

mis[®]
4BONE™ BCH

Synthetic
Bone Graft

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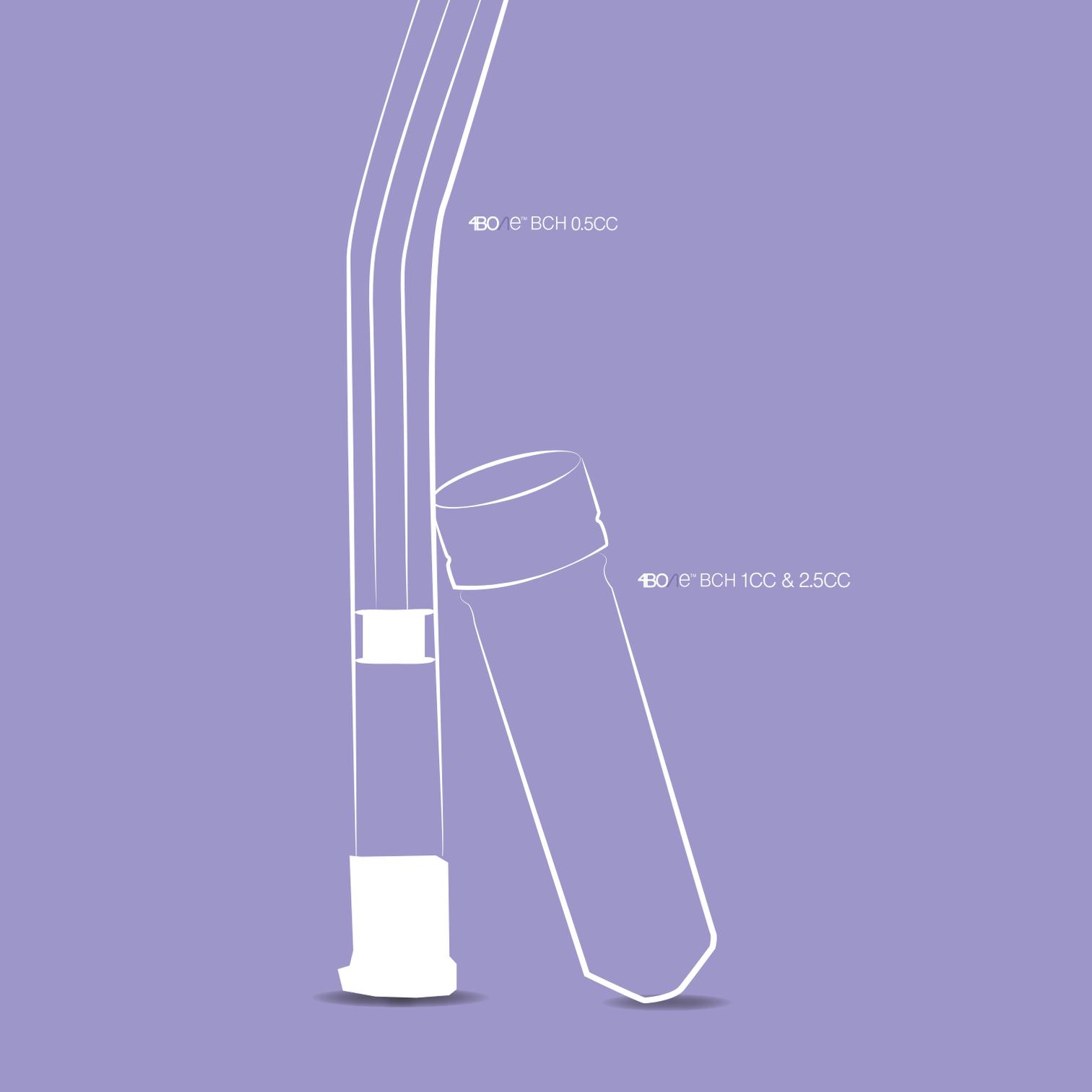
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