MEGA'GEN

bone & tissue regeneration

botiss biomaterials

cerabone®

NATURAL BOVINE BONE
GRAFTING MATERIAL

Scientific and clinical evidence

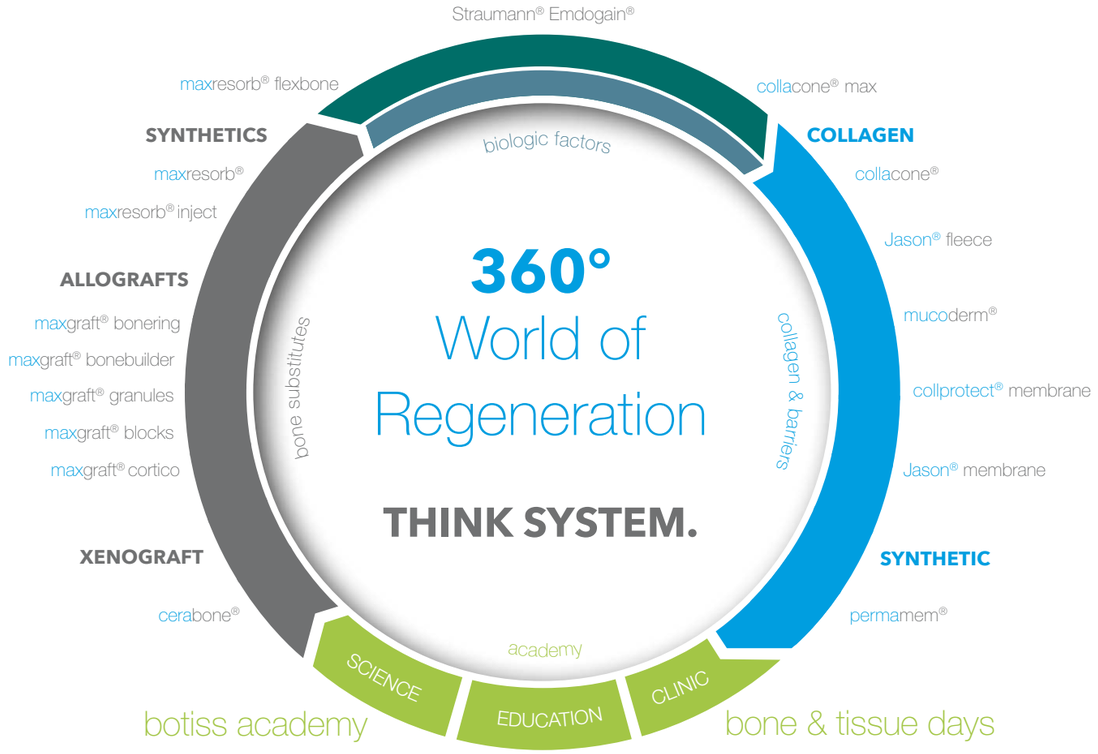
hard tissue

natural

safe

pure

botiss regeneration system



Development / Production / Distribution

cerabone®

Natural bovine bone graft

maxgraft® cortico

Processed allogenic bone plate

maxgraft®

Processed allogenic bone graft

maxgraft® bonebuilder

Patient matched allogenic bone implant

maxgraft® bonering

Processed allogenic bone ring

maxresorb® inject

Synthetic injectable bone paste

maxresorb®

Synthetic biphasic calcium phosphate

maxresorb® flexbone

Flexible blocks (CaP / Collagen composite)

Straumann® Emdogain®

Enamel matrix derivative

collacone® max

Flexible cone (CaP / Collagen composite)

collacone®

Collagenic hemostat (Cone)

Jason® fleece

Collagenic hemostat (Sponge)

mucoderm®

3D-stable soft tissue (Collagen) graft

collprotect® membrane

Native collagen membrane

Jason® membrane

Native pericardium GBR / GTR membrane

permamem®

High-density PTFE barrier membrane

Bone and regeneration techniques

cerabone® 0.5 - 1.0 mm

cerabone® 1.0 - 2.0 mm

THE USE OF BONE GRAFT MATERIALS

Bone graft materials are applied to replace and regenerate bone matrix lost by various reasons such as tooth extraction, cystectomy or bone atrophy following loss of teeth or inflammatory processes. For the filling of bone defects, the patient‘s own (autologous) bone is considered the „gold standard“, because of its biological activity due to vital cells and growth factors. Nevertheless, the harvesting of autologous bone requires a second surgical site associated with an additional bony defect and potential donor site morbidity.

In addition, the quantity of autologous bone is limited. Today, due to a constant development, bone graft materials provide a reliable and safe alternative to autologous bone grafts.

Clinicians can choose between a variety of different bone graft materials and augmentation techniques.

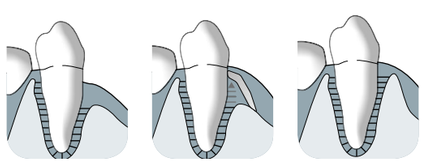
Bone graft materials are classified by their origin into four groups (see classification on right side).

The GBR/GTR technique

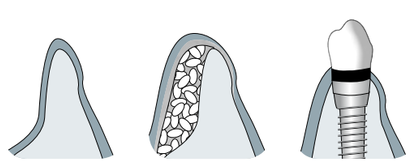
The principle of Guided Bone Regeneration (GBR) or Guided Tissue Regeneration (GTR) is based on the separation of the grafted site from the surrounding soft tissue by application of a barrier membrane. Membranes act as a barrier to avoid the ingrowth of the faster proliferating fibroblasts and/ or epithelium into the defect, and to maintain the space for controlled regeneration of bone.

