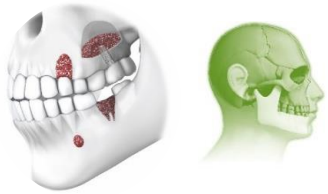
NORAKER®

THE BIOGLASS® COMPANY

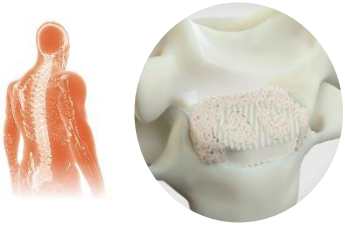
# *Summary of Safety and Clinical Performance (SSCP)*

*Surgeons version*

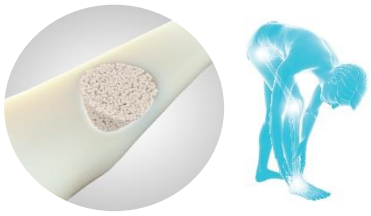
# Granules Range



BiologicGlass
Bioactive Bone Substitute



GlassBone®
Bioactive Bone Substitute



AktiBone®
Bioactive Bone Substitute

**This summary of safety and clinical performance is intended to provide public access to the main aspects of the safety and clinical performance of the device.**

**The summary of safety and clinical performance is not intended to replace the Instructions for Use as the main document to ensure the safe use of the device, nor is it intended to provide diagnostic or therapeutic suggestions to intended users or patients.**

**Version A.1 (EN) of this summary of safety and clinical performance has been validated by a notified body.**

**The following information is intended for users/healthcare professionals.**

# I. Device identification and general information

## 1. Brand name

**GlassBone Granules**

It is available in different volumes: 0.5cc, 1cc, 5cc, 10cc and 16cc and different granule sizes: 0.5-1 mm and 1-3 mm.

There are several other trade names (brands) under which the GlassBone Granules (GB) device is marketed: these devices are identical, only the name changes.

These brands are: AktiBONE Granules (XAK-G), BiologicGlass Granules (XBG-G) and MECTA-Glass (XMG). The volumes and granule sizes available are the same as GlassBone Granules.

| GlassBone Granules (GB-G) | AktiBONE Granules (XAK-G) | Bio Logic Glass Granules (XBG-G) | MectaGlass Granules (XMG-G) | Granule size | Volume |
|---|---|---|---|---|---|
| GB05.1/05-U | XAK-GM0.5 | XBG-GM0.5 | XMG-GM0.5 | 0.5-1 mm | 0.5 cc |
| GB05.1/1-U | XAK-GM1.0 | XBG-GM1.0 | XMG-GM1.0 | | 1 cc |
| GB05.1/5 | XAK-GM5 | XBG-GM5 | XMG-GM5 | | 5 cc |
| GB1.3/1-U | XAK-GL1.0 | XBG-GL1.0 | XMG-GL1.0 | 1-3 mm | 1 cc |
| GB1.3/5 | XAK-GL5 | XBG-GL5 | XMG-GL5 | | 5 cc |
| GB1.3/10 | XAK-GL10 | XBG-GL10 | XMG-GL10 | | 10 cc |
| GB1.3/16 | XAK-GL16 | XBG-GL16 | XMG-GL16 | | 16 cc |

When "GlassBone Granules" is cited in the document, this includes all the brands mentioned above.

## 2. Name and address of the manufacturer

Name: NORAKER

Address: 60 avenue Rockefeller – 69008 LYON - France

Phone: +33 4 78 93 30 92

SAS CAPITAL 300 000 €

N° RCS Lyon 483 190 518

SIRET: 483 190 518 000 41

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## 3. Unique manufacturer registration number

**FR-MF-000000325**

## 4. Unique Device Identifier (UDI-DI)

Basic UDI-DI for GlassBone Granules range of products is: 0376019113DT731M2 (control key: M2).

## 5. Nomenclature

GMDN: 16966 - Prosthesis, internal, bone, synthetic

EMDN: P900402 – IMPLANTABLE PROSTHETICS AND OSTEOSYNTHESIS DEVICES; ABSORBABLE FILLING AND RECONSTRUCTION DEVICES

Regulation 2017/2185 codes are: MDN 1102, MDT 2003, MDT 2006, MDT 2008, MDT 2011, MDS 1005 irradiation and MDS 1008.

### 6. Device class

This product is a medical device in accordance with Article 2 of Regulation 2017/745, class III according to the applicable classification rule 8 of Annex VIII to Regulation 2017/745.

### 7. Year of affixing of the first CE marking

The first affixing of the CE marking and placing on the market dates from 2008.

### 8. Agent, name and unique registration number

Not applicable

### 9. Notified Body, name and unique identifier number

Name: GMED

Unique Identifier Number: 0459

## II. Destination of the device

### 1. Intended use of the device

Glassbone Granules is a synthetic and biocompatible bone substitute device (bioactive glass 45S5), intended for the filling, reconstruction and/or fusion of bone defects or gaps in the skeletal system, in orthopaedic, neurosurgery, cranio maxillo facial and otorhinolaryngology surgery.

### 2. Indications and target population

Loss or lack of bone substance for bone defects of traumatic, pathological or surgical origin when autologous solutions are not applicable or sufficient in orthopedics, neurosurgery, cranio maxillo facial and otorhinolaryngology surgery in adult and pediatric population (more than 10 kg):

- Fusion or reconstruction of deformities and degenerative diseases in spine
- Fusion or reconstruction of deformities and degenerative bone pathologies in orthopedic
- Filling and reconstruction of bone defects due to resection of tumors, cyst or infection and in case of prosthetic revision
- Filling after surgical bone defect (donor sites after removal of autograft, …)
- Filling after removal of cholesteatoma
- Filling and reconstruction due to maxilla and periodontium pathologies

*Note: GlassBone Granules can be used for filling any bone cavity after **surgical procedure** without direct indication and without having a direct therapeutic or diagnostic function themselves.*

| Destination | Granular size | | Population | Lifetime |
|---|---|---|---|---|
| | 0.5 – 1 mm | 1 -3 mm | | |
| Spine | | x | Adult & Child | 12 months |
| Ortho | | x | Adult | 12 months |
| CMF | x | | Adult & Child | 12 months (pediatric population<br>9 months (adult population) |
| ENT | x | | Adult | 10 months |