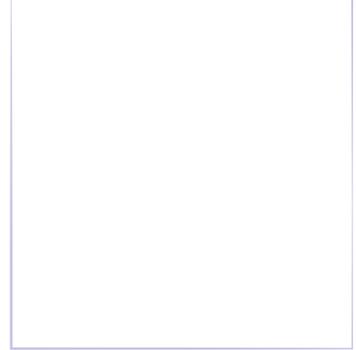
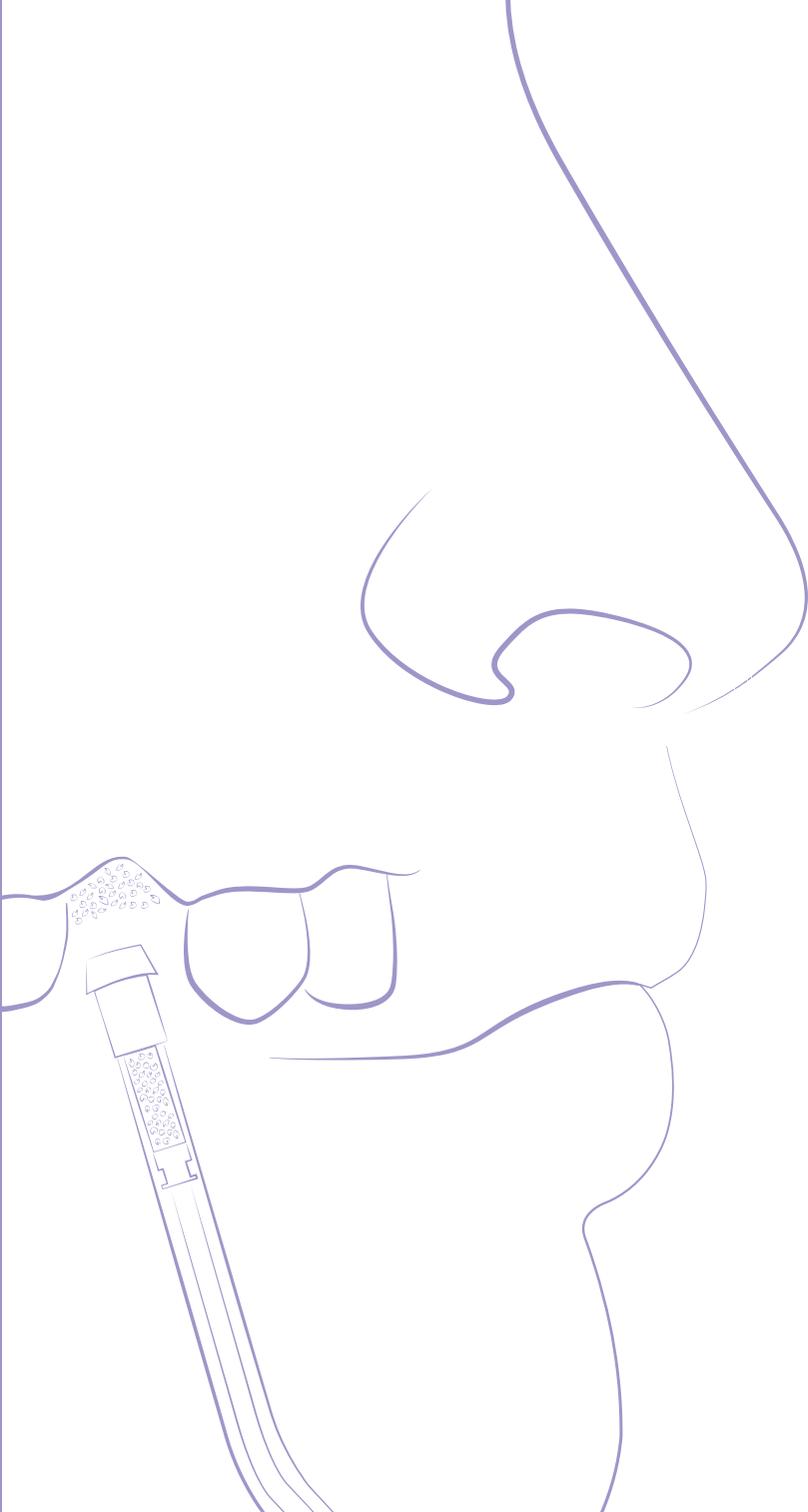
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4BO/e™ BCH 0.5CC

4BO/e™ BCH 1CC & 2.5CC



MIS Bone Grafting Solutions.

