The East of England
Priorities Advisory Committee
Hosted by PrescQIPP

GUIDANCE STATEMENT

EXOGEN® ultrasound bone healing system for the management of bone fractures

PAC recommendations

PAC recommends the use of EXOGEN® for the treatment of non-union fractures in long bones, with a fracture gap of <10 mm which have failed to heal after nine months but less than 12 months in patients aged >18 years, in accordance with defined process criteria (see page 4).

PAC does not recommend the use of EXOGEN®:

- For the treatment of non-union fractures in long bones in cases of unstable surgical fixation, where not well aligned or where inter-fragment gap is >10mm.
- In patients with delayed healing fractures that have no radiological evidence of healing after three months.
- Any other indication.

Background

The EXOGEN® ultrasound bone healing system delivers low-intensity pulsed ultrasound (LIPUS) waves with the aim of stimulating bone healing. It is thought that healing is promoted by stimulating the production of growth factors and proteins that increase the removal of old bone, increase the production of new bone and increase the rate at which fibrous matrix at a fracture site is converted to mineralised bone.[1-3]

The EXOGEN® system is a single hand-held device with two treatment options: EXOGEN® 150 and EXOGEN® 250. These are equivalent to the former versions EXOGEN® Express and EXOGEN® 4000+ respectively.[1-3] It consists of a main operating unit with a permanently connected transducer and a separate fixture strap. The strap is placed around the fractured bone, coupling gel is applied to the transducer head (to aid conduction of ultrasound) and the transducer is secured directly over the fracture site by a fixture on the strap. The ultrasound signal emitted by the device is derived from a combination of defined electrical signal parameters and the proprietary transducer design, which generate an acoustic wave pattern specific to EXOGEN®. If the patient's limb is immobilised in a cast then a hole is cut in the cast to allow access of the transducer to the skin. The device is programmed to deliver ultrasound in 20 minute sessions, and these are self-administered by the patient each day. It is intended to be used in the patient's home.[1-3]

EXOGEN® is a potential alternative to surgery for adult patients >18 years with stable and well aligned long bone fractures, with approximately one third of tibial fractures suitable for treatment. EXOGEN® is not indicated for use in fractures of the skull or vertebrae or in children or adolescents because of their skeletal immaturity.[1,2]

Long bone fractures are usually treated immediately by closed or open reduction (re-alignment of bone ends which can involve surgery), with the affected link immobilised using a cast or by internal

or external fixation. Patients with delayed healing at three months do not usually have surgery at this time unless the fracture is complex. If surgery is required this usually takes place between three and nine months after the fracture and could involve internal or external fixation and bone grafting (with harvesting from the patients' iliac crest).[1,2]

Evidence

The National Institute for Health and Care Excellence (NICE) originally published Medical Technology Guidance (MTG12) for EXOGEN® in January 2013. This was updated in October 2019 to reflect a change in costs and includes the following recommendations.[1,2]

The case for adopting the EXOGEN® ultrasound bone healing system to treat long bone fractures with non-union (failure to heal after nine months) is supported by the clinical evidence, which shows high rates of fracture healing.[1,2]

The EXOGEN® ultrasound bone healing system to treat long bone fractures with non-union is associated with an estimated cost saving of £2,407 per patient compared with current management, through avoiding surgery.[1,2] This level of cost-saving has not been established locally.

There is some radiological evidence of improved healing when the EXOGEN® ultrasound bone healing system is used for long bone fractures with delayed healing (no radiological evidence of healing after approximately three months). There are substantial uncertainties about the rate at which bone healing progresses without adjunctive treatment between three and nine months after fracture, and about whether or not surgery would be necessary. These uncertainties result in a range of cost consequences, some cost-saving and others that are more costly than current management.[1,2]

The 2013 NICE MTG guidance included 17 clinical studies (1,710 patients) in its assessment, including three randomised controlled trials, 13 case series and one prospective comparison. Of these, 13 studies reported on non-union fractures, two reported on delayed healing and two reported on both types of fracture. There were no controlled or randomised studies in which EXOGEN® and surgery were compared directly in the treatment of either non-union or delayed fractures. However, independent estimates of healing rates for EXOGEN® and surgery were available from non-comparative case series for non-union fractures. The age of study participants ranged from 13 to 92 years and follow-up across the studies ranged from two months to six years. None of the studies were carried out in the UK. Healing rates for non-union long bone fracture ranged from 62% to 100% depending on the long bone involved and duration of non-healing.[1]