***Table 1 : Glassbone Granules destinations***

### 3. Contraindications and limits

Glassbone Granules must not be used:

- In case of chronic or acute infection not treated with appropriate therapy.
- In patients who have suffered severe trauma with external wounds open near the defect, which could become infected.
- In patients with a known allergy to bioactive glass or its constituents ($Ca^{2+}$, $PO_4^{3-}$, $Na^+$ and $Si(OH)_4$),
- In patients with pre-existing conditions or disease that may interfere with the good healing of tissues
- In the irradiated bone (according to radiological criteria indicating osteonecrosis).
- To replace structures subjected to high mechanical stresses.
- During severe renal and hepatic infections.
- In conjunction with a treatment known to affect the skeleton.
- In case of unsutured meningeal breach in cranio-spinal surgery.
- In neonatology service.

To date, we do not have any studies conducted in pregnant women or data related to use during breastfeeding. As a safety measure, the implantation of GlassBone Granules is not recommended during the periods of pregnancy and lactation. In addition, a warning is required for patients treated in special clinical situations (tumor, ongoing chemotherapy and radiation therapy, immunodeficiency ...).

# III. Device description

### 1. Description

GlassBone Granules is a synthetic, resorbable and bioactive bone substitute with osteoconduction properties for filling bone defects in the skeletal system in adult and pediatric population (more than 10 kg).

- Composition: 45S5 bioactive glass granules

45S5 bioactive glass granules are only composed of elements naturally present in bone tissue (Calcium, Phosphate, Sodium, Silicon). The release of these ions during the resorption of bioactive glass will allow the

formation on the surface of a layer of carbonate hydroxyapatite whose composition and structure are similar to the mineral phase of the bone. This layer provides GlassBone Granules an osteoconduction property and creates a strong link between granules and living tissues.

This medical device does not contain any medicinal substance or tissues of human origin.

The radio-opacity of GlassBone Granules makes it possible to discern bone substitute granules following their implantation. As the granule's resorption, the radio-opacity of the bone defect approaches that of the surrounding bone.

It is a single-use device.

Bone defects are consolidated in about 9 - 12 months (see table 1) and the bioactive glass granules are gradually resorbed. It should be considered that after 12 months; the device no longer fulfils its function even if the device is not totally degraded.

The current expiration date is 5 years after gamma sterilization.

The device is MR safe and sterile.

- Operating principles and mode of action

Implantation of GlassBone Granules is done after elimination of all soft and/or pathological tissue from the implantation site. Once the surgical site has been prepared, the blister is open as explained in instruction for use. GlassBone Granules can be mix with another constituent in sterile cup (saline serum, autologous bone from the implantation site and/or from another operating site, bone marrow, and/or patient blood). To perform the application of GlassBone Granules, the defect must have sufficient bone wall. The defect is completely fill using a sterile instrument without material compression (not apply excessive pressure to the defect) in the site nor blotting the blood/moisture in the positioned graft. GlassBone Granules maintains its volume it does not shrink or expand. It is recommended to avoid placing granules outside of the bone defect. It is necessary to remove them if it happens. Finally, it is recommended to avoid direct contact of GlassBone Granules with the skin.

After placement of Glassbone Granules, ensure the primary closure of the soft tissues at the graft site. Resorbable or non-resorbable membranes can also be used for the closure. The closure of the operative site depends on the surgery performed and the surgical site (membrane, sutures, etc.). An adequate closure of the graft site is mandatory (e.g., with cortical bone window, collagen membrane, mucosal-periosteum flap, fascia or muscle flap).

To note Glassbone Granules does not have sufficient mechanical strength to withstand load bearing before hard tissue is formed. When used in load bearing areas, standard internal or external stabilization techniques should be followed to achieve rigid stabilization in all planes. It is necessary to follow the usual post-operative treatment and rehabilitation procedures associated with bone grafts.

After implantation the interstitial spaces between the granules allow fluid circulation and cellular and vascular colonization. The resorption of bioactive glass will allow the formation on the surface of a layer of carbonate

hydroxyapatite, which composition and structure are similar to the mineral phase of bone, preventing graft rejection. This layer gives the granules their osteoconduction property and makes it possible to create a link between the granules and the living tissues. Following the carbonate hydroxyapatite layer reactions, bone growth continues, and bioactive glass continues to degrade and serves as a scaffold for bone regeneration.

### 2. Reference to previous model(s) and description of changes

There is no previous model for this device.

### 3. Description of accessories intended for use with the device

No accessories are used with our device.

### 4. Description of other devices intended for use in combination with the device

No accessories or compatible devices are sold with GlassBone Granules.

However, when implanted GlassBone Granules can be mix with another constituent in sterile cup (saline serum, autologous bone from the implantation site and/or from another operating site, bone marrow, and/or patient blood[1]).

## IV. Risks and warnings

### 1. Residual risks and adverse effects

The residual risks of the device itself, i.e., the risks remaining after the implementation of the risk management measures, concern the allergic risks. To date, no adverse effects directly related to the device are reported or detected.

Post-surgical symptoms (pain, redness, inflammation, oedema, hematomas, seroma, swelling, bleeding, ...), postoperative infection, recurrence/residual disease, otorrhea, pulmonary embolism, vein thrombosis, wound leakage, nerve palsy or paresthesia, mechanical failure, delay in consolidation, loss of fracture reduction, fusion failure, fracture, loss of bone graft, protrusion of the graft. These complications are the same as those that can occur with autologous bone grafting (see part 6. Other therapeutic solutions).

[1] Based on clinical data

Possible adverse event is not more severe than those expected of similar products if the instructions are followed correctly by a qualified surgeon familiar with bone grafting techniques.

| Device-related complications | Frequency of occurrence | Source |
|---|---|---|
| Allergy to the constituents of the device | Not detected to date out of 63,896 sales | PMS and available clinical data |
| Surgical adverse event | Not more than those expected of similar products | |

The profit/risk ratio is positive since the benefit is greater than the risk with an acceptable residual risk.

