# SUMMARY of SAFETY and CLINICAL PERFORMANCE (SSCP) for HEALTH CARE PROFESSIONALS
# NANOGEL®

*Foreword*

This Summary of Safety and Clinical Performance (SSCP) is intended to provide public access to an updated summary of main aspects of the safety and clinical performance of the device.

The SSCP is not intended to replace the Instructions For Use as the main document to ensure the safe use of the device, nor intended to provide diagnostic or therapeutic suggestions to intended users or patients

The following information is mainly intended to users (health care professionals such as surgeons). A summary intended for patients can be found at the end.

## 1. Device Identification and general information

1.1. Device Trade Name(s): **NANOGEL®**

The medical device has also the following private labels: Mectagel®, Neve®, Optifuse®, Ostibone®, Nanotek®, IB Fluid, Teknigel®, Cgel, B-Paste.

1.2. Manufacturer name and address(es):

| **TEKNIMED SAS** | | |
|---|---|---|
| *Headquarters*<br>8, rue du Corps Franc-Pommiès<br>65500 Vic en Bigorre<br>France | *Production and facilities*<br>ZI de Montredon - 11-12, rue d'Apollo<br>31240 L'Union<br>France | *Distribution site (labelling)*<br>ZI de la Herray<br>65500 Vic en Bigorre<br>France |

1.3. Manufacturer's SRN (Single Registration Number): **FR-MF-000001224**

1.4. Basic UDI-DI: **376017704B09DA**

1.5. Medical device nomenclature description / EMDN nomenclature: **P900401 – substitutive devices, bone and tendon**

1.6. Class of device: **III**

1.7. Year when the first certificate (CE) was issued covering the device: **2008**

The medical device has been introduced for the first time in the following countries:

| Country | Year of introduction |
|---|---|
| EUROPE | 2008 |
| RUSSIA | 2012 |
| ARGENTINA | 2015 |
| COSTA RICA | 2015 |
| ISRAEL | 2015 |
| AUTRALIA | 2016 |
| UKRAINE | 2016 |
| VIETNAM | 2016 |
| BRAZIL | 2017 |
| MACEDONIA | 2017 |
| INDONESIA | 2018 |
| SAOUDIE ARABIA | 2019 |
| THAILAND | 2020 |

| | |
|---|---|
| UNITED ARAB EMIRATES | 2020 |
| LIBANON | 2020 |
| MOROCCO | 2020 |
| COLOMBIA | 2021 |

1.8. Authorised representative if applicable; name and SRN: NA as the manufacturer is located in the EU.

1.9. NB's name (the NB that will validate the SSCP) and single identification number: BSI Netherlands (CE 2797)

## 2. Intended use of the device

### 2.1. Intended purpose

NANOGEL® is an osteo-conductive hydroxyapatite synthetic gel for bone ingrowth, intended to be used for filling gaps or bone defect in orthopaedic or spine surgery.

### 2.2. Indication(s) and target population(s)

*INDICATIONS:* NANOGEL® is indicated for the filling of bone defects due to bone injury (such as trauma, disease) or surgical procedure (such as arthrodesis, intervertebral cage filling).

*TARGET POPULATIONS*: Adult patients with a bone defect due to bone injury or surgical procedure.

### 2.3. Contraindications or restriction for use

- Procedures other than those stated in the INDICATIONS section
- Use in vertebroplasty procedures
- Treatment of large bone defects which could impact the stability of bone structure without implementing a mechanical stabilisation system (such as plate(s), screw(s), nail(s), cage(s))
- Subcutaneous use
- Patients susceptible to allergic reactions to the products components
- Due to non-sufficient available clinical evidence, NANOGEL® is contraindicated in paediatric patients, and breast-feeding or pregnant women.

## 3. Device description

### 3.1. Description of the device

*General description of the device*: NANOGEL® is a synthetic osteoconductive bone substitute. Its chemical composition and its crystalline structure correspond to the mineral phase of native bone. It is designed as a substrate for filling osseous defects that are not intrinsic to bone stability or for filling intervertebral cages in spine fusion procedures.

*Operating principles and mode of action*: As a gel, NANOGEL® can be applied directly out of the prefilled syringe and does not have to be pre-moulded to the shape of the defect. Following placement in the bone void or gap, NANOGEL® resorbs during the natural bone remodelling and defect repair processes, and is progressively replaced with bone, allowing to restore bone integrity. NANOGEL® offers wide possibilities of use to surgeons, for open surgeries or for percutaneous injections to fill closed bone defects.



*Design characteristics:* NANOGEL® is a gel of pure hydroxyapatite (HA) particles in aqueous solution. Some particles can be of nanometric size.

| Chemical composition | Concentration |
|---|---|
| Water: $H_2O$ | 70 % |
| Hydroxyapatite: $Ca_5(PO_4)_3(OH)$ | 30 % |

NANOGEL is provided as a prefilled syringe, available in 5 volumes:

| Designation | Volume | Reference |
|---|---|---|
| NANOGEL® | 0.5 ml | T860005 |
| NANOGEL® | 1.0 ml | T860010 |
| NANOGEL® | 2.5 ml | T860025 |
| NANOGEL® | 5.0 ml | T860050 |
| NANOGEL® | 10.0 mL | T860100 |

*Lifetime:* NANOGEL® is an implantable device, intended to be totally absorbed after a minimum of 1 year. The lifetime period may vary depending on the size of the defect, the indication and the physiological condition of the patient. NANOGEL® is not intended to be removed and does not need any maintenance, unless a medical complication would require a surgery.