The 2019 update identified a further three systematic reviews (of limited benefit), and five observational studies reporting healing rates for long bone non-union fractures ranging from 32.8% to 88% (depending on the long bone involved and the duration of non-healing). Results from three audits on a total of 87 long bone non-union fractures showed a healing rate ranging from 39%-72%.[2]

No studies were identified that included avoiding surgery as a result of treatment with EXOGEN® as an outcome measure. In addition, no studies presented data on return to weight bearing and normal daily living after EXOGEN® treatment, compared with surgery.[1,2]

The NICE committee concluded that although the evidence on using EXOGEN® for long bone fractures with non-union was from observational studies and related to a limited number of outcomes, it suggested good clinical results after treatment with EXOGEN®, with the observed healing rates supporting the efficacy of EXOGEN® in promoting healing of these fractures, and that its use meant that many of these patients avoided surgery. However, the committee also noted that the clinical evidence comparing EXOGEN® with surgery was very limited and that the efficacy of EXOGEN® may differ depending on which long bone is being treated. Evidence for the use in delayed healing of long bone fractures was considered to be more limited.[1]

Non-union most commonly occurs in fractures of the tibia. Any effective treatment that avoids or reduces the need for surgery is of significant benefit to patients and has potential advantages to the

NHS in terms of resource use. Such advantages might include reducing the duration of NHS care, the number of outpatient visits or the number of X-rays that patients need.[1]

In 2018, NICE published a more general assessment of the use of low-intensity pulsed ultrasound (LIPUS) to promote healing of delayed-union and non-union fractures, as interventional procedural guidance [IPG623]. This assessment advised that, although the gathered evidence raised no major safety concerns, the evidence of efficacy was of inadequate quality and recommended that this procedure should only be used with special arrangements for clinical governance, consent and audit or research.[4]

NICE guideline [NG38] on assessment and management of non-complex fractures does not include either LIPUS or more specifically the EXOGEN® device.[5]

Unlike NICE TAs, adoption of NICE interventional procedures guidance and medical technologies guidance are not currently mandatory for Integrated Care Boards (ICBs) and their system partners.[6,7]

Safety

EXOGEN® has only been approved for use in the UK in persons that are 18 years or older and skeletally mature. There is no maximum age limit.[3,8]

The company website states that there are no contra-indications to the use of the device.[3] However, there are a number of warnings and precautions listed in the device user guide.[8]

None of the clinical studies included in the NICE assessments reported device-related adverse events, and no significant safety concerns were identified in relation to EXOGEN®. Adverse effects reported by the FDA and the Manufacturer and User Facility Device Experience (MAUDE) database, included three cases of skin irritation (from the coupling gel), and one report of chest pain (associated with a cardiac pacemaker), during a one year period. The manufacturer stated that approximately 55,000 EXOGEN® devices were used by patients in the USA over this time period.[1]

In contrast, reports on surgical treatment of non-union and delayed healing fractures documented adverse events including, postoperative wound infection, osteomyelitis and pain.[1]

The safety and effectiveness of EXOGEN® if used for more than one daily 20 minute treatment period has not been studied.[8]

Financial and commissioning considerations

The prevalence of complications due to fractures in the UK population is difficult to determine.

Tibial fractures have the highest incidence of non-union (0–15%), followed by femur fractures (1–11%) and humerus fractures (0–13%).[9]

The EXOGEN® device costs £2,562.50. The NICE MTG updated in 2019 estimates a cost saving of £2,407 per patient compared with current management, through avoiding surgery. This is an increase from the estimated cost saving of £1,164 in the original 2013 assessment, with the increase in savings being primarily due to an increase in length of stay following surgery from 4.9 days to 7 days, in the 2019 cost analysis.[1,2]

Bioventus offer the EXOGEN® Performance program, which guarantees to refund the cost of EXOGEN® to the buyer if the requirements of the program are met, and no healing progression is shown after 120 days of treatment. To be eligible for the program, patients must treat their fracture with EXOGEN® for 20 minutes a day, for a minimum of 120 days, with a minimum of 90% adherence to the treatment regimen. The non-union fracture must be stable, non-displaced, with a fracture gap of less than 10 millimetres.

