Teknimed

NANOGEL®

Technical Guide

Injectable Bone Substitute Gel

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1 PRODUCT OVERVIEW

1.1 Description

1.1.1 Design

NANOGEL® bone replacement material is an osteoconductive apatite gel designed for filling osseous defects not intrinsic to bone stability.

This innovative product is a resorbable bone void filler which gives a very quick bone ingrowth for a bone reconstruction.

Percutaneous insertion of NANOGEL® is a simple process, allowing the surgeon to use it for closed cavity filling indications.

NANOGEL® composition is comparable to the mineral composition of human bone, providing a scaffold for new bone ingrowth.

NANOGEL® is resorbed progressively, and is replaced by bone tissue during the remodeling process.

NANOGEL® offers to surgeons wide possibilities of use; open or percutaneous surgery to fill bone defects.

COMPOSITION

- Hydroxyapatite: 30%
- H_2O: 70%
- Particles between 100 nm to 200 nm[1]
- Specific surface higher than 80 m^2/g

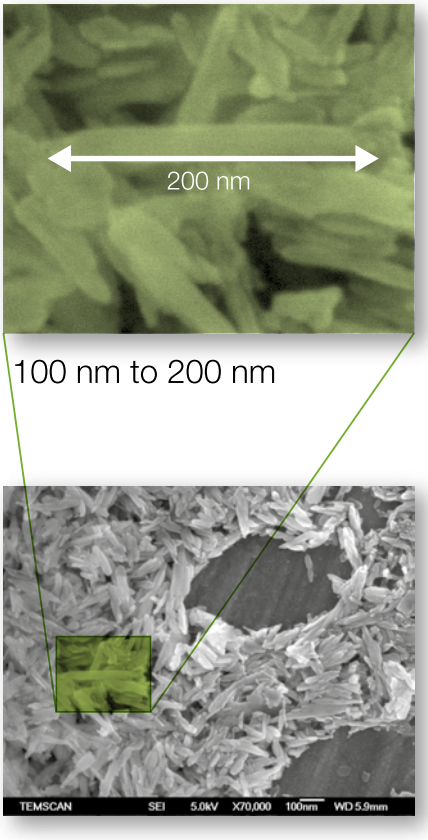


Figure 1: NANOGEL® structure (x70 000 MEB) Source: Teknimed Files

1 The size of the Hydroxyapatite particles that form a part of the amorphous and crystalline mixture are on the nanometer scale.

The size of the crystalline structures was measured by scanning electron microscope to be less than 100 to 200 nanometers.

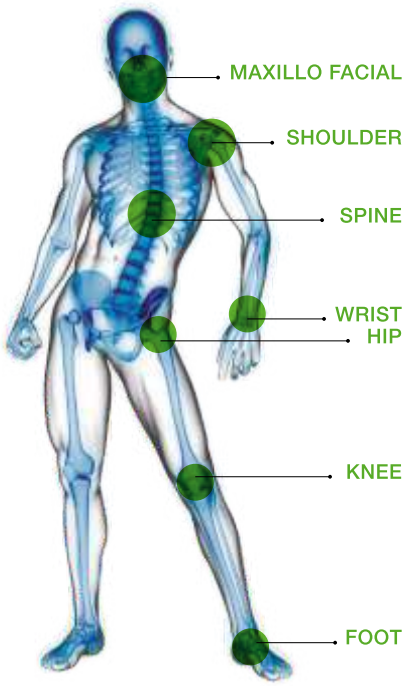
1.1.2 Intended Use and indications

Intended use

NANOGEL® is designed as a material intended for filling osseous defects that are not intrinsic to bone stability.

Indications

The use of NANOGEL® is recommended for:



Orthopaedic surgery:

- Filling after surgical curettage (cysts or benign tumors)
- Osseous defects caused by a traumatic bone lesion
- Filling of cervical or lumbar cages.

Spine surgery:

- Spine fusion
- Interbody cage filling

Dental surgery:

- Filling after surgical curettage (cysts or benign tumors)
- Osseous defects caused by a traumatic bone lesion
- Treatment of alveolar wall and crest defects.

In sites where there are high mechanical stresses, NANOGEL® may only be used as a complement to osteosynthesis equipment.

1.1.3 Claims

NANOGEL® calcium phosphate gel has numerous properties:

	NANOGEL®
Performance claims	• **Resorbable** • **Osteoconductive** • **Injectable gel** • **Percutaneous use**
Safety claim	• **Biocompatible** • **Synthetic** (no risk of infection or cross contamination)

Biocompatibility

NANOGEL® is perfectly tolerated and biocompatible[2]. It is free of any biological substance of animal or human origin, it is sterile and contains no preservatives.