*Sterilization:* The product is supplied sterile, ready to use. It is sterilized by gamma irradiation at 25kGy. Sterility is guaranteed until the expiry date if the packaging has not been opened or damaged.

NANOGEL® is a single use product.

### 3.2. Reference to previous generation(s) or variants if such exist, and a description of the differences

NANOGEL® is not issued from any previous generation and has no variant.

### 3.3. Description of any accessories which are intended to be used in combination with the device

For open surgery, a luer-lock extender is provided with the prefilled syringe for a more comfortable filling.
For percutaneous injection, the use of a gauge trocar less than 13G must be respected.

### 3.4. Description of any other device or products which are intended to be used in combination with the device

No other specific devices are intended to be used in combination with NANOGEL®.
Yet, as NANOGEL® has no mechanical properties, and as mentioned in the Contraindications section (Cf. § 2.3 above), treatment of large bone defects which could impact the stability of bone structure necessitates the implementation of mechanical stabilisation systems, such as plates, screws, nails, cages or any other osteosynthesis material.

## 4. Risks and warnings

### 4.1. Residual risks and undesirable effects

During risk management analysis, 1 residual risk specific to NANOGEL® has been identified:

- Secondary fracture due to implantation in a load-bearing site without mechanical stabilisation system. Even if it has never been reported in the literature or to Teknimed PMS vigilance (actual occurrence of 0%), this event remains susceptible to occur if the patient puts load on a non-stabilized operated limb before the bone is fully remodelled and rebuilt and the NANOGEL® fully absorbed (i.e.: at the end of its lifetime of 1 year).

During Post-Market Surveillance, 1 complaint involving NANOGEL® has been recorded:

- 1 case of inflammatory reaction and bone osteolysis, consecutive to a subcutaneous implantation in the thumb and diagnosed 3 weeks after the surgery. This kind of event was reported only once to Teknimed PMS vigilance, representing a risk of occurrence of 0.007%.

Both residual risks have been added in the 'Contraindications' and 'Side effects' sections of the IFU.

Another risk, still never reported for NANOGEL® but inherent to any device implantation, has been identified in the risk management analysis and mentioned in the 'Contraindications' section of the IFU:

- Allergy to a component of the product.

Any serious incident occurring in relation to the device must be reported without delay to TEKNIMED and the competent local authority where the user and/or the patient is established.

### 4.2. Warnings and Precautions

Read instructions for use carefully prior to use and follow preparation and handling instructions of medical device. Ignoring the instructions for use may lead to potential undesirable effects.
For an optimum use of NANOGEL®, it is essential to perform a thorough pre-operative review of the patient before the intervention in order to confirm the indication and plan the surgical technique.

*Conservation*

- It is strictly forbidden to re-sterilise the product. This product is supplied sterile unless package has been opened or damaged.
- This device is packaged and sterilised for single use only. Do not reuse, reprocess or resterilise. Reuse, reprocessing, or resterilisation may compromise the structural integrity of the device and/or lead to device failure which may result in patient injury or illness. Also, reprocessing or resterilisation 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.
- Before use, check the protective wrapping carefully to ensure that it has not been opened nor damaged in a way that could affect its sterility.
- Do not use this product after the expiration date printed on the package.

*Before Use*

- Examine the product visually to identify any defects such as crack or deformation. Do not implant products with defects.
- When removing the product from its wrapping, be sure to follow asepsis rules.
- if packaging is unintentionally opened before use or damaged, do not use the product.

*Precautions for Use*

- Implantation must not be done in a site requiring structural support due to the rheology of the product
- For open surgery, the covering must be complete and hermetic by suture of the deep plane.
- For percutaneous surgery, implantation must be done under radiological control to assess the filling of the bone defect and follow the distribution of the product in situ.

### 4.3. Other relevant aspect of safety, including a summary of any field safety corrective action (FSCA) if applicable

None.

## 5. Summary of clinical evaluation and relevant information on post-market clinical follow-up (PMCF)

### 5.1. Summary of clinical data related to equivalent device, if applicable

Non applicable. No devices are claimed equivalent.

### 5.2. Summary of clinical data from conducted investigations of the device before the CE-marking, if applicable

Non applicable. No clinical investigations have been conducted before the CE-marking.

### 5.3. Summary of clinical data from other sources, if applicable

4 articles reporting clinical and radiological outcomes of NANOGEL® have been published in the scientific literature.

