module (THM).
- The Treatment Head Module (THM) delivers a specific low-intensity ultrasound signal to the treatment site using coupling gel.

In addition, the device uses a nonelectrical plastic component, the Retaining and Alignment Fixture (RAF), which is mounted in the cast or is used with a Velcro® strap if no cast is present. The RAF insures proper positioning and attachment of the THM in the cast during the 20-minute treatment period. A protective cap and round felt pad are inserted in the RAF during the non-treatment period to maintain even pressure on the skin at all times other than the 20-minute treatment period.

Neither you nor the patient can select or change any of the SAFHS® ultrasound signal specifications.

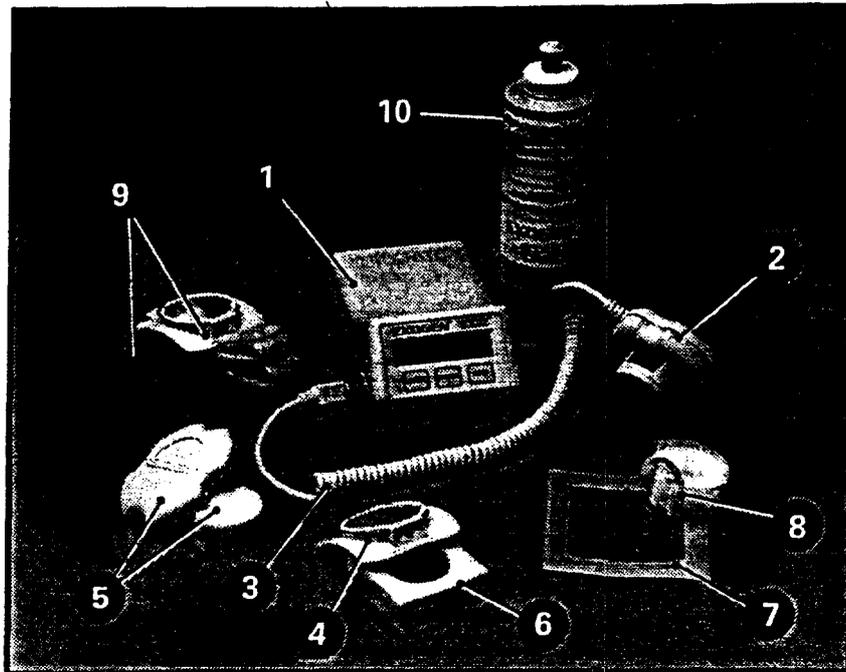


Fig. C.1 THE SAFHS® SYSTEM COMPONENTS

(Each component is identified by number in the Figure and in the description below)

1. **The Main Operating Unit (MOU)** is powered by a non-replaceable and non-rechargeable lithium battery. The MOU's function is to control and monitor the proper attachment and operation of the Treatment Head Module. The MOU also records the use of the device by the patient. After twenty minutes of treatment, a built-in timer automatically disables the THM and alerts the patient that treatment is complete with a visual message on the display and an audible signal. The MOU is capable of controlling two THM's in time-sharing mode when the physician prescribes two THM's for treatment of an extensive nonunion area or a segmental nonunion.

2. **The Treatment Head Module (THM)** is powered by the MOU battery, with a life of approximately 150 treatment periods of twenty-minutes each. The THM is connected to the MOU by a flexible cable. The transducer on the THM is spring loaded and is capable of 12 degrees of angular motion which allows the transducer transmitting surface to make proper contact with the skin surface regardless of cast thickness or skin contour. During the treatment period, the THM is positioned in the Retaining and Alignment Fixture (RAF) directly over the nonunion site. The THM monitors the correct amount of coupling gel on the transducer surface and alerts the patient with a message on the display and an audible signal if not enough gel is present.

3. **THM Interconnecting Cable.** This cable is a permanent part of the THM. The plug at the cable's end allows the THM to be connected to the MOU. The cable provides power to the THM and transmits signals for control and monitoring purposes.
4. **Retaining and Alignment Fixture (RAF).** The RAF is either mounted in the cast if the nonunion is casted and provides for correct placement of the THM, or it is attached with a Velcro strap directly to the treatment site when no cast is present. The THM is inserted into the RAF circular opening by aligning the grooved silver section on the THM transducer barrel with the black dot (●) on the side surface of the RAF. After insertion, the THM is rotated 1/4 turn in either direction. The locking metal spring on the RAF interfaces with the silver grooves on the barrel of the THM and locks the THM in place. This locking mechanism also insures proper operation of the THM. The RAF is provided with a red plastic protective cap for use during cast mounting.
- Note: The system will not operate unless the THM is correctly inserted and locked in the RAF.**
5. **Round Felt Plug and RAF Cap.** The round felt plug and RAF cap are placed into the center hole of the RAF between treatment periods. They protect the skin surface at the treatment site and maintain even pressure on the skin, thereby minimizing the possibility of window edema. The RAF cap has alignment arrows on its top surface. Either of these arrows should be aligned with the black dot (●) on the side surface of the RAF for easy insertion of the cap into the RAF. The cap is then rotated 1/4 turn in either direction to lock it in place.
6. **Square Felt Pad.** Two pads of different thickness are provided to accommodate cast thickness variations. This square pad is placed under the RAF in the cast window prior to the incorporation of the RAF in the cast. The pads may be peeled to an appropriate size to accommodate cast thickness.
7. **Cast Window Template.** The template is used to outline and mark the area of the cast that will be removed to accommodate the RAF.
8. **Nonunion Site Locating Ring with Velcro® Strap.** This component is used for positioning the RAF relative to the nonunion site.
9. **RAF with Velcro® Strap and Foam Pad** is provided to position the THM over the nonunion site when a cast is not used. The foam pad is used under the RAF plastic assembly as padding for the skin. Note: A spare foam pad is provided for replacement as needed. (Detailed instructions on page 16).
10. **Coupling Gel.** Two bottles of hypoallergenic ultrasound coupling gel, which is 96% water based, are provided with the device. The gel must be applied to the transducer surface of the THM at the start of each treatment period in order to allow transmission of the SAFHS® ultrasound signal from the THM transducer surface to the skin at the nonunion site.

Each bottle contains 70 teaspoons (355 ml) of coupling gel. A teaspoon (5 ml) portion is the recommended amount of coupling gel for each treatment session. There are other coupling mediums which can be used if any skin reaction is noted with the standard gel. Please call the Exogen Customer Service Department if this occurs.

Note: SAFHS® ultrasound coupling gel is the recommended gel for use with this system. Do not substitute other gels as they may damage the THM transducer surface or impede signal transmission.

A Product Bulletin, a Patient Instruction manual for operating the SAFHS® device and a clear Airbill pouch containing instructions for completing the Airbill form for returned devices are included with the SAFHS® device.

D. ADVERSE EFFECTS

In laboratory, animal and clinical research, the SAFHS® output intensity (power level) was assessed for its potential for producing significant temperature increases in body tissue, the most common and best understood effect of conventional ultrasound. Conventional therapeutic ultrasound applications utilize ultrasound intensities of approximately 1,000 to 50,000 mW/cm² and must be applied in a stroking manner to avoid tissue necrosis caused by excessive temperature increases that can result in a stationary application. The output intensity of the SAFHS® device of 30 mW/cm² is typically only 1% to 5% of the output intensity of conventional therapeutic ultrasound devices and therefore can be used in a stationary application. The SAFHS® ultrasound intensity is comparable to diagnostic ultrasound (1 to 50 mW/cm²), such as the intensities used in obstetrical sonogram procedures (fetal monitoring). The results of the PMA safety report on the SAFHS® device⁽²²⁾ and SAFHS® PMA research indicate that the SAFHS® device is incapable of producing harmful temperature increases in body tissue and there is also no evidence of non-thermal adverse effects.

No significant adverse reactions or medical complications related to the use of this device were reported during the clinical studies and post-market registry involving over 700 nonunion cases and in over 5,000 completed cases from general prescription use for fracture healing.

During the clinical studies, only 22 cases reported minor complaints involving discomfort, mild pain and sensations normal to a fracture or nonunion condition and were not considered to be device-related complaints. All complaints were resolved by corrective action by the physician. Two patients (less than 0.4%) reported mild skin irritation caused by skin sensitivity to the hypoallergenic coupling gel. Both were resolved by a change of coupling medium to mineral oil or glycerine.

E. INSTALLING THE RAF AT THE TREATMENT SITE

The SAFHS® device is designed for use with or without cast immobilization. When a cast is used, the Treatment Head Module (THM) is inserted into the

Retaining and Alignment Fixture (RAF) which is incorporated into the cast directly over the nonunion site. A cast window for the RAF must be located directly over the nonunion site. A Locating Ring and a Window Template are provided with each device to assist you in the placement of the RAF over the nonunion site. The following steps are recommended to assure proper location of the cast window and RAF placement for a tibia fracture as an example:

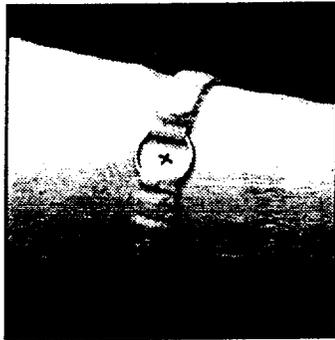


Fig. E.1

- 1. Locating the RAF Relative to the Nonunion Site.** Once casted, the location of the nonunion is determined by a radiograph taken with the Locating Ring affixed to the cast surface in the approximate area of the nonunion. The position of the ring is marked on the cast before removing the ring. The radiograph verifies the position of the ring in relation to the nonunion site and an appropriate correction mark is made on the cast (Fig. E.1).

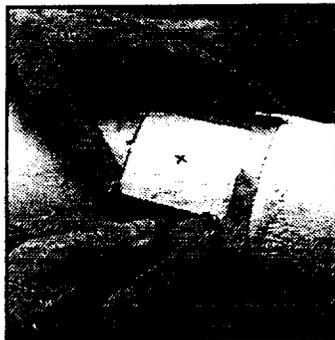


Fig. E.2

- 2. Marking the Cast for a Cast Window.** The yellow Window Template is centered over the marked location of the nonunion site with the notches of the inner edge in the proximal and distal direction. The outline of the inner edges of the template opening is drawn on the cast (Fig. E.2). Use only the yellow template for the SAFHS 2000® since it is a different internal size than the blue one used for the SAFHS® 2A.