The biocompatibility of hydroxyapatite gel was tested in an animal study during a period of 12 weeks. Integration of the gel to the tissue (cortical and medullary) was observed. No rejection phenomenon, no inflammatory

2 Animal study referenced 097/3/EA and histological analysis report n°08-02TEKNIMED / Nanoparticules HAP). Rapport CIT Animal studies n°08-02 – Internal report

reaction was observed within the host bone, which indicates the perfect biocompatibility of the product.

Bone regeneration

NANOGEL® is composed of hydroxyapatite nano particles in aqueous solution. Its chemical composition and its crystalline structure correspond to those of calcium phosphate of natural bone.

In contrast to other materials, the gel is not sintered; the nano sized particles increase the specific area which accelerates the resorption of the biomaterial.

The gel is osteoconductive and therefore enhances bone synthesis. It allows the bone ingrowth during the healing process; NANOGEL® particles are phagocytized. The gel is completely infiltrated and replaced by autogenous bone.

Quick regeneration

The vascularization of NANOGEL® is an early and rapid bone regeneration process which occurs in less than 1 year.

In most radiological studies, monitoring was carried out up to 6 months of implantation of NANOGEL®.

The results of different tests have shown a complete elimination of the product. Crystals of HA resorb in less than one year[3].

Kinetics of colonization & resorption

In opposition to bio-inert ceramics (alumina, zirconia), NANOGEL® is bioactive, and thus provides chemical exchanges with living tissue.

After implantation, the gel undergoes a dissolution and a metabolic degradation, depending on its chemical (HAP, ß-TCP, BCP), and physical (material porous) structures and on the environment.

The biological fluids in contact with the gel stimulate the apatite crystal precipitation with those of the adjacent bone (process of calcification and not of ossification).

Calcium Phosphate gel is osteoconductive and requires an intimate contact with the bone receiver and the absence of movement between bone and implant.

The clinical results will depend on the kinetics of colonization and resorption, which are conditioned by the chemical and physicochemical characteristics of the implant; these criteria will have thus to be controlled perfectly.

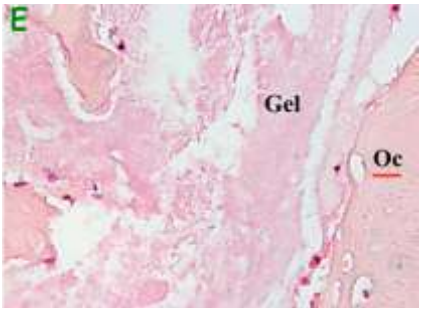
1 week after implantation

During the animal study[4], as early as 1 week after implementation, a thin purple border line was observed around the implanted gel, corresponding to a start of bony mineralization within medullar tissue, witness of a new bone ingrowth.

4 weeks after implantation

After 4 weeks, bony cells could be observed within NANOGEL®.

1week after implantation *(section x40)*



4weeks after implantation *(section x40)*

3 Lifetime report SG150719 – Internal report

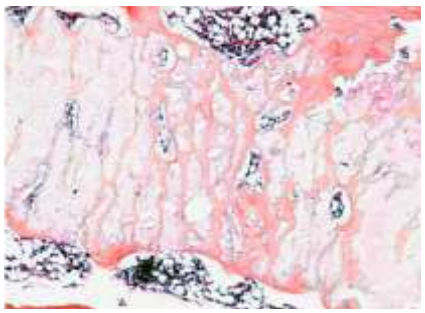
4 Nanogel-Animal study-08-02 - Internal Report

Examination of the gel/bone interface (Oc); no inflammatory response detectable at the interface. The gel is well tolerated.

8 weeks after implantation

Section allowing inspection of the gel scattered within a dense network of almost neo-formed osseous trabeculae.

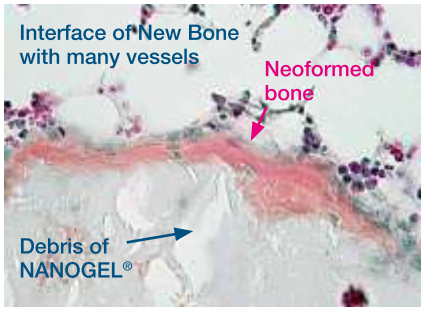
The gel is penetrated by vessels which allow bone ingrowth, suggesting a high activity of bone regeneration; large bone tissue surrounding residual gel is observed.



