Is cerabone® a safe product?

Can a disease/BSE transmission be excluded?
Because of the choice of the raw material (food industry) and the unique manufacturing process, cerabone® can be considered a maximum safe product.

The raw material undergoes a step-wise heating process (up to >1200 °C), which removes all organic components, including potential bacteria, viruses and prions. Heating above 800 °C ensures a complete inactivation of the infectivity of potential prions.\textsuperscript{1,2,3,4} According to the directive EN ISO 22442-1, heating of the material above 800 °C leads to an “acceptable TSE risk” (BSE belongs to the group of TSEs).

Furthermore, the choice of raw material contributes to the safety of cerabone®. Cattle from certified slaughterhouses in New Zealand are used as source for the bovine bone (femoral heads). New Zealand is “recognized as having a negligible BSE risk” according to the World Organization for Animal Health (OIE Resolution No. 20, 27 May 2016). In addition, the animals undergo veterinary inspection and a health certificate is issued for each animal. Processes for control of the raw material and traceability are implemented in the form of a quality agreement with the suppliers. The adherence to the agreements is regularly monitored in audits. Moreover, muscle and skeletal tissue of cows is classified as tissue without demonstrated risk of BSE-infectivity or prions (PrPTSE) by the WHO (WHO Tables in Tissue Infectivity Distribution in Transmissible Spongiform Encephalopathies, 2010).

cerabone® and its production processes fulfill all guidelines and safety regulations of Germany and the EU for bovine bone grafting material including DIN EN ISO 22442-1, DIN EN ISO 22442-2 and DIN EN ISO 22442-3. The end product is gamma-sterilized and stored in a double-sterile barrier packaging.
A patient exhibits an inflammatory reaction (swelling, redness) after treatment with cerabone®. Could this be caused by insufficient biocompatibility of the material, or an allergic reaction against the material?
cerabone® is pure hydroxyapatite that has been produced by elevated heating (>1200°C) of bovine bone. This treatment eliminates all proteins, potential infectious agents (even prions) and antigenic components. Therefore, allergic reactions to cerabone® can be virtually excluded. The product is supplied sterile.

cerabone® has been on the market since 2002 and is distributed in about 100 countries and has been successfully applied in more than 800,000 patients. From our experience, most problems appear as a result of allergic reactions against antibiotics or as a result of contaminations of the material with saliva prior to implantation. Nonetheless, in case of complications customers are encouraged to lodge a complaint. The complaint must include the LOT number of the applied material(s), a description of the incident and the problems occurred.
Will the natural bone structure be impaired or destroyed by the high temperature treatment?

Why is the porous structure and rough surface important for a bone grafting material?
The natural bone structure is preserved during the production process (sintering).\textsuperscript{6}

cerabone\textsuperscript{®} is a highly porous bone grafting material with a porosity of \textasciitilde65-80\% and a mean pore size of \textasciitilde600-900 \textmu m.\textsuperscript{7} Macro pores enable a fast ingrowth of blood vessels and bone cells, while micro pores support fast blood uptake by the capillary effect. Scanning electron microscopic pictures (SEM) also demonstrate the highly structured surface of cerabone\textsuperscript{®}. The rough surface facilitates the adherence of serum proteins and cells. Only adhering osteoblasts can initiate the formation of bone matrix, leading to the osseous integration of the particles.
Is cerabone® hydrophilic and why is hydrophilicity an important factor of a bone grafting material?
The rough surface and interconnected pores of cerabone® lead to an excellent hydrophilicity.

A strong capillary effect enables a fast and efficient penetration with fluid, blood and nutrients into the three-dimensional trabecular network of the particles. Following rehydration the particles stick together, which facilitates their application. In addition, the adhesion of proteins and signaling molecules from the blood improve the biologic properties of cerabone®.
Is there a difference in the hydrophilicity between cerabone® and BioOss®?
cerabone® as well as BioOss® show a good hydrophilicity and take up liquids easily. However, some clinical users have the feeling that cerabone® particles are not as “sticky” as BioOss® particles following rehydration.

This perception may be caused by the smaller particle size of BioOss®, i.e. the bigger range in the size of the small BioOss® granules (0.25-1.0 mm for BioOss® compared to 0.5-1.0 mm for cerabone®). Mixing small particles with fluids yields a different consistency compared to large particles, which can lead to the different perception of the rehydration properties of the two materials.

