

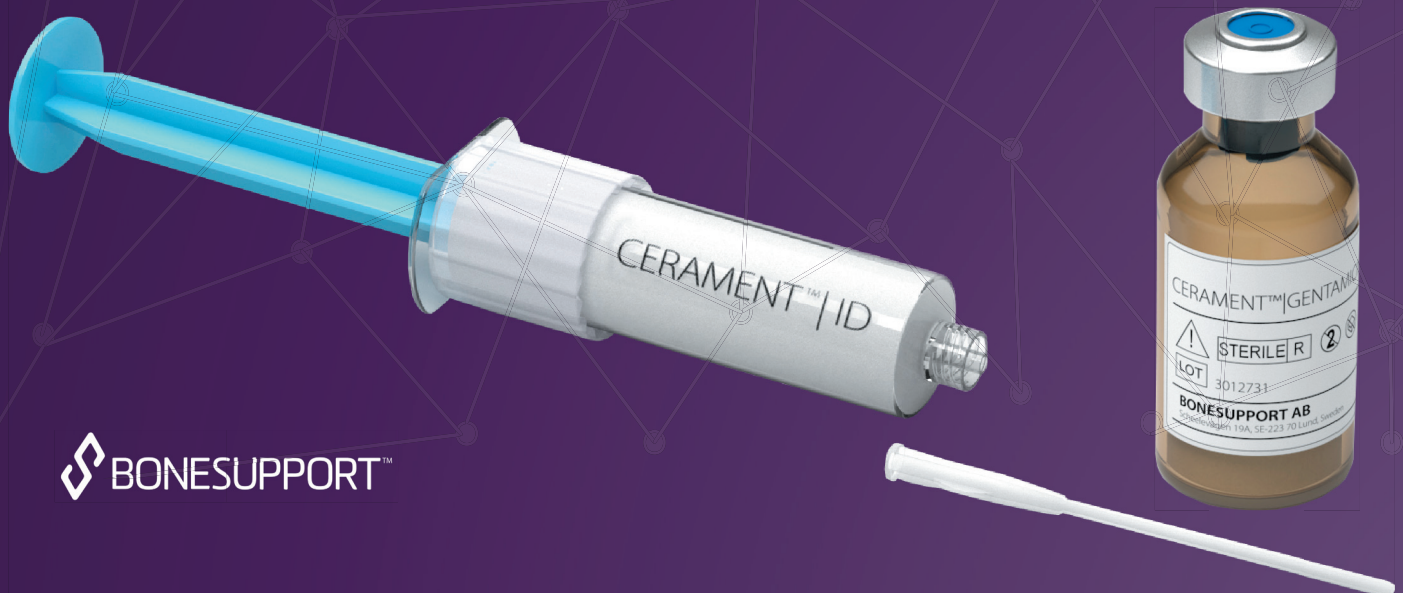
CERAMENT® G
with Gentamicin

VALUE ANALYSIS GUIDE

The First and Only Injectable Antibiotic-Eluting Bone Graft

Indicated for use in management of bone infection

- PROMOTE BONE HEALING
- LOCAL ANTIBIOTIC ELUTION
- LOWER COST OF CARE



 BONESUPPORT™

About BONESUPPORT

BONESUPPORT is a Swedish orthobiologics company that develops, manufactures, and markets CERAMENT® — an innovative portfolio of injectable and drug-eluting bone void fillers with a proven ability to remodel into bone⁴ and reliably elute local broad spectrum antibiotics.^{8-10, 13}

Backed by more than 240 peer reviewed studies and publications, our products are effective in the management of patients with bone voids and infections caused by trauma, disease or related surgery.

Advances in Bone Infection

The best protection against bone infection is healthy bone. The traditional way of managing osteomyelitis (bone infection) is to first clear the infection site of any dead and/or poorly perfused bone by surgical debridement, leaving an empty void. For optimal management of bone voids and gaps, we created CERAMENT® G.

- Proven bone remodeling⁴
- Local, broad spectrum antibiotic elution
- 96% success in eradication of infection
- Supports a single-stage treatment pathway
- Lowers cost of care while improving patient quality of life²⁰
- Consistent antibiotic elution that is safe and reliable

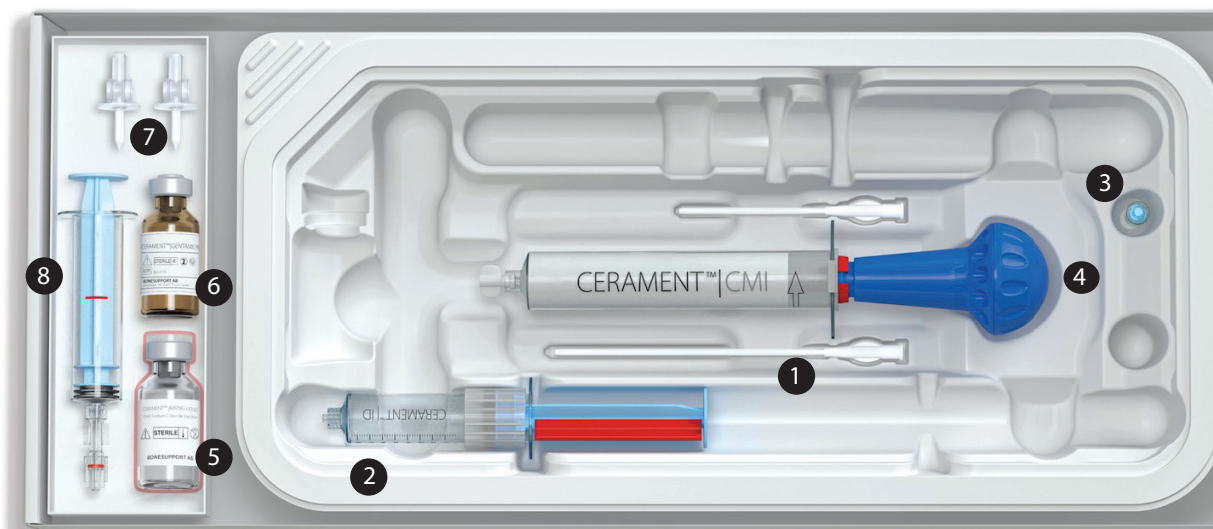
Our Mission - Restoring health to improve the quality of life for patients with bone disorders.