8weeks after implantation *(section x40)*

12 weeks after implantation

Twelve weeks after implantation, very few traces of gel are observed (resorption); NANOGEL® is being replaced by a dense vascularized bone tissue. No inflammatory response can be detected, the sound neo-formed bone is rich in osteocytes.



12weeks after implantation *(section x40)*

Mechanical properties

Calcium phosphate gels have low mechanical resistance due to their rheology.

In case of load-bearing application, gels should be used with materials of osteosynthesis.

1.2 Instructions and precautions of use

1.2.1 Instructions for use

Teknimed products should only be implanted by qualified operators, with an in-depth knowledge and perfect mastery of the specific operating techniques for Teknimed products.

The surgeon is responsible for any harmful complications or consequences that may result from an erroneous indication or operating technique, poor use of the equipment and non-observance of the safety instructions shown in the operating instructions. These complications cannot be ascribed to the manufacturer or the relevant Teknimed representative.

NANOGEL® bone replacement material is available in the form of an osteocon ductive apatite gel intended for bone filling.

⚠ WARNINGS

For percutaneous injection the use of **gauge trocar less than 13G must be respected**

1.2.2 Precautions of use

Thorough preoperative cleaning and preparation of the site to be filled is needed to ensure that the product is spread evenly in the bone defect area for close contact with the receiver bone.

For open surgery, the provided Luer lock extender allows a more comfortable filling.

Installation with closed foci must take place under radiological control to assess the filling level of the Osseous defect and monitor the product's distri - bution in situ. In this case, the use of a gauge trocar less than 13G must be respected.

⚠ WARNINGS

In site where there are high mechanical stresses, use only in complement of osteosynthesis equipment

The surgeon is responsible for the combination of any medicinal substances with NANOGEL® during implantation.

In sites where there are high mechanical stresses, NANOGEL® may only be added as a complement for osteosynthesis equipment for bone filling.

Do not implant NANOGEL® in contact with skin.

This device is packaged and sterilized for single use only. Do not reuse, reprocess or re-sterilize. Reuse, reprocessing, or re-sterilization may compromise the structural integrity of the device and/or lead to device failure that in turn may result in patient injury, illness or death. Also, reprocessing or re-sterilization of single use devices may create a risk of contamination and/or cause patient infection or cross-infection, including, but not limited to, the transmission of infectious disease(s) from one patient to another. Contamination of the device may lead to injury, illness, or death of the patient.

1.2.3 Side effects

No side effects have been determined to date.

Use during pregnancy and breast- feeding: no contraindications known to date.

Use for children treatment: no contraindications known to date.

Interactions with other agents: none known to date.

1.2.4 Contraindications

The contraindications are the same as those applicable to any bone graft:

- Metabolic conditions
- Use for vertebroplasty
- Use in an infected area (osteomyelitis, tuberculosis)
- In an area with no possibility for regeneration.

2 STATE OF THE ART

2.1 Clinical

2.1.1 Bone

Anatomy

Bones are composed of cortical (compact) and cancellous (trabecular) bone tissues. Their shape and construction are determined by their function and the forces exerted on them.

Cortical bone forms the cortex, or outer shell, of most bones. It is much denser,harder, stronger and stiffer than cancellous bone. Cortical bone facilitatesbone's main functions such as: support of the whole body, rotection for organs, lever for movement, and storage and release of chemical elements, mainly calcium.

Cancellous bone is less dense than cortical bone, which gives it softer, weaker, and more flexible characteristics. It is also known as spongy bone because it resembles a sponge or honeycomb, with many open spaces connected by flat planes of bone known as trabeculae. Cancellous bone is typically found at the ends of long bones and within the vertebrae. It is highlyvascularized and frequently contains red bone marrow where hematopoiesis,the production of blood cells, occurs.

Figure 2 : Mineral part of cancellous bone (Source Wikipedia)

Histology and cytology

Bone is composed of cells, protein matrix, and mineral deposits.

The cells are of three types: osteoblasts, osteocytes, and osteoclasts. Osteoblasts are involved in bone formation by secreting a bone matrixof collagen and ground substances (glycoproteins and proteoglycans).

