Mechanism of Action

Activating bone healing at every stage
EXOGEN® Ultrasound Bone Healing System

The EXOGEN Ultrasound Bone Healing System is an FDA-approved bone healing device that uses low-intensity pulsed ultrasound (LIPUS) technology to stimulate the body’s natural bone healing process.¹

EXOGEN is osteoinductive, stimulating cells to differentiate into osteoblasts that begin the formation of new bone. EXOGEN is safe and effective for non-union† fractures with metal fixation or implants² (see EXOGEN User Guide).
1. **Stimulation**
   EXOGEN sends ultrasound waves through the skin and soft tissue to the fracture.

2. **Activation**
   EXOGEN ultrasound activates cell surface mechanoreceptors called integrins, initiating an intracellular cascade that leads to upregulation.

3. **Upregulation**
   EXOGEN ultrasound increases upregulation of genes and expression of proteins and growth factors critical to bone healing.

**COX-2**
Vital to the production of PGE2, critical for bone repair

**Cell Differentiation**
Converts stem cells to osteoblasts

**VEGF**
Stimulates the growth of new blood vessels

**BMP2; BMP4; BMP6; BMP7**
Essential to the creation of new bone

**Mineralization**
Increases bone mineral density
A clear biological response

The lower image shows EXOGEN's impact on the formation of the cytoskeleton (in green) and focal adhesions (orange dots) in osteoblasts in vitro, caused by the clustering of integrins.7
Bridging the fracture gap

Micro-computed tomography shows that EXOGEN treatment increases the removal of original cortical bone and enhances endochondral ossification. The image on the right shows the growth of new, less-dense bone (in green) bridging the fracture gap of older, denser bone (in red).
EXOGEN at every stage of the fracture healing process

**Inflammation**
EXOGEN's ultrasound signal increases cell division among periosteal cells in culture and upregulates growth factors that trigger the formation of new blood vessels.\(^4\)

**Soft Callus**
The ultrasonic treatment enhances the TGFβ-triggered differentiation of chondrocytes in culture and accelerates the formation of extracellular matrix.\(^9,10\)

**Hard Callus**
EXOGEN upregulates endochondral ossification\(^11,12\) and enhances osteoblast differentiation\(^13\) and mineralization.\(^4\)

**Bone Remodeling**
Accelerating both the formation and resorption of bone, EXOGEN ultrasound treatment yields faster remodeling of the mineralized callus.\(^8\)
EXOGEN accelerates healing throughout the fracture healing process.

Maximum torsional torque of the EXOGEN-treated femurs was significantly greater than the placebo controls at each phase of fracture healing in an animal model.¹
EXOGEN can easily penetrate soft tissue to reach both deep and superficial fractures

The depth and breadth of the EXOGEN signal enable it to treat superficial and deep indicated fractures, as well as non-union fractures with metal fixation or implants. \(^2\)\(^,\)\(^14\) Because the ultrasound waves travel easily through adipose tissue, it is suggested that EXOGEN therapy is effective for normally weighted and obese patients.\(^15\)

Depth and breadth of penetration:\(^15\)

- Beam reaches a depth of more than 260 mm
- Effective diameter of the ultrasound beam is more than 5 cm
- Therapeutic span is 3.4 cm, even after passing through 20 cm of soft tissue
EXOGEN shows results in special patient populations:

- Smokers\textsuperscript{16}
- Infected non-union\textsuperscript{17}
- Deep or superficial fractures\textsuperscript{14}
- Atrophic non-union\textsuperscript{14}
- Hypertrophic non-union\textsuperscript{14}

EXOGEN is effective on non-unions with metal implants:\textsuperscript{14}
- Cells respond even if the fracture is fixed with metal implants

EXOGEN used on animal models with metal fixation has been shown to be:
- Safe\textsuperscript{2}
- Non-cavitating\textsuperscript{18}
- Non-thermal\textsuperscript{19}

0\% of EXOGEN-treated smokers developed a delayed union\textsuperscript{16}

\begin{figure}
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\includegraphics[width=\textwidth]{chart.png}
\caption{Comparison of EXOGEN and Control groups.}
\end{figure}
EXOGEN treatment accelerates healing in both cortical and cancellous bone

Analysis of these studies showed an 83% reduction in delayed unions.\textsuperscript{16}

EXOGEN is a unique fracture healing device that has demonstrated the ability to accelerate fresh fracture healing.

In a prospective, randomized, double-blind, placebo-controlled (Level I) study of 67 tibial fractures, EXOGEN treatment accelerated healing by 38\% \textsuperscript{20} – a difference of more than 8 weeks.

A separate Level I trial of 61 distal radius fractures also reported a 38\% acceleration of healing, as well as significantly greater fracture alignment.\textsuperscript{21}
EXOGEN has been shown to successfully resolve 86% of non-union fractures. The EXOGEN ultrasound signal is safe and effective as an adjunct to conservative treatment or surgical management, including metal fixation and implants.

In a study on non-union fracture healing, bone mineral density showed an estimated 34% increase in subjects treated with EXOGEN for 20 minutes a day. EXOGEN also demonstrated a significant benefit in fracture gap reduction compared to the control group.
Backed by a full suite of patient support tools, EXOGEN is the only bone healing device with documented 91% treatment compliance.\(^6\)

**EXOGEN Performance Program**

The EXOGEN Performance Program guarantees progression of non-union fracture healing. If program requirements are met and no healing progression is shown, Bioventus will refund all out-of-pocket costs.

**20-Minute Treatment**

With treatments lasting just 20 minutes, EXOGEN can fit easily into the patient’s daily routine.

**Customer Support**

EXOGEN Customer Support is available to answer questions and help maintain continuity of treatment.

**Smartphone App with Treatment Reminder**

EXOGEN CONNECTS is a free smartphone app that sends automated treatment reminders and provides helpful healing information.

1. **Download**
   The EXOGEN CONNECTS app, available on the App Store, is easy to download and activate.

2. **Receive**
   Patients receive daily treatment reminders on their smartphone.

3. **Treat**
   Automated reminders encourage patients to complete their daily 20-minute treatment.

4. **Heal**
   Using EXOGEN as prescribed can help put patients on the road to faster healing.
Treatment Tracking Calendar

EXOGEN’s built-in treatment tracking calendar tracks device usage, making treatment compliance tracking convenient for patients and verifiable for physicians.
The EXOGEN Ultrasound Bone Healing System is indicated for the non-invasive treatment of established non-unions excluding skull and vertebra. In addition, EXOGEN is 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.

There are no known contraindications for the EXOGEN device. Safety and effectiveness have not been established for individuals lacking skeletal maturity, pregnant or nursing women, patients with cardiac pacemakers, on fractures due to bone cancer, or on patients with poor blood circulation or clotting problems. Some patients may be sensitive to the ultrasound gel. Full prescribing information can be found in product labeling, at www.exogen.com, or by calling customer service at 1-800-836-4080.

A non-union is considered to be established when the fracture site shows no visibly progressive signs of healing.

**Summary of Indications for Use:**


15. Based on mathematical simulation through soft tissue. DOS 12000.04.


Count on EXOGEN.

- High treatment compliance\(^6\)
- Proven clinical effectiveness\(^{20-22}\)
- Successful fracture healing outcomes