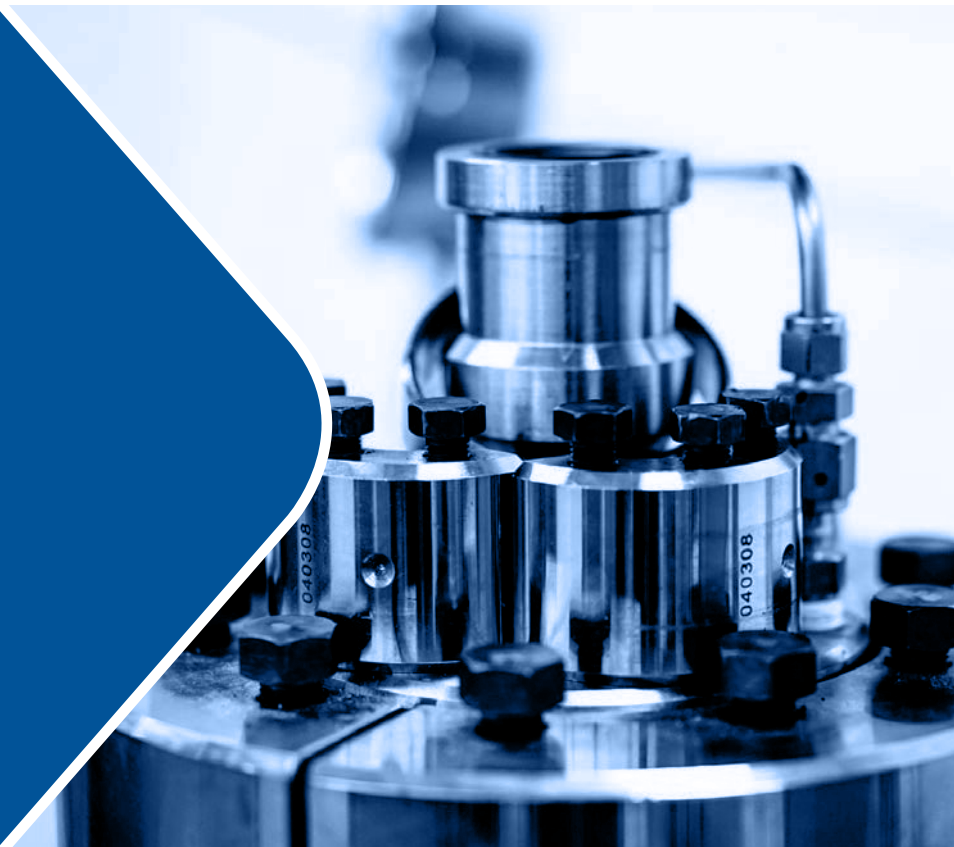




BIOBANK BONE GRAFT
TECHNICAL BROCHURE



ORTHOPAEDIC RANGE

1. ORIGIN OF THE BONE GRAFTS

BIOBank is a French tissue bank authorised by ANSM (French National Safety Agency for Health Products) for the storage, transformation and distribution of bone grafts. The BIOBank grafts are human femoral heads (allografts) which have been taken from living donors during hip arthroplasties.

All samples are obtained in France by orthopaedic surgeons. Donors are selected on the basis of strict observation of health safety criteria, clinical criteria recommended by the French Biomedicines Agency and regulatory serological criteria.

The human femoral heads are converted into virally inactive sterile bone grafts using an exclusive, patented Supercrit® procedure based on the use of supercritical CO₂ which has “process/product” authorisations granted by ANSM.

2. PROCESSING STAGES

BIOBank uses Supercrit® process stages in its specially designed equipment laboratory with high performance clean rooms.

The Supercrit® process is based on an extraction technology using supercritical CO₂ (SC CO₂) to and decontaminate bone tissue. This technology is used in the pharmaceutical and farming-foodstuffs industries for fractionation, extraction and decontamination of biological materials (1). BIOBank is using the Supercrit® process for the first time in human bone tissue.

After mechanical removal of cartilage and osteophytes, the femoral head is subjected to the effect of CO₂ in the supercritical state under action of pressure and temperature. SC CO₂ has the viscosity of a gas and very powerful fat dissolution properties which provides it with its diffusion properties into bone tissue and extraction properties for fats contained in the bone trabeculae.

Through the SC CO₂, fat is completely removed from the humoral head regardless of the head dimensions with a final fat content of under 0.5%. In addition, the SC CO₂ is non-toxic, has antiviral activity (2) and its action on the bone, mineral and collagen framework is entirely neutral.

A chemical process is then used to complete the action of the supercritical CO₂:

- Hydrogen peroxide to oxidise residual proteins in the bone marrow,
- Molar soda to inactivate the prions pursuant to international regulations,
- Ethanol to dehydrate the bone tissue and ensure it is perfectly preserved.