In their examination of 65 patients treated with PEEK intervertebral cages filled with HA gel (NEVE®) in ALIF procedures, Norotte and Barrios (2018) observed significant post-operative clinical improvements for patients. The mean difference

in pre- and post-operative Oswestry Disability Index (ODI) was 39.0 ± 9.7 points, representing an improvement of 63.2%. Likewise, the mean difference between the pre- and post-operative VAS score was 5.7 points, representing a statistically significant decrease in pain. According to Macnab's criteria for patient satisfaction, 46 patients (71.0%) reported 'excellent' results 24 months after surgery. Only 4 cases (6.2%) mentioned a 'fair' level of satisfaction because of intermittent pain of sufficient severity that curtailed or modified their work or leisure activities. Radiological examination confirmed that fusion was complete in 62 patients (95.4%). The authors conclude that HA without autologous bone graft is an effective and safe treatment option for ALIF procedures. HA combined with PEEK cages and post-operative bracing can achieve high fusion rates and clinical improvements comparable and even superior to the published results for ALIF using autografts or BMP. Furthermore, they argue that the use of HA nanoparticles as a graft material avoids the complications specific to these materials.

The study by Pojskic et al. (2021) presented the results of 72 patients treated with NANOGEL® in XLIF procedures. All patients presented with back pain and radiculopathy and spinal claudication was present in 41 patients (56.9%). The mean difference between the pre- and post-operative VAS score was 6 points, representing a statistically significant decrease in pain. Following surgery, 45 patients (62.5%) presented an improvement in preoperative neurological deficits and 21 (29.2%) were unchanged. Fusion was complete in 64 patients (89%). Only 1 patient developed symptomatic non-fusion (pseudoarthrosis).

Of the 5 patients treated with MIDLF procedure using interbody devices, NANOGEL® autologous bone chips and cortical bone trajectory (CBT) instrumentation, in the study by Bielecki et al. (2016), 4 were satisfied with the outcomes and 1 was dissatisfied due to recurring pain and sciatica. The mean lower back pain decreased from 6.6 points prior to surgery to 4.4 at the 3-month follow-up. For leg pain, the mean VAS values were 6.6 prior to surgery and 1.8 at the 3-month follow-up. The mean ODI scores were 52% before surgery and 33% at 3-month follow-up. Immediate post-operative X-rays showed satisfactory CBT screw placement in all patients. In radiographs at 6-month after the surgery, there were no signs of screw loosening or other hardware failures such as angulation, fracture or disconnection.

Likewise, in their study of 40 patients with the same treatment, the same authors (Bielecki et al. 2020) found no hardware abnormalities in the early post-operative radiographic images for their series. In total, the authors evaluated 50 fused levels, 178 screws, and 77 interbody devices. Asymptomatic mobility at the fused level was observed in 1 (3%) patient. Solid bone union in situ was achieved at 47 (92%) operated levels, collapsed unions occurred at 2 (4%) levels, a non-union occurred at 1 (2%) level, and 1 patient (1 level, 4 screws) was lost to follow-up. At the most recent follow-up (mean 52.5 months), the average scores for leg pain and back pain decreased by 6 points and 5 points, representing an improvement of 82% and 74% respectively. The average ODI score decreased by 28 points, representing an improvement of 66.7%. Authors conclude that the CBT technique is effective in achieving spinal fusion and clinical improvement and is related to low risk of hardware complications.

### 5.4. Overall summary of the clinical performance and safety

NANOGEL® is a legacy product issued from a long-known technology which has been used in spine and orthopaedic surgeries for many years. It allows successful bone void or intervertebral cage filling, leading subsequently to clinical benefits for the patients such as pain alleviation and improvement in quality of life. Claims for performance and safety of NANOGEL® have been verified and confirmed through Post-Market Clinical Follow-up (PMCF), and Clinical Evaluation:

A first post-market clinical data collection had been conducted by Teknimed in 2015. In this clinical study, 2 different cohorts of patients were followed:

- *Spine cohort*: 56 patients who underwent surgery for spinal fusion (6 PLIF and 50 ALIF procedures). At follow-up (mean 14-month), all patients were free of pain, thanks to the stabilisation of spinal segments, and X-ray images showed that the product was integrated into bone. No complications and no signs of inflammation were observed.
- *Orthopaedic cohort*: 23 patients who underwent surgery following trauma (17 wrists, 4 humerus, 1 clavicle and 1 knee). 6 patients were treated by open surgery and 17 by percutaneous filling. At follow-up (mean 14-month) average VAS pain score dramatically decreased from 7.8 at baseline to 1.2 at follow-up. In case of proximal humeral reconstruction, patients had a good restoration of function. No displacements of fractures were observed. In wrist fractures, at 3-month FU, X-rays showed that the product was in process of resorption. In proximal humeral reconstruction, at 3-month FU,

X-rays showed a good integration of the product with new trabecular bone ingrowth. No complications and no adverse events have been reported.

To conclude, this study demonstrated that NANOGEL® synthetic bone substitute can be used safely and efficiently, not only in small defects, but also in larger load-bearing areas when associated with osteosynthesis material, providing a safe and predictable alternative for autografts and allografts.

### 5.5. On-going or planned post-market clinical follow-up

Teknimed is currently conducting a post-market clinical follow-up to assess clinical, safety and usability outcomes for its Bone Substitutes family of products, including NANOGEL®.