The FDA designated CERAMENT® G a Breakthrough Device

Reserved for therapies that treat serious and life-threatening conditions and which have demonstrated substantial improvement over other therapies and/or is the first of its kind.

One complete kit

1. 2 x 11G tip extenders with tapered ends in 50mm & 100mm lengths
2. Injection Device (ID) syringe
3. Valve
4. Combined Mixing and Injection (CMI) syringe pre-filled with hydroxyapatite (HA)/calcium sulfate (CaS) powder
5. Mixing Liquid, sodium chloride 9 mg/mL liquid
6. Gentamicin sulfate, provides 17.5 mg gentamicin/mL paste
7. Dispensing pins
8. Syringe for preparing the gentamicin solution



CERAMENT G® with Gentamicin

CERAMENT® G is the first combination bone graft substitute and antibiotic indicated as part of the management of osteomyelitis. Unlike other treatment options, CERAMENT® G is injectable and can be delivered in a single-stage procedure because of its unique ability to simultaneously remodel into bone and elute an antibiotic to protect bone healing. With a 96% success rate in reducing chronic osteomyelitis, healthcare resources and costs are reduced while clinical outcomes are improved.⁵

Challenges of Bone Infection

Osteomyelitis is an infection of the bone that can arise from fractures, placement of orthopedic implants, and diabetic foot ulcers.

Osteomyelitis is a devastating disease that can be irreversibly debilitating and can lead to limb amputations.¹¹ Patient comorbidities play an important role in the propagation of the infection, and the disease requires substantial dedication from the patient and the entire multi-disciplinary medical care team to eradicate.^{12,5} The overall healthcare burden to patients, providers and payers is significant.

CONSIDER THE IMPACT OF BONE INFECTION

CHRONIC OSTEOMYELITIS

Underlying osteomyelitis due to trauma may present itself post-surgery. While the infected bone is removed through surgery, the infection often recurs.

~2
PER 10,000

People diagnosed annually with osteomyelitis in the US¹¹

20-30%

Long term recurrence rate (despite antibiotic/surgical advancements)^{15,16}

FRACTURE-RELATED INFECTIONS

Infection can quickly establish itself after a fracture. For Gustilo-Anderson type III open tibial fractures, the estimated rate of infection is 12.3% for IIIB and 16.1% for IIIC.³⁰

UP TO 30%

Infection rate after open fractures³¹

3-5%

Amputation rate to treat FRI¹⁷

DIABETIC FOOT OSTEOMYELITIS

Diabetic foot ulcers are the consequence of neuropathy and vascular disease. They are worsened by infection which, if it reaches the bone, may require surgical resection or amputation.

20%

Diabetic patients with infected foot ulcers have underlying osteomyelitis¹⁸

15%

Patients will require amputation¹⁹

1 OF 5

Patients will be readmitted within 30 days of lower extremity amputation(s)²¹

Osteomyelitis Treatment and Limitations

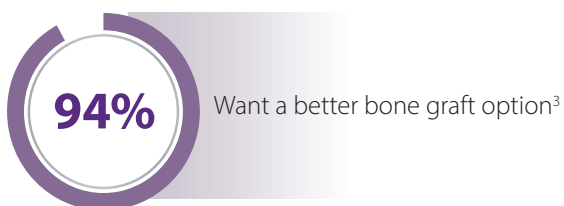
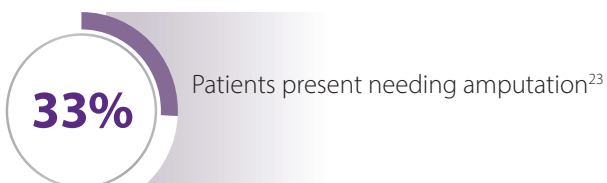
Surgical management of bone infection consists of debridement, tissue sampling and excision of dead/necrotic (infected) bone. The resulting dead space requires management to regenerate the lost bone and mitigate reinfection.¹²

Common practice is a two-stage or multi-stage surgical approach in which the first stage incorporates antibiotic-loaded polymethyl methacrylate (PMMA) beads. The beads are then removed in a subsequent surgery and replaced with a resorbable bone graft to fill the dead space.²³

Clinical advancements have cleared the path for a single-stage surgery, but typically entails off-label manual mixing of calcium sulfate with antibiotics. This results in inconsistent and unpredictable local antibiotic delivery and little bone remodeling due to fast absorbing calcium sulfates.

