

Physician's
Instructions
for Use
& Package
Insert



EXOGEN 4000+[◇] **Bone Healing System**

Low-intensity Ultrasound Bone Healing
System for the Treatment of Nonunion
and Fresh Fractures

Caution: Federal Law (U.S.A.) restricts this device to sale, distribution, or use by or on the order of a physician or properly licensed practitioner. The device is only intended for use by the individual for whom it is prescribed.

DEFINITION OF SYMBOLS



Attention, consult manual.



Refer to Instructions for Use



A blinking addition (+) symbol with an audio tone means you need to add gel to the transducer face.



Pulsing Treating Symbol indicates device is operating properly



Treatment Stop or Treatment Lockout Symbol



Type B APPLIED PART



CE Mark indicates conformity with European Council Directive of 14 June 1993 concerning Medical Devices (93/42/EEC).

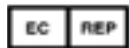


EU: Not for General Waste

The wheelie bin symbol denotes that this device should not be disposed of with ordinary household waste at the end of its life. For details of how to dispose of this item correctly, please contact your local government waste disposal agency or contact your local Smith & Nephew representative.



Manufacturer



Authorized Representative in the European Community

SN

Serial Number (First four digits of serial number indicate month and year of manufacture)



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A. Indications for Use

The EXOGEN 4000+[®], or any other EXOGEN Bone Healing System, is indicated for the non-invasive treatment of established nonunions[†] excluding skull and vertebra. In addition, they are indicated 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 orthopaedically 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, General Warnings and Precautions

Contraindications:

There are no known contraindications to the use of this device.

Nonunion Indication:

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 or 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 EXOGEN® device; therefore, evaluation during EXOGEN treatment by the attending cardiologist or physician is recommended.

- Cell phones may cause interference and patients should avoid cell phone use during treatments.
- Patients in the clinical studies were instructed to apply the device for one treatment period of 20 minutes each day. The safety and effectiveness of the EXOGEN device when used for more than one daily 20-minute treatment period is unknown.
- The age ranges of the patients in the PMA nonunion studies were 17–86. The effect of EXOGEN therapy on patients outside this age range is unknown.

Complications:

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 glycerin.

Fresh fracture indication:

Warnings:

The safety and effectiveness of the use of this device has not been established for the following:

- Fracture locations other than the distal radius or tibial diaphysis.
- Fractures with post-reduction displacements of more than 50%.
- Fractures that are open Grade II or III or that require surgical intervention or with internal or external fixation or that are not sufficiently stable for closed reduction and cast immobilization.
- Individuals lacking skeletal maturity or who are pregnant/nursing women.
- Pathological fractures due to bone pathology or malignancy.
- Individuals with thrombophlebitis, vascular insufficiency, abnormal skin sensitivity, sensory paralysis, alcoholism and/or nutritional deficiency.
- Individuals receiving steroid, anti-coagulant, prescription nonsteroidal anti-inflammatory, calcium channel blocker and/or diphosphonate therapy. Individuals using these therapies were excluded from the studies because of the possible effects of these therapies on bone metabolism.

Precautions:

- Animal studies conducted to date do not suggest any long term adverse effects from the use of this device. Clinical studies conducted for the EXOGEN PMA with long term patient follow up for up to 78 months do not suggest any

long term adverse side effects from the use of this device. However, possible longer-term adverse effects in humans are unknown.

- This device will not correct or alter post-reduction aspects of a fracture such as displacement, angulation or other malalignment.
- The age ranges of the patients in the fresh fracture PMA study were 17–67 years of age (54% were 31 years of age or older) in the tibia study and 20–78 (74% were 50 years of age or older) in the distal radius (Colles') study. The effect of EXOGEN® therapy on patients outside this age range is unknown.
- Operation of active, implantable devices, such as cardiac pacemakers, may be adversely affected by close exposure to the EXOGEN device. The physician should advise the patient or other person in close proximity during treatment to be evaluated by the attending cardiologist or physician before starting treatment with the EXOGEN device.
- Cell phones may cause interference and patients should avoid cell phone use during treatments.
- The clinical studies for the EXOGEN PMA required only one daily treatment period of 20 minutes. Although the EXOGEN device can be used more than once per day, the effects of multiple daily treatments are unknown; therefore, it is important that you prescribe only one daily 20-minute treatment period.

Complications:

No device-related adverse reactions or medical complications related to the use of this device were reported during the tibia or distal radius studies. In the distal radius study, one patient complained of pain during treatment but this resolved by the next follow up visit and one patient, complaining of pain, withdrew from the study.

C. Device Description

1. The EXOGEN 4000+ Bone Healing System

The EXOGEN 4000+ device provides a non-invasive therapy for the healing of nonunions and the acceleration of fresh fracture healing that the patient administers at home or at work, once daily, for 20 minutes. Treatment continues until you determine the fracture to be sufficiently healed to discontinue device use. The device transmits a low intensity ultrasound signal to the fracture site through coupling gel. The device provides low intensity ultrasound of 30 mW/cm² which is comparable to diagnostic ultrasound levels used in sonogram (fetal monitoring) procedures. Due to the very low intensity of the ultrasound, little or no sensation is felt by the patient during the treatment. A design feature alerts the patient in case of improper application or performance of the device. The EXOGEN 4000+ low-intensity ultrasound Bone

Healing System consists of one unit and a transducer permanently connected by a coiled electrical cable.

- The battery operated Main Operating Unit (MOU) provides the treatment control circuitry and also monitors the operation of the transducer at the fracture site.
- Neither the physician nor the patient can select or change any of the signal specifications.

2. Technical Specifications of the EXOGEN 4000+^o Ultrasound Signal

Ultrasound frequency	1.5 ± 5% megahertz (MHz)
Modulating signal burst width	200 ± 10% microseconds (µs)
Repetition rate	1.0 ± 10% kilohertz (KHz)
Effective radiating area	3.88± 1% square cm (cm ²)
Temporal average power.....	117 ± 30% milliwatts (mW)
Temporal maximum power	625 ± 30% milliwatts (mW)
Peak power	1.25 ± 30% watts
Spatial avg.–temporal avg. (SATA).....	30 ± 30% mW/cm ²
Spatial avg.–temporal maximum (SATM) ...	161 ± 30% mW/cm ²
Beam non-uniformity ratio (BNR).....	4.0 maximum

The device also uses a non-electrical, plastic locating component, the Retaining and Alignment Fixture (RAF).