*Title*: Safety and Clinical Performance Assessment of Bone Substitutes used for Bone Voids Filling - A Post-Market Clinical Follow-Up

*Justification/Context*: TEKNIMED has developed several bone substitutes currently used in various types of surgery. Due to their increasing use, there is a need of real-life safety and efficacy data on these products.

*Objective*: The objective is to collect immediate, medium and long-term data (up to 5-year), on the related clinical functional outcomes and complications of market-approved TEKNIMED bone substitutes to assess performance and safety of these products in their current clinical use.

*Study design*: Global, non-controlled, multi-centric, ambispective observational study. Patients will be followed as per local standard medical practices of the investigational sites. Data will be collected pre-operatively, at surgery and at standard of care follow-up visits. A total of 100 patients will be included for NANOGEL® (50 with an orthopaedic indication and 50 with a spine indication).

*Primary endpoint*: Successful bone repair, evaluated through the rate of revision surgery due to failure of the substitute.

*Performance endpoints*: Bone remodelling, well-being and satisfaction of patients, usability and satisfaction of surgeons

*Safety endpoints*: Adverse events will be documented during the study and categorized as whether they are serious and whether they are related to the TEKNIMED device.

*Statistical Analysis*: Statistical analyses will primarily be descriptive as no hypotheses are enunciated to be demonstrated. Each outcome will be reported for each product separately. There are no intentions to compare or test data across products unless requested for a publication or other clinical evidence need.

*Results*: Inclusions started in September 2021 and a first interim report was prepared in October 2021. 2 cohorts of patients were followed:

- *Spine cohort*: 18 patients (8 female and 10 male, mean age 64.78-year-old). 16 patients suffered from degenerative disease and 2 patients presented with a scoliosis. 4 spine levels were treated: L2L3 (n=3), L3L4 (n=8), L4L5 (n=11), L5S1 (n=3) (5 patients treated at 2 levels). Most surgeries (89%) were performed via XLIF procedure (Extreme Lateral Interbody Fusion), 1 via ALIF (Anterior LIF) and 1 via PLIF (Posterior LIF) procedure.
  NANOGEL® was filled directly into the intervertebral cage, without any other addition. The investigator assessed the filling phase as 'easy' in all but 1 procedure (95%), and the device handling/usability as 'good' in all procedures (100%). No perioperative complications were reported.
  All patients (100%) reported a clear alleviation of their pain after the surgery, from a mean level of 7.7 at baseline, to a mean level of 3.6 at follow-up. The global ODI score decreased from a mean value of 48.1% at baseline to a mean value of 18.8% at follow-up. This difference of 30% is well above the minimum of 10% for the difference to be considered significative. A majority patients (73%) were satisfied with their surgery and all of them (100%) reported an improvement (80%) or a stability (20%) in their health status. Yet, 3 of them wouldn't redo the surgery again.
  No adverse events or complications related to NANOGEL® were reported at follow-up.
- *Orthopaedic cohort*: 33 patients (13 female and 20 male, mean age 61.3-year-old). 21 were operated on for prosthesis revision, 5 for arthrodesis, 2 for bone cyst, 2 for fracture and 3 for other reason.
  NANOGEL® was filled directly into the bone void in half of the procedures (n=16) and in association with allograft in the other half (n=17). The investigator assessed the filling phase as 'easy' in all but 1 procedure (95%), and the device handling/usability as 'good' in all procedures (100%). No perioperative complications related with NANOGEL® were reported.
  Patients reported a clear alleviation of their pain, from a mean level of 5.9 at baseline, to a mean level of 1.4 at long term FU. At mid-term follow-up, only 4 (29%) patients reported consumption of antalgic while they were 12 (55%)

before the surgery. At long-term FU, all patients (100%) were satisfied with their surgery and all of them reported an improvement (87%) or a stability (13%) in their health status. Stable osteointegration was observed for all grafts (100%) and bone regeneration was observed in all (95%) but 1 operated site. No cases of osteolysis were observed. No adverse events or complications related to NANOGEL® were reported at follow-up.

To conclude, this interim analysis tends to confirm the previously reported outcomes from the first PMCF study and suggest that NANOGEL® is an effective and safe device relevant to be used in procedures requiring filling with a bone substitute. Yet, a larger cohort will be needed to confirm these conclusions. Inclusions are still current.

## 6. Possible diagnostic or therapeutic alternatives

Bone grafting is required when the size of the void to be rebuilt is important or when the rebuilding is at risk of being slow (delayed union, disease, old patient…). Several categories of bone grafts exist, which encompass a variety of materials and origins, such as:

- Autografts (58% of bone grafts) which are harvested from the patient's own bone tissue, typically the iliac crest;
- Allografts (34% of bone grafts) which are obtained from banked freeze-dried bones of human cadavers;
- Xenografts which are harvested from one individual and transplanted into another individual of a different species. The commonly available xenografts are from coral, porcine, or bovine origin.