The application of a bone graft material into the defect prevents a collapse of the membrane, acting as a place holder for the regenerating bone and as an osteoconductive scaffold for the in-growth of blood vessels and bone forming cells.

Guided Tissue Regeneration (**GTR**)



Guided Bone Regeneration (**GBR**)



Classification

Autologous:
- Patient‘s own bone, mostly harvested intraorally or from the iliac crest
- Intrinsic biological activity

Allogenic:
- Bone from human donors (multi-organ donors or femoral heads of living donors)
- Natural bone composition and structure

Xenogenic:
- From other organisms, mainly bovine origin
- Long-term volume stability

Alloplastic:
- Synthetically produced, preferably calcium phosphate ceramics
- No risk of disease transmission

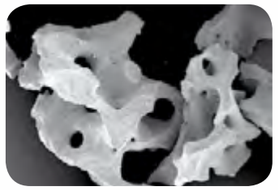
For large defects a mixture of autologous or allogenic bone, which has excellent biological potential, and a bone graft material for volume stability of the grafting site, is recommended.

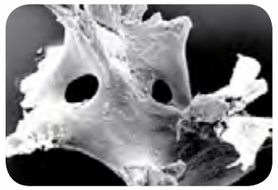
Xenogenic bone graft materials

Xenogenic bone grafts are derived from animals, preferably of bovine origin. Bovine bone materials can be deproteinized by heating (sintering) to minimize the risk of allergic reactions and disease transmission[1].

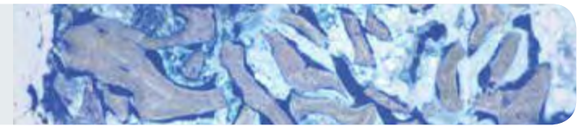
Bovine bone materials have a long tradition, are very well documented, and their clinical application has found wide-ranging acceptance. The removal of all proteins transforms them into biologically derived hydroxyapatite ceramics. It's important to chose a manufacturing process that preserves the natural three-dimensional bone structure with interconnecting pores, so that the material strongly resembles the human bone. In addition, a highly structured surface supports the formation of new bone matrix and thus the osseous integration that is the basis for an excellent volume stability of the augmented site.

SEM: cerabone® macro- and micropores resembling human bone





SEM picture of human bone



Histology of cerabone® six months after sinus lift; optimal integration and bone healing

cerabone® – NATURAL BOVINE BONE GRAFTING MATERIAL

cerabone® is derived from bovine bone in an established high-temperature heating process (sintering) guaranteeing high safety.

Beside safety and reliablity of the product and the production process, the material fulfills all other important requirements for the clinical success of a bovine bone graft material:

- Phase pure hydroxyapatite without organic components
- Rough and open porous structure comparable to native human bone
- Excellent hydrophilicity enabling a rapid uptake of blood
- Optimal biocompatibility proven in various *in vitro* and *in vivo* tests
- Rapid and controlled osseous integration

These characteristics are the basis for the excellent clinical results of cerabone® demonstrated by high volume stability of the grafted site, complete integration into newly formed bone matrix and the resulting high bone density[2].

cerabone® has excellent biofunctionality; superior hydrophilicity and blood uptake

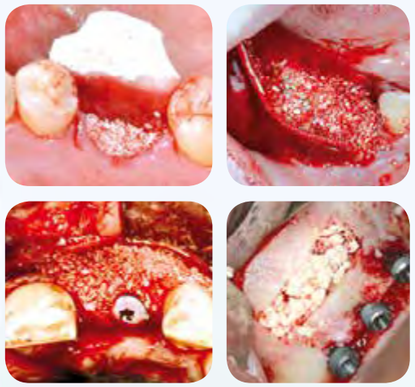
[1] Murugan et al. (2003). Heat-deproteinated xenogeneic bone from slaughterhouse waste: Physico-chemical properties. *Bull Mater Sci* 26:523–528.
[2] Rothamel et al. (2011). Sinus floor Elevation using a sintered, natural bone mineral. *zzi* 27(1).

Indications for cerabone®

Periodontology
Intraosseous defects (1 - 3 walls)
Furcation defects (class I - II)

Implantology and Oral and CMF Surgery

- Sinus floor elevation
- Horizontal augmentation
- Vertical augmentation
- Ridge preservation
- Peri-implant defects
- Socket preservation
- Bone defect augmentation



Product Specifications

cerabone® granules

Art.-No.	Particle Size	Content
1510	0.5 - 1.0 mm	1 x 0.5 ml
1511	0.5 - 1.0 mm	1 x 1.0 ml
1512	0.5 - 1.0 mm	1 x 2.0 ml
1515	0.5 - 1.0 mm	1 x 5.0 ml
1520	1.0 - 2.0 mm	1 x 0.5 ml
1521	1.0 - 2.0 mm	1 x 1.0 ml
1522	1.0 - 2.0 mm	1 x 2.0 ml
1525	1.0 - 2.0 mm	1 x 5.0 ml

cerabone® block

Art.-No.	Dimension	Content
1720	20 x 20 x 10 mm	1 x block

cerabone®: Safety and reliability made in Germany

cerabone® is made of cancellous bone from the femoral heads of domestic cattle. The processes of procurement and processing/production of this bovine material meets strict safety requirements. Thus the risk of BSE transmission can be considered negligible.