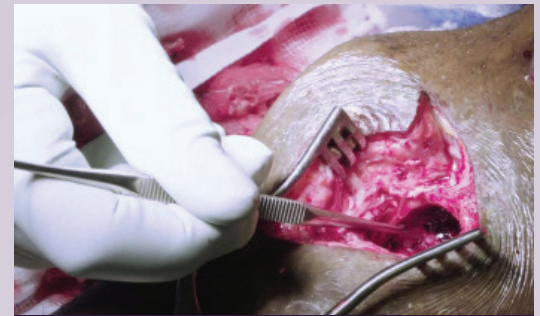
The lack of a standard of care along with improvised treatment options contribute to the high rates of reinfection, amputations, increased mortality and associated healthcare costs.

Survey Results: Hospital Admins & Surgeons



FILLING A BONE VOID WITH CERAMENT® G AFTER SURGICAL DEBRIDEMENT IN A SINGLE-STAGE PROCEDURE

CERAMENT® G's dual mode of action provides bone remodeling with predictable elution of gentamicin in a single-stage procedure.



1. Dead bone is removed leaving a void



2. CERAMENT injected into bone void



3. Bone void is completely filled



4. CERAMENT has set and wound is closed

A New Pathway for Bone Infection

CERAMENT® G provides a pathway for a one-stage approach to the management of osteomyelitis with its unique dual mode of action that delivers proven bone remodeling with reliable elution of a local broad spectrum antibiotic.⁵

CERAMENT® G is an implantable device/drug combination bone void filler and was granted Breakthrough Device Designation by the Food and Drug Administration (FDA). This important designation is reserved for devices that provide for more effective treatment or diagnosis of life-threatening or irreversibly debilitating human disease or conditions and are first of its kind.

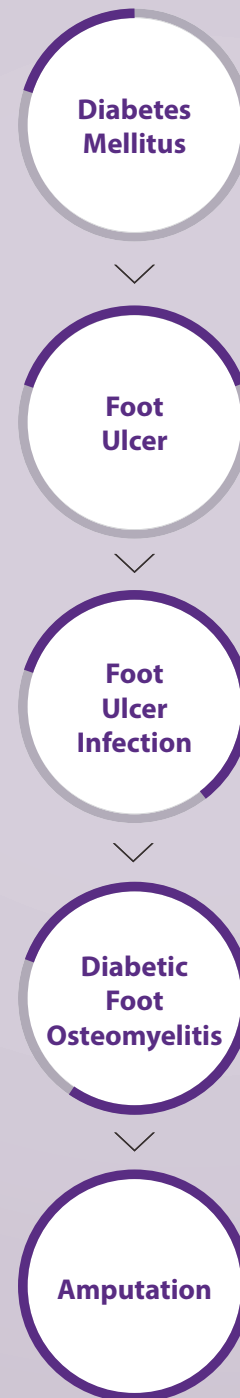
Additional Surgical Option for Diabetic Foot Infection

CERAMENT G can enable a surgical pathway for challenging diabetic patients. It is an additional option available to preserve limb length, saving mobility and reducing costs by averting amputations.

The high costs of treating diabetic foot patients is well documented, beginning with an average of \$17,245 for management of a diabetic foot ulcer. This can escalate quickly if amputation is needed, ranging from \$43,000 to over \$63,000 per event.²⁸

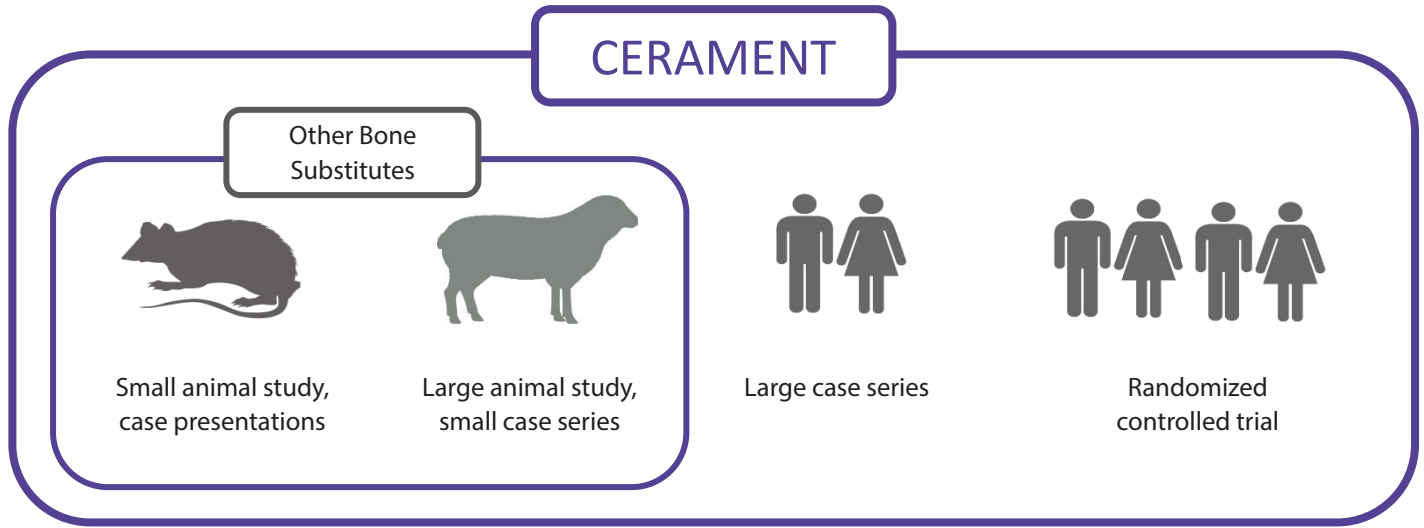
**Limb salvage attempt:
debridement and filling with CERAMENT® G**

CERAMENT® G offers a surgical option for diabetic patients progressing towards amputation.