MIS offers a variety of advanced bone and tissue regeneration products aimed at a wide range of clinical conditions and surgical requirements. All products in this category are packed in varying weights and volumes and in user-friendly containers and utensils, allowing practitioners to choose the precise quantity required for each procedure.

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6.

MIS 4BONE BCH is a fully synthetic bone graft material made of HA (60%) and TCP(40%). Its osteoconductive structure, porosity 70% interconnected macro-porosity and micro-porosity, promotes colonization of osteogenic cells and allows the diffusion of biological fluids.

The combination of 4BONE BCH optimized morphology and resorption properties enables predictable treatment outcomes.



Product Description.

Porosity

The optimized morphology featured by 4BONE BCH forms an ideal habitat for vital bone growth. 4BONE BCH features both micro-pores and macro-pores, providing the material with an overall porosity rate of 70% and compatibility with the bone generating cells size.

The unique combination it offers between macro and micro-porosity is of great importance when it comes to penetration of biological fluids. This permeability allows for vascularization of biological fluids into the 4BONE BCH granule. Once biological fluids flow into the granule, micro-porosity acts as a sieve that attracts bone generating cells, allowing the formation of new bone from inside the granule.

Macro-porosity

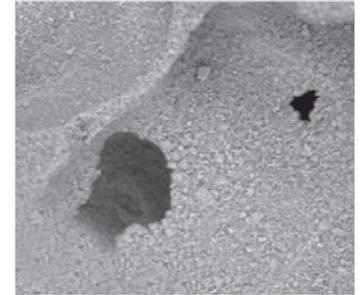
Comprised of 300-600 μm macro-pores, 4BONE BCH 2/3 macro-porosity promotes a deep invasion of osteogenic cells by osteoconduction.

Micro-porosity

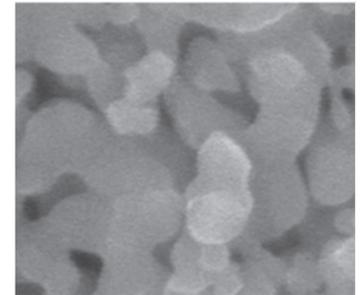
With pores smaller than 10 μm , 4BONE BCH 1/3 micro-porosity comprises interconnected micro-pores allowing for biological fluid diffusion.

Osteogenic Properties

By nature, 4BONE BCH supports the regeneration of new vital bone tissue. Hydroxyapatite which comprises 4BONE BCH, is a specific form of calcium phosphate, that mimics natural bone. Thanks to its small crystal dimensions (HA crystals at nano levels), obtained by a low temperature sintering process, the 4BONE BCH is completely resorbable.



Macropores 400 μm , 70-80% macroporosity



Micro-pores <10 μm , 20-30% micro-porosity

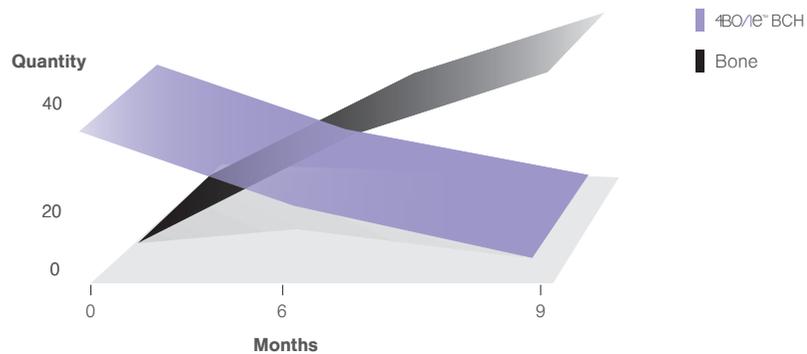
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Bone Resorption/Substitution.