## 2. Warnings and Precautions

GlassBone Granules should be used by qualified surgeons (orthopaedists, neurosurgeons, maxillofacial surgeons, stomatologists and otorhinolaryngologists) trained in bone grafting and fixation techniques who have read these instructions for use.

***Regarding the surgical procedure***

- The general principles of asepsis and patient medication must be observed when using Glassbone Granules.
- GlassBone Granules does not substitute antibiotic therapy treatment during infection.
- The combination of any drug substance with Glassbone Granules during implantation is the responsibility of the surgeon.
- Manipulate Glassbone Granules with a surgical instrument to avoid piercing surgical gloves.
- It is advisable to revive the recipient site before implantation.
- Completely fill the defect with Glassbone Granules. It is possible to perform the application of GlassBone Granules if the defect has sufficient bone wall.
- Avoid placing granules outside of the bone defect. Remove them if necessary.
- Avoid direct contact of GlassBone Granules with the skin.
- If it moves/migrates, the bioactive glass can cause wear of the joints and interfere with movement. Prevention of movement and granule migration is essential for proper bone formation.
- Do not apply excessive pressure to the defect. Excessive pressure may cause embolization of fat in the bloodstream.
- GlassBone Granules maintains its volume that is to say it does not shrink or expand.
- Glassbone Granules does not have sufficient mechanical strength to withstand load bearing before hard tissue is formed. When used in load bearing areas such as mandible fractures, standard internal or external stabilization techniques should be followed to achieve rigid stabilization in all planes.
- It is necessary to follow the usual post-operative treatment and rehabilitation procedures associated with bone grafts.

- The closure of the operative site depends on the surgery performed and the surgical site (membrane, sutures, etc).
- An adequate closure of the graft site is mandatory (e.g., with cortical bone window, collagen membrane, mucosal-periosteum flap, fascia or muscle flap).

***Regarding the medical device***

- Glassbone Granules is a device that resorbs over time to make way for regenerated bone. There is currently no clinical study available that demonstrates complete resorption of the granules.
- This device does not harden like cement.
- Glassbone Granules is a sterile disposable device and must never be re-sterilized or reused. Reuse may cause contamination and impairment of bone substitute performance.

### 3. Other aspect of security, if applicable

GlassBone Granules has been subject to one FSCA in July 2020 (registered in ANSM under reference: R2010145)

NORAKER launched a voluntary recall to withdraw lot GB1906004 of synthetic bone substitute GlassBone Granules GB05.1/5 (0.5-1mm-5cc) from the market, following an error in packaging. Indeed, the labels of the devices indicated GlassBone Granules 0.5-1mm (GB05.1/5) but the blister packs contained larger granules GlassBone Granules 1-3mm (GB1.3/5).

27 boxes have been recalled, 8 boxes have been destroyed and 10 devices had been already implanted.

No health risk has been identified because GlassBone Granules GB1.3/5 (1-3mm- 5cc) can be used in the same indications as GlassBone Granules GB05.1/5 (0.5-1mm- 5cc) i.e. in orthopedic surgery, spine and CMF/ENT to fill, reconstruct and/or fuse bone defects.

So, no additional action had been required for practitioners who had used this batch of bone substitutes, other than the usual post-operative follow-up.

This FSCA have been closed on the 30, July 2020.

## IV. Summary of Clinical evaluation and Post-Market Clinical Follow-up (PMCF)

### 1. Summary of clinical data on equivalent devices, if applicable

Not Applicable

## 2. Summary of clinical data relating to investigations of the device prior to CE marking, if applicable

Not Applicable

## 3. Summary of clinical data from other sources, if applicable

- **In literature**

Currently, the device Glassbone Granules (EtO sterilized) is found in 14 publications:

⇨ 7 publications in orthopaedics surgery:

➢ **(Aytekin et al., 2020). Comparison of the Results of Glassbone and Tricalcium Phosphate Graft Used in Bone Tumors. AOT Journal (2020) 53(2):pp 332-336.**

41 patients with benign bone tumors (mostly simple bone cysts (SBC) and aneurysmal bone cysts (ABC)) had been treated between either glass graft or tricalcium phosphate graft between 2013-2015. Patients were divided into two groups as those treated with BG (45S5 bioactive glass) and TCP grafts. Graft consolidation was evaluated radiologically with x-rays monthly.

For Glassbone group: 2/22 (9.09%) had residual cyst (treated in revision surgery with the same graft). No infection occured. For TCP group, 1/19 (5.26%) had infection and 1/19 (5.26%) had residual cyst (treated in revision surgery with the same graft). In patients using BG, compared to patients using TCP, radiological consolidation was observed faster between 14.-16. months (p = 0.0001) No harvest graft site was needed.

➢ **(Tetzel & Guyard, 2021) – Saving the lower limb with GlassBONE - Successful surgical revision of pseudarthrosis after infected open proximal tibia fracture type IIIC with bioactive glass grafting - A case report. Trauma Case Rep (2021)31.**

This case report is a 51-year-old male patient, involved in a motorcycle accident, suffered an open proximal tibia fracture, type IIIC, of the left leg. Patient was admitted in January of 2013 to a general orthopedic department for surgical treatment. The immediate surgery consisted of open reduction and internal plate fixation (lateral LCP, antero-lateral approach) and vascular bypass of popliteal artery. The postoperative phase was complicated by severe wound healing disorder, leading to septic osteitis with skin necrosis and bone exposition in March 2013. The patient underwent several surgeries. The final treatment consisted of a two-step therapy (Masquelet-therapy followed by auto- and Glassbone-grafting and plate fixation. Again,multiple bacteriological samples were taken including PCR analysis. The bone defect was filled with extensive auto- and allograft (Iliac crest, Glassbone) within the borders of induced membrane and fixed via medial LCP (locking compression plate). Clinical and radiological follow-up was performed on months 1, 3, 4, 6, 10 and 27 post operatively. Radiographically there was no secondary displacement of material, consolidation had begun. Bacteriological samples and PCR were negative. There was no pain or sign of infection. Progressive weight bearing (15 kg) was started, adding 10 kg each week. During the following clinical controls, (3, 4, 6, and 10 months postoperatively) the patient showed an excellent clinical evolution. Radiographically progressive homogenization of the graft and bone consolidation was noted with no material loosening. At 10-month postoperative evaluation, clinical status was still very satisfying. The pain symptomatology did not restrict the patient's daily life activities. Radiographically, bone consolidation was found and there was no deformity of axe nor signs of material loosening. 2 years postoperatively, radiographs and CT-scan showed transformation of the Glassbone into bone and perfect bone consolidation with no material loosening.