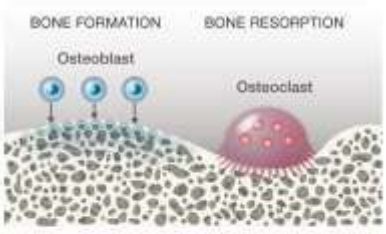


Figure 3 : Principles of bone formation (Source Teknimed)

They provide a framework in which inorganic mineral salts (calcium and phosphorus) are deposited.

Osteocytes are mature bone cells involved in bone maintenance. They are located in lacunae (bone matrix units).

Osteoclasts are multinuclear cells involved in dissolving and resorbing bone.

Structure

Bones are constituted by inorganic (69%) components, consisting of hydroxyapatite (99%); and organic (22%) components, constituted by collagen (90%) and non-collagen structural proteins.

Crystalline hydroxyapatite [Ca_{10} (PO_4)$_6$ ($OH)_2$] is the chief mineral component of bone. Its mineral crystals are deposited along, and in close relation to, the bone collagen fibrils. The end result is a highly organized amalgam of protein, primarily collagen, and hydroxyapatite, that has sufficient structural integrity to serve the mechanical functions of the skeleton.

Bone remodeling

Bone remodeling is a lifelong process wherein old bone is removed from the skeleton, and new bone is added. It involves continuous removal of discrete packets of old bone, replacement of these packets with newly synthesized proteinaceous matrix, and subsequent mineralization of the matrix to form new bone This process also controls the reshaping or replacement of bone following injuries like fractures but also micro-damages which occur during normal activity. Remodeling responds also to functional demands of the mechanical loading.

2.1.2 Bone substitutes

The bone is a dynamic structure which has the property to be renewed and to be rebuilt. The capacities of regeneration are however limited and, in certain circumstances, an osseous filling is necessary to obtain a complete rebuilding of the injured zone. It is the case in particular when the size of the zone to be rebuilt is important (pseudarthrosis, resection of tumors or osseous cysts, important loss of substance at the time of a trauma…) or when the rebuilding is slow (delayed union, disease, old patient…).

Bone substitutes are used in orthopaedic, traumatology, periodontal and orthognathic surgery. They can help recreate a sufficient osseous volume by compensating the thickness or height insufficiencies.

The choice of the type of osseous substitute depends on:

- its nature (synthetic or from animal origin)
- its kinetic of resorption
- the required properties (mechanical continuity or filling)
- the anatomical localization
- the volume to be filled.

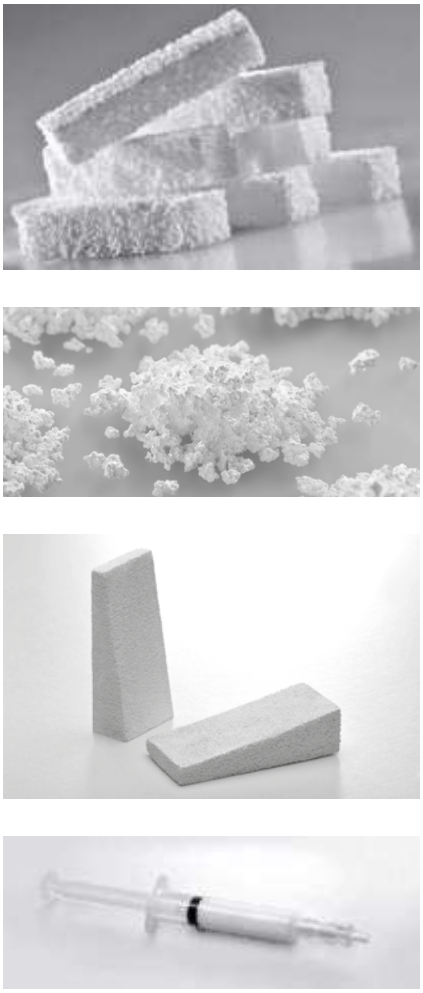


Figure 4: Sticks, granules, wedges and syringe

2.2 Materials

2.2.2 Hydroxyapatite

Because of the difficulties encountered by the use of natural grafts, orthopaedic surgeons and dentists are increasingly turning to synthetic filling materials. Several types of materials are available: bioactive glasses, calcium phosphate compounds, cements, composite materials…

Hydroxyapatite (HA)

HA [$Ca_{10}(PO_4)_6(OH)_2$] is the most stable and the least soluble of all the calcium orthophosphates in physiological conditions. It has a chemical composition similar to the mineral content of bone and teeth. Hydroxyapatite (HA) materials have drawn great interest because they are widely applied as biomedical materials, including such uses as bone fillers, bone tissue engineering scaffolds, bioactive coatings, soft tissue repairs, drug/ protein/gene loading and delivery systems, and column chromatography for rapid fractionation of biomolecules because of their excellent biocompatibility, osteoconductive properties, and similarity to the inorganic component of human bones.