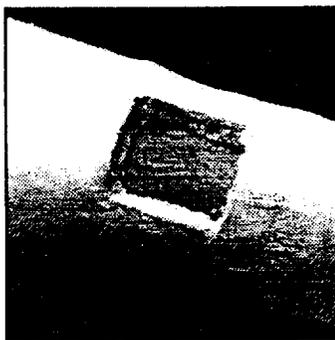


Fig. E.3

- 3. Cutting the Cast.** Cut a cast window following the template markings on the cast. Be sure to make the opening only as large as the interior perimeter of the template (err on the side of being slightly smaller than larger). The RAF's lateral and medial flanges should sit on the surface of the cast. Remove all the loose cast material, including the cast padding and stockinette, to expose the bare skin (Fig. E.3).

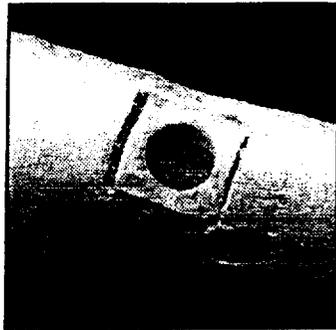


Fig. E.4

- 4. Fitting the Protective Felt Pad in the Cast Window.** The square felt pad with a center hole and the round felt plug should be placed in the window directly on the patient's skin. Thin the felt pad to the thickness of the cast by peeling off appropriate layers and place it back in the window. Remove the round felt plug and peel it to the same dimension as the felt pad. Save it for later use in the installation instructions (Fig. E.4).

Note: Failure to use the felt pad and plug may cause skin irritation or window edema.

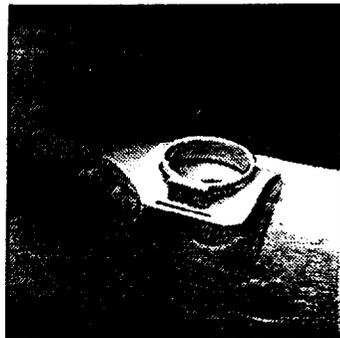


Fig. E.5

- 5. Placing the RAF in the Cast Window.** Place the RAF with the red protective red plastic cap (not shown in Fig. E.5 or E.6) over the cast window with its flat projecting flanges overlapping the window on the medial and lateral sides. The system has been designed so that pressure created when applying the RAF cap or THM is transmitted to the cast and not the nonunion site at the window opening. This is important for the patient's comfort in the early period of treatment when the nonunion site may still be tender (Fig. E.5).



Fig. E.6

- 6. Securing the RAF.** Leave the red plastic cap in place during RAF placement to prevent cast debris from either entering the open area of the RAF or interfering with the operation of the locking spring in the RAF. Secure the RAF to the cast with casting material making sure to cover the medial and lateral flanges. Fig. E.6 shows the RAF with the round felt plug in place after casting.

Note: Cast material must not be allowed to cover any portion of the RAF's circular opening outer perimeter. Avoid getting casting material on the metal locking spring or on the side where the black locating dot is located. Casting material on these surfaces may interfere with the THM or RAF cap insertion and locking procedure. Remove the red protective cap on the RAF after the RAF has been incorporated into the cast.

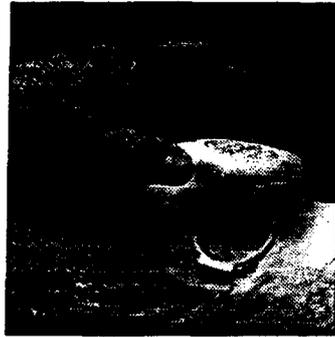


Fig. E.7.A



Fig. E.7.B

7. **Inserting the Protective Felt Plug and RAF Cap.** When the RAF is secured, confirm that the round felt plug is in place. Insert the RAF cap by positioning the alignment arrows on the cap with the black dot (●) on the side of the RAF (Fig. E.7.A). After the RAF cap is inserted, lock it in place with a 1/4 turn in either direction. The cap and felt plug should remain in place at all times, except during the daily 20 minute treatment period (Fig. E.7.B). **During treatment periods, the RAF cap and the felt plug must be removed (Fig. E.7.A).**

F. DEVICE OPERATING INSTRUCTIONS

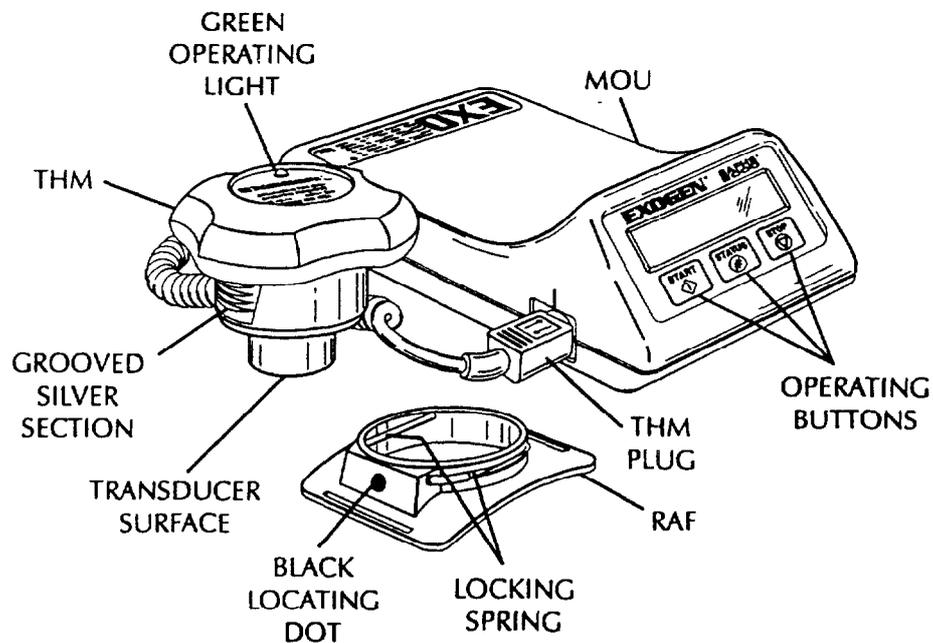


Fig. F.1 - MOU, THM and RAF

(Important Operating Buttons, Components and Characteristics are Indicated)

Note: You will hear a beep every time you press an operating button.

The following instructions, also provided in the Patient Instructions for Operating the Device manual, are to be followed by the patient when using the device:

Beginning a Daily Treatment Period When a Cast is Present

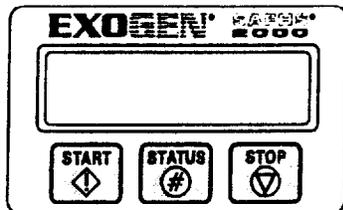


Fig. F.2

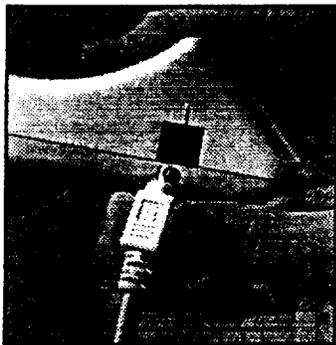


Fig. F.3

- a. Check the MOU to be sure that it is turned off. This is indicated by a blank screen on the display (Fig. F.2). If the "Start (◊)" button was accidentally pressed, wait until the display is blank.

- b. Connect the THM to the MOU by plugging the interconnecting cable connector into the mating socket on the MOU (Fig. F.3).

Note: The MOU receptacle and the THM cable plug are keyed and the plug can only be inserted in one position. The arrow (▲) on the THM cable plug should be aligned with the vertical line (|) above the socket on the MOU for easy insertion. Push straight in. Do not attempt to turn or rotate the cable plug as it may damage the MOU or THM. The patient can leave the THM connected to the MOU between treatment sessions. It is not necessary to disconnect the THM at the end of each treatment session.

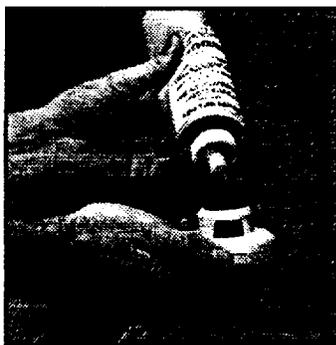


Fig. F.4

- c. Remove the RAF cap by rotating the cap 1/4 turn and lifting it out of the RAF. Remove the round felt plug from the RAF opening.
- d. Prepare the THM by placing approximately 1 teaspoon (5 ml) of coupling gel on the round flat black surface on the THM transducer. Do not spread the gel on the transducer surface. The system is designed so that the gel is spread evenly when the transducer contacts the skin (Fig. F.4).

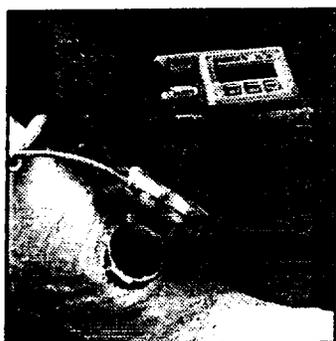


Fig. F.5.A



Fig. F.5.B

- e. After applying the gel, immediately place the THM in the RAF by lining up the grooved silver section on the barrel surface of the THM with the black dot (●) on the side of the RAF (Fig. F.5.A). While applying gentle pressure, turn the THM approximately a 1/4 turn in either direction until it is secured in place. You will feel the THM attach securely as the grooves of the silver section of the THM engage with the metal spring of the RAF to lock the THM in place (Fig. F.5.B). If the THM is not correctly seated in the RAF, remove it and apply it again.

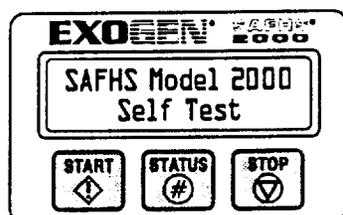


Fig. F.6.A



Fig. F.6.B

- f. Press the "Start (◆)" button and the display will activate. The system will automatically perform a self-test of all operations and functions. The display will indicate "SAFHHS Model 2000 Self Test" (Fig. F.6.A) for approximately 2 seconds and will be followed by a display reading "Press START to BEGIN Treatment" (Fig. F.6.B) which will flash on and off for 5 seconds.