Sintering

Heating up to >1200°C

UNIQUE MANUFACTURING PROCESS

Both, product and process of procurement of the raw material as well as the production process are fulfilling the German and EU-regulatory and security requirements for bovine bone grafts including EN ISO 22442-1, -2 and -3, as well as Commission Regulation (EU) No 722/2012.

The proprietary manufacturing process of cerabone® is based on high-temperature treatment (sintering):

- Cell-friendly, biomimetically structured, rough surface
- Complete removal of organic components and albuminous impurities
- Negligible risk of allergic reactions or rejection

CE MARKING

- CE certification of cerabone® was issued in 2002
- The product is available in the orthopedic field since 2002 and is on the dental market since 2006

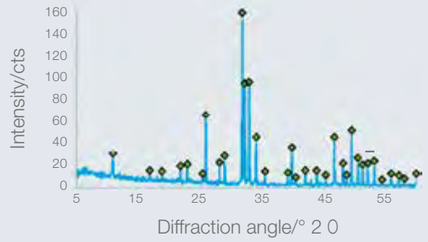
STERILE AND STORABLE

cerabone® is available as granules and in block form, which are sealed in primary and secondary blister packaging and sterilized with gamma irradiation. cerabone® can be stored at room temperature for up to three years.

cerabone®: 100% pure mineral bone phase

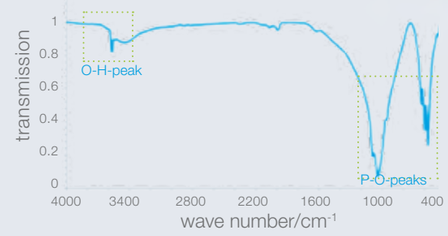
cerabone® consists of the pure mineral phase of bovine bone. No other phases besides hydroxyapatite are detectable. The high phase purity leads to maximal volume stability. In addition, the absence of organic components ensures the high safety of cerabone®.

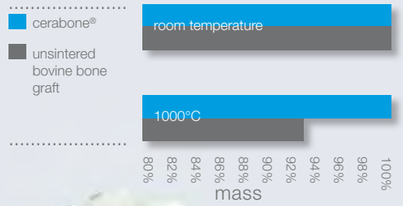
Results from Prof. Dr. C. Vgt, University of Hannover



X-ray diffractometry: mineral phases and crystallinity.
Narrow peaks and low baseline[3].
cerabone® shows high crystallinity and 100% purity.

Infrared spectroscopy: molecular fingerprint. Characteristic peaks of phosphate and hydroxy groups of hydroxyapatite[3].
No other organic phases detectable.





Thermogravimetric analysis showing combustion of organic components.
No mass loss by heating cerabone® up to 1000°C[4].
Complete removal of organic components (cells, collagen) by sintering process.

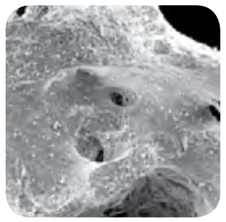
[3] Prof. C. Vogt, Leibniz University Hanover, Protocol on the analysis of bone graft material, 2012.
[4] Tadic et al. (2004). A thorough physicochemical characterisation of 14 calcium phosphate-based bone substitution materials in comparison to natural bone. *Biomaterials* 25:987–994.

Topography and hydrophilicity as key success factors

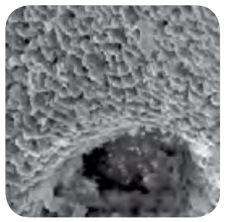
Optimal adhesion and ingrowth of cells, proteins and blood vessels

Scanning electron microscope (SEM) pictures show the highly structured surface of cerabone® as well as the macro- and micropores.

The macroporous structure enables migration of cells, penetration of blood vessels and integration of the particles

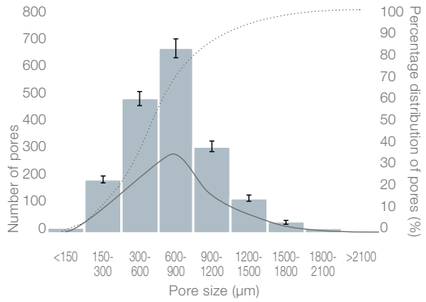


The capillary effect of the micropores leads to a quick blood uptake of the material



The rough surface ensures an excellent and homogenous surface adhesion of cells and proteins

Pore distribution of cerabone®[5]



Excellent hydrophilicity of cerabone®

cerabone®´s rapid and complete hydration with blood or saline solution is crucial for excellent handling characteristics, new bone formation and for the final clinical success.

Its strong capillary action facilitates fast and efficient penetration of the material particles with fluids, nutrients and blood through the three-dimensional, porous trabecular bone network, resulting in excellent handling and reliability in the daily clinical use.