4BONE BCH facilitates architectural bone formation by providing an osteoconductive scaffolding. 4BONE BCH serves as a scaffold for bone deposition during the bone formation process. The mechanical stability of the augmented bone is maintained thanks to the slow resorption rate of hydroxyapatite. Unlike other biphasic calcium phosphates, 4BONE BCH is not only a combination of HA and TCP, but is chemically synthesized as a composite in order to ensure homogenous distribution of the two phases. 4BONE BCH is integrated with the natural human bone remodeling process and is eventually replaced by the natural bone. 4BONE BCH effectiveness, safety and biocompatibility have been clinically and scientifically proven over the past 20 years. It is widely documented and backed by a vast quantity of scientific and clinical literature since 1986.

Recommendations based on clinical experience with 4BONE BCH:

Sinus healing - 6 to 8 months ■ Alveolus filling - 5 to 6 months ■ Healing period may be shortened if 4BONE BCH is mixed with autologous bone.



Comparison Bone Graft Types.

Among the available materials used for pre-implant bone reconstruction, autologous bone is considered to be the gold standard, since it does not require any resorption/substitution process. To overcome autograft limitations, a wide range of biomaterials - natural products of human and animal origins - have been offered, exposing patients to an increased risk of cross-contamination. Consequently, products of synthetic origin were developed, among them, biphasic calcium phosphate, composed of hydroxyapatite (HA) and beta-tricalcium phosphate (β -TCP). With a chemical composition that mimics natural bone apatites and a clinically proven efficiency, 4BONE BCH offers great potential for bone reconstruction.

Type of Bone Graft	Autograft	Allograft (cadaver) Xenograft	Hydroxyapatite TCP	4BONE [®] BCH Synthetic Bone Graft
Origin	Patient bone	Human origin Animal origin	Calcium phosphate	Biphasic phosphate HA/TCP
Quantity	Limited	Unlimited	Chips/blocks	Granules
Benefits	- Fast results - 4 to 6 months to mature in the sinus	- Available in large quantities - Mechanical properties	100% synthetic biocompatible	100% synthetic biocompatible osteogenic
Disadvantages	- Considerable volume needed (5-10cc per side) for typical sinus augmentation - Harvested from intra-oral donor sites - Requires additional invasive surgery	- Dead bone provides limited bone ingrowth - Very slow resorption - Contamination risks - Limited storage	Slow resorption	No initial mechanical properties

10.

4BONE™ BCH Advantages.



Architectural bone remodeling

Specific micro-structures and macro-structures represent a dynamic process, including physico-chemical processes, crystal/protein interactions, cell and tissue colonization and bone remodeling.



Efficient

Bioactive. 4BONE BCH allows cell attachment, proliferation and cell expression.



Safe

100% synthetic. No human or animal origin involved. The product's safety has been well established by twenty years of clinical studies.



Easy

Easy to handle. The granules of 4BONE BCH are easily mixed with the patient's blood or with a physiological solution in a syringe, enabling simple delivery to the augmented site.

0.5cc/1cc Indications.

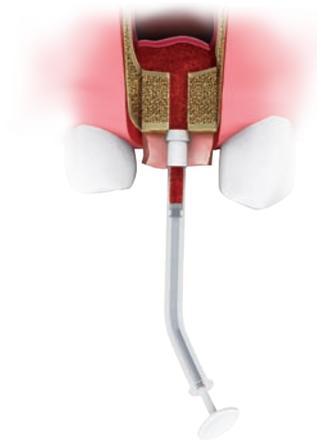
4BONE BCH is intended for use as a bone void filler or augmentation material for use in oral, periodontal or maxillofacial defects. It may also be used as a bone graft extender. 4BONE BCH is intended only for bony voids or gaps that are not intrinsic to the stability of the bony structure. When placed into a bony site, 4BONE BCH is gradually resorbed and replaced with natural bone during the healing process.

Typical uses include:

Periodontal/intra-bony defects ■ Ridge augmentation ■ Extraction sites (implant preparation/placement) ■ Sinus lifting ■ Cystic cavities
 ■ 4BONE BCH is also very efficient in immediate loading procedures and may be used as a bone graft extender.



Easy procedure -
mixing with saline
and/or patient's blood.



Injection of the fully absorbed 4BONE BCH substance into implantation site.



Important

- 1 - Bone granules should be wetted with saline solution.
- 2 - Do not compact or jam 4BONE BCH granules when delivery is attempted.