**The size of the cerabone® particles had been deliberately chosen, with the intention to leave sufficient space between the particles for new bone formation.**

cerabone® is a non-resorbing material, therefore, the formation of vital bone between the particles is of utmost importance for the stability of the grafting site. **Very small particles block these interparticular spaces.**

Nevertheless, cerabone® exhibits a very good hydrophilicity and blood uptake (see above). You can see the efficient blood uptake of cerabone® in comparison to BioOss® in this videos: https://www.youtube.com/watch?v=vnDZPIVwJEO
What is cerabone® composed of and are there any differences in the composition between BioOss® and cerabone®?
Due to the high temperature treatment cerabone® is composed of the pure mineral part of bovine bone without any organic components such as cells or proteins. The high purity of cerabone® was confirmed by various analytical methods. Studies have shown that besides hydroxyapatite no other phases can be found.

cerabone® as well as BioOss® are pure bone minerals of bovine origin without any organic phase. Nevertheless, there are distinctive differences in the composition. cerabone® exhibits a very high crystallinity together with phase purity, i.e. it is 100% pure hydroxyapatite. In contrast, BioOss® shows a residual amount of 3% water. Furthermore, its mineral phase also contains carbonate which is absent in cerabone®. Due to a higher solubility, incorporated carbonate enhances the biodegradation of a grafting material. Therefore, cerabone® may provide a better volume stability when compared to BioOss®.

<table>
<thead>
<tr>
<th></th>
<th>H₂O (wt%)</th>
<th>Soft tissue+organic bone matrix (wt%)</th>
<th>Mineral phase (wt%)</th>
<th>Formal content of CaCO₃ (wt%)</th>
<th>Content of TCP</th>
<th>Formal content of HAP (wt%)</th>
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<tr>
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<td>0</td>
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<td>0</td>
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<tr>
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<td>0</td>
<td>—</td>
<td>100</td>
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<td>\textsuperscript{\textcircled{59.6}}</td>
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<td>59.6</td>
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<tr>
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<td>0</td>
<td>97</td>
<td>3.4</td>
<td>—</td>
<td>93.6</td>
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</table>

Diagram/data based on Tadic et al. 2004, Biomaterials
What happens with cerabone® after implantation?
Due to the natural bone surface structure (micro- and macro pores, rough surface), bone formation starts early following implantation (3-6 weeks).

During the formation of a blood clot, different cell types involved in the wound healing cascade and growth factors originating from the wound area bind to the surface of the scaffold. Precursor cells differentiate into osteoblasts and start to produce new bone matrix.

**After a few months (6-9 months), the cerabone® particles are integrated into the newly formed bone matrix and the surface is completely covered by new mineralized bone resulting in a long-term stable bone situation.** The particles will not be resorbed (or only superficially) and can be found in the augmentation area even after years, ensuring the long-term volume stability of the grafted site. This has been shown by long-term follow-ups of four to eight years.9,10

Histology of a trephine biopsy taken six months after sinus floor augmentation with cerabone® (grey) showing the excellent integration of the particles into the newly formed bone (blue).
When should the re-entry/implantation be performed in case of a two-stage surgery?
It will take about six months until the particles are completely integrated into the newly formed bone matrix. Accordingly, a healing phase of at least six months should be kept to ensure a stable integration of the particles. For smaller defects the healing time can be shorter. Likewise, an earlier re-entry is possible, i.e. after four months, if cerabone® is mixed with autologous or allogenic bone (maxgraft®, ratio 1:1).
Why do human-derived bone grafts (maxgraft® product line) completely resorb while cerabone® does not?
The manufacturing processes of allografts (i.e. human-derived bone grafts) and cerabone® are completely different and therefore, the composition, the bio-physical properties of the materials and the resorption behaviour differ. The high temperature treatment of the bovine bone confers the material into a non-resorbable, purely mineral hydroxyapatite ceramic. The resorption rate decreases as a function of crystal growth during heating; the bigger the crystals, the slower the resorption. Human-derived bone grafts (e.g. maxgraft® product line) are not heat-treated during the production process. The production is based on a wet-chemical process that maintains the natural collagen of the bone matrix. Therefore, maxgraft® will be completely remodeled (natural bone resorption and formation) into patient’s own bone.
Can the cerabone® blocks be used in the same way as allogenic blocks?
No. Augmentation with cerabone® blocks is only a technique for specialists, who have already worked with xenogeneic or synthetic blocks.