When incorporated into the strap, the RAF is used for a Non-Cast application or an On-Cast application. A RAF is also available for incorporation into a cast for In-Cast applications. The RAF Cap Assembly is snapped on the RAF after the insertion of the transducer during treatment periods. In both On-Cast and Non-Cast applications, the RAF/strap is applied to the cast or skin over the fracture site and insures proper positioning during the 20-minute treatment period. During non-treatment periods in In-Cast applications, the transducer is removed and replaced with a felt plug to maintain even pressure on the skin. The RAF Cap is replaced on the RAF during non-treatment periods.

3. The EXOGEN 4000+ System Components

The EXOGEN 4000+ device is composed of a Main Operating Unit (MOU) Assembly with a permanently attached transducer and accessory items, which are shown below in *(Figure 1)*.

- The Main Operating Unit (MOU):** The MOU is powered by a non-replaceable and non-rechargeable lithium battery with a life of a minimum of 150 treatment periods of 20 minutes each. Since the range of the number of total treatment sessions for some patients may exceed this number, your device may require a battery change (see Section J). The MOU is connected to the transducer by a permanently attached coiled inter-connecting cable.

The MOU:

- monitors and controls system operation during treatment.
- verifies operation of the transducer and the MOU and monitors the MOU battery for a low battery condition.
- controls the duration of the 20-minute treatment period.
- monitors the presence/absence of coupling gel on the transducer surface. The MOU then alerts the patient with a visual and an audible beeping sound if gel is not present on the transducer.

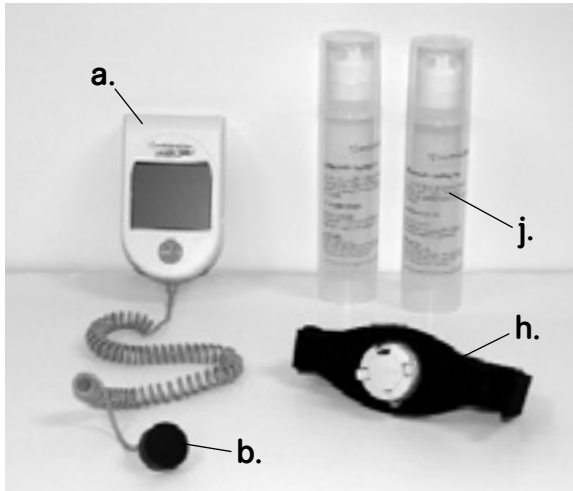


Figure 1

- automatically shuts off at the end of the 20-minute treatment period and alerts the patient with an audio signal that the treatment has ended.
 - maintains a complete record of patient daily use of the device, which is available to you, the physician.
 - monitors compliance with prescribed device use.
- b. **The Transducer:** The transducer is powered by the MOU battery supply and is connected to the MOU by a permanently attached flexible coil cable capable of extending from 1.5 feet (45cm) to approximately 5 feet (1.5m). The round, flat, black transducer surface attached to the coil cable transmits the low intensity ultrasound signal to the skin at the fracture site through a layer of ultrasound coupling gel. Coupling gel is necessary, as air will not transmit ultrasound. The appropriate ultrasound coupling gel is supplied with the device.

In-Cast and On-Cast Application

The EXOGEN® Cast Accessories Kit, supplied as needed, contains the items necessary for In-Cast or On-Cast installations. The EXOGEN Cast Accessories Kit components are shown in (Figure 1a) and are listed below:

- c. **Target Ring Locator:** The locating ring locator with strap is placed on the cast or on the skin over the fracture site, and is used to accurately locate the fracture.

- d. **Retaining and Alignment Fixture (RAF):** The separate RAF is a receptacle for the transducer, and it can be used in either an IN-Cast or a Non-Cast application. For both applications, the snap-on cap with a tethering ring is used to hold the transducer in place within the RAF. The snap-on cap has a spring attached to its inner side which keeps a light pressure on the transducer, thereby ensuring contact of the transducer surface with the skin. The tethering ring attached to the cap is placed around the RAF opening and prevents the possible loss of the

snap-on cap. The transducer is placed in the RAF for the daily 20-minute treatment period. The strap is adjustable for various cast diameters and can be cut to the desired length by the installer. If the strap supplied is too short for the diameter of the cast, strap extensions can be ordered from the Patient Service Department at Smith & Nephew, or may be available from the local sales representative.

- e. **Red Plastic Cap:** Protects the RAF opening during casting.
- f. **Felt and Foam Pads:** Square felt pads are supplied for installation beneath the RAF in 5/8 inch (16mm) and 1/4 inch (6mm) thickness. Their function is to maintain pressure on the skin under the RAF. A round felt plug (5/8 inch [16mm] diameter plugs) is used to maintain pressure on the skin during the time the transducer is not present. In addition, a black round foam disc is provided for placement on top of the transducer to ensure contact of the transducer surface with the skin when the cast thickness is excessive.
- g. **RAF retainer in cast:** The rectangular mesh RAF retainer is used to retain the RAF as it is incorporated into the cast.

EXOGEN® Cast Accessories Kit

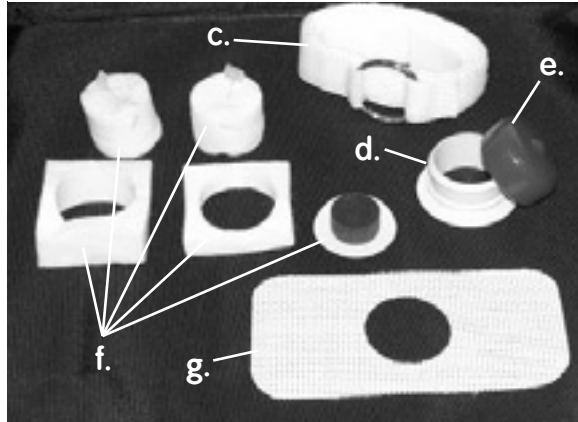


Figure 1a

Non-Cast Applications

The EXOGEN® Strap Kit (see *Figure 1, h.*) contains items listed below for a Non-Cast installation:

- h. **Strap Assembly:** The strap assembly supplied in the strap kit contains the RAF, with the snap-on Cap tethered to the RAF. The snap-on cap has a spring attached to its inner side which keeps a light pressure force on the transducer, thereby ensuring contact of the transducer surface with the skin.
- i. **Foam Pad:** A foam pad with a self-adhesive backing on one surface is used to provide a soft-surface padding under the RAF for contact with the skin in a Non-Cast application.