Through the deep cleaning of the bone trabecular network with SC CO₂, the duration of action of these three solvents is shortened compared to conventional processes. The Supercrit® process does not therefore damage the bone tissue and achieves an extremely high level of viral safety.

Once perfectly deep cleaned, the grafts are then dried by simple hot air flow and packaged in a water-tight packaging sterilised by irradiation at 25 kGy. The long-term sterility of the products and their long term storage at room temperature is therefore guaranteed.

The Supercrit® process is a group of particularly effective mechanisms which respect the integrity of the trabecular bone tissue. The grafts are completely safe and preserve the mechanical resistance of fresh bone.

3. IN VITRO CHARACTERISATION

Viral Inactivation:

Viral inactivation has been assessed by the Pasteur-Textcell laboratory in two studies. The results demonstrate the effectiveness of the four stages of the Supercrit® process in inactivating the most resistant viruses, including Parvovirus, up to the heart of the complete femoral head (2, 3, 4).

Integrity of bone tissue characteristics:

- Biochemical analysis: mineral (Ca, P, Mg, Na) and organic composition (hydroxyproline, glycine, alanine and proline) identical to untreated bone tissue.
- Scanning electron microscopy observation: complete removal of cellular and bone marrow cells preserving the conformation of collagen fibres.
- Histological analysis: organic mineral framework and bone architecture unchanged.
- Immuno-histochemical analysis: no denaturation of type I collagen.

Effectiveness of cleaning:

- Lipid content reduced from 60% to under 0.5% without the use of toxic organic solvents.
- Residual water content under 4%.

Preservation of mechanical properties:

Three studies have been conducted to assess the influence of the Supercrit® process on the mechanical properties of the cancellous bone tissue:

- Compression tests in 2 paired series of 100 bone samples treated compared to fresh bone have demonstrated the biochemical parameters for the BIOBank bone grafts before sterilisation by irradiation, with a maximum rupture force of 10.2 ± 5.2 MPa and an elasticity module of 412 ± 149 MPa. No statistically significant difference was found with fresh bone (6).
- Ultrasound analysis of the influence of the dose of gamma irradiation has concluded that there is no difference between 10 and 25 kGy on the elasticity module of the processed dehydrated cancellous bone tissue compared to unirradiated fresh bone. In light of its efficacy this result adds to the demonstration of the benefit of this type of end-stage sterilisation for bone allografts (7).
- Different treatment processes on the cancellous bone have been compared with ultrasound analysis of matched samples before and after treatment. This shows that the Supercrit® process is a viral inactivation process which has least effects on the elasticity of cancellous bone tissue and therefore confirms its ability to optimise preservation of the structural and architectural qualities of the bone (8).

Storage conditions:

The BIOBank bone grafts have a shelf life of 5 years at room temperature.

4. ANALYSIS OF IN VITRO AND ANIMAL EXPERIMENTS

The toxicity tests have demonstrated the absence of toxic residues on the products after the process:



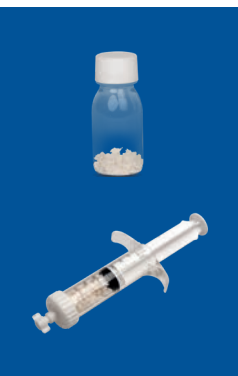
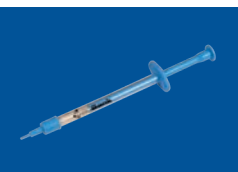
- Negative cytotoxicity test.
- Negative systemic toxicity test.
- No pyrogens.
- Heavy metal content compliant with standard ASTM F 1088-87 ($Pb \leq 30ppm$ - $Hg \leq 5ppm$).

The osteoconduction and tolerability in the intra-osseous site have been assessed in an implantation study in animals. Allogenic sheep bone (one treated series compared to an untreated series) was implanted on condylar site in 12 animals and analysed histologically at 1, 4 and 8 months (4 animals per period) to assess bone healing and tissue tolerance. The results demonstrate improved tolerance and superior and faster bone apposition for the processed samples. The quantitative parameters are all superior for the treated series demonstrating more active bone remodelling (4, 5).