Good hydrophilicity and fast blood uptake of cerabone®[3]

Hydrophobicity of a non sintered bovine bone graft material[3]

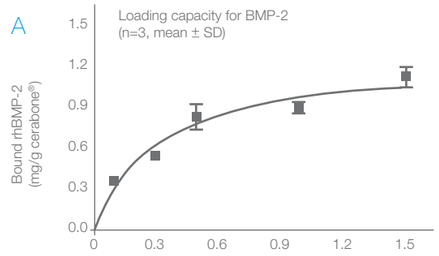
[5] Seidel and Dingeldein (2004). Cerabone® - Bovine Based Spongiosa Ceramic. *Mat.-wiss. u. Werkstofftech.* 35:208–212.

cerabone® serves as an excellent matrix for bone regeneration

cerabone® and growth factors

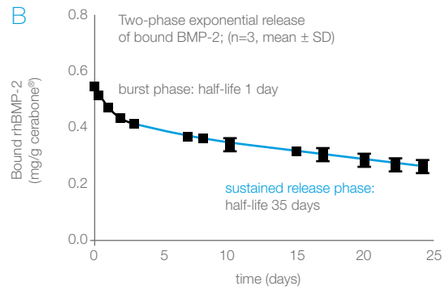
In vitro experiments from Prof. Dr. H. Jennissen and Dr. M. Laub University of Duisburg-Essen/Morphoplant GmbH

A



In vitro experiments show that cerabone® can be loaded with up to 1 mg BMP-2/g.

B



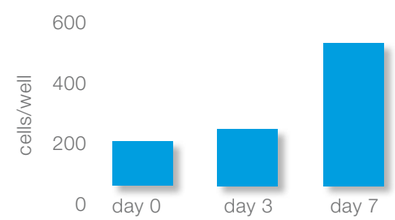
Two-phase controlled exponential release of BMP-2 may provide cerabone® with enhanced osseointegration (Morphoplant GmbH; patent application WO 2009/056567).

Growth of osteoblasts and osteoclasts on cerabone®

In vitro results from Prof. Dr. Dr. D. Rothamel, Clinic Mönchengladbach, University of Düsseldorf and PD Dr. C. Reichert, University of Bonn

The rough surface also promotes the adhesion of serum proteins and cells onto the surface. Osteoblast-like cells quickly adhere to the cerabone® particles. Only attached osteoblasts can start to produce new bone matrix leading to the osseous integration of the cerabone® particles. Another study indicated that the good adherence of osteoclasts promotes the superficial remodeling of the particles.

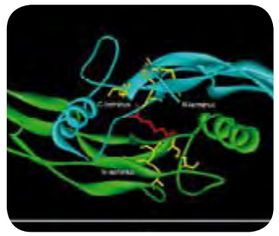
Proliferation of osteoblasts on cerabone®



[6] Konermann et al. (2014). Bone substitute material composition and morphology differentially modulate calcium and phosphate release through osteoclast-like cells. *International journal of oral and maxillofacial surgery* 43:514–521.

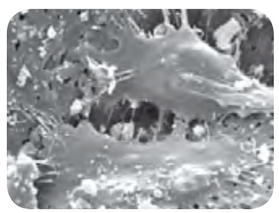
Bone biology:

Scientific results from *in vitro* experiments



BMP-2 structure

Colonialization of cerabone® by osteoblasts
Prof. Dr. Dr. D. Rothamel, Clinic Mönchengladbach



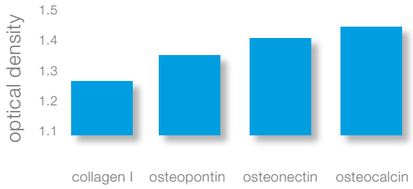
Osteoclastic resorption of cerabone®
PD Dr. C. Reichert, University of Bonn[6]

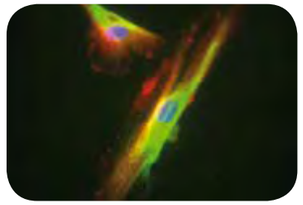
Stem cell research

Interaction of cerabone® with stem cells

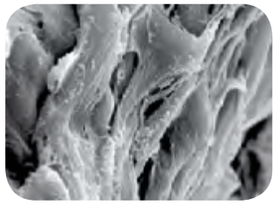
In vitro results from Prof. Dr. B. Zavan, University of Padova

cerabone® supports the differentiation of attached stem cells into osteoblasts that produce new bone matrix.
Collagen, osteopontin, osteonectin and osteocalcin are proteins of the extracellular bone matrix that can be used as markers for bone formation. Their detection 14 days after seeding stem cells on cerabone® indicates the correct differentiation of the cells.





Immunofluorescence staining of stem cells

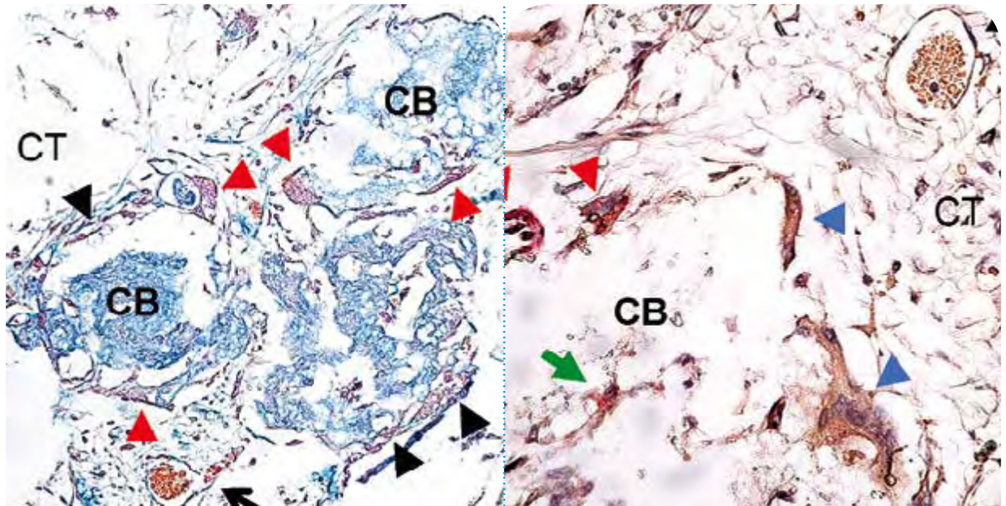


Stem cells seeded on cerabone®

Tissue integration and cellular degradation

In vivo data from a mouse model by Prof. Dr. Dr. S. Ghanaati, University of Frankfurt a. M.