Other Accessories

- j. **Coupling Gel:** Two containers of hypoallergenic ultrasound coupling gel, which is 96% water, are provided with the EXOGEN device. Coupling gel must be applied to the transducer surface at the start of each treatment period in order to permit transmission of the ultrasound signal from the transducer surface to the skin over the fracture site. Each container has 200ml of coupling gel. A single pump (1.4cc) portion is the recommended amount of coupling gel for each treatment session. Each bottle will provide enough gel for approximately 140 treatments. Please replace the clear plastic top on the get bottle

after dispensing gel. There are other coupling mediums, which can be used if a skin reaction is noted with the standard gel. Please call the Patient Service Department at Smith & Nephew, Inc., if this occurs.

Note: EXOGEN ultrasound coupling gel supplied is the recommended gel for use with this system. Do not substitute other gels as they may damage the transducer surface or impede signal transmission. Please call the Patient Service Department at Smith & Nephew, Inc., if the patient needs more coupling gel.

Manuals: Patient Instructions for Use, Quick Instruction Guide, and the Physician Instructions for Use are included with the device.

D. Adverse Effects

In laboratory, animal and clinical research, the EXOGEN device output intensity (power level) (see C. Device Description, Technical Specifications) 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 5,000 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 device your patient received is 30 mW/cm² and 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 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 EXOGEN[®] device⁵¹ and EXOGEN PMA research indicate that the EXOGEN device is incapable of producing harmful temperature increases in body tissue and there is also no evidence of non-thermal adverse effects.

E. System Installation

This section of the manual is intended to provide directions for the installation of the EXOGEN device. Assistance in this installation can be obtained from the **Smith & Nephew, Inc. Patient Service Department at 1-800-836-4080, option #2, in the United States; or (+49) 746-22080 in Europe; and (+1) 901-396-2121 (USA) in other countries.**

1. RAF “On-Cast” Installation:

a. Getting the Cast Ready for an “On-Cast” Installation:

If the patient is casted, a window must be cut in the cast immediately over the fracture site, and the RAF applied in the following manner:

1. The target ring locator is placed over the fracture site, (*Figure 2*) and an X-ray is taken to assure that the locator is centered over the fracture site. If the locator is not centered over the fracture site, it should be moved to the appropriate position, and an “X” should be drawn in the center of the locator ring.
2. Using the square felt pad, trace the outline of the window on the cast (*Figure 3*).
3. The marked area is then removed with a cast saw (*Figure 4*).
4. The cast padding and stockinette are then cut away to reveal the skin overlying the fracture site (*Figure 5*).
5. Layers of the square felt pad, either of the 5/8 inch (16mm) or of the 1/4 inch (6mm) thickness are removed until the pad is the same thickness as the cast (*Figure 6*). The pad is placed in the window.
6. From the Strap Kit, remove the strap assembly. The foam pad is not used in the ON-Cast situation. Position the RAF securely over the cast window. The strap should be tightened, utilizing the hook and loop, to prevent the RAF from sliding out of place. It should not be so tight as to cause discomfort (*Figure 7b*).



Figure 2



Figure 3



Figure 4



Figure 5

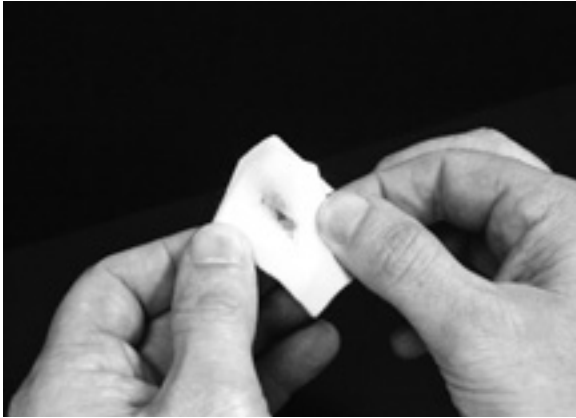


Figure 6



Figure 7a

7. The round felt plug with tab, layered to match cast thickness, is placed in the RAF hole during no-treatment periods (*Figure 7a*).

8. (*Figure 7b*) shows the RAF strap assembly in place, with cap closed.

2. RAF “In-Cast” Installation:

- a. **RAF “In-Cast” Assembly:** RAFs without a securing strap are provided in the EXOGEN® Cast Accessories Kit if you wish to incorporate the RAF into the patient’s cast. The following instructions detail this



Figure 7b

procedure. When the cast is complete and has dried sufficiently to permit “windowing,” the following procedure is performed:

1. The target locating ring is placed over the fracture site, as shown in *(Figure 2)*. An X-ray is taken to assure that the locating ring is centered over the fracture site. If the locating ring is not centered over the fracture site, it should be moved to the appropriate position, and an “X” should be drawn in the center of the locating ring.
2. Using the RAF mesh retainer, trace the outline of the window on the cast, as shown in *(Figure 3)*.



Figure 8

3. The marked area of the cast is then removed with a cast saw *(Figure 4)*. The cast padding and stockinette are then cut away to reveal the skin overlying the fracture site as shown in *(Figure 5)*.
4. Layers of the square felt pad, either of the 5/8 inch (16mm) or of the 1/4 inch (6mm) thickness are removed until the pad is the same thickness as the cast, as shown in *(Figure 6)*. The pad is placed in the window.
5. Place the RAF mesh retainer onto the RAF. Place red cap on the RAF, and place over the cast window as shown in *(Figure 8)*.

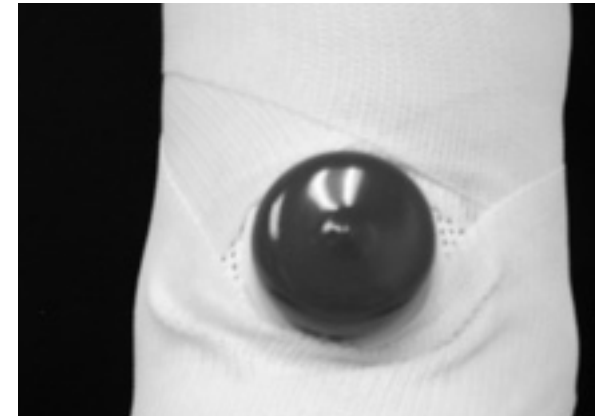


Figure 9

6. The physician or cast technician incorporates the RAF using appropriate width casting material.
7. Ensure that the RAF is completely and firmly installed in the cast (*Figure 9*).
8. When the RAF is securely incorporated in the cast, the red cap may be removed and discarded. The round felt plug is placed in the RAF and the tethered cap assembly is snapped in place on the RAF. (*Figure 10*) shows the incorporated RAF with the cap off and (*Figure 11*) with the cap snapped in place.