All these grafts give good clinical results but, for the patient, they remain at risk of immune reaction leading to acute inflammation, and of infection at the harvesting site of the graft. Synthetic bone substitutes, fully biocompatible, have been designed to avoid these types of adverse events.

| **Therapeutic alternatives** | **Benefits for the patient** | **Risks for the patient** |
|---|---|---|
| *Natural bone grafts* | | |
| Autograft | No risk of immune reaction<br>Good osteoinduction properties | Longer surgery time<br>Complications at the harvesting site |
| Allografts | No complications at the harvesting site<br>Good osteoinduction properties | Low risk of immune reaction<br>Low osteoinduction properties |
| Xenograft | No risks of morbidity at harvesting site | Risk of immune reaction<br>Poor osteoinduction properties |
| *Synthetic bone substitute* | | |
| Biphasic calcium phosphate | No risk of inflammatory reaction<br>Good osteoconduction properties | No osteoinduction properties<br>No mechanical properties |
| Hydroxyapatite | No risk of inflammatory reaction<br>Good osteoconduction properties | No osteoinduction properties<br>No mechanical properties |
| Tricalcium phosphate | No risk of inflammatory reaction<br>Good osteoconduction properties | No osteoinduction properties<br>No mechanical properties |
| Calcium sulphate | No risk of inflammatory reaction<br>Good osteoconduction properties | No osteoinduction properties<br>No mechanical properties |

No consensus has been clearly established in the literature, relative to which graft is more indicated in which bone defect. The choice belongs to the surgeons, considering the patient's condition (allergies, risk of inflammatory response…), the shape (surgical osteotomy, bone cyst curettage…) and the size (wide or small defect) of the bone defect, or the usage (bone void filling, cage filling) of the graft.

## 7. Suggested profile and training for users

Implantation of TEKNIMED products should only be performed in an adapted environment (operating room) and by qualified health care professionals (surgeons, interventional radiologists) having a sound knowledge and full mastery in surgical procedures and preparation techniques specific to NANOGEL®. Preparation techniques may be acquired from the distributors qualified by TEKNIMED. The operator is responsible for any complications or harmful consequences which might result from an erroneous indication or operative technique, an improper use of the equipment and/or a failure to comply with the safety rules provided in the instructions for use. Neither TEKNIMED as manufacturer nor the authorized TEKNIMED representative can be held responsible for these complications.

## 8. Reference to any harmonized standards and CS applied

| Standard reference | Standard revision | Standard title | Applicability |
|---|---|---|---|
| > General standards | | | |
| EN ISO 13485 | 2016 / AC:2018 | Medical devices - Quality management systems - Requirements for regulatory purposes | Fully whenever applicable |
| EN ISO 14630 | 2012 | Non-active surgical implants - General requirements | Fully whenever applicable |
| EN ISO 14971 | 2019 | Medical devices - Application of risk management to medical devices | Fully whenever applicable |
| EN 62366 | 2015 / A1:2020 | Medical devices – Application of usability engineering to medical devices | Fully whenever applicable |
| EN ISO 14155 | 2020 | Clinical investigation of medical devices for human subjects — Good clinical practice | Fully whenever applicable |
| > Product standards | | | |
| ISO 13779-3 | 2018 / A1:2021 | Implants for surgery — Hydroxyapatite — Part 3: Chemical analysis and characterization of crystallinity and phase purity | Fully whenever applicable |
| ASTM F 1088 | 2018 | Standard Specification for Beta-Tricalcium Phosphate for Surgical Implantation | Fully whenever applicable |
| ASTM F 1185 | 2003 | Standard specification for composition of hydroxylapatite for surgical implants | Fully whenever applicable |
| > Biocompatibility standards | | | |
| EN ISO 10993-1 | 2020 | Biological evaluation of medical devices — Part 1: Evaluation and testing within a risk management process | Fully whenever applicable |
| EN ISO 10993-2 | 2006 | Biological evaluation of medical devices — Part 2: Animal welfare requirements | Fully whenever applicable |
| EN ISO 10993-5 | 2009 | Biological evaluation of medical devices —— Part 5: Tests for in vitro cytotoxicity | Fully whenever applicable |
| EN ISO 10993-10 | 2013 | Biological evaluation of medical devices — Part 10: Tests for irritation and skin sensitization | Fully whenever applicable |
| EN ISO 10993-11 | 2018 | Biological evaluation of medical devices — Part 11: Tests for systemic toxicity | Fully whenever applicable |
| EN ISO 10993-12 | 2021 | Biological evaluation of medical devices — Part 12: Sample preparation and reference materials | Fully whenever applicable |
| EN ISO 10993-17 | 2009 | Biological evaluation of medical devices — Part 17: Establishment of allowable limits for leachable substances | Fully whenever applicable |
| EN ISO 10993-18 | 2020 | Biological evaluation of medical devices — Part 18: Chemical characterization of medical device materials within a risk management process | Fully whenever applicable |
| ISO TR 10993-22 | 2017 | Biological evaluation of medical devices — Part 22 Guidance on nanomaterials | Fully whenever applicable |
| EN ISO 10993-23 | 2021 | Biological evaluation of medical devices — Part 23: Tests for irritation | Fully whenever applicable |
| > Labelling and packaging standards | | | |
| EN ISO 14698-1 | 2003 | Cleanrooms and associated controlled environments — Biocontamination control — Part 1: General principles and methods | Fully whenever applicable |
| EN 556-1 | 2001 / AC:2006 | Sterilization of medical devices. Requirements for medical devices to be designated "STERILE". Part 1 : requirements for terminally sterilized medical devices | Fully whenever applicable |