Only CERAMENT® is backed by a robust body of data

CERAMENT® has the largest amount of animal and clinical data to prove bone remodeling and is the only bone graft substitute with patient reported outcome measures (PROMs) data. No other bone graft offers this level of clinical data.



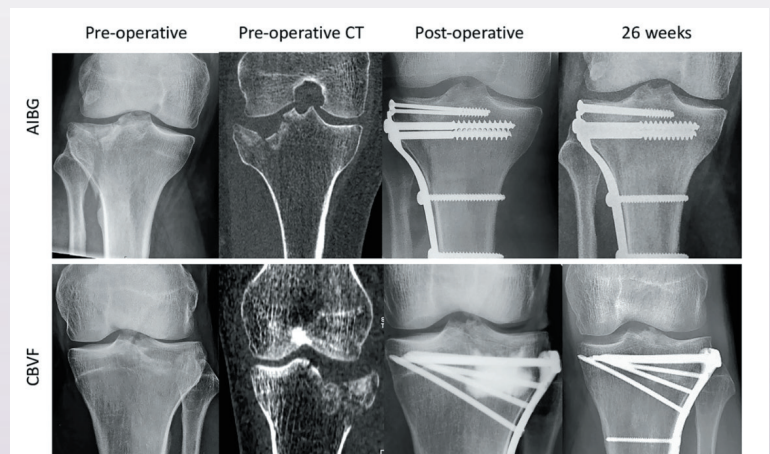
A LEVEL 1 STUDY COMPARING CERAMENT® BONE VOID FILLER TO “GOLD STANDARD” AUTOGRAFT

ABOUT THE STUDY

Published in the *Journal of Bone and Joint Surgery American* (2020), CERTiFY is a Level I, multi-center, prospective, randomized controlled trial of patient-reported outcome measures (PROMs) in 135 patients²⁴

RESULTS

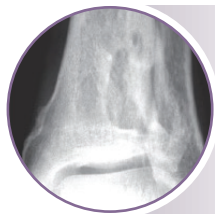
- CERAMENT was found to be as good as autograft
- Proven bone remodeling with CERAMENT
- Less post-op pain with CERAMENT
- Less blood loss with CERAMENT
- Results confirmed by PROMs and radiographs



CERAMENT® G Dual Mode of Action

PROMOTE BONE HEALING

- Proven bone remodeling



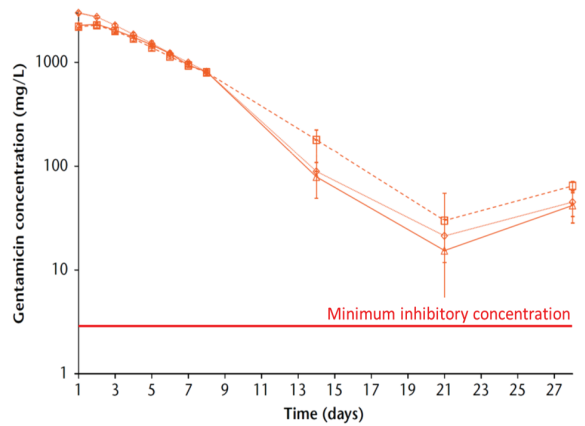
Debridement and injection of CERAMENT G: CERAMENT is highly flowable to completely fill voids and cracks.



The bone is healed at 6-12 months: The CaS in CERAMENT is fully resorbed, HA is embedded in bone and natural bone building continues increasing mechanical strength