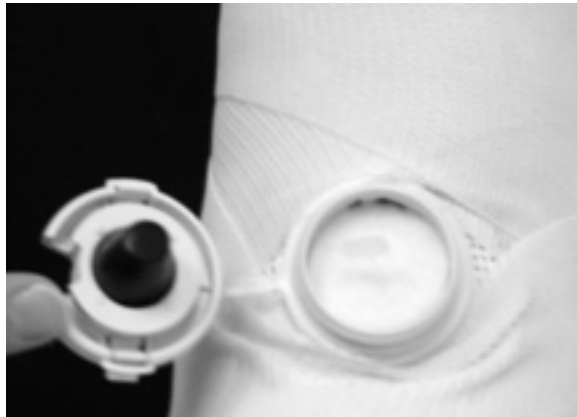


Figure 10

F. Device Operating Instructions

1. General Operating Instructions:

- a. **Starting a Daily Treatment Period:** The instructions shown below are to be followed when using the EXOGEN® 4000+ device with an ON-cast or IN-cast application. (See Section I for instructions on device use when you are not using a cast or you wish to continue treatment without a cast or utilize a removable cast or splint).

1. Remove the RAF Cap (*Figure 12*) by gently squeezing the tabs on the Cap Assembly with an inward motion



Figure 11

and lift it off of the RAF. Remove the round felt plug from the RAF opening. The cap is tethered to the RAF.

2. Prepare the transducer by placing a single pump (1.4cc) of coupling gel on the round flat black surface of the transducer (see *Figure 13*). **Do not spread the gel over the transducer surface.**

Note: The system is designed so that the gel spreads evenly when the transducer contacts the skin. You should use the recommended amount of gel. The device will alert you if insufficient gel is present. (See Section J — “Trouble Signals and Corrective Action.”)

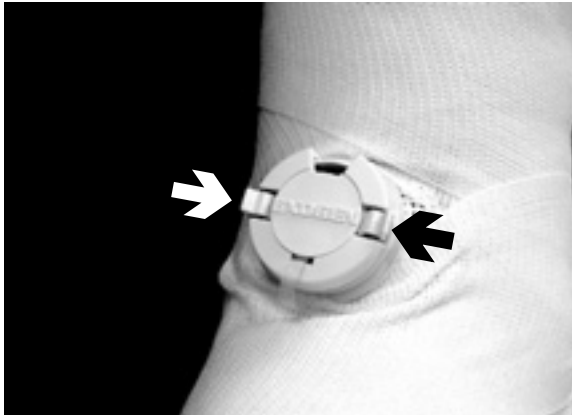


Figure 12



Figure 13



Figure 14

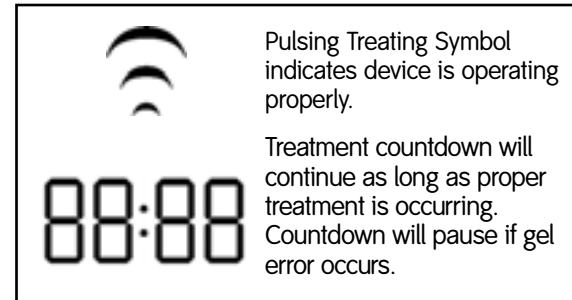
3. Insert the transducer, with the gel applied, into the RAF opening (*Figure 14*). Align the transducer cable with the cap slot before snapping the cap in place.

b. **Turning “On” the EXOGEN 4000+° Model for the Daily Treatment Period:** Press and release the “On/Off” button once on the MOU (see *Figure 15*) to turn ON the system. When the “On/Off” button is pressed to turn ON the system the following steps occur:



Figure 15

1. The system will emit a two-tone beep and run its built-in testing circuit that checks the unit operation. This self-test takes approximately 2 seconds during which the display will show all icons.
2. The device will display the total number of FULL treatments completed.
3. The device will display the total number of PARTIAL treatments.
4. The device will then start treatment. The Pulsing Treatment Symbol and the countdown clock will be shown on the display.



The LCD display will provide a warning message if either insufficient gel has been applied or a fault or problem has been detected. After the 20-minute

treatment period, the unit will emit a two-tone beep and turn itself off.

The EXOGEN 4000+[®] device is intended for one 20-minute treatment period per day. It is recommended that there be at least 12 hours between treatments although this spacing may not always be possible to maintain. As an example, if the treatment started at 10:00 p.m. on Monday, Tuesday's treatment should be performed after 10:00 a.m. In any case, the patient should always follow the treatment schedule as prescribed by you.

Note: *Each time the device is turned on, and used for at least 3 minutes, a record of the use will be stored in the device. Instructions on the procedure to obtain a device use record is available in Section G.*

- c. **At the End of a Daily Treatment Period:** The device will automatically stop treatment after 20 minutes. A two-tone beeping sound will indicate that treatment has been completed followed by the LCD turning off.
1. Remove the transducer from the RAF. The transducer must be removed from the RAF after each treatment session.
 2. 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 (see *Figure 16*).



Figure 16



Figure 17

Clean the inside surface of the RAF and the transducer after each treatment to remove any gel that may have accumulated, as this may cause difficulty during the next treatment.

3. Replace the round felt plug with tab into the RAF (see *Figure 17*).
4. Snap on the RAF cap tethered to the RAF by positioning it over the RAF hole and pushing down until it snaps securely in place.

G. Treatment Schedule

It is recommended that you prescribe only one daily 20-minute treatment period for your EXOGEN device treated patients. The EXOGEN® device should be used daily until you judge the fracture to be sufficiently healed to discontinue therapy. Please note that ultrasound therapy is automatically shut off after each treatment period. However, the transducer should be removed from the RAF after each treatment period to allow for proper cleaning and storage.

1. Treatment Log of Patient Use

The EXOGEN 4000+ device contains an internal patient use timer, which monitors and records the daily use of the device.

When the device turns ON it initially performs a self-test after which it displays the total number of FULL treatments completed, then the number of PARTIAL treatments.

- **Partial treatments** are from more than 3 minutes to 18 minutes.
- **Full treatments** are from more than 18 minutes to 20 minutes.

H. Interruption of a Treatment Period

It is recommended that each treatment period be a continuous, uninterrupted 20-minute period. During a treatment period, if for any reason the patient must attend to something for a short period of time (e.g., answer a telephone or a doorbell), the MOU can be carried by the patient. In this instance, it is not necessary to turn off the device. However, if the patient does not want to carry the MOU to attend to the interruption, the patient has 30 seconds before the device shuts off. If the device shuts off, the patient will need to begin a new 20 minute treatment.