| | | | |
|---|---|---|---|
| EN 868-5 | 2018 | Packaging for terminally sterilized medical devices — Part 5: Sealable pouches and reels of porous materials and plastic film construction — Requirements and test methods | Fully whenever applicable |
| EN ISO 11607-1 | 2020 | Packaging for terminally sterilized medical devices — Part 1: Requirements for materials, sterile barrier systems and packaging systems — Amendment 1 | Fully whenever applicable |
| EN ISO 11607-2 | 2020 | Packaging for terminally sterilized medical devices — Part 2: Validation requirements for forming, sealing and assembly processes — Amendment 1 | Fully whenever applicable |
| ISO 15223-1 | 2021 | Medical devices. Symbols to be used with medical device labels, labelling and information to be supplied. General requirements | Fully whenever applicable |
| EN ISO 20417 | 2021 | Medical devices — Information to be provided by the manufacturer | Fully whenever applicable |
| ASTM D 4169 | 2016 | Standard Practice for Performance Testing of Shipping Containers and Systems | Fully whenever applicable |
| ASTM D 4332 | 2014 | Standard Practice for Conditioning Containers, Packages, or Packaging Components for Testing | Fully whenever applicable |
| ASTM D 4728 | 2017 | Standard Test Method for Random Vibration Testing of Shipping Containers | Fully whenever applicable |
| ASTM D 5276 | 2019 | Standard Test Method for Drop Test of Loaded Containers by Free Fall | Fully whenever applicable |
| ASTM D 999 | 2008 | Standard Test Methods for Vibration Testing of Shipping Containers | Fully whenever applicable |
| ASTM F 1929 | 2015 | Standard Test Method for Detecting Seal Leaks in Porous Medical Packaging by Dye Penetration | Fully whenever applicable |
| ASTM F 88 | 2015 | Standard test method for seal strength of flexible barrier materials | Fully whenever applicable |
| ASTM F1980 | 2016 | Standard Guide for accelerated aging of sterile medical packages | Fully whenever applicable |
| ASTM D642 | 2020 | Standard Test Method for Determining Compressive Resistance of Shipping Containers, Components, and Unit Loads 1 | Fully whenever applicable |

> Microbiology standards

| | | | |
|---|---|---|---|
| EN ISO 11737-1 | 2018 | Sterilization of medical devices — Microbiological methods — Part 1: Determination of a population of microorganisms on products | Fully whenever applicable |
| EN ISO 11737-2 | 2020 | Sterilization of medical devices — Microbiological methods — Part 2: Tests of sterility performed in the definition, validation and maintenance of a sterilization process | Fully whenever applicable |
| EN ISO 11138-1 | 2017 | Sterilization of health care products — Biological indicators - Part 1: General requirements | Fully whenever applicable |

> Sterilisation standards

| | | | |
|---|---|---|---|
| EN ISO 11137-1 | 2015 / A2:2019 | Sterilization of health care products — Radiation — Part 1: Requirements for development, validation and routine control of a sterilization process for medical devices | Fully whenever applicable |
| EN ISO 11137-2 | 2015 | Sterilization of health care products — Radiation — Part 2: Establishing the sterilization dose | Fully whenever applicable |
| EN ISO 11137-3 | 2017 | Sterilization of health care products — Radiation — Part 3: Guidance on dosimetric aspects | Fully whenever applicable |

## 9. Revision history

| Revision number | Date issued | Change description | Revision validated by the Notified Body |
|---|---|---|---|
| 1.0 | 29 OCT 2021 | Creation | ☐ Yes, language: English<br>☒ No |
| 1.1 | 23 MAR 2022 | Modification following Round 1 of questions during MDR clinical review:<br>- quantification of potential occurrence of residuals risks (§ 4.1.)<br>- update of inclusion numbers and clinical outcomes from the currently conducted PMCF study (§ 5.5.)<br>- update of suggested profile and training for users (§ 6.) | ☐ Yes, language: English<br>☒ No |
| 1.2 | 10 JUN 2022 | Modification following Round 2 of questions during MDR clinical review:<br>- precision on the adult population (§ 2.2.)<br>- reformulation of many sections in the lay person part | ☐ Yes, language: English<br>☐ No |

*A summary of the safety and clinical performance of the device, intended for patients, is provided on next page.*

**SUMMARY of SAFETY and CLINICAL PERFORMANCE (SSCP) for PATIENTS - English Version**
**NANOGEL®**

Document revision: 1.2
Date issued: JUN 2022

*This Summary of Safety and Clinical Performance (SSCP) is intended to provide public access to an updated summary of the main aspects of the safety and clinical performance of the device. The information presented below is intended for patients or lay persons. A more extensive summary of its safety and clinical performance prepared for healthcare professionals is found in the first part of this document.*

*The SSCP is not intended to give general advice on the treatment of a medical condition. Please contact your healthcare professional in case you have questions about your medical condition or about the use of the device in your situation. This SSCP is not intended to replace an implant card or the Instructions For Use to provide information on the safe use of the device.*

## 1. Device Identification and general information

### 1.1. Device Trade Name: **NANOGEL®**

The medical device has also the following private labels: Mectagel®, Neve®, Optifuse ®, Ostibone®, Nanotek®, IB Fluid®, Teknigel®, Cgel®, B-Paste®.