4BONE BCH is supplied within an easy-to-use syringe.

Quantity: 0.5cc
Granule size: 0.5-1mm

2.5cc Indications.

When large defects and volumes are involved, particles require greater spaces around them in order to allow cell colonization. Using larger particles of 4BONE BCH provides a larger contact surface for cell attachment and bone ingrowth spaces.

4BONE BCH Synthetic Bone Graft injections of 2.5cc, are indicated for large augmentation sites, where long resorption time is crucial for successful results.



Packaging.

4BONE BCH is supplied in a sterile syringe or vial. The syringe packaging facilitates both mixing of the substance with saline and/or with the patient's blood and an easy placement into the augmented site.



4BONE BCH is available in three quantities:

BS-4BS01

0.5cc, granule size:
0.5-1mm syringe

BS-4BS1S

1cc, granule size:
0.5-1mm, vial packaging

BS-4BS25

2.5cc, granule size:
1-2mm, vial packaging

FAQs.



1

What is 4BONE BCH?

Approximately 15 years ago, Dr. Daculsi (France) and Drs. Lynch, Nery, and LeGeros (United States) developed a bio-active product based on biphasic calcium phosphate (MBCP = 4BONE BCH) ceramics. This product combines hydroxyapatite (HA) with Tricalcium Phosphate (TCP), creating a unique combination of HA as the stable phase and TCP as a more soluble phase. 4BONE BCH promotes the formation of new bone by releasing calcium and phosphate ions into the surrounding area. The bio-active process, which is based on the dissolution/transformation processes of HA and TCP into bone, can be used as bulk, coating and injectable bio-material. At the calcium phosphate (CaP)/bone interface, a dynamic process occurs, which includes a physico-chemical processes, crystal/protein interactions, cell and tissue colonization, bone remodeling, and finally a total replacement by a natural functional bone. 500 publications and numerous techniques have documented the outstanding physico-chemical and biological performance of 4BONE BCH. These materials, used for many years in preclinical and clinical trials, have shown that effective bone augmentation, bone reconstruction and bone in-growth efficacy are possible due to the unique characteristics of micro-porous MBCP bio-ceramics.

2

Why use a 100% synthetic bone graft?

While autograft may be hard to collect and while the use of allograft (human) and xenograft (animal) materials may be rejected by your patient, synthetic materials are abundant, effective and completely safe. More than 25 years of fundamental and clinical evaluation have confirmed 4BONE BCH as a bone regenerative material.

3

What is 4BONE BCH comprised of?

4BONE BCH is comprised of a 100% synthetic material which has a composition that is similar to the mineral structure of human bone. The use of hydroxyapatite (HA), which has a slow resorption rate and tricalcium phosphate (TCP), which has a faster resorption rate, guarantees a perfect balance, unique to 4BONE BCH. These characteristics allow 4BONE BCH to be replaced by living bone without a significant loss of volume. Since 4BONE BCH is synthetic, any fears related to pathogen transmission are avoided, securing the patients' safety and wellbeing.

4

Is 4BONE BCH bio-active?

4BONE BCH elicits a spectrum of responses from bone cells and other cells *in-vitro* and *in-vivo* which are similar to those elicited by natural bone. The material allows cell attachment, proliferation and expression. Immediately after the placement of 4BONE BCH, biological fluid diffusion is followed by cell colonization. Macrophages are replaced by mesenchymal stem cells, osteoblasts and osteoclasts, which fill the macro-pores of the material. 4BONE BCH transforms into a living bone with new vascularization due to its angiogenic and osteogenic properties.

2.

Is 4BONE BCH fully resorbable?

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During the process of regeneration 4BONE BCH is fully replaced by bone. Its global porosity >70% at the nanometer level and optimal surface, allow a direct contact with the natural bone turnover process. The micro-structure, approximately 30% of the global porosity, allows for favorable penetration of biological fluids that carry proteins and other growth factors required for bone tissue in-growth with new vascularization, as well as a highly osteogenic matrix. The bio-degradation of 4BONE BCH includes a dissolution of the individual HA and TCP crystals. The resorbability (reflected by *in-vivo* dissolution) of a 4BONE BCH bone graft depends on the TCP/HA ratio - the higher the ratio, the faster the resorbability.