Within 30 seconds, the patient must complete the following:

1. Open the RAF cap and remove the transducer from the RAF.
2. Attend to the reason for the interruption.

3. Reapply coupling gel to the transducer, as necessary.
4. Replace the transducer in the RAF.
5. Snap the RAF cap back on.
6. If the total response time for the above steps took less than 30 seconds, the treatment will continue to completion. However, if the total time of response exceeds 30 seconds, the device will turn off. It will be necessary to follow steps 1–5 above before pressing the “On” button to start a new, complete 20-minute treatment period.

I. Instructions when No Cast Is Used or when the Cast Is Removed and Treatment Is Continued

Included with this device is a RAF Strap Assembly (*Figure 1*). Treatment with the EXOGEN® device in these situations can be administered by using the RAF Strap Assembly directly on the skin over the fracture site; cinching the assembly in-place with the hook and loop; inserting the transducer into the RAF after putting coupling gel on the transducer surface; and commencing treatment as described above in Section F.1.

1. Starting a Non-Cast Application:

- a. The following instructions will be helpful when placing the EXOGEN device for a non-cast application.
- b. In addition, when cast immobilization has initially been used and is discontinued, you may wish to continue EXOGEN® treatment while protecting the fracture with a removable splint or brace. If a brace or splint is being used, instruct the patient how to remove the splint or brace prior to beginning treatment and reinstall the splint or brace after treatment.
- c. In any “non-cast” applications, 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. You will need to place a mark over the fracture site, or indicate an area on the skin as a landmark to insure proper placement of the device for each treatment (*Figure 18*).
- d. For daily treatment with the EXOGEN 4000+, the RAF with the attached foam pad and strap is used to secure the RAF over the fracture site. The circular opening in the RAF must be centered over the treatment area (*Figure 19*).



Figure 18



Figure 19

- e. The strap should be tightened, utilizing the hook and loop to snug it up enough to prevent the RAF from sliding out of place. It should not be so tight as to cause discomfort.
- f. The strap assembly must be secured in place over the treatment site BEFORE the transducer with gel applied is inserted into the RAF. This will ensure that the coupling gel placed on the transducer is applied directly to the treatment site.
- g. Follow directions provided in Section F.1. for starting treatment. The patient should remain in a resting position during a treatment period to minimize movement of the transducer and RAF Strap/Cap assembly.

2. At the End of a Non-Cast Treatment Period

- a. Open the cap and remove the transducer from the RAF Strap Assembly to allow for proper cleaning.
- b. Remove the RAF Strap Assembly, and 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 gel residue from the RAF Strap Assembly (Figure 20).
- d. Clean any coupling gel from the transducer with a soft cloth, tissue or paper towel, to prevent gel from drying on the transducer surface and interfering with the following treatments. Use a damp cloth or paper towel to remove any dried gel. Replace the removable splint or brace if applicable. The device should be placed in its device container or a safe place until the next treatment period.

Never immerse the EXOGEN 4000+° device in water.



Figure 20

J. Trouble Signals and Corrective Action

Please do not attempt to open the device. There are no user serviceable parts in the EXOGEN° device.

At the start of the treatment self-test sequence, the MOU monitors the correct operation of the EXOGEN 4000+ system. During the entire treatment period, the MOU continues to monitor system operation. It detects whether:

- sufficient gel is present on the transducer surface,
- the internal battery has reached a low battery condition, and
- the device is operating properly.

If an alarm occurs, do not turn the device off. The MOU display indicates the type of problem by displaying an icon message on the LCD display along with an audible tone. The following alarm displays may occur during system operation.

1. Please Add Gel Symbol



- a. This symbol appears on the LCD display along with a fast pulsing audio tone of 0.1 second on and 0.1 second off lasting for 30 seconds after which the device turns “off.”

b. Correct this condition as follows:

1. Remove the transducer from the RAF Strap Assembly.
2. Apply one pump of gel to transducer and replace cap on bottle.
3. Re-insert the transducer and snap on cap making sure it properly snaps in place. If the problem has been corrected within 30 seconds of the alarm, the Please Add Gel Symbol will be replaced by the countdown of the remaining treatment time. If the problem is corrected after 30 seconds, the device will turn "Off." It will be necessary to press the "On/Off" button to turn the device back "On" for a new, complete 20-minute treatment period.

2. Error or Problem Messages

Note: The following fault conditions require that you contact Smith & Nephew, Inc.'s Patient Service Department.

Attention: Consult Manual symbol



The MOU alerts you of an error or problem condition in the device.

An error or problem message is shown on the LCD display as the Attention symbol and is accompanied by an audible alarm consisting of a slow pulsing tone with 2 seconds "on" and 0.1 seconds "off" (long beep "on" followed by a very short "off" period) lasting for 30 seconds. This denotes a problem with the operation of the device. The device turns "off" after the 30 seconds. If the Attention symbol appears, turn the device OFF and wait approximately one minute. Press the "On/Off" button once to turn on.

If the device still displays the Attention icon there is a problem with the device, please call Patient Services at **1-800-836-4080, option #2, in the United States; or (+49) 746-22080 in Europe; and (+1) 901-396-2121 (USA) in other countries.**

Treatment Stop or Treatment Lockout symbol



This symbol indicates that the current 20-minute treatment period has been completed.

K. Care and Handling of the EXOGEN 4000+[◇] System

Do not use cleaning agents or solvents on any of the components of the system. Use a soft cloth, tissue, paper towel, or cotton swab to clean the transducer or the RAF. Use a damp cloth or paper towel to remove any dried gel residue. Never immerse the unit in water. The EXOGEN 4000+ device is intended for home or office use and, therefore, should be operated within the typical room temperature conditions expected in a home/office environment 60°–100° F (16°–38° C). If the 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 device should not be stored, moved or transported in temperature conditions below 0° F (-18° C) or above 130° F (54° C) range, or damage may result to internal electronic components. The device shall operate in normal use under the following conditions:

- Ambient temperature range: 50° F (10° C) to 104° F (40° C).
- Relative humidity range: 30% to 75%.
- Atmospheric pressure range: 700 hPA to 1060 hPA.

When the EXOGEN 4000+ device is outside its protective packaging, 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. Please exercise care while handling the transducer as rough handling may adversely affect the device operation. Please save the packaging for device safekeeping and transport. Periodically inspect the transducer and the transducer cable for cracks, or other signs of damage, which may allow the entrance of conductive fluids or exposure of conducting wire. Contact the Patient Service Department of Smith & Nephew, Inc., if you detect any problems with the device.