### 1.2. Manufacturer name and address(es):

| **TEKNIMED SAS** | | |
|---|---|---|
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### 1.3. Basic UDI-DI: **376017704B09DA**

### 1.4. Year when the device was first CE-marked: **2008**

## 2. Intended use of the device

### 2.1. Intended purpose

NANOGEL® is a paste made of synthetic bone (hydroxyapatite). It is used by surgeons to fill gaps or defects in bones. This paste supports ingrowth of newly formed bone.

### 2.2. Indication(s) and intended patient groups

*INDICATIONS:* NANOGEL® is used to fill bone defects due to bone injury or surgical procedure.

*TARGET POPULATION:* Adult patients with a bone defect due to bone injury or surgical procedure.

### 2.3. Contraindications

- Procedures other than those stated in the INDICATIONS section
- Injection into a vertebra (vertebroplasty procedure)
- Treatment of large bone defects without reinforcement by plate, screw, nail, cage… because the bone could be damaged.
- Use directly under the skin (subcutaneous)
- Use in patients susceptible to allergic reactions to the products components

- Not enough data are available on some categories of patients. NANOGEL® cannot be used in children. NANOGEL® cannot be used in breast-feeding or pregnant women.

## 3. Device description

NANOGEL® is a paste made of synthetic bone (hydroxyapatite). The composition is similar to new bone. This product is used by surgeons to fill gaps or defects in bones. It supports ingrowth of newly formed bone. This paste has no mechanical properties. It should therefore not be used alone in large bone defects. Around large bone defect external mechanical support is needed (plate, screws…).

As a gel, NANOGEL® is provided inside a prefilled syringe. It can be used directly out of the syringe. No preparation is needed. Once in place, NANOGEL® will naturally resorb during the healing process. It will be progressively replaced with bone. Bone will restore its integrity.

NANOGEL® can be used in open surgeries. The product is injectable. It can thus be used in surgeries made through small holes (percutaneous injections).




NANOGEL® is a gel of synthetic bone particles (hydroxyapatite) and water. Some particles can have a very small size (nanoparticles).

| Chemical composition | Concentration |
|---|---|
| Water: $H_2O$ | 70 % |
| Hydroxyapatite: $Ca_5(PO_4)_3(OH)$ | 30 % |

*Lifetime:* NANOGEL® is an implantable device. It is totally absorbed after a minimum of 1 year The lifetime of the product in patient's body depends on different factors: size of the defect, location, clinical condition of the patient. NANOGEL® is not intended to be removed and does not need any maintenance, unless a medical complication would require a surgery.

## 4. Risks and warnings

*Contact your healthcare professional if you believe that you are experiencing side-effects related to the device or its use or if you are concerned about risks. This document is not intended to replace a consultation with your healthcare professional if needed.*

### 4.1. Remaining risks and undesirable effects

- New fracture due to use in a too large bone defect. Even if it has never been reported in the literature or to Teknimed vigilance (actual occurrence of 0%), this event remains susceptible to occur in case that the operated site hasn't been stabilised with osteosynthesis material (such as a plate or screw(s)) and if the patient puts load on the operated limb, before the bone is fully remodelled and rebuilt and the NANOGEL® fully absorbed (i.e.: at the end of its lifetime of 1 year).
- Heat, pain, redness, swelling or loss of function (inflammatory reaction) and bone destruction, consecutive to implantation under the skin. This kind of event has been reported only once to Teknimed PMS vigilance (inflammation of the thumb, diagnosed 3-week after the surgery), representing a risk of occurrence of 0.007%.

- Allergy to a component of the product is another risk. It has still never been reported for NANOGEL®. It is however inherent to any device implantation. Any serious incident occurring in relation to the device must be reported without delay to TEKNIMED and the competent local authority where the user and/or the patient is established.

### 4.2. Warnings and Precautions

No warning and precautions for patients. This device is only used by healthcare professionals.

### 4.3. Summary of any field safety corrective action (FSCA) if applicable

None. No FSCA have been issued since the release of NANOGEL® on the market

## 5. Summary of clinical evaluation and post-market clinical follow-up

### 5.1. Clinical background

Synthetic bone substitutes have been developed more than 50-year ago. They offer an alternative to the bone grafts of human or animal origins which can induce infection at the sampling site (often the pelvis).
NANOGEL® is a well-known legacy device which has been sold for more than 12 years. A long history of surveillance of its safety since its release on the market has proved that it carries no significant risks.