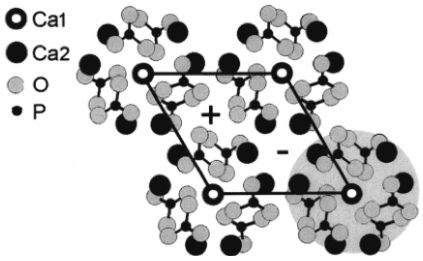


Figure 5 : Source: Symmetry of Posner's Cluster (researchgate.net)

In biomedical applications, the main strength of HA is its excellent biocompa - tibility and osteoconductive properties. HA bio ceramics are usually implanted in the form of granules and porous scaffolds.

However, the major limitation to use HA as load-bearing biomaterials are their low mechanical properties.

The recently developed interest for nanotechnology in many fields, is producing interesting applications for nano-hydroxyapatite, which presents crystals ranging in size between 50 and 1000 nm. The nano-hydroxyapatite has a strong ability to bond with proteins. Besides, nano-hydroxyapatite also acts as filler because it repairs small holes and depressions, a function enhanced by the small size of the particles that compose it. Thanks to its chemical and crystallographic affinity with inorganic components that constitute the bone, hydroxyapatite is able to establish chemical bonds to bone and surrounding tissues.

2.2.3 Functions and properties

Several processes are involved in the successful reconstitution of a bone defect: osteogenesis, osteoconduction and osteoinduction.

Osteogenesis is the formation of new bone by precursor cells that are in the grafting material. In appropriate host conditions, these precursors proliferate and differentiate and then generate new bone.

Osteoconduction is the provision of a scaffold over which new bone formation can be propagated. This facilitates the development of new bone, and also integration with the host skeleton. It depends on many factors such as porosity and surface roughness.

Osteoinduction is the proliferation and differentiation of bone-producing cells from precursors cells in the surrounding host tissues. This is stimulated by a number of molecules such as inflammatory cytokines and bone morphogenetic proteins.

The ultimate aim of porous degradable ceramics implanted into bone is natural organ replacement at void-filling sites. Normal tissue interacting with these ceramics is supposed to replace the implant in time. The degradation rate of HA may change depending on its manufacturing, pore size, porosity, composition, and sintering temperature.

Ceramics, so far, have been identified as compatible and biologically active materials. They are not toxic and do not cause cell death at the surrounding tissue. Biological response to these ceramics follows a similar cascade observed in fracture healing. This cascade includes hematoma formation, inflammation, neovascularization, osteoclastic resorption, and new bone formation. Surrounding tissue is supposed to replace these ceramics as they degrade. A fibrous tissue capsule rarely occurs, and an interfacial bond between the ceramic and the bone is established. Macrophages are presented to be the major infiltrating cells when HA is implanted.

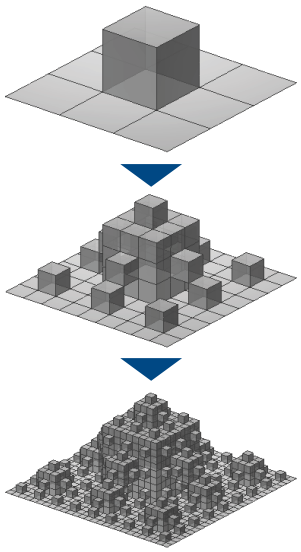


Figure 6 : Principle of surface interaction increased by the reduction of particle sizes

3 SURGICAL TECHNIQUE

3.1 Uses

	SURGERY		USE - ASSOCIATION WITH		
Applications	**Percutaneous Surgery**	**Opened Surgery**	**Associated with AUTOGRAFT**	**Associated with ALLOGRAFT**	**SIMPLE APPOSITION**
Spine		X	X		
Wrist	X			X	X
Shoulder		X	X	X	
Collarbone		X		X	X
Femur		X		X	

NANOGEL® can be used in all types of bone surgery and offers successful long-term outcomes across surgical applications[5], including:

- Cage filling in spine surgery for posterior (PLIF) or anterior (ALIF) lumbar interbody fusion Wrist plate fracture,
- Proximal humerus fractures,
- Clavicle fracture, knee fracture,
- Dental sinus lift augmentation.