- **Mora-Zúñiga A, Cárdenas-Arellano F, Cruz-Munguía JD, Hernández-Carrillo JE. Osteomielitis crónica de tibia; uso de vidrio biactivo como complemento de tratamiento. Acta Ortopédica Mexicana, 2021 Oct.**

This case report is 42-years-old male with a diagnosis of chronic tibia osteomyelitis, with sequelae of previous surgical interventions, multiple antibiotic treatments and type IV B classification by Cierny-Mader. A two-stage surgical treatment was chosen. Firstly, extensive bone and soft tissue debridement, placement of cement beads medicated with amikacin in the medullary cavity and osteoclast system for irrigation with vancomycin. In the second stage, free fibular bone grafting, fixation and stabilization with screws, bioactive glass placement in areas of interface between stabilized fibula and posterior tibial cortex. The case was assessed one month after surgery, with clean healed surgical wounds, closed fistulas with no evidence of infection, complete arches of movement, muscular hypotrophy, radiographic control with graft in the integration phase with no evidence of instability of osteosynthesis material and continued rehabilitation exercises. At 3 months, the patient walk without support and laboratory tests are within normal parameters. Radiography shows an osseointegration of the fibula into the tibia. At 12-months follow-up, the patient has no evidence of infection and has recovered 90% of the function of the affected limb.

- **(Gravina_2022) Gravina P, De Francesco F, Pangrazi PP, Marchesini A, Neuendorf AD, Campodonico A, Gigante A, Riccio M. A case report of upper limb loss of substance: Use of functional gracilis free flap, brachioradialis transposition and bioglass for bone regeneration. Trauma Case Rep. 2022 Jan 31**

This case report is a 27- year-old male with complex upper limb trauma and loss of a proximal third of the posterior forearm structure as well as loss of active finger extension, ulnar and radial nerve territory anesthesia and ulnar fracture. The patient underwent several surgeries: at first, a fixation of the ulnar bone by external fixator, then 6 days after a debridement, fasciotomy of dorsal hand was performed, and Negative Pressure Therapy was applied on the wound at the distal third of forearm and 45 days after a composite nerve-tendon-muscle-skin gracilis free flap was harvested from the contralateral leg, related to tendon transfer, to supply active hand extension. Six months after surgery the ulnar fracture was affected by pseudoarthrosis. Bioactive glass was implanted in the site of the bone defect previously prepared with a biologic camera.

Three months later and five months later, the patient was monitored, and we observed satisfactory outcomes in the injury site. After one-year follow-up, there were clinical optimal outcomes in finger, thumb, and wrist flexion.

- **(Gravina_2022) Gravina P, De Francesco F, Pangrazi PP, Gigante A, Riccio M. A Large Osteoid Osteoma of Trapezium: A Regenerative Approach and a Review of Literature. Journal of Hand Surgery Global Online. 2022 Sept**

This article describes a rare case of a large (1.3 cm) osteoid osteoma of the trapezium in a 19- year-old male patient treated surgically with resection and curettage of the osteoid. The patient had intense pain localized at the right thumb basal joint until 1 year. The pain was dull and persistent. The patient underwent filling and reconstruction surgery: enucleation of the nidus (curettage) and filling the bone defect with bioactive glass mixed with fresh blood.

At the latest follow-up (60 days), all clinical examination tests improved significantly ($P < .05$) with VAS score at 0, Pinch test at 20 kg, and Kapanji scores at 9. The brief Michigan Hand Outcomes Questionnaire global score (showed subjective evaluation of the functional and aesthetic outcomes) was slightly significantly better at 60 days after surgery (70.83%). No recurrence was observed until 12 months after surgery.

- **(Cuvillier at al., 2022) Masquelet's induced membrane technique associated with Reamer Irrigation Aspiration grafting and intramedullary Nailing (MaRIAN) for chronic diaphyseal osteomyelitis of the lower limb. *Orthopaedics and Traumatology: Surgery and Research* (2022).**

This article is a case series patients with chronic osteomyelitis of the femur or tibia. The first surgical stage consisted of bone resection in the healthy zone and use of a gentamicin cement spacer to fill the bone defect. The second stage consisted of the placement of a statically locked intramedullary nail associated with a bone autograft using the RIA technique. Eight patients had a transplant by RIA alone. In 4 patients, the graft was associated with an osteoinductive protein (Osigraft, Olympus, USA), or mixed with a bone substitute (GlassBone, Noraker, Lyon, France) in a patient. 12 men with diaphyseal osteomyelitis were operated; 9 tibial and 2 femoral, and 1 knee non-union, the mean bone defect was 7.3 cm (± 6.7). At a minimum follow-up of 18 months, with an average of 5 years, consolidation was complete without infectious recurrence. Despite the statistical weakness related to the size of the cohort, the resumption of early weight bearing and nail dynamization seemed to have an impact on the formation of complete consolidation. Corticalization appeared on average after 1.6 months (range, 1–3 months) and complete callus was obtained after 9.1 months postoperatively (range, 3–36 months). This short series, compared to the literature, demonstrated that the proposed technical modifications improved the overall management of this rare and challenging condition while maintaining the reliability of the original technique.

- **(Ilyas, 2022) İlyas G, Kaya A, İncesu M. Is a Bioceramic Glass Bone Graft Superior to Spongious Allografts in Femoral and Tibial Benign Bone Lesions? J Tepecik Educ Res Hosp 2022;32(1):122-30**

47 patients (19 men and 28 women) were randomized to receive either human-induced cancellous graft (29 patients) or bio ceramic glass graft (18 patients). The treatment consisted in curettage-grafting surgery for patients with benign tumor in long bones whose measurements are between 7 and 150 cm and average volume of 43.15 $cm^3$. The main follow-up was 16 months [6-48].