Note: The "Press START to BEGIN Treatment" will alternate with "Attention: 12 hrs have not elapsed" during this 5 second period if the patient's last treatment period was less than 12 hours from the new treatment. The SAFHHS® clinical studies used one twenty minute treatment session per day for all patients. It is recommended that there be at least approximately 12 hours between treatments although this spacing may not always be possible to attain.

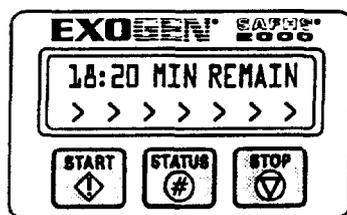


Fig. F.7

- g. Press the “Start (◊)” button again within this 5 seconds to start the 20-minute treatment period. The display indicates the remaining time of the 20-minute treatment period (Fig. F.7). The green light on the back of the THM will light indicating that the THM is emitting ultrasound. The device will shut off and the display will be blank if the “Start (◊)” button is not pressed within this 5 seconds and steps F.1.a through F.1.e must be repeated.

Note: Each time the device is turned on (Fig. F.7) by pressing the “Start (◊)” button, a record of use is stored in the Patient Compliance Monitor (PCM). The PCM records completed, partial, and terminated treatments. The patient should avoid turning the device on and immediately off repeatedly because there is a data storage capacity limit in the PCM.

At the End of a Daily Treatment Period When a Cast is Used

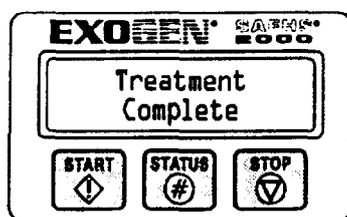


Fig. F.8

- a. The device will automatically stop treatment after 20-minutes. A beeping sound of 1 beep per second will indicate that treatment is complete and the display will read “Treatment Complete” (Fig. F.8). The green light on the THM will go out.

- b. After 10 seconds, the SAFHS 2000® will automatically turn off, the audible alarm will stop and the display will turn blank.

- c. **The THM must be removed from the RAF immediately after each treatment period.** Gently turn the THM counter-clockwise approximately 1/4 turn and lift it out of the RAF.



Fig. F.9

- d. Using a soft cloth, tissue, paper towel or a cotton swab, gently clean the skin area at the treatment site to remove the coupling gel. Remove any gel that may have accumulated on the RAF as this may cause difficulty in locking the THM into the RAF (Fig. F.9).

- e. **Replace the round felt plug on the skin through the hole in the RAF.** Replace the protective cap by lining up either of the arrows (▲) on the top surface of the RAF cap with the black dot (●) on the RAF and, while applying gentle pressure, turn a 1/4 turn in either direction (as shown in Section E., Fig. E.7.A and Fig. E.7.B).

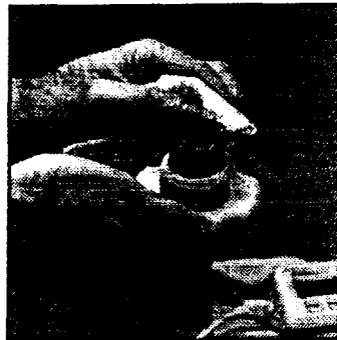


Fig. F.10

- f. **Clean the coupling gel from the THM transducer surface with a soft cloth, tissue or paper towel.** This is very important to prevent the gel from drying on the transducer surface and interfering with its spring-loaded mechanism (Fig. F.10). Use a damp cloth or paper towel to remove any dried gel residue. **Never immerse the THM in water.**
- g. Leave or place the device in a safe place until the next treatment period. **It is not necessary to unplug the THM at the end of each treatment period.** The MOU can remain connected to the THM.

Interruption of a Treatment Period

It is recommended that each treatment period be a continuous, uninterrupted 20-minute period. However, interruptions are sometimes unavoidable. During a treatment period, if for any reason a treatment period must be interrupted for a short period of time (e.g., to answer a telephone or a doorbell), the MOU can be carried as it is completely portable. However, interruptions where the patient may not wish to carry the MOU are sometimes unavoidable. The appropriate steps for the interruption of a treatment period are provided in the *Patient Instructions, Section F: Interruption of a Treatment Period*.

G. TREATMENT SCHEDULE

Exogen recommends that you prescribe only one daily 20-minute treatment period for your SAFHS® treated nonunion patients. The SAFHS® device should be used daily until you judge the nonunion to be sufficiently healed to discontinue therapy. Following the treatment schedule with SAFHS® therapy will provide the clinical benefit of healing the nonunion that was shown in the SAFHS® clinical studies. Nonunions were defined as a minimum of 9 months from initial injury date, with no signs of healing and a minimum of 3 months

prior to start of SAFHS® therapy with no surgical procedure. Nonunions meeting this rigorous definition were classified as the core group and those that did not meet all the requirements were the non-core group. Three studies (Germany, Netherlands, and the United States) used the same rigorous definition of nonunion and a similar study design where each nonunion was its own control based on the prior result of failed orthopaedic treatment. A total of 378 cases met the rigorous definition of nonunion and were included in the core group of nonunion. The use of SAFHS® therapy in this challenging nonunion population healed 81% (306/378) with a significance of $p < 0.00001$. The average healed time was 168 ± 5.1 days and a median heal time of 148 days. Ninety percent healed in 265 days or less, with 50% healed in 148 days or less. The mean fracture age for the healed cases was 664 ± 49.1 days (1.8 years) with a median of 418 days. Twenty-five percent of the nonunions had fracture ages greater than 593 days (1.6 years) from initial injury and 75% had fracture ages of greater than 10 months.

An analysis of all healed and failed cases including both core and non-core groups showed a combined total of 534 cases with an 83% (443/534) healed rate with an average healed time of 165 ± 4.2 days (median of 142 days) and an average fracture age of 679 ± 37.6 days or 1.9 years from initial injury date.

The effects of low-intensity ultrasound on the healing of non-unions was first reported by Xavier and Duarte in 1983.⁽¹⁹⁾ They utilized a low-intensity signal similar to the SAFHS® signal with daily treatments of 20 minutes for a minimum of 45 days to a maximum of 120 consecutive days in 28 cases of nonunions. Union was achieved in 70% of the treated nonunions (average fracture age of 12 ± 2.2 months). Choffie and Duarte⁽¹⁾ reported on a series of 86 ununited fractures with an average fracture age of 8.6 months with 26 nonunions that were greater than 9 months post-fracture. All of the nonunions healed with an average time to a healed fracture of 3.4 months. There were 37 fractures with internal fixation (screws, plates, or rods) present from the initial fracture treatment at injury or from subsequent secondary procedures. The overall success rate was 92% (34/37) in nonunions with metal fixation with an average time to a healed fracture of 3.6 months. The success rate and heal time varied by bone location with 93% healed in 2.1 months for scaphoid nonunions, 87% healed in 4.6 months in femoral nonunions and 87% healed in 3 months for tibia nonunions. At the 20th SICOT World Congress in 1996, Duarte, Xavier, and Choffie⁽³⁾ reviewed their treatment of 385 nonunions with an average fracture age of 14 months (range 6 to 60 months). The overall success rate was 85% in 166 tibia cases, 85% in 40 ulna cases, 81% in 47 radius cases and 60% in 5 clavicle cases. Similar healed rates were noted by Strauss, et al.,⁽¹⁶⁾ Frankel (80%),⁽⁵⁾ and Mayr and Ruter (80%)⁽⁸⁾ in their treatment of nonunions by pulsed low-intensity ultrasound. Meani⁽⁹⁾ reported on the successful use of SAFHS® in the healing of recalcitrant infected nonunions.

In additional studies, Heckman and Kristiansen, for their prospective, randomized, double-blind, and placebo-controlled multi-centered studies, utilized the SAFHS® low-intensity 30mW/cm² signal developed by Duarte.⁽¹⁵⁾ Heckman, et al.⁽⁶⁾ studying the influence of low-intensity ultrasound in tibial diaphysis fractures, demonstrated a significant 38% acceleration in the time to a healed fracture from a placebo mean of 154 to 96 days with SAFHS® (p<0.0001). Similar results were reported for distal radius metaphyseal fractures by Kristiansen, et al.⁽⁷⁾ who demonstrated a significant 38% acceleration in the active low-intensity ultrasound treated fractures with a healed time of 61 days as compared to the placebo group average heal time of 98 days (p<0.0001). The results of these two studies were stratified as to patient smoking habits by Cook, et al.⁽²⁾ who reported that the negative effects of nicotine on the fracture-repair process were mitigated by SAFHS® ultrasound treatment.

Duarte, with a rabbit study, was the first to demonstrate that low-intensity pulsed ultrasound therapy could affect bone healing and showed that it caused a significant increase of callus.⁽⁴⁾ The evidence that low-intensity pulsed ultrasound not only has a positive influence on the quantity of callus, but also significantly increases the mechanical strength and stiffness of the callus was demonstrated by Pilla, et al. in a rabbit model.^(10,11) Wang, et al.,⁽¹⁷⁾ Yang, et al.,^(20,21) and Wu, et al.⁽¹⁸⁾ reported a significant increase in aggrecan mRNA, a cartilage related gene and proteoglycan synthesis, and an increase in *α1(II)* procollagen mRNA in the callus of a rat fracture model.

In *in-vitro* studies, Ryaby^(12,13,14) demonstrated that use of pulsed, low-intensity ultrasound produces a significant increase of calcium absorption in isolated mesenchymal cells as well as cartilage cells. Ryaby also showed an effect on adenylate cyclase levels and TGF- β in osteoblastic cells.