5. PRESENTATIONS AND INDICATIONS

Forms and presentations:

The BIOBank bone grafts are available as different shapes, tailored to the needs for bone regeneration in orthopaedic surgery and neurosurgery

	Family	BIOBank bone grafts designation	Product code
	Anatomic forms	Whole femoral head	90001
		Half femoral head	90003
	Geometric Forms	Cancellous bone dowels 28x09 mm	900909
		Cancellous bone dowels 28x10 mm	900910
		Cancellous bone dowels 28x11 mm	900911
		Cancellous bone dowels 28x12 mm	900912
		Cancellous bone dowels 28x13 mm	900913
		Cancellous bone dowels 28x14 mm	900914
		Cancellous bone block 30x20x10 mm	90011
		Cancellous bone block 20x10x10 mm	90012
		Bone wedge 30x30x6 mm 6 °	90019
		Bone wedge 30x30x8 mm 8 °	90015
		Bone wedge 30x30x10 mm 10 °	90016
Bone wedge 30x30x12 mm 12 °	90017		
Bone wedge 30x30x14 mm 14 °	90018		
	Granules forms	<i>Vial presentation:</i>	
		Cancellous bone granules 3-4 mm 7 cc	90072
		Cancellous bone granules 3-4 mm 18 cc	90074
		Cancellous bone granules 3-4 mm 25 cc	90075
		<i>Presentation in syringe:</i>	
		Cancellous bone granules 3-4 mm 7 cc	90082
Cancellous bone granules 3-4 mm 18 cc	90084		
Cancellous bone granules 3-4 mm 25 cc	90085		
	Powders forms	<i>Presentation in syringe:</i>	
		Cancellous bone powder 0.5 mm 0.5 cc	90035
		Cancellous bone powder 0.5 mm 1 cc	90036
Cancellous bone powder 0.5 mm 2 cc	90037		

Therapeutic indications:

- ◆ The therapeutic indications for the BIOBank grafts are **filling and structural grafts** in:
 - Segmental substance loss during arthroplasties revisions;
 - Curettage of benign bone tumours;
 - Fracture with osteosynthesis;
 - Osteotomy with osteosynthesis;
 - Spinal arthrodesis.

Under these conditions of substantial use depending on the case in question, osteosynthesis may be combined with gradual tailored weight bearing, depending on the primary stability of the reconstruction.

6. PRESCRIPTION AND DISTRIBUTION

The BIOBank grafts is provided on a **personal medical prescription** for single use. The patient must be informed of the use of tissue of human origin.

The prescription should be sent to BIOBank by the grafting surgeon prior to the surgery, by fax +33(0)1.64.42.59.60, or by email. The prescriber can use the model prescription form provided separately by BIOBank.

The information required to deliver the grafts are:

- The name and contact details of the prescribing surgeon (RPPS no.).
- The First name, name, age, date of birth and sex of the recipient.
- The date of the surgery.
- The shape and amount of each graft prescribed.
- The address where the grafts should be sent to.

7. INSTRUCTIONS AND PRECAUTIONS FOR USE

The BIOBank graft is dispensed for immediate use. It must not be frozen or refrigerated.

On receipt and before opening, the integrity of the outer packaging and inner packaging, shelf life of the graft and traceability documents must be checked.

The graft must not be used if the inner or outer packaging are not intact. If it is not used, the graft must be returned to BIOBank in its packaging.

Implantation of several combined graft is the responsibility of the surgeon who must then pay greater attention to management of the traceability documents.

Operating procedure:

The transformed bone tissue needs to be rehydrated in order to confer its natural elasticity. Rehydration allows optimal finishing and adjustment of the graft to the environment of the graft site. The different phases for this preparation must be conducted following very strict aseptic conditions.

Use of anatomical and geographical forms:

- Open the outer bag and recover the internal bag on the sterile operating site.
- Open the internal bag and transfer the graft into a cup.

Use of granule forms in vial:

- Open the outer bag and recover the bottle on the sterile operating site.
- Open the bottle and transfer the granules into a cup.

Use of granule and powder forms in syringe:

- Open the double external packaging and recover the syringe onto the sterile operating field.
- Transfer the rehydration liquid into the syringe following the instructions for use leaflet provided with the graft.

The graft is rehydrated by immersing it in a sterile sodium chloride solution.

The rehydration time depends on the size of the product and should be:

- 30 minutes for femoral heads and half heads.
- 15 minutes for bone blocks or bone wedge.
- 10 minutes for granules.
- Few minutes for powders.

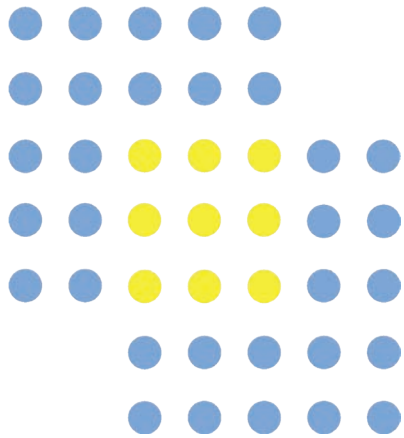
8. TRACEABILITY AND BIOVIGILANCE

To ensure traceability of each graft it is essential that the completed implantation form be returned to BIOBank and that the graft identity form be archived in the patient's records.

Any adverse effects due to or liable to be due to the product must be reported to the local biovigilance representative for the facility in which the product is used or failing this, to BIOBank.

9. BIBLIOGRAPHICAL REFERENCES

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