L. General Information

Patients should be instructed to notify you if any of the following conditions occur:

- Any problems with immobilization such as soft, loose or damaged cast or splint, etc.
- Any reactions/complications during treatment.

Patients should notify the Patient Service Department of Smith & Nephew, Inc., if:

- The device malfunctions or develops a problem.
- The patient does not have sufficient coupling gel to complete their prescribed therapy.

M. Guidance and Manufacturer's Declaration—Electromagnetic Emissions and Immunity Testing

Electromagnetic Environment Guidance: The EXOGEN 4000+° device uses radio-frequency (RF) energy only for its internal function. Therefore, its RF emissions are very low and are not likely to cause any interference in nearby electronic equipment.

Interference with proper operation of the EXOGEN 4000+ device may occur in the vicinity of equipment marked with this symbol.



This equipment includes portable and mobile communications units. If abnormal operation of the EXOGEN 4000+ device is observed due to the electromagnetic environment where the device is being used, additional measures may be necessary to correct the problem. These measures include relocating the EXOGEN 4000+ device at a further distance from the interfering equipment or reorienting the EXOGEN 4000+ device in relation to the interfering equipment.

Electromagnetic Compatibility Testing

Summary:

Testing Report for:
Smith & Nephew, Inc.

Equipment Under Test:
EXOGEN 4000+^o

Used for Life Support:
No

Use in shielded enclosure:
No

Test Description	Published Test Level or Class	Pass/Fail, Comments
IEC 60601-1-2:2001		
IEC 61000-4-2 Electrostatic Discharge	±6kV contact discharge ±8kV air discharge	Pass
IEC 61000-4-3 RF Electromagnetic Field	1 kHz sine wave (80% AM) 80–2500 MHz , 3 V/m	Pass
IEC 61000-4-4 Electrical Fast Transient/Burst	AC or DC power ports, ±2kV	Not Applicable. The EUT is battery operated.
	Signal and I/O ports, ±1kV	Not Applicable. The EUT cable is less than 3m long.
IEC 61000-4-5 Surge	AC or DC power ports, ±2kV Line to ground and ±1kV line to line	Not Applicable. The EUT is battery operated.
IEC 61000-4-6 Conducted RF Immunity	AC or DC power ports, 0.15–80 MHz, 3 or 10 V	Not Applicable. The EUT is battery operated.
	Signal and I/O ports, 0.15–80 MHz, 3 or 10 V	Not Applicable. The EUT cable is less than 3m long.
IEC 61000-4-8 Power frequency Magnetic Field	3A(rms)/m, @ 50 Hz and 60 Hz	Pass
IEC 61000-4-11 Voltage Dips, Short Interruption	> 95% (10ms), 60% (100ms), 30% (500ms), > 95% (5000ms)	Not Applicable. The EUT is battery operated.
IEC 61000-3-2 Harmonics	Class A, B, C or D	Not Applicable. The EUT is battery operated.
IEC 61000-3-3 Flicker	See standard specifications	Not Applicable. The EUT is battery operated.
CISPR 11 Radiated Emissions	Class B Limits	Pass
CISPR 11 Conducted Emissions	Class B Limits	Not Applicable. The EUT is battery operated.

Test Report # 3066582-27-1-0, November 24, 2004. Testing performed by: Intertek, 1950 Evergreen Blvd, Suite 100, Duluth, GA 30096.

N. Background Information on the EXOGEN[®] Bone Healing System

1. Safety

a. Gross pathology

Several studies were conducted to assess the safety of the EXOGEN device as part of the FDA summary of safety & effectiveness. Results from a placebo controlled in-vivo study on rabbits with bilateral mid-shaft fibular osteotomies showed no deleterious effects of EXOGEN as evidenced by pathological, hematological, and histological analysis.⁴⁰

b. DNA analysis

Analysis of the effects of EXOGEN on chromosome of bone marrow cells from a rabbit mid-shaft radius osteotomy reported no measurable, significant, detrimental effects.²

c. Temperature

The EXOGEN device's acoustic output is 20 to 100 times less than that of other therapeutic ultrasound devices currently available. An independent university-based medical expert in ultrasound⁵¹

concluded the EXOGEN device is incapable of producing temperature elevations greater than 1° C. Such temperature elevations are not considered significant and the potential for detrimental thermal effects is not a concern.

d. Metals & Implants

Several reference articles have focused on conventional therapeutic ultrasound's effect on surgical metallic implants. Lehman et al.²⁰ reported that, based on histological studies, ultrasound applied in the presence of metal implants did not produce any untoward effects. In addition, it has been shown (PMA 900009, supplement 6) that low intensity ultrasound does not compromise the integrity of a standard orthopaedic stainless steel fixation plate. After 30 hours of continuous exposure, no changes or effects could be detected.

Temperature—Gersten¹² reported that temperature rises were smaller with metal than with bone at the same depth, and that the presence of metal was not a contraindication to the use of ultrasound.

Migration—Lotsova²³ 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.

Degradation—Skoubo-Kristiansen and Sommer⁴¹ concluded that as a result of ultrasound treatment no effect was observed on fixation screws or the torques necessary for loosening the screws in an in-vivo study. The compatibility of the EXOGEN[®] ultrasound signal on bioabsorbable screws has also been investigated in-vitro and clinically. Handolin et al^{15, 16} showed treatment with the EXOGEN device had no effect on the mechanical or molecular properties of biodegradable self-reinforced poly L-lactide screws and thus biocompatibility between the screws and Exogen was good, with no effect on the biodegradation rate.

Apart from Handolin et al, the studies reported above used 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 EXOGEN bone healing device. It is reasonable to conclude that metal present in a healing fracture would not affect the safety or effectiveness of the EXOGEN bone healing system.

e. Clinical

No device-related adverse reactions or medical complications related to the use of this device have been reported during the clinical studies^{3, 4, 6–10, 14, 15, 17–19, 21, 24–31, 33, 36, 39, 42, 43, 47, 49}.

2. Effectiveness

a. Pre-clinical

Studies reported for the PMA summary of safety and effectiveness for *fresh fracture* indications:

- Pilla et al.^{33, 34}, in two rabbit bilateral fibular osteotomy placebo-controlled studies, reported statistically significant acceleration of ultrasound-treated fibulae versus the placebo side 1.7 and 1.4 times faster, respectively.