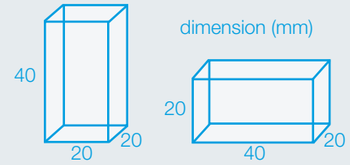
15 days after implantation into the subcutaneous tissue (CT) of mice, cerabone® (CB) is embedded within a well vascularized granulation tissue (blood vessels marked by arrows). No fibrous encapsulation or inflammatory reactions are observed. Mononuclear and multinuclear cells (arrow heads) indicate the onset of cellular degradation of the cerabone® particles.



Maximal stability and good osseous integration of cerabone®

Histological studies on cerabone®

Compressive force (N)	1670±120	4510±770
Compressive resistance (N/cm²)	420±32	564±96
Shear force (N/cm²)	124±35	338±200



Animal study

cerabone® – osteoconduction and bony regeneration

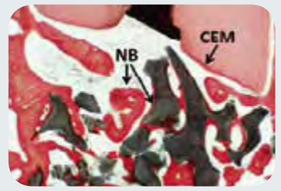
Optimal bone regeneration after bone defect treatment with cerabone® was demonstrated in an animal study.

Bony defects following apicoectomy, were filled with cerabone®.

The histological examination showed a complete bridging of the osteotomy orifice after three months and a well established new bone (NB) and cementum formation (CEM) around the cerabone® particles.

In vivo

Results from Prof. Dr. Z. Artzi, University of Tel Aviv [7]



Section of maxillary block stained with Stevenels blue and Van Gieson's picro fuchsin

Clinical study

cerabone® – osseous integration and optimal stability

Sinus lift study from Prof. Dr. Dr. D. Rothamel, Clinic Mönchengladbach, University of Düsseldorf [8]

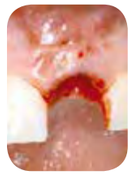
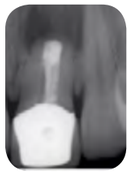
A study on 12 patients showed that cerabone® acts as an osteoconductive material that supports the regeneration of bone after sinus floor elevation surgery. After six months the particles of all biopsies were completely integrated into the newly formed bone matrix, while the grafted area showed excellent volume stability.

Biopsy taken six months after sinus floor elevation. cerabone® particles are covered by a layer of newly formed bone matrix

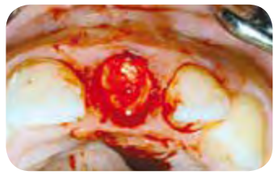
[7] Artzi et al. (2012). Effect of Guided Tissue Regeneration on Newly Formed Bone and Cementum in Periapical Tissue Healing after Endodontic Surgery: An In Vivo Study in the Cat. *Journal of Endodontics* 38:163–169.
[8] Rothamel et al. (2011). Sinus floor elevation using a sintered, natural bone mineral - A histological case report study. *zzi* 27(1): 60.

CLINICAL CASE BY
Dr. Marius Steigmann, Neckargemünd, Germany

CERABONE® FOR COVERAGE OF IMPLANT DEHISCENCE AND RIDGE AUGMENTATION

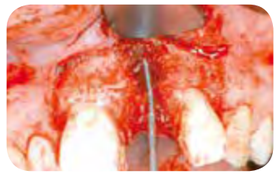



Extraction of tooth 21 after endodontic treatment



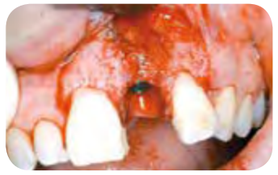
Application of collacone® for stabilization of the blood clot

Buccal bone defect after eight weeks healing time

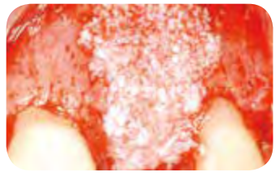


A periodontal probe demonstrates the vertical extension of the defect

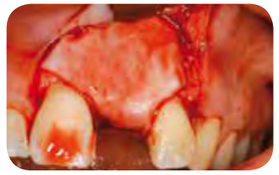
Implant placed into the former extraction socket



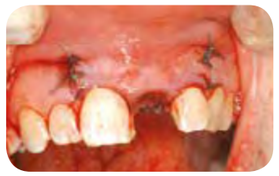
Surface of the implant is covered with autologous bone



Coverage of the autologous bone with cerabone® (0.5 - 1.0 mm)

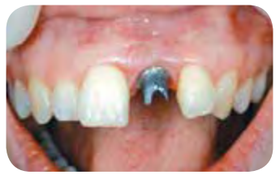


Covering of the bone substitute with Jason® membrane

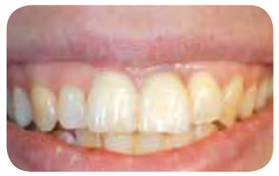


Closure of the site using single sutures after periosteum slitting

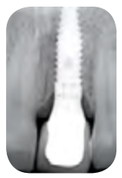
Tension-free suturing maintains undisturbed healing



Abutment installation after implant uncovering, six months after implantation



Final prosthetic restoration with a full-ceramic crown



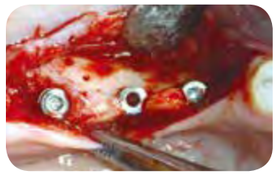
Radiographic control five years post-operative

Contour maintenance
For augmentations in the aesthetic region cerabone® provides long-term dimensional stability and therefore a good bone bed to support an optimal contour of the soft tissue and sustained aesthetic result.