Physician's Access to Record of Patient's Usage of the SAFHS® Device

The record of device usage is stored on a real time basis in the Patient Compliance Monitor (PCM) of the SAFHS® device. This information can be accessed by the physician through simple operations of the three front panel buttons on the MOU. **The THM does not have to be connected to obtain this data.** The procedure shown below should be followed at the patient's scheduled follow-up visit:

- a. Hold the MOU in both hands with the left hand positioned so that the left thumb is over the "Start (↕)" button and right hand positioned so that the right thumb is over the "Stop (⊖)" button. With the device off, which is denoted by a blank screen, simultaneously press the "Start (↕)" and "Stop (⊖)" buttons momentarily (Fig. G.1) then immediately press the "Status (⊗)" button using either thumb (Fig. G.2).

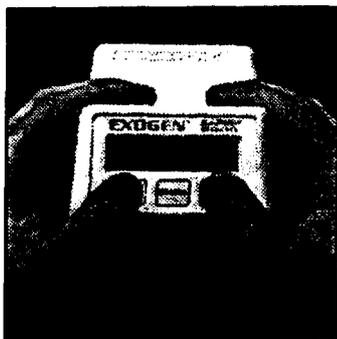


Fig. G.1



Fig. G.2

This step places the MOU into the PCM access mode. The MOU screen will display the following message:

“SAFHS Model 2000 Self Test”

In approximately 2 seconds the display will automatically switch to the following display (Fig. G,1):

11/21/95 13:54
S/N 01960111

Month/Day/Year
Greenwich time (Eastern Standard Time + 5 hours)
Serial Number (S/N)

- b. To obtain the information available from the PCM, you must press the “Status (#)” button within 10 seconds. The screen display will show the following information as you consecutively press the “Status (#)” button (examples of typical displays are presented for each status message):

1st Press = “Total Treatments 0047”

Total number of completed, partial and terminated treatments since the start of therapy:

2nd Press = “Treatment Days 0037”

Total number of treatment days to date.

The number of treatment days when compared to the total number of treatments provides an indication of whether the patient has either used his SAFHS® device more than once per day or has terminated treatments because of various reasons.

3rd Press = "Accumulated Time 12:10:15"

Accumulated treatment time in hours, minutes and seconds.

This accumulated treatment time includes complete 20 minute periods and the time of partial treatments due to premature termination, from treatment start date to present date.

4th Press = "Partial - 0001
Terminated - 0009"

Partial: Number of treatments that were interrupted and never resumed.

Terminated: Number of treatments that were terminated prematurely by the patient by turning the device off.

The number of completed treatments can be calculated by subtracting the sum of partial and terminated treatments from the total number of treatments.

5th Press = "Trouble - 0005
Gel Error - 0002"

Trouble: Number of times the device sensed an operating problem and automatically stopped treatment

Gel Error: Number of times the device notified the patient that an insufficient amount of coupling gel had been used by the patient for treatment periods.

The device does not shut down automatically for a "Gel Error" and will continue to emit ultrasound signal.

Note: Pressing the "Status (Ⓢ)" button a sixth time will start the sequence again and each press of the button will continue the same sequence described above.

Please note that when viewing the PCM data, each depression of the "Status (Ⓢ)" button must occur within 10 seconds of the last button press or the MOU will automatically turn "Off". If this occurs, you can start the process of reviewing PCM data by following the instructions above from Step G.1.

A printed record of your patient's use of the SAFHS 2000® device is available from Exogen after the device is returned to Exogen at the end of therapy.

This record documents the date, time and length of each treatment period, alarms or interruptions, gel sensing alerts and total accumulated time of the patient's use of the SAFHS® device. Please call our Customer Service Department at 1-800-396-4325 or the Exogen sales representative in your area if you want this record for your patient file.

Patient Access to Record of Usage of SAFHS® Device

The patient can check the total number of treatment periods at any time by pushing the "Status (⊕)" button. The display will immediately indicate the number of treatments (includes full, partial and interrupted treatments), e.g., "Total Treatments 057".

H. SAFHS® TREATMENT WHEN CAST IMMOBILIZATION IS NOT PRESENT

Location of the Treatment Site

You must carefully instruct the patient as to the exact location of the treatment site. It is helpful to mark the skin at the treatment site or instruct the patient to measure the distance to the treatment site from a specific anatomic landmark.

- a. The Velcro® strap RAF assembly is supplied with two foam pads. The foam pad prevents movement of the RAF on the skin surface and provides patient comfort when the Velcro® strap is secured in place. Note: The second foam pad is provided as a replacement if needed.
- b. Instruct the patient to align the RAF strap assembly with the markings you have made or according to your instructions so that the THM transducer is directly over the nonunion site. The RAF strap assembly with the Velcro® strap must be securely in place over the treatment site **BEFORE** the THM is attached. This allows the patient to look through the opening in the RAF to make sure that it is correctly placed at the treatment site. It will also insure that the conductive gel placed on the transducer surface of the THM is applied directly over the treatment site.
- c. The patient should follow the instructions in the *Patient's Instructions for Operating the Device* manual for attaching the RAF and starting treatment.
- d. The patient should tighten the RAF Velcro® strap so that it is snug while ensuring that the THM and RAF are correctly positioned. Patients should remain in resting position during a treatment period to minimize movement of the THM.

Beginning a Daily Treatment Period

The patient is to follow the instructions given in the *Patient Instructions for Operating the Device* manual (also see page 9 of this manual, Beginning a Daily Treatment Period).

At the End of a Daily Treatment Period

The patient is to follow the instructions below for disconnecting the device and cleaning the skin at the end of a treatment session:

- a. Remove the THM from the RAF then remove the RAF with the Velcro® strap.

Note: The THM should be removed from the RAF immediately after each treatment period to allow for proper cleaning and storage.

- b. Using a soft tissue, paper towel or cotton swab, gently clean the skin area at the treatment site to remove the coupling gel.
- c. Replace the removable splint or brace if applicable.
- d. Clean any coupling gel from the THM with a soft cloth, tissue or paper towel. This is **VERY IMPORTANT** to prevent gel from drying on the transducer surface and interfering with its spring loaded mechanism. Use a damp cloth or paper towel to remove any dried gel residue. **Never immerse the THM in water.**
- e. Leave or place the device in a safe place, such as the device container until the next treatment period. The MOU can remain connected to the THM.

I. TROUBLE SIGNALS AND CORRECTIVE ACTIONS

The MOU monitors the correct operation of the SAFHS® system at the start of treatment self-test sequence, during the entire treatment period, including detection of insufficient coupling gel, and determines if the internal battery has reached a low battery condition.

The MOU display indicates the specific problem and the audible alarm sounds when a problem exists and must be corrected. **There is no concern if this occurs.**

1. "Trouble detected with THM"

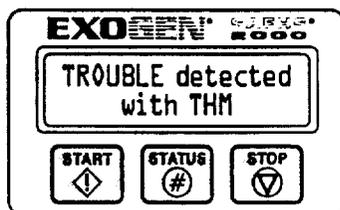


Fig. 1.1

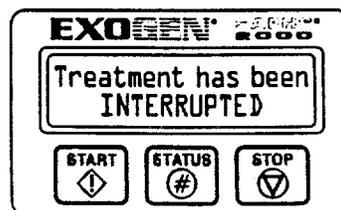


Fig. 1.2

Display reads “Trouble detected with THM” (Fig. I.1) followed by “Treatment has been INTERRUPTED” in sequence (Fig. I.2). The audible alarm beeps rapidly at 4 beeps per second. This alarm indicates that the THM may not be correctly placed in the RAF. Remove and reinsert the THM to verify that it is correctly seated in the RAF. **A feature in the device automatically stops SAFHS® treatment when the trouble alarm activates. If an alarm occurs, do not turn the device off.**

2. “There is no THM connected”

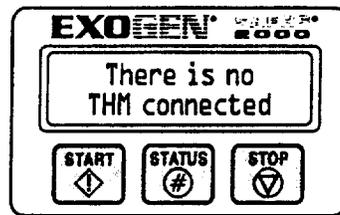


Fig. I.3

Display reads “There is no THM connected” (Fig. I.3). The audible alarm beeps at 2 beeps per second. This alarm indicates that the connector is not securely placed in the receptacle in the MOU. Remove and reinsert if necessary.

If the above steps have corrected the problem and you have completed your checks within four minutes of the alarm, the display will show the remaining time of the treatment period, the audible alarm will cease and the SAFHS® treatment will continue for the remainder of the treatment period. If more than four minutes have passed since the alarm began the device will turn off. Press the “Start (◇)” button to reactivate the device for a treatment period. **A feature in the device automatically stops SAFHS® treatment when the trouble alarm activates. If an alarm occurs, do not turn the device off.**

3. “Insufficient GEL ERROR”

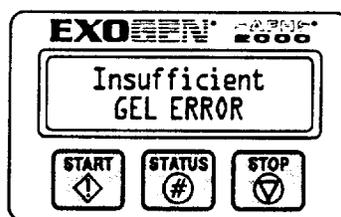


Fig. I.4

The THM transducer has the ability to sense if coupling gel is present on the transducer surface for correct ultrasound transmission to the skin. Insufficient coupling gel will cause the display to read “Insufficient GEL ERROR” (Fig. I.4) and the audible alarm to pulse on and off with 2 rapid beeps followed by a pause within each second. This condition is corrected by the following steps:

- a. Remove the THM from the RAF.
- b. Add gel to the transducer surface.
- c. Reinsert the THM into the RAF.
- d. If the “Gel Error” problems have been corrected, the system will start operating properly for the balance of the treatment period.

4. "Low Battery Condition"

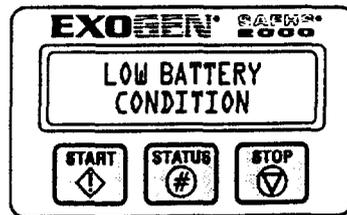


Fig. I.5

The SAFHS® system provides an audible and visual alarm when the internal battery reaches a discharged condition. Display reads "LOW BATTERY CONDITION" (Fig. I.5). The SAFHS® system should be returned to Exogen for replacement should this occur.