At the end of follow-up, the average pain score, according to VAS, over 10, was found as 1.07 ± 0.96 in human-induced cancellous graft group while the Glassbone group was 1.0 ± 0.84. No harvest graft was needed for both groups. The average lower extremity function score percentage (LEFS score) was 93.75% ± 3.67% in human-induced cancellous graft group while it was 94.51% ± 3 in Glassbone group. The average consolidation ratio at the end of follow-up was found as 82.58% ± 15.55 (35-98) in human-induced cancellous graft group, while 93.78% ± 3.67 was found in Glassbone group (87-99).

⇨ 2 publications in neurosurgery:

- **(Barrey et al., 2019) Barrey 2019: Clinical and radiographic evaluation of bioactive glass in posterolateral cervical or lumbar spinal fusion. European Journal of Orthopaedic Surgery & Traumatology. (2019).**

30 consecutive patients with indications for a posterolateral spinal fusion procedure were operated by the author and consecutively included in the study. Appropriate decompressive surgery was performed with subsequent fixation using posterior instrumentation as appropriate and filled with bioactive glass. GlassBONE Granules (1 – 3.15 mm) were mixed with local autograft harvested from the surgical site and blood.

All patients underwent posterior spinal fusion either in the cervical or the thoraco-lumbar spine. Multi-level fusions represented the majority of the cohort (43% of patients with more than seven levels treated). Radiographic imaging demonstrated excellent fusion rates (93%) at final follow-up, equivalent to the outcomes reported in the literature for autogenous bone, with excellent bone bridging and no spinal implant loosening. Only two cases of non-union were encountered. Additionally, 90% of the patients demonstrated recovery at 1 year after surgery with a pain reduction of 60%. Resorption was observed on all CT-Scan.

- **(Courvoisier et al. 2023) Courvoisier A, Maximin M-C, Baroncini A. Safety and Efficacy of Stand-Alone Bioactive Glass Injectable Putty or Granules in Posterior Vertebral Fusion for Adolescent Idiopathic and Non-Idiopathic Scoliosis. Children 2023, 10, 398.**

43 patients with scoliosis and requirement of posterior fusion posterior instrumentation were included. 18 patients underwent surgery using GlassBone Granules (1-3mm) and 25 using GlassBone Injectable Putty. For GlassBone Granules group, the mean aged is 15.7 ± 1.7 [13–19]. 9 patients had adolescent idiopathic scoliosis, 7 patients had neurologic scoliosis and 2 had neuromuscular scoliosis. 78% received 10 cc of GB-G (1-3 mm) and 22% received 20 cc. Each patient's last follow-up was performed at 24 months and included clinical and radiological evaluations. Four of all operated patients (GB-G and Putty) experienced adverse events. 2 patients (4.7%) had surgical site infection which was treated with revision and cleaning, and 1 patient had an extended stay in the intensive care unit (2.3%). All these adverse events were due to surgical intervention. No other causes were identified. 1 case (2.3%) of late mechanical complications was observed 24 months after surgery. Surgical revision was performed, and the instrumentation was removed. At the latest follow-up, bony fusion was documented in all patients (100%). Cobb angle measurements reflected a significant reduction in spinal deformity. No significant loss of correction occurred between the immediate post-operative examination and the 24-months. There was no sign of non-union, screw loosening, implant displacement or rod breakage. The results shows that the massive use of bioactive glass in posterior fusion, when combined with proper surgical planning, hardware placement and correction, is effective in providing good clinical and radiological outcomes.

⇨ 5 publications in CMF surgery:

- **(Adam et al. 2016) . Adam S, Sama HD, Dégardin N, Gallucci A, Bellot-Samson V, Bardot J. The gingivo periosto plastic surgery with osseous substitute: technique and first results. Annales Chirurgie Plastique Esthetique (2016). Vol 61, numéro 4, 257-62.**

A retrospective study was conducted since January 2012 to December 2012 including 23 cases of gingivoperioplastic surgery using Glassbone Granule (0.5-1mm). There were 6 patients aged 4 to 6, 9 patients aged 7 to 9 and 8 patients aged above 10 years old. There were 17 unilateral clefts and 6 bilateral clefts, and 18 narrow clefts and 5 wide clefts. 20 patients received volume less 1 cc and 3 higher than 1 cc.

At 18 months, no adverse effects were observed: neither inflammation nor infection. One case of bleeding was noted 2 days after surgery but it was due to lack of respect of instructions. Technique of gingivo periosto plastic surgery with osseous substitute is simple and our results are globally satisfactory. We observed less morbidity of the operating site.

- **Bahammam, MA. Effectiveness of bovine-derived xenograft versus bioactive glass with periodontally accelerated osteogenic orthodontics in adults: a randomized, controlled clinical trial. BMC Oral Health. 2016, 30;16(1):126.**

In this prospective, single-masked clinical trial, 33 orthodontic patients (20 women, 13 men; mean age 21.2), were randomly allocated to one of three groups. Group 1 underwent a modified corticotomy technique on the labial side only, whereas group 2 was treated with the same technique combined with periodontally accelerated osteogenic orthodontics (PAOO) using a bovine-derived xenograft and group 3 was treated in the same way but combining PAOO with bioactive glass (0.5-1mm). At the end of the study period, there was a significantly greater increase in bonedensity in the two groups that had been treated with bone grafting when compared with the group that had been treated with a modified CAOT alone. Moreover, patients who were treated with the bovine derived xenograft showed a greater (albeit not statistically significant) increase in bone density than those who were treated with bioactive glass.