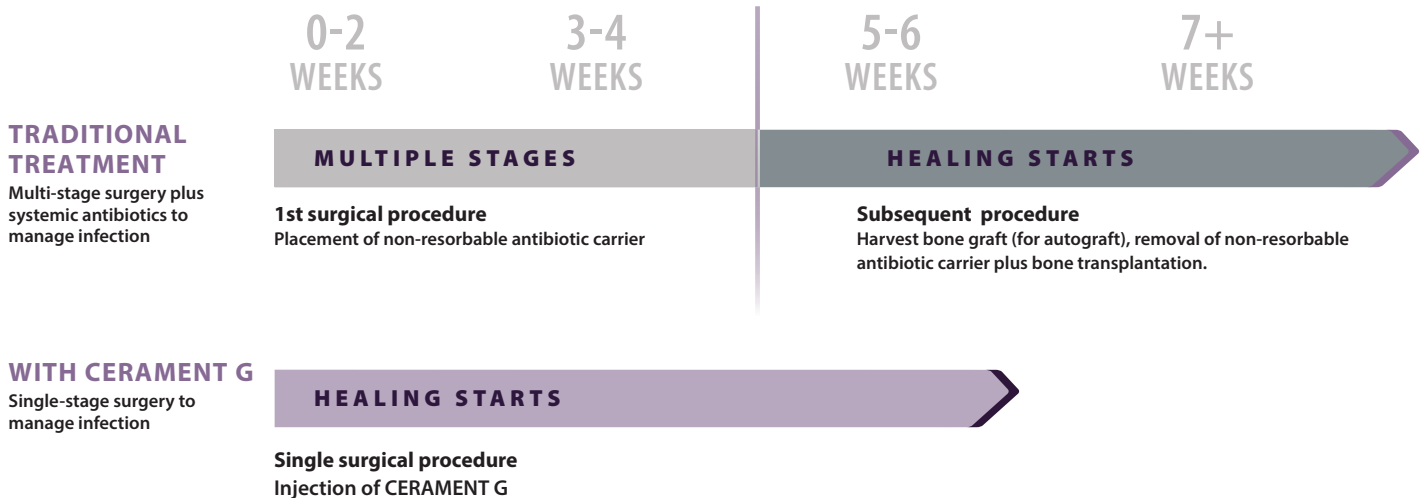
PROTECT BONE HEALING

- High burst of a local broad spectrum antibiotic.
- Sustained release above MIC* for 28 days.
- Serum levels well below systemic toxicity levels.⁸
- Consistent elution independent of surface area as demonstrated on the graph below.⁸



*The minimum inhibitory concentration (MIC) is the lowest concentration of a chemical, usually a drug, which prevents visible growth of bacterium.¹⁴

Managing bone infections is simplified with CERAMENT G



96% of patients were infection-free after surgical management and CERAMENT G in a one-stage approach.

A reduction in hospital-related costs with CERAMENT® G has been shown in the largest analysis of hospital episode statistics for NHS England carried out for a bone graft substitute to date.²⁰

The study was carried out at Oxford University Hospital, a world leader in osteomyelitis treatment and pioneer of the multi-disciplinary team (MDT) service (orthopaedics, plastics and microbiology).

In the analysis, 25,006 patients diagnosed with osteomyelitis in England between 2013 and 2017 were included and split between two groups: patient treated in a MDT service with CERAMENT® G as part of their treatment and patients treated in the rest of England.^{20,27}

Oxford Protocol Results²⁰

- 79% lower mortality rate
- 58% reduction in readmissions
- 39% reduction in length of stay
- 7% reduction in all hospital visits
- 48% reduction in Emergency Room visits over a 24 month post surgery period

CERAMENT® G in a Distal Tibial Osteomyelitis Case

Figure 2a

Pre-op X-ray of the tibia with haematogenous osteomyelitis present for more than ten years.



Figure 2b

MRI image demonstrates a cortical defect communicating with the skin sinus and central active infection, identified as Staph aureus.

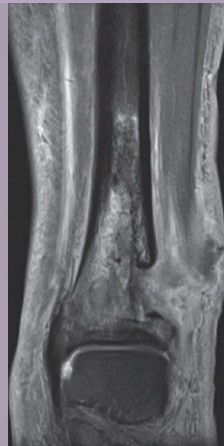


Figure 2c

3 days post-op, good contact between CERAMENT and bone surface can be seen.



Figure 2d

6 weeks post-op the margin is more diffused and a 'reactive zone' around CERAMENT G is visible in the cancellous bone and on the surface.

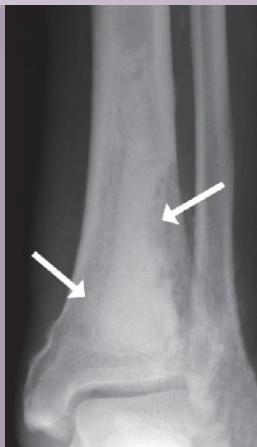


Figure 2e

At 6 months, residual CERAMENT is seen distally (black arrow) along with the reappearance of trabecular markings in the central zone (white arrow).

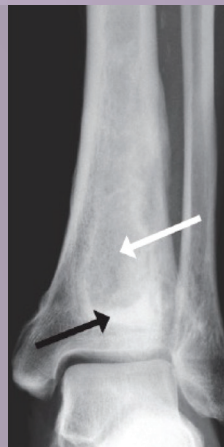
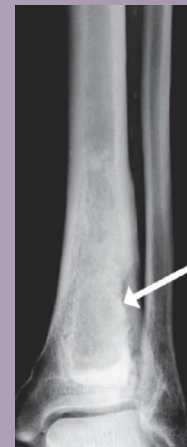


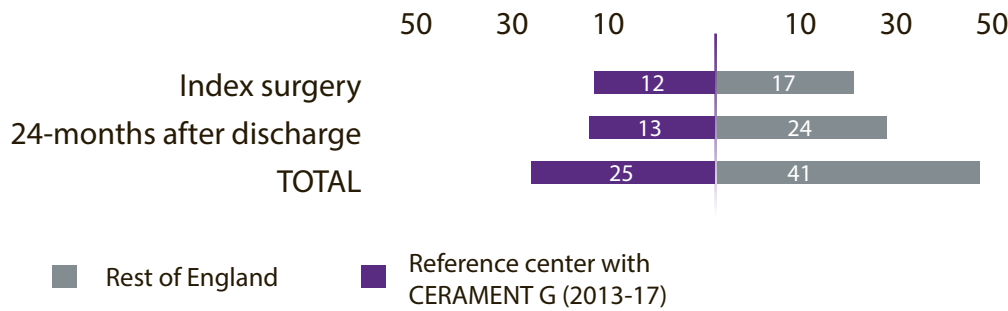
Figure 2f

At 18 months CERAMENT has undergone further remodeling, with increased density in the peripheral zone and the lateral cortex more defined.