Studies reported for the PMA summary of safety and effectiveness for nonunion indications:

- Wang et al⁴⁶ and Yang et al⁴⁸ reported on ultrasound fracture treatment in a model of bilateral closed femoral shaft fractures made in rats and stabilized by a Kirschner wire, serving as an intramedullary rod. Ultrasound 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.

Other studies:

- Numerous pre-clinical studies have been conducted and these indicate the acceleration of bone healing induced by the EXOGEN® ultrasound signal has no negative impact on the quality of bone. Further in-vivo studies in rat fracture models^{1,11} have confirmed the earlier work in rabbits by Pilla et al.^{33, 34} in which low intensity pulsed ultrasound accelerated fracture healing, as evidenced by increased mechanical properties at the fracture site. Azuma et al.¹ through histological analysis and micro-computed tomography were able to determine that fracture healing in the ultrasound-treated group, whilst accelerated, was typical of normal bone healing, and showed an impact at early, mid and late stages of fracture healing with maximum impact achieved when treatment with the EXOGEN bone healing system was applied throughout the healing process. Takikawa et al.⁴⁴ studied the impact of the Exogen bone healing system in a hypertrophic nonunion model demonstrating 50% resolution in the active group versus 0% in the control group at 6 weeks.

b. Clinical

Studies reported for the PMA summary of safety and effectiveness for fresh fracture indications:

- The pivotal works demonstrating the benefits of low intensity pulsed ultrasound in fresh fractures were reported by Heckman et al.¹⁷ and Kristiansen et al.¹⁹. These prospective, placebo-controlled, randomized, double-blind, multi-center studies were two of the first examples of such rigorously designed studies reported in the orthopedic literature. Heckman et al.¹⁷ included 67 conservatively treated closed or grade-I open, cortical tibial fractures in their trial. This study demonstrated that the EXOGEN bone healing system induced a 38% acceleration of clinical and radiographic healing (96±4.9 days in the active group versus 154±13.7 days in the control group; p<0.0001). The median duration of treatment was 10 weeks (5–23 weeks). The second pivotal study by Kristiansen et al.¹⁹ included sixty one conservatively treated cancellous radial fractures. EXOGEN ultrasound treatment accelerated healing by 38% (61±3.4 days in the active group versus 98±5.2 days in the control group; p<0.0001). Median treatment time was 9 weeks (6–11 weeks). Cook et al.³ pooled the data from the tibia and distal radius studies to analyze the impact of low

intensity pulsed ultrasound on the incidence of delayed unions, and on the healing time of smokers. Using a 150 day definition of delayed union, Cook et al.³ determined that the EXOGEN[®] bone healing system had a statistically significant effect ($p < 0.003$) on the rate of delayed unions (treated group 6% versus control group 36%). Cook et al.³ also demonstrated a significant reduction in the healing time of smokers for fractures of the tibia and distal radius.

Studies reported for the PMA summary of safety and effectiveness for nonunion indications:

- Three studies, undertaken in the USA, Germany and the Netherlands, were submitted to the FDA³⁵ as the basis for approval of the EXOGEN bone healing system to treat established nonunions. The studies were prospective and self-paired, in that the nonunion fractures had been established for a minimum time, and had no recent surgical intervention in order to rule out the possibility of spontaneous healing from that treatment. The only change in treatment regimen was the application of low intensity pulsed ultrasound. Analyzing the data from Germany, the completed cases had a healed rate of 86% (64/74) with a mean time to a healed fracture of 163 ± 9.4 days. The median heal time

was 142 days with a range of 53 to 375 days. The median fracture age for the healed cases was 494 days with a range of 257–6011 days. Appendix 1 presents the healed rate results that 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 (time from initial fracture to the start of ultrasound treatment) stratum of over 5 years (>1827 days). The scaphoid nonunion heal rate of 33% (2/6) was attributable to the three scaphoid nonunion failures that were all more than 10 years in fracture age and, therefore, were very difficult and challenging cases. Cases with metal present during ultrasound treatment such as those with ORIF and those cases with IM rods had an 88% (21/24) and 100% (16/16) healed rate, respectively. The results of this nonunion paired design clinical study established the safety and efficacy of the EXOGEN bone healing system in treating nonunions. This includes cases that had long fracture ages of up to 5 years but suggests that nonunions of more than 5 years duration may have a decreased response to ultrasound treatment. Nolte et al³¹, reporting on the Netherlands study,

confirmed the 86% success rate and showed the average heal time to be around 5 months. There were high success rates seen with atrophic and oligotrophic nonunions (80% and 92% respectively) where some biological deficiency may contribute to the original nonunion. Additionally the application of EXOGEN® to hypertrophic nonunions, which might usually be considered as requiring revised treatment to correct fracture instability, was successful in 80% of cases. Success was seen for a range of bones, all types of typical primary fracture management, and across all patient age ranges. For the United States study, the completed cases group had an 82% (352/429) heal rate.

Other *nonunion* studies:

- Frankel and Mizuno⁶ in their analysis of the 1,546 USA patient nonunion registry demonstrated that for patients with risk factors that may impair fracture healing, such as substance abuse, diabetes, vascular problems, or steroid use, there was no significant change in the efficacy of the EXOGEN bone healing system. Frankel⁷ provided further insight to the USA patient registry by stratifying the data to include early delayed unions (91–150 days) and late delayed unions (151–269 days), in addition to fresh fractures and nonunions (270 days or greater). Again high success rates

were achieved for all bones, regardless of fracture age, but there was a trend towards higher success rates and faster healing with earlier intervention.

- Duarte et al.⁴ presented data from one of the largest cohorts of patients treated with low intensity pulsed ultrasound (1996). 380 non-responding delayed and nonunions (averaging 14 months old) were treated with the EXOGEN ultrasound signal and achieved an 85% success rate across a range of bones.
- Romano et al.³⁶ reported on prospective longitudinal studies in infected nonunions and pseudoarthrosis respectively, suggesting high success rates with low intensity pulsed ultrasound in both situations.

Other fresh fracture studies:

- In addition to long bones the effect of the EXOGEN® bone healing system on fractures of other types of bone has also been clinically studied. A single-center, prospective, randomized, double-blind, placebo-controlled study of 40 scaphoid fractures²⁷, demonstrated a statistically significant 31% acceleration in the primary end-point of clinical plus radiographic healing (active 43 days; control 62 days; $p < 0.01$) and 41% improvement in % trabecular bridging at 6 weeks (active 81%, control

55%, $p < 0.05$). A smaller ($n=20$) single-center, prospective, randomized, double-blind, placebo-controlled study of Jones' fractures⁴³ showed all actively-treated fractures healed within 56 days whilst only 60% of placebo-treated fractures had healed by 87 days, and 20% had still not healed after 140 days. In addition the actively-treated group reached pain free status 31 to 70 days earlier than the placebo group, and on average took only half the rehabilitation time.