The cerabone® blocks are purely mineral and accordingly very brittle and inflexible. Therefore, they are quite hard to handle. The handling and biological properties of cerabone® blocks are not comparable to allogeneic blocks, which contain collagen. Cutting with piezo instruments is possible when the blocks are dry. The risk of breaking is high when trying to fix the blocks with screws, it is therefore recommended to place the blocks without fixation. In this case immobilization by a membrane is required. When fixation is indispensable, carefully prepare a pilot hole and slowly fix without applying any pressure.
Are there any recommendations concerning which product, cerabone® or maxresorb®, is preferred for which indication - or do both products work equally well for all indications?
Generally, both products can be used for the same indications. The optimal material for a certain indication depends on the patients’ health status, aesthetical requests as well as the projected restoration.

The very slow resorption kinetics of cerabone® makes the material the ideal choice in cases where long-term stability is of utmost importance. In older patients with less adequate bone quality, cerabone® may be preferred because of its long-term stability. In younger patients, the use of maxresorb® may be preferred since it will fully resorbs over time and allows complete bone regeneration with optimal biological structure.

In certain clinical situations the long-term stability of cerabone® can be advantageous. In the anterior region where the bony support of the soft tissue is essential to achieve optimal aesthetic results, the long-term stability of a non-resorbable material (cerabone®) supports long-term aesthetic outcomes. If implantation is not foreseen within one to two years following tooth extraction, but a bridge restoration is planned, then cerabone® would be the biomaterial of choice since it remains within the augmentation area and permits to preserve the shape of the ridge. Without the presence of an implant that transfers a physical load to the ridge, the newly formed bone integrating the graft material may resorb. cerabone® is also the material of choice in block augmentation, to cover and protect allogenic or autologous bone blocks from resorption.
In which indications would you recommend the small cerabone® particles and in which one the large particles?
The small particles are particularly advantageous for contouring, e.g. for augmentation in the aesthetic region or to fill remaining gaps when a block grafting is performed. Furthermore, small particles are preferably used for the regeneration of smaller defects and intraosseous defects. Large particles are favorable if large volume defects (e.g. sinus floor elevation) are filled. In addition to the higher volume, there is more space between the large particles which enables a better revascularization of bigger defects.
Before I have only used BioOss®, which is distributed in grams – how can I compare the weight of BioOss® to the cerabone® volumes?
To determine the required amount of a grafting material it is important to estimate the size of the defect and the volume needed to fill that defect. Accordingly, the volume cc (ml) should be compared instead of the weight (g) of a material.

0.25 g BioOss® small granules (0.25-1.0 mm) have a volume of 0.5 cc (ml). The smallest package of BioOss® corresponds to the smallest package of cerabone® (0.5 cc (ml), 1510).

0.5 g of the large BioOss® particles (1.0-2.0 mm) have a volume of 1.5 cc (ml). There is no direct equivalent for cerabone®, you can either chose 1cc (ml) (1520) or 2 cc (ml) (1521).

The volumes of the packages can also be found on the Geistlich price list.

<table>
<thead>
<tr>
<th>BioOss®</th>
<th>Grams</th>
<th>Volume</th>
<th>cerabone® equivalent</th>
<th>Volume</th>
</tr>
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<tr>
<td>BioOss® (0.25 - 1 mm)</td>
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<td>0.5 cc (ml)</td>
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<td>6 cc (ml)</td>
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In the course of the healing process I can sometimes observe particles migrating through the soft tissue or particles in the soft tissue/flap when I perform the re-entry?

What has happened and what should I do?
Particles in the mucosa are often observed, if the augmented site (or filled extraction socket) was not or only incompletely covered with a membrane or if the membrane has resorbed too quickly due to exposure. However, it can also happen that particles are visible in the soft tissue if the augmentation site is covered adequately. This might be caused by the hardness of the cerabone® particles promoting their migration through the tissue. Particles in the soft tissue pose no risk to the patient and do not adversely affect the healing process, as their appearance is not associated with an inflammation. Particles visible in the superficial part of the mucosa will grow out. Particles at the inner aspect of the flap, visible at time of re-entry, can be removed with forceps. Also, loose particles in the most coronal part of the augmentation site that are not embedded in bone matrix can be scratched away. To avoid a migration of particles it is of utmost importance to stabilize the grafting area by covering with a membrane. A fixation of the membrane (e.g. with pins) can be advantageous. Furthermore, mixing of the particles with PRF or hyaluronic acid may also help to stabilize the particles and prevent migration.
Literature:
1. Becker, Organikum, Ambrosius Verlag, Leipzig 1993
2. Morrison, Boyd, VCH 1986