### 5.2. Clinical evidence for CE marking

NANOGEL® was first CE marked and placed on the market in 2008. At that time, the clinical safety was shown by equivalence with another product. This equivalent product was already approved and sold on the market.
More recently, Teknimed performed two clinical studies. They confirm the performance and safety.
A first post-market clinical data collection had been conducted in 2015. In this clinical study, 2 different groups of patients were followed: (i) Spine cohort: 56 patients who underwent surgery for spinal fusion; (ii) Orthopaedic cohort: 23 patients who underwent surgery following trauma (17 wrists, 4 humerus, 1 clavicle and 1 knee).

- *Spine cohort*: 14 months after the surgery, all patients were free of pain, thanks to the stabilisation of the vertebrae, and radiographic images showed that the product was integrated into bone. No complications and no signs of inflammation were observed.
- *Orthopaedic cohort*: 6 patients were treated by open surgery and 17 by percutaneous filling. 14 months after the surgery, the level of pain dramatically decreased, from 7.8/10 at baseline to 1.2/10 at follow-up. In case of proximal humeral reconstruction, patients had a good restoration of function. No displacements of fractures were observed. In wrist fractures, after 3 months, radiographs showed that the product was in process of resorption. In humeral reconstruction, after 3 months, radiographs showed a good integration of the product with new bone ingrowth into the gel. No complications and no adverse events have been reported.

To conclude, this study demonstrated that NANOGEL® can be used safely and efficiently in small defects and in large load-bearing areas when it is associated with supportive material, providing a safe and predictable alternative for autografts and allografts.

Teknimed is currently conducting a second clinical study (post-market clinical follow-up). Its goal is to confirm performance and safety. In this study, 2 cohorts of patients are followed:

- *Spine cohort*: 18 patients (8 female and 10 male, mean age 64.78-year-old, 16 patients with degenerative disease and 2 patients with scoliosis). No perioperative complications were reported.
  All patients (100%) reported a clear alleviation of their pain after the surgery, from a mean level of 7.7/10 at baseline, to a mean level of 3.6/10 at follow-up. The global ODI score (a performance score specific for the spine) decreased significatively of more than 30% at follow-up. A majority of patients (73%) were satisfied with their surgery and all of them (100%) reported an improvement (80%) or a stability (20%) in their health status. Yet, 3 of them wouldn't redo the surgery again.
  No adverse events or complications related to NANOGEL® were reported at follow-up.
- *Orthopaedic cohort*: 33 patients (13 female and 20 male, mean age 61.3-year-old). 21 were operated on for prosthesis revision, 5 for arthrodesis, 2 for bone cyst, 2 for fracture and 3 for other reason.

NANOGEL® was filled directly into the bone void in half of the procedures (n=16) and in association with allograft in the other half (n=17). No perioperative complications related with NANOGEL® were reported.
Patients reported a clear alleviation of their pain, from a mean level of 5.9/10 at baseline, to a mean level of 1.4/10 at long term FU. At mid-term follow-up, only 4 (29%) patients reported consumption of antalgic while they were 12 (55%) before the surgery. At long-term FU, all patients (100%) were satisfied with their surgery and all of them reported an improvement (87%) or a stability (13%) in their health status. Osteointegration was observed for all patients (100%) and bone regeneration was observed in all (95%) but 1 operated site. No cases of osteolysis were observed. No adverse events or complications related to NANOGEL® were reported at follow-up.

Conclusion: this on-going study confirmed that NANOGEL® is an effective and safe device. It can be used in procedures requiring filling with a bone substitute.

### 5.3 Safety

Teknimed is always doing clinical studies (Post-Market Surveillance and Clinical Follow-up). They document and evaluate the benefits and risks of using NANOGEL®.
Benefits for the patients are a pain alleviation and a better health status.
Only 3 residual risks were identified: new fracture due to use in a too large bone defect; heat, pain, redness, swelling or loss of function (inflammatory reaction) and bone destruction, consecutive to implantation under the skin and; allergy to one component. Patients with a risk of allergy to synthetic bone (hydroxyapatite) should discuss this with their surgeon.
When looking at risk versus benefits, the product is considered safe.
Teknimed is currently conducting a new clinical study on NANOGEL®. Its goal is to check safety and performances.

## 6. Possible diagnostic or therapeutic alternatives

Replace missing bone (one grafting) is required when bone defect is large or bone rebuilding slow.. Several categories of bone grafts exist, such as:

- Grafts from the patient itself (Autografts (58% of the bone grafts) which are harvested from the patient's own bone tissue, typically the pelvis);
- Grafts from other human donors (Allografts (34% of bone grafts) which are obtained from banks of human freeze-dried bones);
- Grafts from an animal (Xenografts which are harvested from one individual and transplanted into another individual of a different species. The common available xenografts are of coral, porcine, or bovine origin).

All these grafts give good clinical results. They however remain at risk of reaction from the body (acute inflammatory reactions, even up to the rejection of the graft). Synthetic bone substitutes, fully biocompatible, have been designed to avoid these types of adverse events.
The choice of the best type of graft to use belongs to the surgeons. Multiple factors must be considered: patients' health status (allergies, risk of inflammatory response…), the shape and the size of the bone defect, or the kind of indication (bone void filling, cage filling).

## 7. Suggested profile and training for users

Product should only be used in clinics or hospitals. It should be used by qualified health care professionals. They need to be expert in orthopaedic surgery.