Why use hydroxyapatite and not just tricalcium phosphate?

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Hydroxyapatite (HA), the closest synthetic equivalent to human bone mineral, is bio-compatible and bio-active *in-vivo*. Hydroxyapatite may or may not be resorbable. Resorption rate depends on the size of the HA crystals obtained after synthesis. 4BONE BCH hydroxyapatite is wholly resorbable due to its nano scale crystal size. Bone apatite crystals are formed immediately after cell colonization into the micro-pore. The residual HA acts as a scaffold for the precipitation of the bony crystals. These newly-formed crystals have a large specific surface area, and integrate the osteogenic growth factor of the patient. It has been demonstrated that the HA/TCP micro-structure (micro-pore) combination provides an osteogenic/osteoinductive substitute and promotes angiogenesis.

How long does it take to replace the 4BONE BCH with bone?

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Clinical experience shows that 6 to 8 months are required for the formation of a normal bone. The healing process starts with the colonization of the macro-pores and is followed by the differentiation of mesenchymal stem cells into osteoblasts and osteoclasts. 4BONE BCH supports these processes by functioning as a biocompatible scaffold, similar to bone in its mechanical properties. 4BONE BCH is osteoconductive, however it is important to note that the regeneration speed is affected by the age, medical condition and gender of the patient. The augmentation speed corresponds to the bone physiopathology, bone turn-over and remodeling.

What is the quality of the regenerated bone?

8

4BONE BCH granules form a solid architectural bio-active matrix, which, through its ability to interact with environmental cells, favors vascularization and progressive bone colonization to totally replace the matrix by living bone architecture, similar to normal bone.

What is the main difference between bovine bone and 4BONE BCH?

9

Bovine is a biological apatite that contains carbonated phosphate calcium similar to hydroxyapatite. This is why bovine is characterized by slow degradation when coupled with a collagenous matrix. Bovine bone is considered a synthetic material only if it is sintered in temperatures higher than 1100°C. Without sintering, it shares the risks associated with all biological materials. Xenograft is partially resorbed due to its high density.

3.

What is the main difference between 4BONE BCH and other biphasic calcium phosphates?

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Dr. Daculsi et al. determined the effect of sintering conditions on micro-porosity of cell proliferation and bone in-growth on biphasic calcium phosphate (BCP) bio-ceramics. The resorption of the BCP and bone in-growth are directly related to the sintering temperature - the higher the temperature, the lower the resorption rate and bone in-growth. In-vivo studies have demonstrated that optimum micro-porosity (30%) and large crystal specific surface area of BCP bio-ceramics elicit the optimum cell response and can significantly affect bone in-growth. 4BONE BCH satisfies these specifications: HA/TCP content, 30% micro-pores for bone crystal precipitation, high specific crystal surface area for dissolution, resorption and also – a complete replacement of the micro/macro-porous biphasic calcium phosphate by bone.

How should I use 4BONE BCH for the first time?

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4BONE BCH granules are available either in a vial or syringe for better handling comfort, and in two convenient granule sizes: 0.5-1 mm and 1-2mm. For larger defects (>2.5 cc), 4BONE BCH large granules (1-2 mm) are recommended. The spaces between the granules optimize vascularization. For smaller defects (<2.5 cc), 4BONE BCH small granules (0.5-1 mm) are recommended. Sterile package opening: open the two blisters and remove the vial or syringe.

Vials: Dispense the contents of the vial into a sterile dish. Just before use, hydrate 4BONE BCH with sterile physiological saline to promote cells and soluble protein diffusion. Alternatively, add fresh blood to the soaked granules before use. It is critical that 4BONE BCH is placed on healthy, fresh bone to maximize vascularization of the graft.

Syringe: Hydrate the contents of the syringe by aspirating the sterile physiological saline through the filter until liquid level is slightly higher than the granule level. Expel excess liquid by slightly pressing on the syringe plunger before use.

4BONE BCH can be mixed with autogenous bone to accelerate new bone formation. In large defects (>2.5 cc), it is recommended to mix 4BONE BCH with autogenous spongy bone (or bone marrow). This 4BONE BCH/autogenous bone mixture must be used immediately to preserve cell vitality.