5. Instructions for Problems that Cannot be Resolved and Termination of a Treatment Period

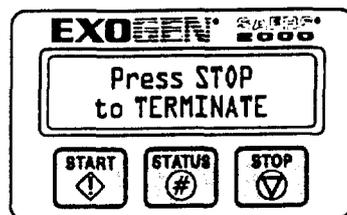


Fig. I.6

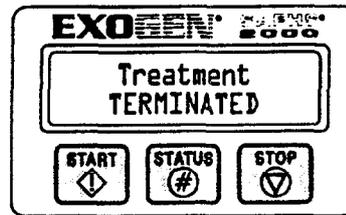


Fig. I.7

If the steps taken in 1 through 4 above do not resolve a problem or if you wish to terminate a treatment period for any reason, a treatment period can be terminated at any time by pressing the "Stop (⏏)" button. The display will show "Press STOP to TERMINATE" four times in 10 seconds (Fig. I.6). You must press the "Stop (⏏)" again during those 10 seconds or the treatment will continue. When you press the "Stop (⏏)" button the second time, the display will show "Treatment TERMINATED" for 10 seconds (Fig. I.7) accompanied by a slow pulsing audible alarm of 1 beep per second following which the audible alarm will cease and the display will be blank.

6. Other Problems

Other problems may be indicated on the MOU display, such as, "Self Test - ERROR #91" followed by "Return this unit for service." This display accompanied by a steady audible tone will remain for 8 seconds and then the display will become blank. This alarm indicates an electronic problem exists in either the MOU or THM. If this occurs, the SAFHS® device must be returned to Exogen for service.

Notify Exogen's Device Service Department at 1-800-836-4080 if a device problem is not resolved.

J. CARE AND HANDLING OF THE SAFHS® DEVICE

Do not use cleaning agents or solvents on any of the components of the system. Use only a soft cloth, tissue, paper towel or cotton swab to clean the THM or the RAF. Use a damp cloth or paper towel to remove any dried gel residue. Never immerse the MOU or the THM in water.

It is important to protect the device from impact, exposure to moisture, liquid spills, sand, dirt, debris, freezing or excessively hot temperatures (such as radiators or heating vents) to avoid possible damage.

The SAFHS® device is intended for home use and, therefore, should be operated within the typical room temperature conditions expected in a home environment (e.g., 60° to 100°F). If the SAFHS® device is stored, moved or transported in temperature conditions other than those described above, the device temperature should be allowed to return to room temperature conditions before using. This device should be handled with the same care as any home electronic equipment.

K. GENERAL NOTES FOR THE PATIENT

Patients should notify you and Exogen of:

- Any reactions, complications or problems that occur during treatment.

Patients should notify Exogen if:

- The device malfunctions or develops a problem.
- They do not have sufficient coupling gel to complete their therapy.

L. REFERENCES

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Date of Insert: 6/18/98 U7-00000-0

SAFHS 2000[®]

SONIC ACCELERATED HEALING SYSTEM
FOR THE TREATMENT OF NONUNION

Patient
Instructions
For Operating
The Device

**Caution: Federal law restricts this device
to sale, distribution or use by or on the
order of a physician. Use is restricted to
the individual for whom it is prescribed.**

EXOGEN[®] Inc.

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Exogen's toll free number is 1-800-836-4080.

Please call Exogen if any problem arises with the SAFHS® device that cannot be resolved following the instructions in this manual.

You are an active participant with the physician during the course of therapy.

Your understanding of the proper use of the SAFHS® device is an important part of the process.

Please read this entire Patient Manual before using the SAFHS® device.

Call your physician should you have any questions about SAFHS® therapy.

Please save the shipping container or boxes for return shipments. The SAFHS® device is the property of Exogen, Inc. and is provided to you for the treatment of your fracture at the prescription order of your physician. Please refer to Section K of this manual for return shipping instructions, if you encounter a problem with the device that requires return shipment of a component, or if your physician directs you to return the device.

Replacement
pp. 1 + 2 for
Patient
Labeling

A. INDICATIONS FOR USE

The Exogen 2000® or Sonic Accelerated Fracture Healing System (SAFHS®) is indicated for the non-invasive treatment of established nonunions* excluding skull and vertebra, and for accelerating the time to a healed fracture for fresh, closed, posteriorly displaced distal radius fractures and fresh, closed or Grade I open tibial diaphysis fractures in skeletally mature individuals when these fractures are orthopedically managed by closed reduction and cast immobilization.

*A nonunion is considered to be established when the fracture site shows no visibly progressive signs of healing.

B. CONTRAINDICATIONS

There are no known contraindications for the SAFHS® device.

C. WARNINGS AND PRECAUTIONS

Warnings:

- The safety and effectiveness of the use of this device has not been established in nonunions for the following:
 - nonunions of the vertebra and the skull.
 - individuals lacking skeletal maturity

Precautions:

- The safety and effectiveness of the use of this device in pregnant/nursing women has not been established.

- Careful consideration of the use of this device must be decided on an individual basis in the presence of malaligned nonunion since the device will not correct or alter displacement, angulation or other malalignment.
- With active, implantable devices, such as cardiac pacemakers, operation may be adversely affected by close exposure to the SAFHS® device; therefore, evaluation during SAFHS® treatment by the attending cardiologist or physician is recommended.
- Patients in the clinical study were instructed to apply the device for one treatment period of twenty-minutes each day. The safety and effectiveness of the SAFHS® device when used for other than one daily twenty-minute treatment is unknown.
- The age range of the patients in this PMA nonunion study was 17- 86. The effect of SAFHS® therapy on patients outside this age range is unknown.

D. DEVICE DESCRIPTION

The SAFHS Device

The SAFHS® is a non-invasive device that the patient administers at home with daily 20-minute treatment periods. The device transmits a low- intensity specific ultrasound signal to the nonunion site which stimulates the nonunion gap tissue to develop into a healed bone. Little or no sensation is felt by the patient during the treatment and a design feature alerts the patient in case of improper application or performance of the device. The SAFHS® devices have been designed both for use in a cast and for use with a Velcro® strap assembly when no cast is present.

Technical Specifications of the SAFHS Ultrasound Signal

Ultrasound frequency	1.5±5% megahertz
Modulating signal burst width	200±10% microseconds
Repetition rate	1 ± 10% kilohertz
Effective radiating area	3.88±1% square centimeters (cm ²)
Temporal average power	117 ± 30% milliwatts (mW)
Temporal maximum power	625 ± 30% mW
Peak power	1.25±30% watts
Spatial average-temporal average (SATA)	30±30% mWkm ²
Spatial average-temporal maximum (SATM)	161 ± 30% mW/cm ²
Beam nonuniformity ratio (BNR)	2.16

Device Components

The SAFHS 2000® device consists of two electronic sub-units which are interconnected by an electrical cable:

- The battery powered Main Operating Unit (MOU) provides for the control of the 20-minute treatment duration and also monitors the proper attachment and operation of the Treatment Head Module (THM).
- The Treatment Head Module (THM) delivers the specific low-intensity ultrasound signal to the treatment site using coupling gel.

In addition, the device uses a nonelectrical plastic component, the Retaining and Alignment Fixture (RAF), which is mounted in the cast or is used with a Velcro® strap if no cast is present. The RAF insures proper positioning and attachment of the THM in the cast during the 20- minute treatment period. A protective cap and round felt plug are inserted in the RAF during the non-treatment period to maintain even pressure on the skin at all times other than the 20-minute treatment period.

Neither you nor your physician can select or change any of the SAFHS® ultrasound signal specifications.

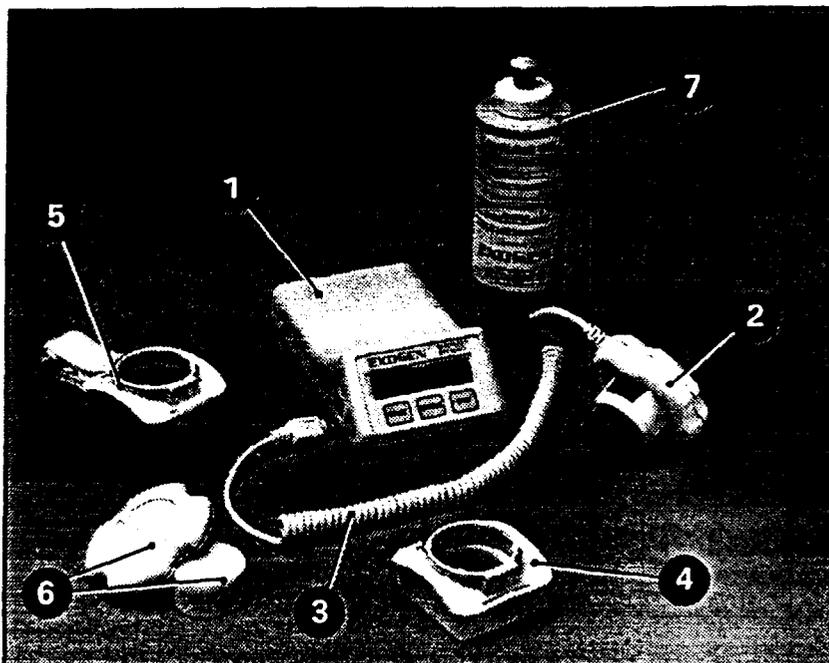


Fig. C.1 THE SAFHS® SYSTEM COMPONENTS

(Each component is identified by number in the Figure and in the description below)

1. The Main Operating Unit (MOU) is powered by a non-replaceable and non-rechargeable lithium battery with a life of approximately 150 treatment periods of twenty-minutes each. The MOU is connected to the Treatment Head Module (THM) by inserting the plug of the THM's interconnecting cable into the receptacle on the left front side of the MOU.

The MOU's function is to:

- Monitor and control the operation of the THM.
- Verify cable connections between the THM and the MOU and monitor the MOU battery for a low battery condition.
- Control the duration of the 20-minute treatment period.
- Alert you if you do not have enough coupling gel on the THM transducer surface.

- Shut off the SAFHS® device at the end of the 20-minute treatment period and alert you that the treatment is complete by a "Treatment Complete" message on the display and an audible signal.
- Monitor and record the daily use of the device. This record is available to your physician at your follow-up visits and a complete record of your daily use is available to your physician at the end of your therapy. You can monitor the number of treatments (includes full, partial and terminated treatments) that you have applied to your nonunion by following the procedure in Section H.