- **Graillon N 2018. Graillon N, Degardin N, Foletti JM, Seiler M, Alessandrini M, Gallucci A. Bioactive glass 45S5 ceramic for alveolar cleft reconstruction, about 58 cases. J Craniomaxillofac Surg. 2018 Oct;46(10):1772-1776.**

In this clinical case series, 58 patients aged 3 to 15 years (7.6 years on average) were included who have undergone a unilateral or bilateral alveolar cleft. The alveolar cleft was grafted with 0.5 to 2 cc of GlassBone (size: 0.5 - 1mm) depending on the volume of the graft and 11 patients on one side with bioactive glass because

the other side was grafted with iliac bone before the beginning of the study. Hospitalization, social eviction and antalgic consumption were reduced. Bone continuity was achieved in 63.8% of the cases. Bilateral cleft and dental agenesia increased grafting failure. In the subgroup of 25 patients with isolated unilateral cleft without dental agenesis, 80% had bone continuity at one year. We noted 10.3% of alveolar fistula recurrence. They are two cases (3.4%) of mucosal dehiscence.

- **El Hawary 2021. El-Hawary HE, Shawky M. Assessment of the sticky bone preparation of bioactive bone glass in grafting critical-sized surgical bony defects. Egyptian Dental Journal. 2021 Jul; 67: 1899-1908.**

In this randomized clinical controlled trial, 24 were divided into two equal groups for cystic bony lesions. Cystic lesions exceeding 2 x 2 cm were enucleated, and the defect was obliterated with bioactive bone glass particles in group 1 and bioactive glass sticky bone in group 2 (bioactive glass granules + platelet rich fibrin).

In group 1, the percentage of decrease in the bone density during the first three months is higher in group 1 than group 2 that was then increased by nearly the same percentage at the six months interval, although statistically there is no significant difference between the two groups throughout the study period. The defects were completely filled in the 2 groups without loss of substitute. The healing went uneventful through all the cases. The surgically reconstructed defects did not show postoperative infection nor wound dehiscence or graft rejection throughout the healing phase. After resolving the postsurgical phase's signs, none of the patients exhibited any complaint during the whole study interval. The defect was reconstructed.

- **Hassan 2022. Hassan C-H, Malheiro E, Béquignon E, Coste A, Bartier S. Sublabial bioactive glass implantation for the management of primary atrophic rhinitis and empty nose syndrome: Operative technique. Laryngoscope Investigative Otolaryngology. 2022;7(1):6-11.**

This is a two cases report: Two patients were operated for nasal obstruction: empty nose syndrome (ENS) and atrophic rhinitis (AR) are two chronic and socially disabling nasal diseases. The objective of the current study was to describe an innovative technique of a sub mucoperiosteal bilateral Glassbone granules bioactive glass.

Results demonstrated a postoperative satisfying endoscopic and sinus CT-scan results with filling of the nasal cavities, with less crusts and a complete wound healing. They had no short-term complications.

- **PMCF Follow-up**

Following the implementation of a post-market clinical follow-up study, 6 studies have been completed with GlassBone Granules (EtO sterilized):

- **Spine**

In a retrospective study (CHU St Etienne), 127 patients, representing 130 cases, were included to confirm the safety and tolerability of GlassBone Granules under its normal conditions of use in spinal pathologies with a minimum setback of 6 months (France). The majority of patients had degenerative disc disease and in 42% of cases, GB-G was used mainly for posterior fusion. Immediate post-surgery complications during the hospital stay were noted: 1 infection (0,8%), 3 mechanical (2,4%) and 2 neurological (1,6%). Complications during clinical follow-up were identified: 4 surgical site infection and 3 mechanical complications (material expansion/replacement) at 2 months and only 1 mechanical complication at 6 months. These complications were not related to the substitute. No adverse event was noted at 12 months.
Pain was thus improved for 90% of patients and fusion was acquired for 91% of patients, partial fusion for 5% and 5% of non-union.

- **Spine**

Surgical treatment of idiopathic scoliosis in children and adolescents by posterior vertebral instrumentation, arthrodesis and fusion of the instrumented segments with the GlassBone Granules (GlassBone-G). Pr Courvoisier: Published.

A retrospective study (grade C) was to conduct at CHU Grenoble (France) to confirm the performance and tolerability of the GlassBone G device in idiopathic scoliosis in children and adolescents (deformation and degeneration of the spine). GlassBone G device was used in posterior thoracolumbar spinal fusion for paediatric patients with idiopathic scoliosis. GlassBone G is used for fusion of the instrumented vertebrae allowing consolidation of the instrumentation after surgery. The safety and bone fusion are evaluated.

23 paediatric patients, all operated by Prof. Courvoisier, were included in the study. The average age was 14.9 ± 3.1 years [3 - 19] with a distribution of 12 women (52.2%) and 11 men (47.8%). Before 6 months, there were two surgical site infections that required surgical revision for lavage (at 2 months post-op) and there was 1 internal bleeding. At the final follow-up, 1 patient had PJK with kyphosis at the top of the highest instrumented level. Glassbone G was well in place during revision. All these adverse events are related to the surgical practice and not to the device. At the last postoperative follow-up [12-24 months], all patients (n=23) had an acquired fusion. No pseudoarthrosis was found during follow-ups. The reduction in Cobb angle for the included patients is significant ($p<0.05$). The loss of correction is 1,7 ± 4,9° and 2 ± 4,4° for the 3-6-, 12/24-months postoperative follow-ups compared to the immediate postoperative radiograph measurements (no significant difference).

- **Spine**

Post-market, retrospective, observational, monocentric clinical study to confirm the performance and tolerance of the GlassBone Granules device.
A retrospective study was to conduct in Hospital Pierre Wertheimer (69). This study assesses GlassBone Granules (GB-G) synthetic bone substitute in real life and aims to provide sufficient evidence of the device's clinical performance and safety. 100 patients who had undergone spine surgery with GlassBone Granules bioactive glass between September 2019 and September 2021 for reconstruction of deformities and degenerative diseases were included. The population represented 48 women (48%) and 52 men (52%). 19% of patients underwent surgery for cervical pathology and 81% for lumbar pathology. The pathologies concerned are 45% discopathies, 40% deformations, 11% traumas and 4% tumors. Pain was improved at 12 months in 85.6% of patients and bone fusion at 12 months in 96% of patients. A total of 24% of complications were found in a population of 24 patients of which only 6 were under 65 years of age. Safety was confirmed because no serious adverse events occurred and adverse events which was detected were not related to the device. Performance was confirmed with a good fusion rate.