CERAMENT® G can help reduce hospital admissions, length of stay and costs

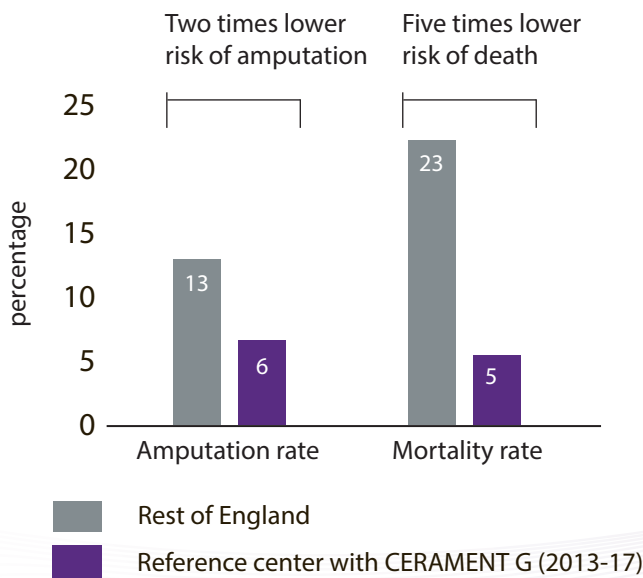
16 fewer bed days during index surgery and 24-months after discharge generates large cost savings per patient²⁰



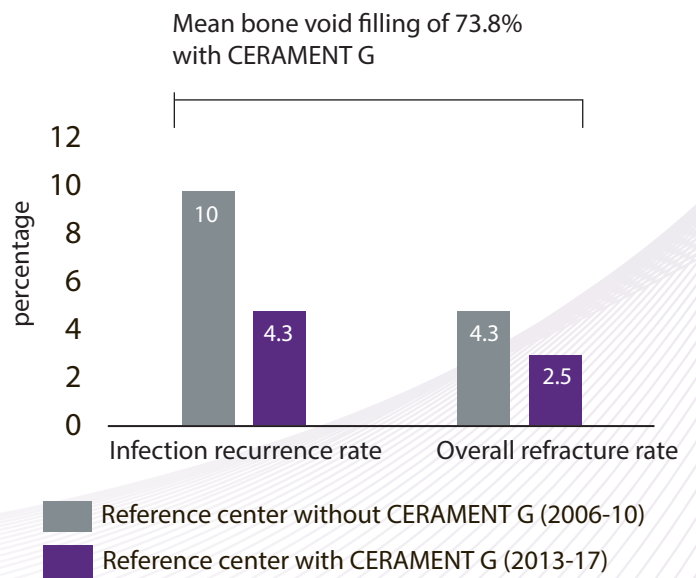
\$10,266 Direct cost savings per patient from reduced length of stay*

*Average cost per bed day of £500; the average annual exchange rate between pound sterling and US dollars for 2020 was used (£1 = \$1.2832); data sourced from the Office for National Statistics (ons.gov.uk)

Improved patient outcomes at the reference center relative to the rest of England²⁰



Use of CERAMENT G contributes to improved clinical outcomes at the reference center^{4,7}



CERAMENT® G Difference

Improve Osteomyelitis Outcomes & Reduce Costs

Value is about achieving the best outcomes per dollar spent. When bone healing fails, and infection occurs or reoccurs after surgery, more resource-intensive procedures are required. The quality of life for patients also worsens as a result.

Calculating the Value of CERAMENT® G

CERAMENT® G is uniquely positioned to decrease healthcare costs while improving patient's lives. To support CERAMENT® G's value and ease the decision between cost and care, BONESUPPORT is developing tools and pursuing product focused reimbursement pathways.

1. A cost-effectiveness analysis to demonstrate how the use of CERAMENT® G in a single-stage approach can reduce healthcare-related expenses (vs. multi-stage approaches) while improving patient quality of life.
2. An interactive companion to the VAC Guide showcasing different ways that adopting CERAMENT® G can help hospitals make managing bone infections more effective.
3. CMS has proposed to approve new technology add-on payments (NTAP) for CERAMENT G. This will be a cost off-setting resource to help adoption and support health systems to gain access to new technology and provide the most advance care for their patients.

Reimbursement

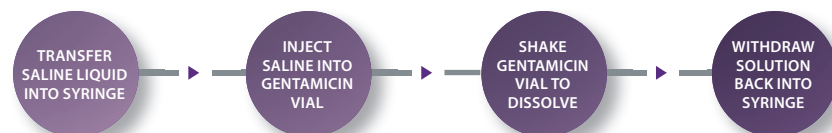
Currently all bone void fillers get allocated under the primary DRG in a bundled payment. BONESUPPORT, through it's FDA Breakthrough Designation, was awarded a unique ICD-10 Procedure Code and NTAP is expected to go into effect October 1st 2022. NTAP will provide inpatient hospital stays with additional payment for the use of CERAMENT G when the hospital costs exceeds the payment threshold.