- Strauss and Gonya⁴² described the effects of low-intensity pulsed ultrasound on two difficult cases of Charcot nonunions with multiple prior failed surgical procedures. Both cases healed within 5.5 months when treated with the EXOGEN bone healing system.

3. Mode of Action

a. Mode of Action

The low-intensity pulsed ultrasound delivered by the EXOGEN bone healing device is a mechanical stimulus. This has been clearly demonstrated by experimental work on cadavers in which tissue around an osteotomized bone moved in response to the ultrasound signal at a frequency of 1kHz, the

same frequency as the pulse of the EXOGEN ultrasound signal. Tissue motion has been calculated to be of the order of 0.5nm, approximately 1000 times less than "micromotion." As well as soft tissue movement it was demonstrated that the bone moved also, albeit on a smaller scale¹³. This work shows stimulation with the EXOGEN bone healing system provides motion on a nanometer scale, suggesting the mode of action is independent of fixation methods such as casting or external fixation.

Mechanical energy is transformed into biochemical energy by transduction at the cell membrane. One family of cell membrane receptors that are responsible for this transduction are integrins and on a model system of cultured fibroblasts it has been demonstrated that the EXOGEN ultrasound signal stimulates cells through an integrin pathway⁵⁰.

Within this integrin pathway, cytoskeletal organization, transcription factor activation, gene upregulation, protein synthesis and increased cell proliferation have all been observed.

b. Review information on fracture healing and bone formation

Two review articles^{14, 37} have assessed the clinical and basic science evidence for the EXOGEN® bone healing system. Their analyses suggested the EXOGEN bone healing system induced cellular reactions at each phase of fracture healing from inflammation through to endochondral ossification³⁰.

c. Modes

Effects on chondrocytes—Chondrocytes have been shown to respond to Exogen by an increase in proteoglycan synthesis (mediated by calcium signaling) and the increase in aggrecan mRNA demonstrated in fracture callus in vivo⁴⁸ has also been demonstrated in chondrocytes in vitro³².

Response of marrow cells to the EXOGEN ultrasound signal—Mesenchymal cells derived from the bone marrow give rise to chondrocytes and osteoblasts in a fracture site and work published in Tissue Engineering⁵ demonstrated that the Exogen signal accelerated the differentiation of mesenchymal cells when cultured in a system designed to promote chondrocytic differentiation.

Periosteal cell response—Human periosteal cell cultures were studied by Leung et al.²² who clearly demonstrated they respond to low intensity pulsed ultrasound by increasing expression of alkaline phosphatase, osteocalcin and VEGF. In addition long term treatment (4 weeks of 20 minute daily treatment) increased the level of mineralization in these cultures.

Osteoblast differentiation—MMP13 and alkaline phosphatase are two enzymes key to the process of mineralization and Unsworth et al.⁴⁵ demonstrated an increase in both these enzymes in MC3T3-E1 cultures after stimulation with Exogen. Further evidence that ultrasound affects the mineralization process comes from Saito et al.³⁸ who demonstrated accelerated calcium accumulation in MC3T3-E1 cultures. Significant increases (8.6-fold and 3.6-fold higher than untreated controls) were seen at day 25 and day 35 respectively. Collectively the findings of these studies demonstrate that in a pre-osteoblastic culture system PLIUS accelerates differentiation along the osteoblastic lineage, as shown by the rise in alkaline phosphatase synthesis, and the raised level of MMP13 expression. These phenotypic changes facilitate an increased degree of mineralization. Such effects in a fracture

environment can benefit the formation of a mineralized callus, stabilizing the fracture and increasing the strength of the bone, as has been observed in animal studies.

Clear evidence exists that the EXOGEN® bone healing system accelerates the healing process at all stages of fracture repair. In-vitro evidence supports this by demonstrating effects on various cell types, stimulating proteins involved in various biological processes and demonstrating acceleration of some processes in organ culture.

Appendix 1

Clinical Study Results for the Nonunion Supplement 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 ^o Treatment	Completed Cases Fisher's 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	20 15 24 15	15 12 23 14	5 3 1 1	75% 80% 96% 93%	0.16

ROW	Categorical Variable Prior to Start of SAFHS Treatment	Completed Cases Fisher's Exact Probability [†]				
		Total	Healed	Failed	% Healed	p-value
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 2 1 6 1 6	26 12 6 5 4 1 1 2 1 6	2 1 1 1 0 1 4 0 0 0	93% 92% 86% 83% 100% 100% 50% 33% 100% 100%	0.03
8	Long Bone vs. Other Bones: Long Bones 28 tibia 13 femur 7 radius 6 humerus 4 metatarsal 1 metacarpal	59	54	5	92%	0.02

ROW	Categorical Variable Prior to Start of SAFHS° Treatment		Completed Cases Fisher's Exact Probability†				
			Total	Healed	Failed	% Healed	p-value
	Other Bones 1 calcaneus 4 clavicle 1 pelvis 1 rib 6 scaphoid 2 ankle		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) Open reduction Internal fixation (ORIF) External fixation; only for long bone cases (N=59)		 43 16 50 24 50 9	 38 16 43 21 46 8	 5 0 7 3 4 1	 88% 100% 86% 88% 92% 89%	 0.31 1.00 0.58

ROW	Categorical Variable Prior to Start of SAFHS Treatment		Completed Cases Fisher's Exact Probability†				
			Total	Healed	Failed	% Healed	p-value
	Conservative (Cast, splint, brace) No Yes		58 16	51 13	7 3	88% 81%	0.44
	IM rod, or ORIF, or External Fixation, or conservative No Yes		10 64	7 57	3 7	70% 89%	0.16
13	Prior failed Lithotripsy therapy: No Yes		 72 2	 62 2	 10 0	 86% 100%	 1.00
14	Smoking status: Missing Never smoked Stopped smoking prior to SAFHS start Smoker at SAFHS start		 (2) 34 10 28	 (2) 31 8 23	 (0) 3 2 5	 91% 80% 82%	0.47
15	Nonunion type: Missing Atrophic Hypertrophic		 (22) 41 11	 (17) 36 11	 (5) 5 0	 88% 100%	0.57

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Product No. 81032987
11/06