Should I take any precautions while using this material?

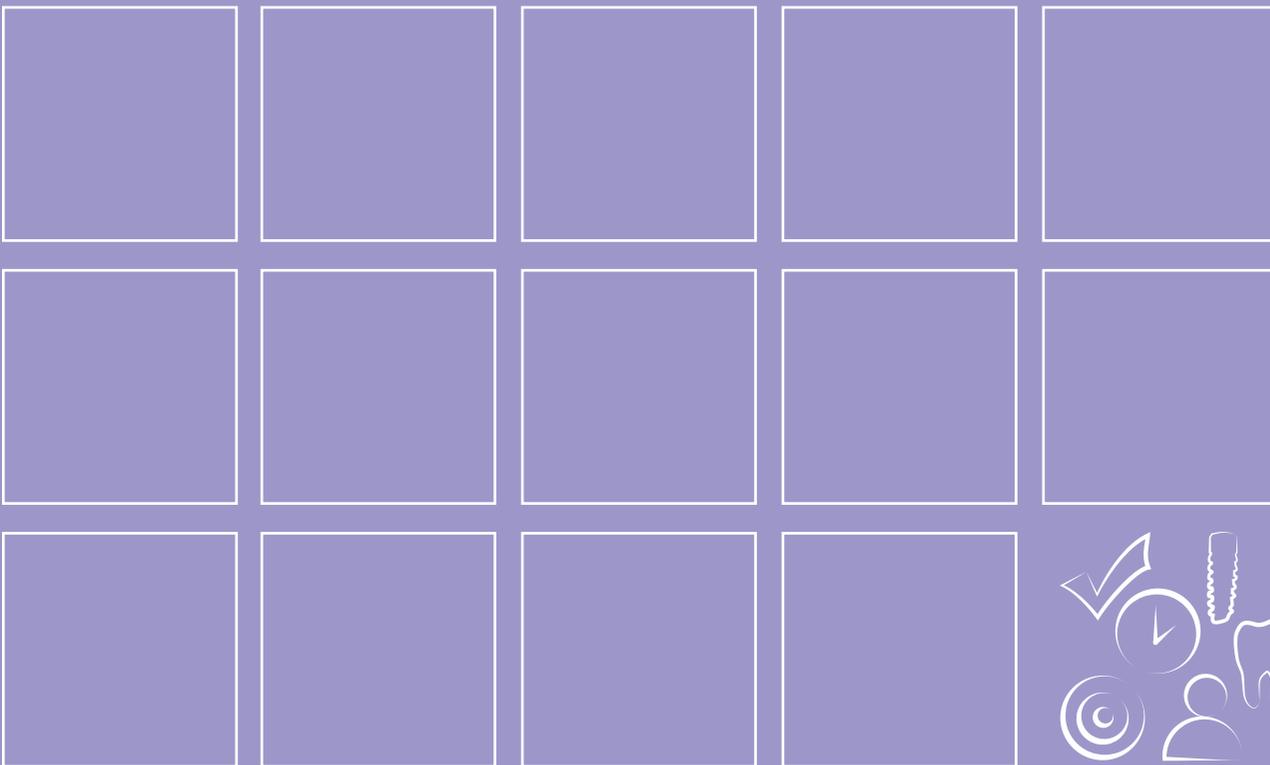
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4BONE BCH does not have any initial mechanical properties so the micro-porous structure must be preserved during handling. Do not press, jam or compact the granules in order to preserve the delicate structure of the material. Fill the defect without any pressure; do not overfill. It is very important to leave space between the grains to allow for bone colonization.

Does any clinical data exist on 4BONE BCH?

13

Over 500 *in-vivo* and *in-vitro* studies on HA/TCP are available. 4BONE BCH is a leading product among synthetic bio-active materials.





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MIS Quality System complies with international quality standards: ISO 13485:2003 - Quality Management System for Medical Devices, ISO 9001: 2008 - Quality Management System and CE Directive for Medical Devices 9342/EEC. MIS products are cleared for marketing in the USA and CE approved.