3.2 Bone filling surgery

1) Connect NANOGEL® to the trocar (Gauge 11)

2) Press the syringe to fill the bone defects

Cf. video: Nanogel Uses 1 - YouTube
https://www.youtube.com/watch?v=ckO-sAv4mEQ

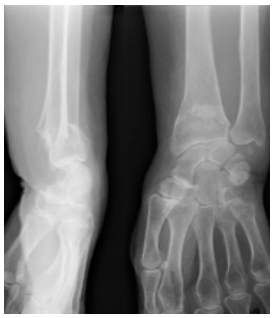
⚠ WARNINGS
In site where there are high mechanical stresses, use only in complement of osteosynthesis equipment

CLINICAL CASE STUDY N°5 [5]

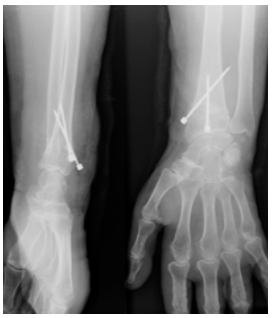
Woman, 78-year-old

Treated for a wrist fracture by arthrodesis with K-wires and injection of NANOGEL®.

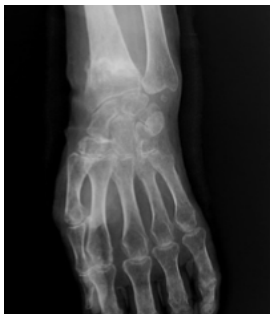
Outcome: at 3-month follow up, fusion of the bone was complete. Good reconstruction.



Pre-op



Post-op



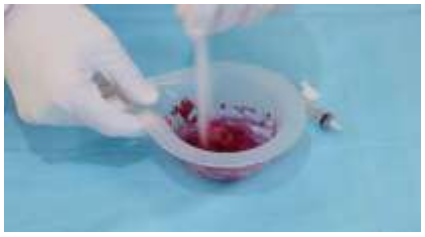
3 months Post-op

3.3 Bone filling paste surgery

The application of the NANOGEL® can also be done in association with blood, autograft, or allograft.

1) Put the NANOGEL® with the Bone & blood mixture in a bowl. (Teknimed Bowl & Spatula, ref: T060404)

2) Mix with the spatula and do the application of the mixture.

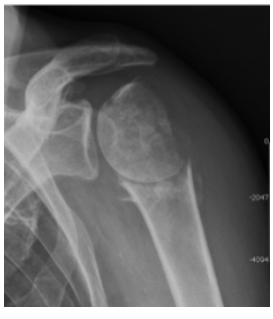


Cf. video: Nanogel Uses 3 - YouTube
https://www.youtube.com/watch?v=7A68M2C8CG0

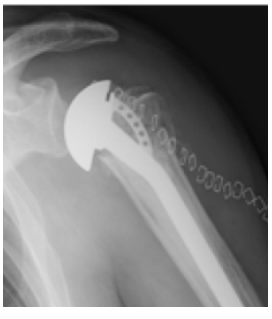
CLINICAL CASE STUDY N°9 [5]

Man, 52-years-old, treated for a proximal humerus fracture with a shoulder prothesis and bone filling with autograft and Nanogel.

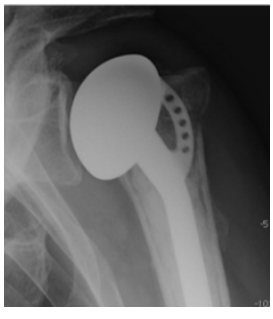
Outcome: at 3 months follow up, bone remodeling can be observed.



Pre-op



Post-op



3 months Post-op

⚠ WARNINGS

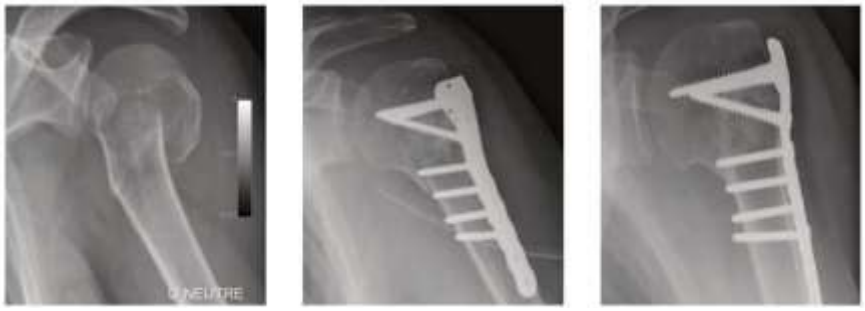
In site where there are high mechanical stresses, use only in complement to osteosynthesis equipment

Do not implant Nanogel in contact with skin and soft tissue, always in cavity.