- **ENT**

A study (Clinique Causse (42), France)) was conducted with the aim of confirming the safety and performance of Glassbone Granules (GB-G) under its normal conditions of use in mastoid obliteration after cholesteatoma resection with a conventional follow-up of 10 months (France).
Eighty-seven patients were enrolled in this study; the average age is 49.8 years with a distribution of 37 women and 50 men. There was no extrusion of bioactive glass material no complications occurred due to the bioactive glass material. 65% of patients had none post-operative complications. Complications were vertigo, intermittent Otorrhoea, persistent Otorrhoea, EAC healing delay, EAC stenosis, infection with retroauricular fistula, secondary facial paresis, cerebrospinal fluid in perioperative time. No allergy was noted. All these adverse events are related to the surgical practice and not to the device GlassBone Granules.
During the follow-up period cholesteatoma recidivism was observed in 2% of the patients (2 patients). Overall, both air conduction thresholds and air bone gap were slightly lowered when comparing post-operative values to pre-operative values.

- **Ortho: filling after tumour resection**

This is a retrospective study that was conducted in June 2022 including 36 patients who undergone tumor resection. Glassbone Granules was used after the resection to fill the defect. No fracture occurred during the follow- up (mean 22 months [6: 58]) and 78% have a consolidation acquired or partial (in progress) according the Neer classification, that is compliant with the performance criteria: the healing rate is 100%.

No complications occurred after surgery.

- **Ortho: osteomyelitis**

Performance and safety of Aktibone (45S5, synthetic bone substitute) used in orthopaedic surgery, in osteomyelitis indication. Retrospective study on 87 adult patients.
This is a retrospective study with 87 patients who underwent osteomyelitis surgery and grafted with AktiBone bioactive glass granules between January and December 2021. Aktibone Granules has been used to fill bone defects due to debridement of osteomyelitis localized mainly in femur (48.3%) and tibia (12.6%). Data from clinical follow ups including bone remodelling, maintenance of bone volume and side effects (complications and recurrence) were analysed. The safety and performance of bioactive glass have been evaluated.
The population represented 39 women (77.8%) and 48 men (55.2%). The average age at the time of surgery was 52.4 years old. The main isolated pathogen is Staphylococcus aureus (64.4%). According to Cierny–Mader classification, anatomic osteomyelitis is type 3 (localized osteomyelitis- 62.1%) and 4 (diffuse osteomyelitis- 37.9%). No immediate post-surgery complications during the hospital stay were noted. No recurrence of osteomyelitis occurred during clinical follow-up. All patients are safe of their osteomyelitis at 4 months and 12 months. To note, patients had an antibiotic treatment until 4 months. No extrusion of bone substitute occurred.
The use of Aktibone in a one-stage procedure, with no second operation required and no harvesting of autologous graft from the iliac crest, makes Aktibone G as a cost-effective, as well as a rapid method in the treatement of osteomyelitis. It can provide a safe and effective alternative to autograft and allografts. Aktibone G can provide an effective and long-term solution for reconstructive procedures following curettage of infected bone and it safe and well tolerated by patients and with successfully remodelled bone defect.

## 4. Overall Summary of Clinical Performance and Safety

The clinical claimed clinical performance is the filling, reconstruction and / or fusion of bone defects allowing the regeneration of the bone. The claimed performance is consistent with the results we currently have:

| Reference | Population | GlassBone Granules | Destination | Indication | Performance (%) | Follow-up (months) |
|---|---|---|---|---|---|---|
| Graillon et al.,2018 | Child | Sterilized EtO<br>Granular size: 0.5-1 mm | CMF | Alveolar cleft | 80% reconstruction | 12 |
| Barrey, 2019 | Adult | Sterilized EtO<br>Granular size: 1-3 mm | Spine | Cervical and lumbar degenerative diseases | 93% fusion | 12 |
| Aytekin et al., 2020 | Adult and Child | Sterilized EtO<br>Granular size: 1-3 mm | Ortho | Benign bone cyst | 100% filling and consolidation | 16 |
| Ilyas, 2022 | Adult | Sterilized EtO<br>Granular size: 1-3 mm | Ortho | Benign bone lesions | 95% reconstruction | 16.5 |
| Courvoisier et al, 2023 | Child | Sterilized EtO<br>Granular size: 1-3 mm | Spine | Spine deformities | 100% fusion | 24 |
| RETRO_StEtienne | Adult | Sterilized EtO<br>Granular size: 1-3 mm | Spine | Cervical and lumbar degenerative diseases | 91% fusion | 12 |

| | | | | | | |
|---|---|---|---|---|---|---|
| SCOGRAPE | Child | Sterilized EtO<br>Granular size: 1-3 mm | Spine | Lumbar deformative diseases | 100% fusion | 12 |
| CAUSSE | Adult | Sterilized EtO<br>Granular size: 0.5-1 mm | ENT | Cholesteatoma | 100% filling | 10 |
| TUGRA | Adult | Sterilized EtO<br>Granular size: 1-3 mm | Ortho | Benign bone tumor | 100% filling and consolidation | 22 |
| Bresil_TRAUMA | Adult | Sterilized EtO<br>Granular size: 1-3 mm | Ortho | Osteomyelitis | 100% filling and consolidation | 12 |
| DEFGRAD | Adult and Child | Sterilized EtO<br>Granular size: 1-3 mm | Spine | Lumbar and cervical spine disease | 100% fusion | 12 |

Current clinical results indicate that the benefits far outweigh the risks since the only risk associated with the identified device would be allergy.

| | Benefits | Risk |
|---|---|---|
| **Manufacturer's claim** | - Reduction of graft site morbidity and/or no other bone harvesting site<br>- Limited recurrent / residual disease<br>- Quality of life improvement | Surgical risk: possible complications but not more severe than those expected of similar products.<br>Device risk: No allergy |
| **Available performance data** | - Orthopaedic, spine, CMF: Reduction of and complication associated with other harvesting graft or absence of morbidity (no harvest graft)<br>- ENT: Limited recidivism and recurrence rate<br>- Spine: Pain and deformity reduction<br>- Orthopaedic: Reduction of fracture rate, tumor rate and bone infection recurrence<br>- CMF: Pain reduction<br>- ENT: Hearing improvement<br><br>All results in accordance with literature research. | No complications related to Glassbone Granules substitute.<br>Surgical complications not more severe than those expected of similar products.<br>No allergy. |