ICD-10-PCS	DESCRIPTION
XW0V0P7	Introduction of Antibiotic eluting Bone Void Filler into Bones, Open Approach, New Technology Group 7

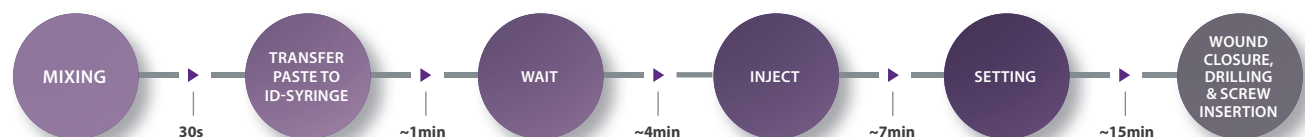
EASY MIXING

Pre-measured, Self-contained, Predictable

Step 1: Prepare the Gentamicin Solution



Step 2: CERAMENT G Mixing and Setting Time



CERAMENT: Summary of Unique Features and Clinical Benefits

FORMULA	DETAILS	CLINICAL VALUE
Proprietary Formula	<ul style="list-style-type: none"> 60% calcium sulfate (CaS) 40% hydroxyapatite (HA) Gentamicin (17.5 mg of gentamicin/mL of CERAMENT paste) 	<ul style="list-style-type: none"> CaS enhances injectability¹ and acts as a carrier for HA and gentamicin HA is highly osteoconductive and provides a longterm scaffold for bone remodeling¹ Inhibits gentamicin-sensitive microorganisms from colonizing the bone void filler to protect bone healing²
Bone remodeling	<ul style="list-style-type: none"> Proven bone remodeling³⁻⁵ 	<ul style="list-style-type: none"> Reduces the risk of re-fracture, non-union and (re)infection^{4,5} and the costs associated with additional treatment Improves patient outcomes⁴
Antibiotic elution	<ul style="list-style-type: none"> Reliable, consistent elution at a concentration and for a time period that is clinically relevant⁸ Far higher local concentrations at site than achievable with systemic antibiotics⁸ No reported risk of systemic toxicity^{8,29} 	<ul style="list-style-type: none"> Gentamicin elution stays above Minimum Inhibitory Concentration (MIC) for at least 28+ days⁸ to reduce the risk of (re)infection^{4,5,9} Reduce readmission rates, length of stay and cost of care²⁰ Protects bone healing⁶ and improves patient outcomes⁴ Reduces overall antibiotic use due to reduction in surgical stages and reinfection rates
Preparation	<ul style="list-style-type: none"> Self-contained, sterile mixing device 30-second mixing 	<ul style="list-style-type: none"> Easy to mix and use Consistent and reliable antibiotic concentration
Handling & Timing	<ul style="list-style-type: none"> Injectable between 4- 7 minutes Drillable after 15 minutes Not temperature sensitive 	<ul style="list-style-type: none"> Intra-operative flexibility to inject, mold and drill, reducing need for multiple products Injectability ensures complete filling of voids to reduce risk of (re)infection
Temperature	<ul style="list-style-type: none"> Not temperature sensitive Product is stored at room temperature (15-25°C / 59-86°F) Isothermic setting process 	<ul style="list-style-type: none"> Product can be used straight off the shelf Setting time is not affected by room or body temperature Isothermic - no heat or cold is given off during setting, so there is no damage to surrounding cells and tissues
Clinical data / FDA / Adoption	<ul style="list-style-type: none"> Over 240 publications and 70,000 patients treated worldwide with the CERAMENT portfolio Received FDA authorization in 2022 Received CE-mark in 2013 	<ul style="list-style-type: none"> 58% reduction in readmissions²⁰ 46% reduction in length of stay²⁰ 7% reduction in all hospital visits²⁰ 48% reduction in Emergency Room visits over a 24 month post surgery period²⁰ Level I study against the gold standard autograft²⁴, CERAMENT BVF demonstrated equivalence to autograft with: <ul style="list-style-type: none"> proven bone remodeling less post-op pain less blood loss trend towards shorter duration of surgery