CLINICAL CASE STUDY N°11 [5]

Woman, 78-years-old, treated for a proximal humeral fracture with plate and screws and bone filling with allograft and Nanogel.

Outcome: at 1 year follow up and removing the osteosynthesis the fusion was done and a good reconstruction.

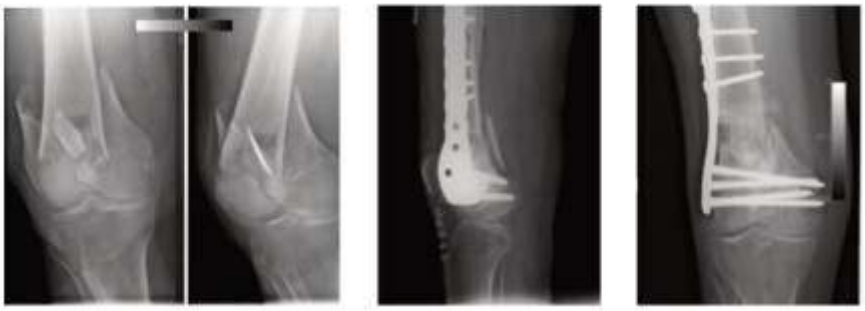


Pre-op | Post-op | 4 months Post-op

CLINICAL CASE STUDY N°14 [5]

Man, 83-years-old, treated for a femoral fracture with plate and screws and bone filling with allograft and NANOGEL®.

Outcome: at 8 month follow up.



Pre-op | Post-op | 3 months Post-op

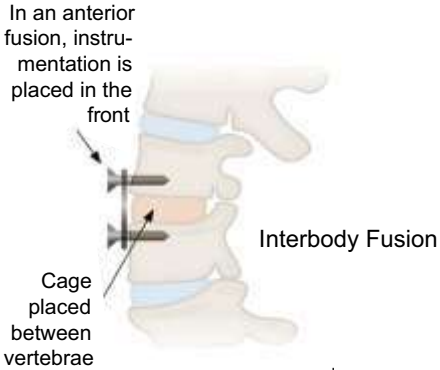
3.4 Spinal Fusion Surgery

Techniques:

In Spinal fusion surgery, bone graft material is placed between two vertebrae in a cage. The material grows and fuses the two vertebrae together.

The bone graft material may be placed between the two transverse processes in the back of the spine (posterolateral fusion), or it may be placed between the vertebral bodies (interbody fusion).

Instrumentation (rods, screws, etc.) is used to hold the vertebrae together while the graft grows and fuses.



4. APPENDIXES

4.1 Technical data

4.1.1 Sterilization

NANOGEL® is sterilized by gamma radiation at 25 kGy.

Before using the product, carefully check the protective packaging to ensure that it has not suffered any damage that may compromise its sterile condition.

Single use. Do not use if the packaging is damaged.

NANOGEL® is delivered sterile, ready for use. When removing the product from its packaging, be careful to observe the asepsis rules

Any re-sterilization of the product is strictly forbidden.

Do not use after the product's expiry date.

NANOGEL® shelf life is 3 years.

4.1.2 Storage

NANOGEL® must be kept in its original unopened packaging at a temperature between + 2°C and + 25°C.

Noncompliance with storage conditions may cause demixtion of the product (Liquid water appears on the gel surface).

⚠ WARNINGS

Risk of product's demixtion:

Do not expose the product at a low temperature under +2°C during shipping and storage.

Please check the color of the temperature indicator on the shipping box.

If the ball has remained transparent the product is compliant, but if it's the ball is purple the product is non-compliant.

4.2 Post Market Surveillance Data

NANOGEL® products are marketed since 2008 by Teknimed.

Since then, post market surveillance (PMS) has been conducted continuously to collect data on NANOGEL® in order to asses if:

- products perform as intended
- any side effects occur
- products are safe
- products are used/applied in the intended way

During the past 5 years, post-market surveillance allowed to conclude that:

- NANOGEL® products are used successfully as bone void fillers.
- No risks of compromising the security of the patients were reported.
- No serious adverse effects have been reported after exposure to NANOGEL® or similar products when used as intended.