2. The Treatment Head Module (THM) is powered by the MOU battery supply and is connected to the MOU by a flexible cable.

The round, flat, black THM transducer surface transmits the low-intensity ultrasound signal to the skin at the nonunion site through a layer of ultrasound coupling gel. Coupling gel is necessary to insure the proper transmission of ultrasound as air does not transmit ultrasound.

The THM has the following functions:

- Transmits pulsed, low intensity ultrasound to the nonunion site through a layer of coupling gel between the skin surface and the round, flat transducer surface. The green light on the top surface of the THM is lit when the THM is on. (*Note: the lit green light may be difficult to see in a brightly lit room*).
- The THM transducer is spring-loaded and is capable of 12 degrees of angular motion. This allows the transducer transmitting surface to make good contact with the skin regardless of the cast thickness or skin surface contour.
- Monitors for the presence of coupling gel on the transducer surface and alerts you with audible sound if not enough gel is present.

3. THM Interconnecting Cable. This cable is a permanent part of the THM. The plug at the cable's end allows the THM to be connected to the MOU. The cable transmits signals for control and monitoring purposes.

4. Retaining and Alignment Fixture (RAF). If your nonunion is immobilized in a cast, your physician has installed this plastic component in your cast. The RAF holds the THM in its proper position during the daily 20 minute treatment period. You insert the THM into the RAF and lock it in place with a 1/4 turn in either direction. The locking metal spring on the RAF engages with the silver grooves on the barrel of the THM and locks the THM in place. This locking mechanism also insures proper operation of the THM.

Note: The SAFHS® system will not operate unless the THM is correctly inserted and locked into the RAF.

5. **RAF with Velcro® Strap and Foam Pad.** Your physician will advise you about the use of this accessory.
6. **Round Felt Plug and RAF Cap.** The round felt plug and RAF cap are placed into the center hole of the RAF between treatment periods. They protect your skin at the treatment site and maintain even pressure on the skin to prevent swelling.
7. **Coupling Gel.** Two bottles of hypoallergenic ultrasound coupling gel, which is 96% water based, are provided with your SAFHS® device. You must apply coupling gel to the transducer surface at the start of each treatment period in order to allow transmission of the SAFHS® ultrasound signal from the THM transducer surface to the skin at the treatment site. Each bottle contains approximately 70 teaspoons (355 ml) of coupling gel. A teaspoon (5 ml) portion is the recommended amount of coupling gel for each treatment session. There are other coupling mediums which can be used if any skin reaction is noted with the standard gel. Please call the Exogen Customer Service Department if this occurs.

Note: SAFHS® ultrasound coupling gel is the recommended gel for use with this system. Do not substitute other gels as they may damage the THM transducer surface or impede signal transmission.

Please call Exogen's Device Service Department at 1-800-836-4080 if you need more coupling gel.

Note: A Product Bulletin, a Patient Instruction Manual, a large shipping PAK envelope, and a clear Airbill pouch containing instructions for completing the Airbill form for returned devices are included with the SAFHS® device.

D. ADVERSE EFFECTS

In laboratory, animal and clinical research, the SAFHS® output intensity (power level) was assessed for its potential for producing significant temperature increases in body tissue, the most common and best understood effect of conventional ultrasound. Conventional therapeutic ultrasound applications utilize ultrasound intensities of approximately 1,000 to 50,000 mW/cm² and must be applied in a stroking manner to avoid tissue necrosis caused by excessive temperature increases due to stationary application. The output intensity of the SAFHS® device of 30 mW/cm² is typically only 1% to 5% of the output intensity of conventional therapeutic ultrasound devices and therefore can be used in a stationary application. The SAFHS® ultrasound intensity is comparable to diagnostic ultrasound (1 to 50 mW/cm²), such as the intensities used in obstetrical sonogram procedures (fetal monitoring). The results of PMA safety report on the SAFHS® device and SAFHS® PMA research indicate that the SAFHS® device is incapable of producing harmful temperature increases in body tissue and there is also no evidence of non-thermal adverse effects.

No significant adverse reactions or medical complications related to the use of this device were reported during the clinical studies and post-market registry involving over 700 nonunion cases and in over 5,000 completed cases from general prescription use for fracture healing.

During the clinical studies, only 22 cases reported minor complaints involving discomfort, mild pain and sensations normal to a fracture or nonunion condition and were not considered to be device-related complaints. All complaints were resolved by corrective action by the physician. Two patients (less than 0.4%) reported mild skin irritation caused by skin sensitivity to the hypoallergenic coupling gel. Both were resolved by a change of coupling medium to mineral oil or glycerine.

E. DEVICE OPERATING INSTRUCTIONS

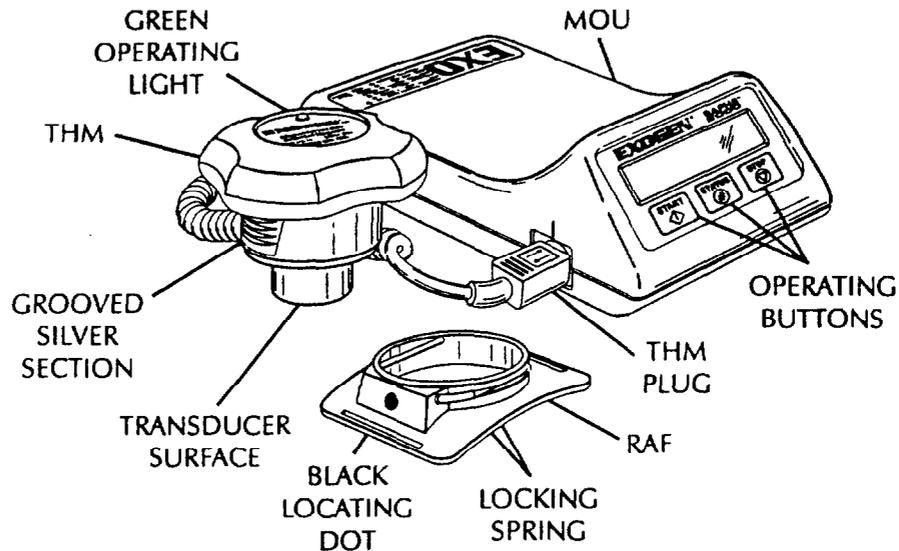


Fig. E.1 - MOU, THM AND RAF

(Important Operating Buttons, Components and Characters are Indicated)

Starting Your Daily Treatment Period

The SAFHS® device is designed for use with a cast or without a cast. If you have a cast, your physician will prepare your cast and install the Retaining and Alignment Fixture (RAF) in your cast at the nonunion location.

The following instructions are to be followed when using the device when a cast is present:

Note: You will hear a beep every time you press an operating button.

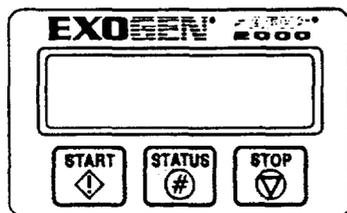


Fig. E.2

- a. Check the MOU to be sure that it is turned off. This is indicated by a blank screen on the display (Fig. E.2). If you have accidentally pressed the "Start (◇)" button, wait approximately 15 seconds until the display is blank.

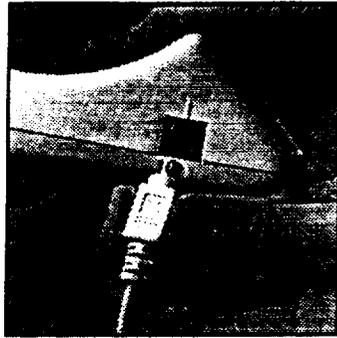


Fig. E.3

- b. Plug the THM cable plug into the receptacle on the left side of the MOU (Fig. E.3).

Note: The MOU receptacle and the THM cable plug are keyed and the plug can only be inserted in one position. The vertical line (|) above the socket on the MOU should be aligned with the arrow (▲) on the THM cable plug for easy insertion. Push the plug straight in. Do not attempt to turn or rotate the cable plug as you insert it as it may damage the MOU or THM. You can leave the THM connected to the MOU until your physician determines that you have completed therapy. It is not necessary to disconnect the THM at the end of each treatment session.

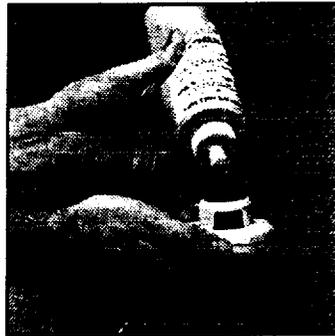


Fig. E.4

- c. Remove the RAF cap by rotating the cap 1/4 turn in either direction and lift it out of the RAF. Remove the round felt plug from the RAF opening.

- d. Prepare the THM by placing approximately 1 teaspoon (5 ml) of coupling gel (about the size of a Hershey Kiss®) on the round flat black surface on the THM transducer. Do not spread the gel on the transducer surface. The system is designed so that the gel is spread evenly when the transducer contacts the skin (Fig. E.4).

Note: You should use the recommended amount of gel. The SAFHS® device will go into alarm if insufficient gel is present. Repeated use of excessive gel could result in gel infiltration into the transducer housing and cause the device not to operate.



Fig. E.5.A

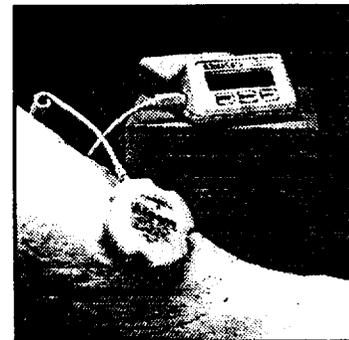


Fig. E.5.B

- e. After applying the gel, immediately place the THM in the RAF by lining up the grooved silver section on the barrel surface of the THM with the black dot (●) on the side of the RAF (Fig. E.5.A). While applying gentle

pressure, turn the THM approximately 1/4 turn in either direction until it is secured in place. You will feel the THM attach securely as the grooves of the silver section of the THM slide into the metal spring of the RAF to lock the THM in place (Fig. E.5.B). If the THM is not correctly seated in the RAF, remove it and apply it again.