1. Nilsson et al. 'The composite of hydroxyapatite and calcium sulphate: a review of evaluation and clinical applications'. *Expert Rev. Med. Devices* 2013; 10(5), 675-684.
2. IFU 0022
3. Hettwer et al. 'Establishment and effects of allograft and synthetic bone graft substitute treatment of a critical size metaphyseal bone defect model in the sheep femur'. *APMIS* 2019; 127: 53–63.
4. Ferguson et al. 'Radiographic and Histological Analysis of a Synthetic Bone Graft Substitute Eluting Gentamicin in the Treatment of Chronic Osteomyelitis'. *J. Bone Joint Infect.* 2019; 4(2): 76-84.
5. McNally et al. 'Single-stage treatment of chronic osteomyelitis with a new absorbable, gentamicin-loaded, calcium sulphate/ hydroxyapatite biocomposite'. *Bone Joint J.* 2016 Sep; 98-B(9):1289-96.
6. Stravinskas et al. 'A ceramic bone substitute containing gentamicin gives good outcome in trochanteric hip fractures treated with dynamic hip screw and in revision of total hip arthroplasty: a case series'. *BMC Musculoskeletal Disorders* 2018; 19:438.
7. Ferguson et al. 'The Use of a Biodegradable Antibiotic-Loaded Calcium Sulphate Carrier Containing Tobramycin for the Treatment of Chronic Osteomyelitis: A Series of 195 Cases'. *Bone and Joint Journal*, 96 B.6 (2014), 829–36.
8. Stravinskas et al. 'Pharmacokinetics of gentamicin eluted from a regenerating bone graft substitute - In vitro and clinical release studies'. *Bone Joint Res.* 2016; 5:427–435.
9. Stravinskas et al. 'Antibiotic Containing Bone Substitute in Major Hip Surgery: A Long Term Gentamicin Elution Study'. *J Bone Joint Infect.* 2018; 3(2):68-72.
10. Colding-Rasmussen et al. 'Antibiotic Elution Characteristics and Pharmacokinetics of Gentamicin and Vancomycin from a Mineral Antibiotic Carrier: An in vivo Evaluation of 32 Clinical Cases'. *J. Bone Joint Infect.* 2018; 3(4): 234-240.
11. <https://my.clevelandclinic.org/health/diseases/9495-osteomyelitis> [accessed 9th February 2021].
12. Metsemakers et al. 'Infection after fracture fixation: Current surgical and microbiological concepts'. *Injury.* 2018 Mar;49(3):511-522.
13. Butini et al. 'In vitro anti-biofilm activity of a biphasic gentamicin-loaded calcium sulfate/hydroxyapatite bone graft substitute'. *Colloids and Surfaces B: Biointerfaces* 2018; 161:252–260.
14. https://en.wikipedia.org/wiki/Minimum_inhibitory_concentration [accessed 24th September 2019].
15. Pande K. Optimal management of chronic osteomyelitis: current perspectives. *Orthop Res Rev.* 2015;7:71-81.
16. Conterno LO, Turchi MD. Antibiotics for treating chronic osteomyelitis in adults. *Cochrane Database of Systematic Reviews* 2013, Issue 9. Art. No.: CD004439.
17. Bezstarosti et al. Insights into treatment and outcome of fracture-related infection: a systematic literature review. *Arch Orthop Trauma Surg* 139, 61–72 (2019).
18. Lipsky. 'Treating Diabetic Foot Osteomyelitis Primarily With Surgery or Antibiotics: Have We Answered the Question?' *Diabetes Care.* 2014; 37:593–595.
19. Murphy-Lavoie et al. 'Diabetic Foot Infections.' Treasure Island (FL): StatPearls Publishing; 2020 Jan. Bookshelf ID: NBK441914, PMID: 28722943.
20. Ferguson et al. "A retrospective cohort study comparing clinical outcomes and healthcare resource utilisation in patients undergoing surgery for osteomyelitis in England: a case for reorganising orthopaedic infection services." *Journal of bone and joint infection* vol. 6,5 151-163. 28 Apr. 2021.
21. Curran et al. 'Risk Factors and Indications for Readmission Following Lower Extremity Amputation in the ACS-NSQIP'. *Journal of Vascular Surgery.* 2014; 60(5): 1315–1324.
22. National Institute for Health and Care Excellence (NICE). 'Diabetic foot problems: prevention and management'. NICE guideline NG19 Published: 26 August 2015.
23. Inspired Health Market Research Survey Data.
24. Hofmann et al. 'Autologous Iliac Bone Graft Compared with Biphasic Hydroxyapatite and Calcium Sulfate Cement for the Treatment of Bone Defects in Tibial Plateau Fractures'. *The Journal of Bone and Joint Surgery: February 5, 2020 - Volume 102 - Issue 3 - p 179-193.*
25. Petrakis et al. Losing a foot versus losing a dollar; a systematic review of cost studies in diabetic foot complications. *Expert Rev Pharmacoeconomics Outcomes Res [Internet].* 2017;17(2):165–80.
26. Ashry et al. 'Cost of diabetes-related amputations in minorities'. *The Journal of Foot and Ankle Surgery.* 1998; 37(3): 186-190.
27. Hospital Episode Statistics (HES) analysis, data on file.
28. Chandra et al. 'Partnerships between podiatrists and vascular surgeons in building effective wound care centers'. *Journal of Vascular Surgery.* September 1, 2017 - Volume 66 - Issue 3 - p 902-905.
29. Muir R et al. 'Does local implantation of gentamicin impair renal function in patients undergoing surgery for chronic bone infection?' *Int J Res Orthop.* 2021 May;7(3):438-443
30. Papakostidis et al. 'Prevalence of Complications of Open Tibial Shaft Fractures Stratified as per the Gustilo-Anderson Classification'. *Injury*, 42.12 (2011), 1408–15
31. Metsemakers et al. 'Prevention of fracture-related infection: a multidisciplinary care package.' *International Orthopaedics (SICOT)* 41, 2457–2469 (2017).

**Get CERAMENT® G with Gentamicin
and get more from your bone graft.**

TO ORDER

us.sales@bonesupport.com



PRODUCTS

CERAMENT® G with Gentamicin 5ml A0450-11
A0535-06

CERAMENT® G with Gentamicin 10ml A0450-10
A0535-05



BONESUPPORT, INC.,
60 William St, Suite 330
Wellesley, MA 02481

T: 1.877.719.6718
E: us.sales@bonesupport.com
W: bonesupport.com