Vertebra and skull fractures are excluded. The EXOGEN® device contains an internal patient usage monitor that records the date, time and duration of each treatment. This monitor is utilised to confirm that the 90% treatment compliance threshold is met and the device has not been modified

or altered. Any devices which have been modified and/or altered will not be eligible to participate in the EXOGEN® Performance Guarantee. A number of other exclusion criteria apply and full details are available on the device promotional website.[10,11]

Bone growth stimulators are currently listed as an excluded device in tab 14a of Annex A – the national tariff workbook, which also states they are currently commissioned by NHS England.[12] Specialist adult orthopaedic surgery and orthopaedic revision are considered to be ready and suitable for greater ICS leadership under the roadmap for transition of specialised services recommendations.[13]

PAC recommendations for funding

EXOGEN® may be considered and funded where ALL the following criteria are met:

- Patient age >18 years
- Long bone non-union of fracture >9 months and <12 months
- The bones are well aligned (i.e. stable and non-displaced)
- The fracture is stable and the inter-fragment gap is <10mm.[1,8,14,15]

Process criteria

- The patient has been screened and referred by a Consultant Radiologist/Consultant Orthopaedic Surgeon following review on at least two occasions at least four weeks apart to allow examination of serial X-rays.
- The patient has received a further assessment in a non-union clinic by surgeon with expertise of dealing with non-union of long bones; appropriateness of EXOGEN® has been determined through agreement of two specialist non-union Consultants.
- The patient has received appropriate counselling and training and is able to use the device and comply with the usage protocol and criteria which includes 90% minimum adherence to the treatment regimen.
- The patient has been counselled and has the ability to comply with usage protocol and criteria in line with the EXOGEN® Performance Guarantee Program which includes a 90% minimum adherence to the treatment.
- The patient is registered on the EXOGEN® Performance Guarantee Program.[10,11,15]

Exclusion criteria

Funding is not recommended in the following circumstances:

- Long bone fracture with delayed healing beyond 12 months
- Pathological fractures due to bone pathology or malignancy
- Non-unions of the vertebra and the skull
- Pregnant or nursing women
- Unstable surgical fixation, not well aligned or where inter-fragment gap is >10mm
- Infection
- Patients with pacemakers
- Individuals with thrombophlebitis (blood clot in a vein), vascular insufficiency, abnormal skin sensitivity
- Individuals lacking skeletal maturity.[3,8]

Individuals receiving steroid, anticoagulant, non-steroidal anti-inflammatory drugs, calcium channel blockers or bisphosphonate therapy were all excluded from the clinical studies because of possible

effects of these therapies on bone metabolism. Consequently safety and effectiveness has not been established in these patients.[8]

Patients with lifestyle factors which are known to delay fracture healing rates, e.g. smoking and excess alcohol intake, should be appropriately counselled and required to eliminate these risks before determining non-union status and ultimately eligibility for EXOGEN®. Where appropriate, referrals to specific support services should be arranged, e.g. smoking cessation service.[15]

Funding for other indications is not recommended.

Prior approval and patient uptake and outcome monitoring may be required and should be agreed locally. See appendix 1 for draft prior approval and monitoring forms for local adaptation. Regular audit of outcomes should be undertaken as agreed locally, including participation in regional network where available. For treatment failures, providers will ensure that a re-imbursement is obtained in accordance with the manufacturer's performance guarantee program. Local commissioners will not fund these patients.

These criteria will be reviewed/updated on publication of new evidence in the form of relevant trial data, updated national guidance or national or local audit outcomes.

Comments sought from: East of England clinicians via PAC members

Author: Monika Wojtowicz & Vicky Gibson

Document history

PAC approval date	16th January 2023
Version	Version 2
Document history	v1 April 2015
Consultation process	East of England clinicians via PAC members
QA process	Katie Smith, Director of Clinical Quality, PrescQIPP. 23rd February 2023

Acknowledgement

This policy is based in part on the South Worcestershire Clinical Commissioning Group (CCG), NHS Redditch & Bromsgrove Clinical Commissioning Group (CCG) & NHS Wyre Forest Clinical Commissioning Group (CCG) commissioning policy for EXOGEN® Ultrasound Bone Healing System for Long Bone Fractures with Non-Union or Delayed Healing.