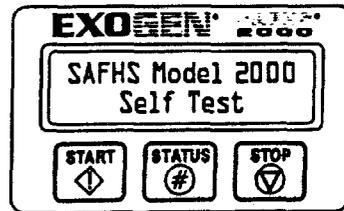


Fig. E.6.A

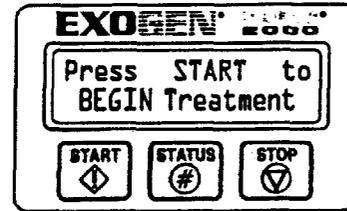


Fig. E.6.B

- f. Press the “Start (◊)” button and the display will activate. The system will automatically perform a self-test of all operations and functions. The display will indicate “SAFHS Model 2000 Self Test” (Fig. E.6.A) for approximately 2 seconds and will be followed by a display reading “Press START to BEGIN Treatment” which will flash on and off for 5 seconds (Fig. E.6.B). The “Press START to BEGIN Treatment” display will alternate with “Attention: 12 hours have not elapsed” during the five second period if your last treatment period was less than 12 hours from this treatment.

Note: The SAFHS® device is intended for one treatment period per day. It is recommended that there be approximately 12 hours between treatments although this spacing may not always be possible to maintain. The MOU display will alert you if less than 12 hours have elapsed since your last treatment. Try to keep your treatments at least 10 hours apart but with only one per day. For example, if you treated yourself at 10:00 PM on Monday, do Tuesday's treatment after 8:00 AM. In any case, you should follow the prescribed treatment schedule as prescribed by your physician.

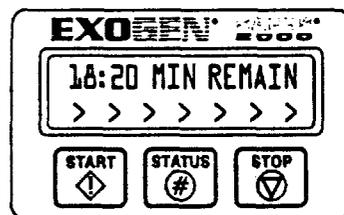


Fig. E.7

- g. Press the “Start (◊)” button again within this 5 seconds to start the 20-minute treatment session. The display indicates the remaining time of the 20-minute treatment period (Fig. E.7). The green light on the back of the THM will light indicating that the THM is emitting ultrasound. The device will shut off and the display will be blank if you do not press the “Start (◊)” button again within this 5 seconds and steps E.1.a through E.1.e must be repeated.

Note: Each time the device is turned on by pressing the “Start (◊)” button, a record of the use is stored in the Patient Compliance Monitor (PCM). The information stored includes, completed, partial, and terminated treatments.

You should avoid turning the device on and immediately off repeatedly because there is a data storage capacity limit in the PCM.

At the End of a Daily Treatment Period

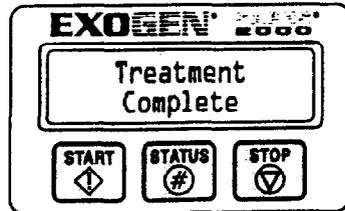


Fig. E.8



Fig. E.9



Fig. E.10



Fig. E.11.A



Fig. E.11.B

a. The device will automatically stop treatment after 20-minutes. A beeping sound of 1 beep per second will indicate that treatment is complete and the display will read "Treatment Complete" (Fig. E.8). The green light on the THM will go out.

b. After 10 seconds, the SAFHS 2000® will automatically turn off, the display will turn blank and the audible alarm will stop.

c. **The THM must be removed from the RAF immediately after each treatment session.** Gently turn the THM approximately a 1/4 turn in either direction and lift it out of the RAF.

d. Using a soft cloth, tissue, paper towel or a cotton swab, gently clean the skin area at the treatment site to remove the coupling gel. Remove any gel that may have accumulated on the RAF as this may cause difficulty in locking the THM in the RAF (Fig. E.9). Verify that the spring is in the proper position as shown in Fig. G.3, page 12.

e. **Replace the round felt plug on the skin through the hole in the RAF (Fig. E.10).**

f. Insert the RAF protective cap into the RAF by positioning either of the arrows (▲) on the top surface of the RAF cap with the black dot (●) on the RAF (Fig. E.11.A). While applying gentle pressure, turn a 1/4 turn in either direction to lock the RAF cap in place (Fig. E.11.B).



Fig. E.12

- g. Clean the coupling gel from the THM transducer surface with a soft cloth, tissue or paper towel. This is very important to prevent the gel from drying on the transducer surface and interfering with its spring-loaded mechanism (Fig. E.12). Use a damp cloth or paper towel to remove any dried gel residue. **Never immerse the THM in water.**
- h. Leave or place the device in a safe place until the next treatment period. **It is not necessary to unplug the THM at the end of each treatment period. The THM can remain connected to the MOU.**

F. INTERRUPTION OF A TREATMENT PERIOD

It is recommended that each treatment period be a continuous, uninterrupted 20 minute period. However, interruptions are sometimes unavoidable. During a treatment period, if for any reason you must attend to something for a short period of time (e.g., to answer a telephone or a doorbell), the MOU can be carried with you as it is completely portable. However, interruptions where you do not want to carry the MOU are sometimes unavoidable. The procedure for the interruption of a treatment period is as follows:

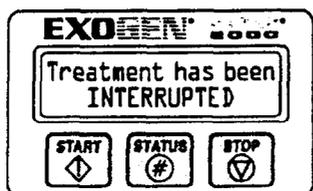


Fig. F.1

Leave the SAFHS® device on. Remove the THM from the RAF. THM removal will cause the display to alternate between "Treatment has been INTERRUPTED" and "TROUBLE detected with THM" accompanied by a rapid pulsing audible alarm (Fig. F.1 and Fig. F.2). The audible alarm beeps rapidly at 4 beeps per second.

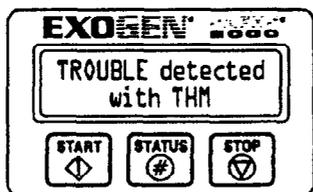


Fig. F.2

The audible alarm and the display will remain until you are ready to start treatment again. You have a total of 4 minutes for the interruption following which the SAFHS® device will **automatically turn off.**

If less than 4 minutes of interruption has passed, reapply coupling gel and replace the THM in the RAF. The treatment will resume and continue for the balance of the treatment period (e.g., if you interrupted treatment period after 8 minutes of treatment and followed the above steps to interrupt and resume treatment, the SAFHS® device would provide 12 more minutes of treatment for a total of one 20-minute treatment period).

G. INSTRUCTIONS WHEN NO CAST IS PRESENT

Starting Your Treatment Period



Fig. G.1

- a. When no cast is present, the THM will be inserted into an RAF with an elastic Velcro® strap which is secured over the treatment site for each treatment period (Fig. G.1).

Your physician will mark your skin at the exact area for treatment or provide you with a measurement from a specific body location near your nonunion site to the RAF location in order that you treat the same area during each daily treatment.



Fig. G.2

- b. Included with this device are a RAF with an elastic Velcro® strap and two foam liners with adhesive on one side. The paper backing should be removed and the adhesive side of the foam placed on the underside of the RAF to provide a padded surface over the nonunion site and to prevent movement of the RAF on the skin surface (an extra foam liner is provided to allow replacement as needed [Fig. G.2]).

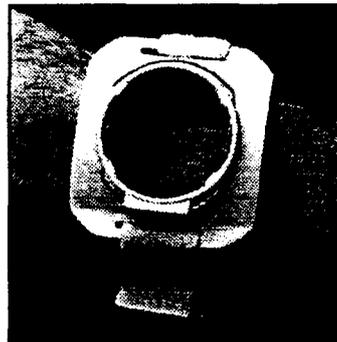


Fig. G.3

- c. For your daily treatment with the SAFHS® device, use the RAF with the attached Velcro® strap and secure the RAF over the nonunion site with the circular opening in the RAF centered over the treatment area indicated by your physician. This allows you to look through the hole in the RAF to make sure that it is correctly placed at the treatment site (Fig. G.3).

- d. The Velcro® strap should be tightened so that it is snug enough to prevent the RAF from sliding out of place. It should not be so tight as to cause discomfort.

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- e. The RAF with attached Velcro® strap must be securely in place over the treatment site **BEFORE** the THM is attached. This will also insure that the coupling gel placed on the THM transducer is applied directly to the treatment site.
 - f. Follow directions provided in Section E.1.e through E.1.g for attaching the RAF and starting treatment. You should remain in a resting position during a treatment period to minimize movement of the THM.

At the End of a Treatment Period

- a. Remove the THM from the RAF with attached Velcro® strap to allow for proper cleaning.
- b. Using a soft tissue, paper towel or cotton swab, gently clean the skin at the treatment site to remove any coupling gel.
- c. **Clean any coupling gel from the THM with a soft cloth, tissue or paper towel. This is VERY IMPORTANT** to prevent gel from drying on the transducer surface and interfering with its spring loaded mechanism. Use a damp cloth or paper towel to remove any dried gel residue.
Never immerse the THM in water.
- d. Place the device in its device container or a safe place until the next treatment period. The MOU can remain connected to the THM.



H. TREATMENT SCHEDULE



You should comply with the recommended daily twenty minute treatment period that has been prescribed by your physician. Following this treatment schedule with SAFHS® therapy can provide the clinical benefit of healing your nonunion as was shown in the SAFHS® clinical studies. The device display will tell you when a treatment is within 12 hours of the previous treatment. This will assist you in avoiding more than one treatment per day.

Please note that ultrasound therapy is automatically shut off after each treatment period. However, the THM should be removed from the RAF after each treatment period to allow for proper cleaning and storage.

Use the device for one 20-minute treatment period each day until your physician advises you to discontinue therapy. The SAFHS® device contains an internal patient use timer which monitors and records the daily use of your device. This record is available to your physician at the end of therapy so that he can evaluate your adherence with the daily treatment schedule. You can check the total number of treatment periods (includes full, partial and interrupted treatments) that you have applied to your nonunion at any time by pushing the "Status (#)" button. The display will immediately indicate the number of treatments (e.g., "Total Treatments 057").

I. TROUBLE SIGNALS AND CORRECTIVE ACTIONS

The MOU monitors the correct operation of the SAFHS® system at the start of the treatment self-test sequence, during the entire treatment period including detection of insufficient gel, and determines if the internal battery has reached a low battery condition.