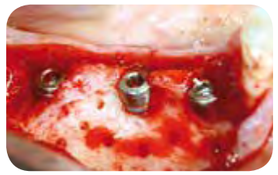
CLINICAL CASE BY
Dr. Viktor Kalenchuk, Chernivtsi, Ukraine

RIDGE AUGMENTATION WITH CERABONE® AND COLLPROTECT® MEMBRANE

Clinical situation with narrow alveolar ridge in the lower jaw



3.5 mm dental implants inserted with inefficient immersion of dental implant platforms



Implants inserted and cortical bone perforated, vestibular view

Alveolar ridge form and size renewal around implants with cerabone®

cerabone® particles size 0.5 - 1.0 mm in place

Covering augmentation site with collprotect® membrane

Situation at re-entry six months post-operative, implants partly covered by new bone matrix

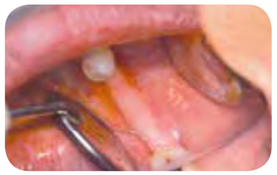
Implants uncovered, good integration of cerabone® particles

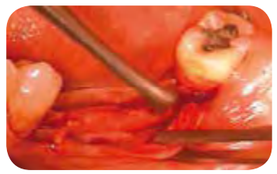
Rehydration
Due to its excellent hydrophilicity, cerabone® particles adhere to each other after mixing with blood or sterile saline solution, allowing optimal handling and good adaptation to surface contours.

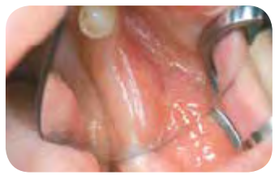
Particle Size
Small cerabone® particles (0.5 - 1.0 mm) allow good adaptation to surface contours; they are especially useful for lateral augmentations or to fill voids when working with autologous bone blocks.
For sinus lift and extensive augmentations the use of large cerabone® particles (1.0 - 2.0 mm) is recommended. The increased space between the large particles enables a better vascularization and improves the regeneration of larger defects.

CLINICAL CASE BY
Dr. Marius Steigmann, Neckargemünd, Germany

CERABONE® FOR HORIZONTAL AUGMENTATION

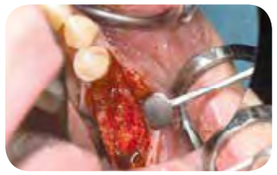

Atrophic alveolar ridge in the left mandible

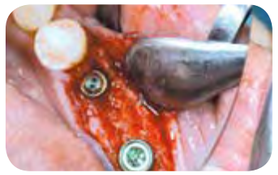

After mucoperiosteal flap elevation, the extensive bone resorption is visible

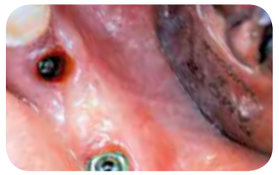

Clinical view six months after augmentation reveals healthy soft tissue situation

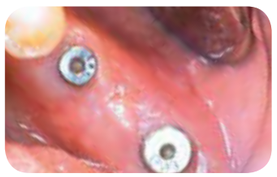


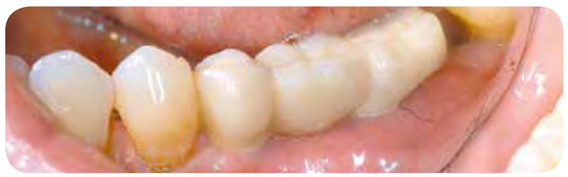
Preoperative cone beam scan revealing good osseous formation of the augmented site


Excellent bone regeneration six months after augmentation with cerabone® particles and Jason® membrane


The wide ridge allows for stable insertion of the two implants


Situation after healing of the soft tissue

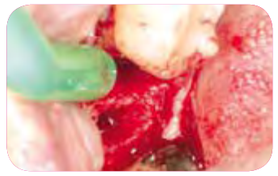

Insertion of gingiva formers allow for soft tissue maturation

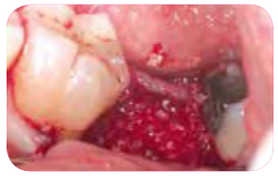

Final prosthetic restoration with ceramic bridge

Antibiotic prophylaxis
Especially before large volume augmentations the patient can be prophylactically adminstered antibiotics, e.g. by starting the antibiosis one day prior to surgery or at least one hour before the surgery by ingestion of a full daily dose.