References

1. NICE. EXOGEN® ultrasound bone healing system for long bone fractures with non-union or delayed healing. Medical technologies guidance [MTG12]. Published January 2013. Last updated October 2019. https://www.nice.org.uk/guidance/mtg12
2. NICE. EXOGEN® ultrasound bone healing system for long bone fractures with non-union or delayed healing. Review Decision. September 2019. https://www.nice.org.uk/guidance/mtg12/evidence/review-decision-september-2019-pdf-6901879069
3. EXOGEN® ultrasound bone healing system. Product Website. https://www.exogen.com/en-gb/
4. NICE. Low-intensity pulsed ultrasound to promote healing of delayed-union and non-union fractures. Interventional procedures guidance [IPG623]. Published July 2018. https://www.nice.org.uk/guidance/ipg623
5. NICE. Fractures (non-complex): assessment and management. NICE guideline [NG38]. Published

February 2016. https://www.nice.org.uk/guidance/ng38

6. NICE. Interventional procedure guidance. https://www.nice.org.uk/about/what-we-do/our-programmes/nice-guidance/nice-interventional-procedures-guidance
7. NICE. Medical technologies guidance. https://www.nice.org.uk/about/what-we-do/our-programmes/nice-guidance/nice-medical-technologies-guidance
8. EXOGEN® ultrasound bone healing system. User guide. https://www.exogen.com/wp-content/uploads/2021/10/81087030-US-2020-User-Guide.pdf
9. Wildemann B, Ignatius A, Leung F, et al. Non-union bone fractures. Nature Reviews Disease Primers 2021; 57(7) https://www.nature.com/articles/s41572-021-00289-8
10. EXOGEN® ultrasound bone healing system. Performance guarantee. Patient Brochure. https://www.exogen.com/wp-content/uploads/2021/11/SMK-000554_EXOGEN_Performance-Guarantee_Patient-brochure-insert_UK_LR-1.pdf
11. EXOGEN® ultrasound bone healing system. Performance program. Physician Brochure. https://www.exogen.com/wp-content/uploads/2021/11/SMK-000556_physician-brochure_UK_iPad.pdf
12. NHS England. 2022/23 national tariff workbook (Annex A). Last updated September 2022. https://www.england.nhs.uk/wp-content/uploads/2020/11/22-23NT_Annex-DtA-National-tariff-workbook.xlsx
13. NHS England. Roadmap for integrating specialised services within Integrated Care Systems. May 2022. https://www.england.nhs.uk/wp-content/uploads/2022/05/PAR1440-specialised-commissioning-roadmap-addendum-may-2022.pdf
14. EXOGEN® ultrasound bone healing system. Treatment pathway. https://www.exogen.com/wp-content/uploads/2022/03/SMK-000801B-EXOGEN-Treatment-Pathway-Poster-UK-DIGITAL.pdf
15. South Worcestershire Clinical Commissioning Group (CCG), NHS Redditch & Bromsgrove Clinical Commissioning Group (CCG), NHS Wyre Forest Clinical Commissioning Group (CCG), commissioning policy for EXOGEN® Ultrasound Bone Healing System for Long Bone Fractures with Non-Union or Delayed Healing, First published September 2014. Updated August 2021. https://herefordshireandworcestershireccg.nhs.uk/policies/clinical-medicines-commissioning/clinical-policies-guidance/musculoskeletal/118-exogen-therapy-commissioning-policy-v1-0-april-2020/file

Assessment against ethical and commissioning principles

Treatment assessed	EXOGEN® ultrasound bone healing system for the management of long bone fractures in adult patients.
East of England Priorities Advisory Committee recommendation	PAC recommends the use of EXOGEN® for the treatment of non-union fractures in long bones which have failed to heal after 9 months but less than 12 months in patients aged >18 years, in accordance with defined process criteria (see page 4). • PAC does not recommend the use of EXOGEN® for the treatment of non-union fractures in long bones in cases of unstable surgical fixation, where not well aligned or where inter-fragment gap is > 10mm. • PAC does not recommend the use of EXOGEN® in patients with delayed healing fractures that have no radiological evidence of healing after three months. • PAC does not recommend use of EXOGEN® ultrasound bone healing system for any other indication.
Clinical effectiveness	The clinical effectiveness for is based on three systematic reviews, three randomised controlled trials, five observational studies, 13 case series and one prospective comparison.
Cost effectiveness	EXOGEN® ultrasound bone healing system to treat long bone fractures with non-union is associated with an estimated cost saving of £2,407 per patient compared with current management, through avoiding surgery (2019 data). Non-union most commonly occurs in fractures of the tibia. Approximately one third of non-union tibial fractures might be suitable for treatment with EXOGEN®.
Equity	Some patients may not be able to use the device due to disability and require additional support to use this treatment. No other issues identified.
Needs of the community	Eligible patients could potentially avoid surgery.
Need for healthcare (incorporates patient choice and exceptional need)	Potential advantages include reduction in the duration of NHS care, the number of outpatient visits or the number of X-rays that patients need.
Policy drivers	None
Disinvestment	None