The MOU display indicates the specific problem and the audible alarm sounds when a problem exists and must be corrected. **There is no concern if this occurs.**

Check all of the device connections as follows:

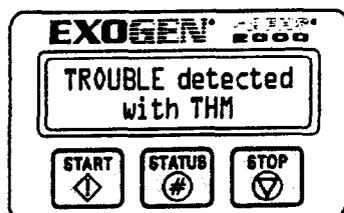


Fig. I.1

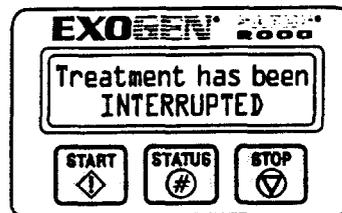


Fig. I.2

1. "Trouble detected with THM"

Display reads "TROUBLE detected with THM" (Fig. I.1) followed by "Treatment has been INTERRUPTED" in sequence (Fig. I.2). The audible alarm beeps rapidly at 4 beeps per second. This alarm indicates that the THM may not be correctly placed in the RAF. Remove and reinsert the THM to verify that it is correctly seated in the RAF. **A feature in the device automatically stops SAFHS® treatment when the trouble alarm activates. If an alarm occurs, do not turn the device off.**

2. "There is no THM connected"

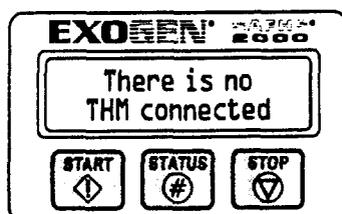


Fig. I.3

Display reads "There is no THM connected" (Fig. I.3). The audible alarm beeps at 2 beeps per second. This alarm indicates that the connector is not securely placed in the receptacle in the MOU. Remove and reinsert if necessary. **A feature in the device automatically stops SAFHS® treatment when the trouble alarm activates. If an alarm occurs, do not turn the device off.**

If the above steps have corrected the problem and you have completed your corrective actions within four minutes of the alarm, the display will show the remaining time of the treatment period, the audible alarm will cease and the SAFHS® treatment will continue for the balance of the treatment period. If more than four minutes have passed since the alarm began the device will turn off. Press the "Start (◇)" button to reactivate the device for a new 20-minute treatment period.

3. "Insufficient GEL ERROR"

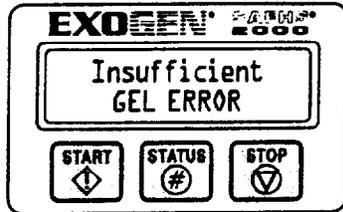


Fig. 1.4

The THM transducer has the ability to sense if coupling gel is present on the transducer surface for correct ultrasound transmission to the skin. Insufficient coupling gel will cause the display to read "Insufficient GEL ERROR" and the audible alarm to pulse on and off with 2 rapid beeps followed by a pause within each second (Fig. I.4). This condition is corrected by the following steps:

- a. Remove the THM from the RAF.
- b. Add gel to the transducer surface.
- c. Reinsert the THM into the RAF.
- d. If the "Gel Error" problems have been corrected, the system will start operating properly for the balance of the treatment period.

4. "Low Battery Condition"

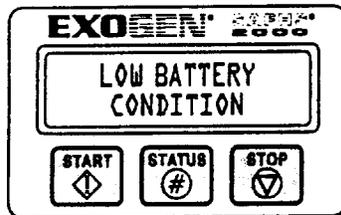


Fig. 1.5

The SAFHS® system provides an audible and visual alarm when the internal battery reaches a discharged condition. Display reads "LOW BATTERY CONDITION" (Fig. I.5). The MOU should be returned to Exogen for replacement should this occur. Call the Customer Service Department immediately upon seeing the Low Battery Warning.

5. Instructions for Problems that Cannot be Resolved and Termination of a Treatment Period



Fig. 1.6

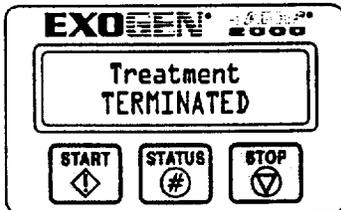


Fig. 1.7

If the steps taken in 1 through 4 above do not resolve a problem or if you wish to terminate a treatment period for any reason, a treatment period can be terminated at any time by pressing the "Stop (▽)" button. The display will show "Press STOP to TERMINATE" four times in 10 seconds (Fig. I.6). You must press the "Stop (▽)" again during those 10 seconds or the treatment will continue. When you press the "Stop (▽)" button the second time, the display will show "Treatment TERMINATED" for 10 seconds (Fig. I.7) accompanied by a slow pulsing audible alarm of 1 beep per second, following which the display will be blank and your treatment will be terminated.



6. Other Problems

Other problems may be indicated on the MOU display, such as, “Self Test - ERROR #91” followed by “Return this unit for service.” This display accompanied by a steady audible tone will remain on for 8 seconds and then the display will become blank. This alarm indicates an electronic problem exists in either the MOU or THM. If this occurs, the SAFHS® device must be returned to Exogen for service.

Notify EXOGEN'S Device Service Department at 1-800-836-4080 if a device problem is not resolved.

J. CARE AND HANDLING OF THE SAFHS® DEVICE

Do not use cleaning agents or solvents on any of the components of the system. Use only a soft cloth, tissue, paper towel, or cotton swab to clean the THM or the RAF. Use a damp cloth or paper towel to remove any dried gel residue. Never immerse the THM in water.

- The SAFHS® device is intended for home use and, therefore, should be operated within the typical room temperature conditions expected in a home environment (e.g., 60° - 100°F). If the SAFHS® device is stored, moved or transported in temperature conditions other than those described above, the device temperature should be allowed to return to room temperature conditions before treatment is started. The SAFHS® device should not be stored, moved or transported in temperature conditions below -0°F or above 130°C range, or damage may result to internal electronic components.
- When the SAFHS® device is outside its protective package, it is important to protect the device from impact, exposure to moisture, liquid spills, sand, dirt, debris, freezing or excessively hot temperatures (such as radiators or heating vents) to avoid possible damage. The device should be handled with the same care as any home electronic device.

K. RETURN SHIPPING INSTRUCTIONS UPON COMPLETION OF SAFHS® TREATMENTS

The SAFHS® device is the property of Exogen, Inc. and is being provided to you for the treatment of your fracture. The SAFHS® device is restricted to use only by the individual for whom it was prescribed. The shipping container has individual boxes for the MOU and the THM. Save both the container and the individual boxes for the final return shipment or if you encounter a component problem during your treatment period.

Note: All shipping containers contain a clear Airbill pouch with an insert labeled *IMPORTANT*** - DO NOT DISCARD. This clear pouch contains instructions for completing the freight forwarder's Airbill. The backing on the clear pouch should be removed to expose the adhesive backing and the pouch applied to the shipper's PAK envelope or the**

shipping box or container. Place the addressed and completed Airbill in the airbill pouch without sealing the pouch. The shipping container also includes a large PAK envelope that can be used for return shipments.

During treatment, you may encounter device problems which require shipping certain components to Exogen. Upon completion of the treatment, the device must be returned to Exogen. Exogen will pay for all shipping costs in either of the above situations. The following instructions will assist you in returning devices or components to Exogen.

Return shipments after treatment is complete:

1. Only the MOU and THM components of the device are returned **when your physician advises you that your treatment is complete.** All other ancillary components (gel bottles, RAF, etc.) can be discarded.
2. The MOU and THM should be packed in the individual boxes that contained the MOU or THM. These individual MOU and THM boxes can be identified quite easily as they are labeled with **Return to: Exogen, Inc., 10 Constitution Ave., Piscataway, NJ 08855 - (800-836-4080).** If you use the individual boxes, they can be placed in the shipper's PAK envelope that was included in your shipping container.

If you do not have or cannot locate the individual boxes and/or the PAK envelope, pack the MOU and THM in the shipping container or in a suitable box using packing material to prevent movement of the MOU and THM during return shipment. If you are using the shipping container or your own box for the return shipment, please label the side of the box with permanent marker as indicated earlier in this paragraph as **Return to: Exogen, Inc., 10 Constitution Ave., Piscataway, NJ 08855 - (800-836-4080).**

Seal the return shipping container or containers with strong shipping tape making sure that the tape does not cover up the return shipping address.

3. Follow the instructions in the Airbill pouch for completing the shipper's waybill. The above **Note:** provides instructions on using the Airbill pouch for the return shipment.
4. When packing is complete and the Airbill pouch has been attached to the return package, call the toll-free freight company number provided on the "instructions" in the Airbill pouch.
5. You will receive a receipt from the freight company. Keep this receipt in case questions arise regarding the return shipment.

Return shipments of the MOU or THM components if problems arise:

1. The MOU or THM should be packed in their individual boxes. Seal the box with tape and place the box in the shipper's PAK envelope for return shipment. If you do not have the individual boxes, place the component in a suitable small box and insert it into the shipper's PAK envelope.

Follow the instructions provided to you in the Airbill pouch for completing the shipper's Airbill.

2. If you cannot locate the individual MOU or THM boxes, use the outer shipping container or a suitable box for the return shipment using packing material to prevent movement of the MOU and THM during return shipment.
3. When packing is complete and the Airbill pouch has been attached to the return package, call the toll-free freight company number provided on the "instruction" insert.
4. You will receive a receipt from the freight company. Keep this receipt in case questions arise regarding the return shipment.

Assistance from Exogen's Customer Service Department:

Assistance is always available from the Exogen Customer Service Department if you have questions on preparing a return shipment, completing the shipper's Airbill or contacting the forwarding freight company. Contact the Customer Service Department at 1-800-836-4080 for any information that you require.

L. GENERAL INFORMATION

1. Your physician will demonstrate the use of the device. Be sure that you understand the use of the device, how it works, what trouble indicators mean and what you should do if you have any problems during your daily treatments.
2. No attempt should be made to modify or repair the SAFHS® device.
3. You should notify your physician or Exogen of:
 - Any reactions, complications or problems that occur during treatment.
4. You should notify Exogen of:
 - Any device problems that cannot be resolved following the instructions in Section I: *Trouble Signals and Corrective Actions*.
 - The requirement for additional coupling gel to complete your therapy.

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