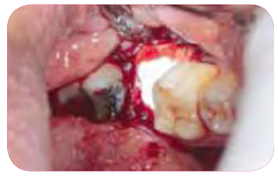
CLINICAL CASE BY
Dr. Paolo Di Capua, Tel Aviv, Israel

SOCKET PRESERVATION WITH CERABONE®, JASON® MEMBRANE AND PERMAMEM®

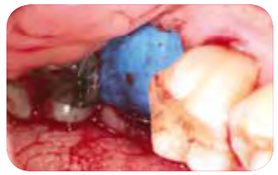

Situation after tooth extraction

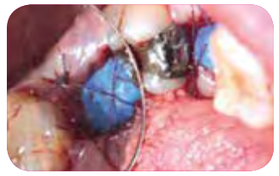

Socket grafted with cerabone®

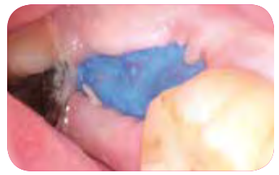

Placement of Jason® membrane over the augmented socket

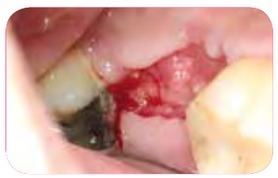

Augmented socket completely covered with Jason® membrane

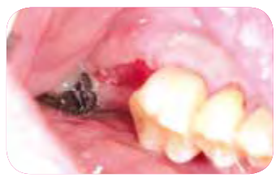

Placement of permamem®

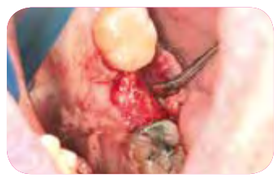

Augmented socket completely covered with permamem®

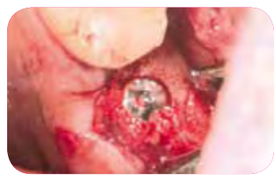

Membrane stabilized with cross suture. Open healing of the membrane


Situation four weeks post-operative

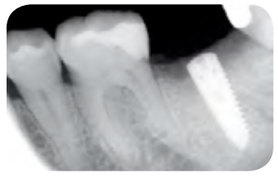

Situation four weeks post-operative after removal of permamem®


Situation five weeks post-operative


Re-entry


Implant placement

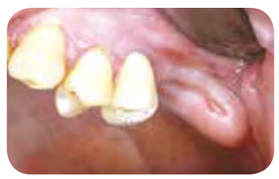

Primary wound closure


Radiographic control

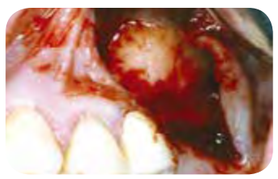
CLINICAL CASE BY

Prof. Dr. Dr. Daniel Rothamel,
Clinic Mönchengladbach, University of Düsseldorf, Germany

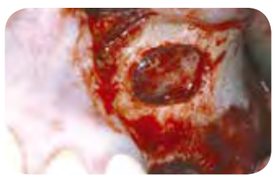
TWO-STAGE SINUS LIFT WITH CERABONE® AND JASON® MEMBRANE



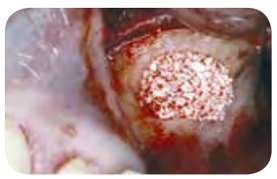
Clinical situation before surgery



Surgical presentation of the atrophic alveolar ridge

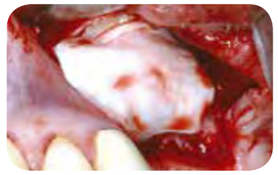


Preparation of lateral sinus window

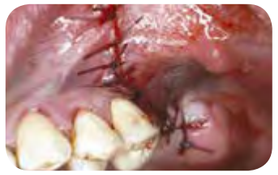


Filling of the sinus cavity with cerabone®

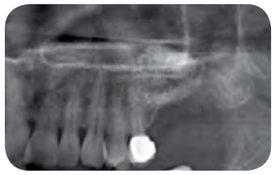
Additional lateral augmentation with cerabone®



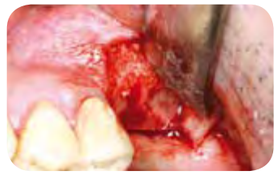
Covering of the augmentation site with the slowly resorbing Jason® membrane



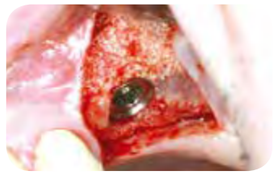
Tension-free wound closure



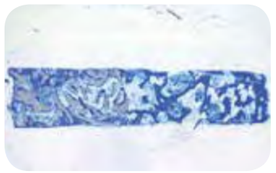
Detail of OPG showing radio-pacity of cerabone®



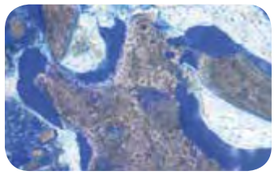
Very good integration of cerabone® particles without soft tissue encapsulation



Implant placed in sufficient bone matrix



Trephine biopsy taken at implant insertion



Detail of the histology showing cerabone® particles covered by newly formed bone matrix

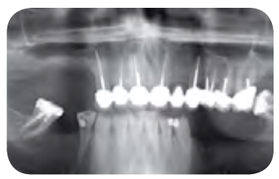
Schneiderian membrane perforation

In case of a small perforation (< 5 mm) of the Schneiderian membrane during sinus floor elevation, the application of a collagen membrane (e.g. Jason® membrane or collprotect® membrane) is a useful tool for perforation coverage. Instruct the patient to avoid sneezing for two weeks and prescribe antibiotics and swelling prophylaxis (e.g. xylomethazoline). Never continue if you find an acute sinusitis with presence of pus.