Use of the product:

1) Open the cap of the syringe and fill the cage with the gel properly on the first face.

Volumes vary depending on the indications and cages manufacturers. We estimate that the average volume required is:

- 0.5ml (0.5cc) and 1ml (1cc) for cervical cages
- 1ml (1cc), 2.5ml (2.5cc) and 5ml (5cc) for lumbar cages.

2) Press and remove excess of NANOGEL®,

3) Turn over the cage and finish filling the cage with NANOGEL®

⚠ WARNINGS

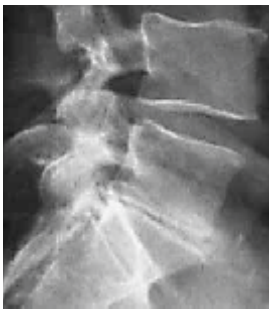
Clean properly the Nanogel in excess on the surface of the cage,

4) Press and remove excess of NANOGEL®

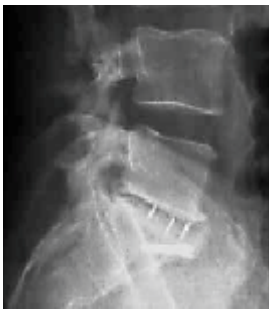
Cf. video: Nanogel Uses 2 - YouTube
https://www.youtube.com/watch?v=6uMo6jtZtSw

CLINICAL CASE STUDY N°18 [5]

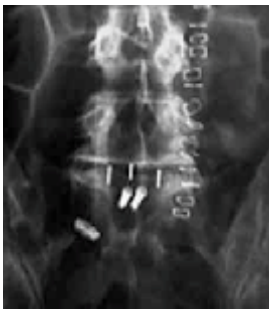
Man, 67-year-old, presenting a degenerative pathology of the lumbar spine (L5- S1). The intervertebral disc is removed and replaced by a cage using an anterior approach. The cage was filled by NANOGEL®



Pre-op



Post-op



1 Year Post-op

5. Extract from PMCF plan on Nanogel, the retrospective multicentric study is an evaluation of 81 clinical cases of patients with a follow up between 6 to 12 months. (PMCF_SO_10)

4.3 Packaging & References

NANOGEL® Gel of nanoparticles of HAP	**Ref.**	**Weight**	**Box size & contents**
0,5ml	T860005	50 g	175 x 135 x 20 mm 1 unit - Packaged in a pre-filled syringe
1m	T860010	50 g	
2,5ml	T860025	50 g	
5ml	T860050	53 g	

4.4 Related products manufactured by Teknimed

TRIHA+®

Granules 3x3x3 mm:

5cc	T824402
10cc	T824405
30cc	T824415

Sticks 5x5x20 mm (x5):

2,5cc	T827104

Sticks 5x5x20 mm (x10):

2,5cc	T827105

Chips 1-2 mm:

10cc	T821210
20cc	T821220

Chips 2-5 mm:

10cc	T822510
20cc	T822520

CERAFORM®

5cc	T804402
10cc	T804405
15cc	T804407
20cc	T804410
30cc	T804415

Sticks (x5) 5x5x20 mm:

2,5cc	T807104

Wedges:

8°	T803008
10°	T803010
12°	T803012

TROCARS

TROCAR TEK:

11Gx125mm	T060430
13Gx125mm	T060431

Bowl + Spatula kit

(pack of 10)	**T060404**

5. FAQ

Is Nanogel radiopaque?

No, it isn't.

Which trocar's minimum measure do you recommend to use with Nanogel?

13G

Is it possible to add a kind of antibiotic to Nanogel? If yes: which one and which volume or percentage?

The surgeon is responsible for the combination of any medicinal substances with NANOGEL® during implantation.

Can we inject Nanogel close to the joint surface?

Installation with closed foci must take place under radiological control to assess the filling level of the Osseous defect and monitor the product's distribution in situ. Care must be taken to avoid contact with skin.

After the injection of the Nanogel injection into the bone defect, Nanogel turn to be solid or still be liquid?

Nanogel will never harden.

Is Nanogel osteoconductive?

Yes, it is.

What is the influence of frost on Nanogel?

If Nanogel has been exposed to frost (or under 2°C) the product is no longer usable because of the water and HAP nanoparticles demixtion.

Is trocar included in the set?

No, it isn't.

Hydroxyapatite and Calcium Phosphate are the same?

Hydroxyapatite (HAP) is part of the calcium phosphate family.

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