## 5. Ongoing or planned post marketing clinical follow-up

The table below lists all ongoing and planned studies or registers concerning this medical device.

| Destination | Indication | Statue | Grade | Objective |
|---|---|---|---|---|
| **Register** | | | | |
| Spine | Pathologies of the spine | Finished | - | Confirm indications and safety per operatively. |
| Ortho | Trauma | Ongoing | - | Confirm indications and safety per operatively. |
| ENT | Cholesteatoma | To be started | - | Confirm indications and safety per operatively. |
| **Prospective studies in progress** | | | | |
| Spine | Degenerative pathology of the lumbar spine | 100/100: Finished | C | - Evaluation of tolerance through analysis of complication rate<br>- Performance evaluation via analysis of fusion |
| **Upcoming clinical investigations** | | | | |
| ENT | Cholesteatoma | Forthcoming<br>0/50 | B | - Evaluation of tolerance through complication rate analysis<br>- and performance through filling analysis |
| CMF | Cleft palate | TBD | B | - Evaluation of performance with bone reconstruction<br>- Evaluation of tolerance |
| Ortho | Benign Bone tumor | TBD | C | - Evaluation of tolerance through complication rate analysis<br>- and performance through consolidation analysis |
| Ortho | Osteomyelitis | TBD | C | - Evaluation of tolerance through complication rate analysis<br>- and performance through consolidation analysis after infection |

For each study, a follow-up of complications is planned throughout the duration of the study. Events should be reported to NORAKER at any time. In addition, post-market surveillance data and other clinical data that will be collected will be incorporated as part of the annual updates of the clinical assessment.

# VI. Other therapeutic solutions

Grafts are used when conservative treatments (first line approaches when pathologies are not severe) have failed and when surgery is required. In this case, they are mainly used in combination with others implants such as rods, screws, plates and prothesis. They can also be used alone or not at all. Their mains functions (prevent progression of disease, mechanical support etc.) are different as bone grafts functions. Thus, these alternative treatments cannot be compared with bone grafts. They are considered as complementary implants.

Likewise, drug treatments, chemotherapy, radiotherapy, physiotherapy… are complementary and can't be considered as a total alternative solution.

Therapeutic alternatives to Glassbone Granules are autologous bone, allograft, xenograft, and other families of synthetic substitutes.

The gold standard remains the autologous bone but involves a sampling site on the patient and therefore a second surgical site that can cause additional complications: pain, infection, fracture, loss of sensation or hematomas. These complications, the lengthening of the operating time, the limited quantity and the variable quality of the available material are the main limitations of autologous transplantation, leading professionals to resort to bone substitutes. The most common options for replacing autograft are: allogeneics, xenografts and synthetic bone substitutes.

Allografts are tissues of human origin and are distributed by tissue banks and are subject to authorization. Xenografts are made from non-viable tissues of animal origin, stripped of their bone marrow, or derivatives made non-viable. They are of various origins: coral, cuttlefish, mammals. Most bone substitutes of animal origin come from cattle. The risk of pathogen transmission is not excluded.

As regards synthetic substitutes, they do not contain any derivative or tissue of biological origin and are not derived from such derivatives. Their composition varies (calcium phosphate, calcium sulfate, bioactive glass...) and can be absorbable or non-absorbable.

Glassbone Granules, like other synthetic bone substitutes, makes it possible to overcome the constraints of the sampling site (morbidity of the donor site) and to achieve the expected performance of the gold standard.

This summary table shows the advantages (+) and disadvantages (-) of other available solutions.

| | Manipulation | Bioactivity | Transmission of possible pathogens | Availability | Osteoconduction | Osteoinducteur | Bioresorbable |
|---|---|---|---|---|---|---|---|
| Autograft | - | - | + | - | + | + | - |
| Allograft | + | - | - | - | + | - | - |
| Xenograft | + | - | - | + | + | - | - |
| Synthetic substitute | + | + | + | + | + | - | + / - |
| BMP | + | - | - | + | + | + | + |
| Bioactive glass | + | + | + | + | + | - | + |

# VII. Suggested profile and training for users

Users are experienced surgeons (orthopaedists, neurosurgeons, cranio-maxillofacial surgeons, stomatologists and ENT surgeons) with bone graft techniques. There is no specific training on the use of the device.

# VIII. Reference to harmonized standards and common specifications applied

At the moment of writing this document, no common specification is published on our product, and only a few standards are harmonized according to Regulation 2017/745.

The list of harmonized standards applied is as follows for this device:

| Number | Year | Title of standard |
|---|---|---|
| EN ISO 11137-1 + A2 (2018) | 2015 | Sterilization of health care products - Radiation - Part 1 : requirements for development, validation and routine control of a sterilization process for medical devices |
| EN ISO 13485 + A11 (2021) | 2016 | Medical devices, Quality management systems, Requirements for regulatory purposes |
| EN ISO 14971 + A11 (2021) | 2019 | Medical devices - Applications of risk management to medical devices |
| EN ISO 11737-1 + A1 (2021) | 2018 | Sterilization of medical devices - Microbiological methods Part 1: Determination of the population of microorganisms on products |
| EN ISO 11737-2 | 2020 | Sterilization of medical devices - Microbiological methods - Part 2 : tests of sterility performed in the definition, validation and maintenance of a sterilization process |
| EN ISO 10993-9 | 2020 | Biological evaluation of medical devices - Part 9: Framework for identification and quantification of potential degradation products |
| EN ISO 10993-10 | 2023 | Biological evaluation of medical devices - Part 10: Tests for skin sensitization |
| EN ISO 10993-12 | 2021 | Biological evaluation of medical devices - Part 12: Sample preparation and reference materials |
| EN ISO 10993-23 | 2021 | Biological evaluation of medical devices - Part 23: Tests for irritation |
| EN ISO 15223-1 | 2021 | Medical devices - Symbols to be used with medical device labels, labelling, and information to be supplied - Part 1: General requirements |