CLINICAL CASE BY

Dr. Damir Jelušić, Opatija, Croatia

SINUS FLOOR ELEVATION WITH CERABONE® AND JASON® MEMBRANE



Preoperative OPG

Preparation of a lateral window for sinus floor elevation

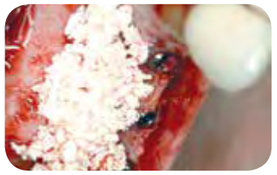
Perforation of the Schneiderian membrane visible after prepara-tion of the lateral window

Jason® fleece inserted into the sinus cavity to cover the Schneiderian membrane

Filling of the sinus cavity with cerabone® (particle size 1.0 - 2.0 mm)

Simultaneous placement of three implants

Jason® fleece covering the lateral sinus window

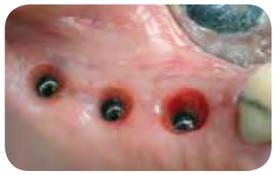


Additional horizontal augmen-tation with cerabone® (particle size 1.0 - 2.0 mm)

Covering of the augmentation site with Jason® membrane

Re-opening six months after implantation, stable integration of the cerabone® particles

Placement of gingiva formers



Good situation after removal of ginigva formers, six weeks after re-opening

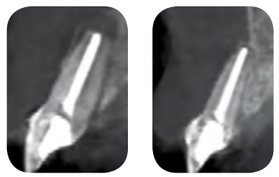
Membrane coverage

For better and more predictable results we always recommend to cover the augmentation area (and the lateral sinus window after sinus floor elevation) with a collagen membrane (e.g. collprotect® membrane or Jason® membrane).

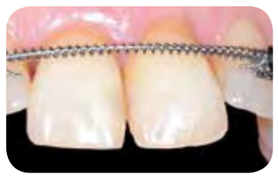
CLINICAL CASE BY

Dr. Damir Jelušić, Opatija, Croatia

SOCKET PRESERVATION WITH CERABONE®

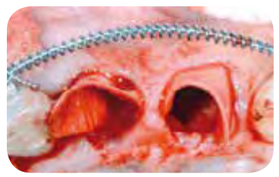


Preoperative CT of teeth 11 and 21 after endodontic treatment

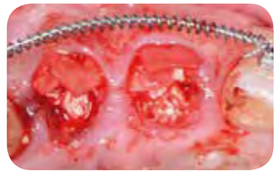


Teeth 11 and 21 not worth saving and planned for extraction

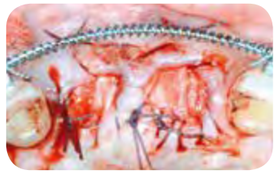
Situation after extraction of the front teeth



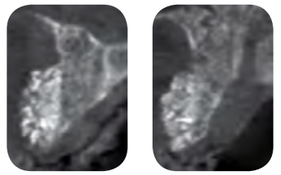
Jason® membranes placed within the extraction sockets



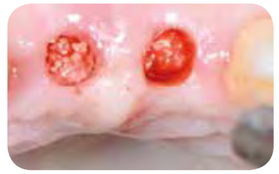
Filling of the sockets with cerabone®



Jason® membrane turned down over the socket and sutured



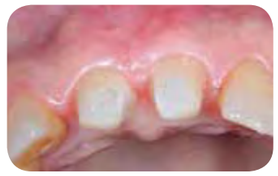
Post-operative CT four months after extraction, good preservation of the ridge



Flapless implant placement (punch technique) four months after socket preparation; good integration of cerabone® particles

Placement of gingiva formers

Final prosthetic situation with individual emergence profile created with provisional crowns (Four months post implantation)



Individualized zirconium abutments

Final prosthetic restoration with ceramic crowns

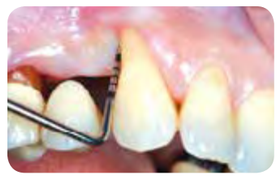
Application of the granules

Avoid to compress the cerabone® particles excessively at the defect site. Open space between the particles permits blood vessel ingrowth and the formation of new bone matrix.

CLINICAL CASE BY

PD Dr. Raluca Cosgarea and Prof. Dr. Dr. Anton Sculean,
University of Marburg, Germany and University of Bern, Switzerland

REGENERATION OF INTRABONY DEFECTS WITH CERABONE® AND COLLPROTECT® MEMBRANE

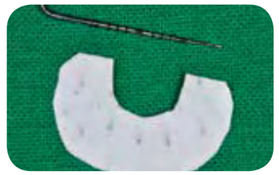


Preoperative defect measurement

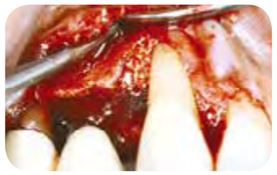
Preoperative x-ray showing intrabony defect

Defect presentation after preparation of mucoperiosteal flap

Rehydration of cerabone® particles



collprotect® membrane cut to shape

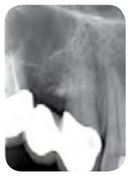


Filling of intrabony defect with cerabone®

collprotect® membrane in place

Wound closure

X-ray control at 12 months post-operative



X-ray at 24 months post-operative

Final prosthetic restoration

Sterile application

Pay attention to sterile application of the substitute, e.g. by using new instruments for granule insertion (and trimming of membranes). Prior contact to saliva may contaminate your graft.

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