SUMMARY of SAFETY and CLINICAL PERFORMANCE (SSCP)

for HEALTH CARE PROFESSIONALS

CERAFORM®

and its Private Label HYDROSUB®

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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): **CERAFORM®**

CERAFORM® has also the following private labels:

Name of the company	Name of the private label
TEKNIMED	HYDROSUB

1.2. Manufacturer name and address(es):

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

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

1.4. Basic UDI-DI: **376017704B08D8**

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: **1998**

			References	
Designation	**Size**	**Quantity**	**CERAFORM®**	**HYDROSUB®**
Granules	3 x 3 x 3 mm	5 cc	T804402	HS804402
		10 cc	T804405	HS804405
		15 cc	T804407	HS804407
		20 cc	T804410	HS804410
		30 cc	T804415	HS804415
	6 x 6 x 6 mm	15 cc	T804507	HS804507
		30 cc	T804515	HS804515
Stick	5 x 5 x 20 mm	2.5 cc	T807104	HS807104

Wedges	8°	1	T803008	HS803008
	10°	1	T803010	HS803010
	12°	1	T803012	HS803012

The device was introduced for the first time in the following countries:

Country	Year of introduction
USA	2004
RUSSIA	2012
SERBIA	2013
SUDAN	2015
ARGENTINA	2015
KOREA	2015
COSTA RICA	2015
UKRAINE	2016
MECEDONIA	2017
BRASIL	2017
BULGARIA	2017
LEBANON	2018
THAILAND	2018
INDONESIA	2018
IRAN	2019
MONTENEGRO	2019
COLOMBIA	2019
SAUDI ARABIA	2019
ECUADOR	2019
MAROCCO	2020
JORDAN	2020
VIETNAM	2020
EGYPT	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

CERAFORM® is an osteo-conductive synthetic ceramic for bone ingrowth, intended to be used for filling gaps or bone defects in orthopaedic or spine surgery.

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

Indication: CERAFORM® is indicated for the filling of bone defects due to bone injury (such as tumour, trauma, disease), or surgical procedure (such as arthrodesis, osteotomy), as follows:

- Granules are indicated for use in tumoral or benign bone cysts (shoulder, hip, knee, foot), fractures (shoulder, knee), osteotomies (knee), and spine fusion procedures,
- Sticks are indicated for use in fractures (knee, shoulder),
- Wedges are indicated for use in fractures (knee, shoulder).

Target population: Patients presenting 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
- Treatment of large bone defects which could impact the stability of bone structure, without implementing mechanical stabilization systems (such as plate(s), screw(s), nail(s), cage(s))
- Patients susceptible to allergic reactions to the product components

Due to non-sufficient available clinical evidence, CERAFORM® 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: CERAFORM® is a macroporous osteoconductive implant made from synthetic beta tricalcium phosphate and hydroxyapatite. It has a multidirectional interconnected porosity structure, similar to that of the human cancellous bone. It is indicated for the treatment of traumatically created injuries to bones or of surgically created osseous defects.

Operating principles and mode(s) of action: Following placement in the bone void or gap, CERAFORM® implant resorbs during the natural bone remodelling and defect repair processes and is progressively replaced with bone, allowing to restore bone integrity.

Design characteristics: CERAFORM® is a biphasic calcium phosphate ceramic. Hydroxyapatite (HA) is a calcium phosphate similar to the mineral phase of bone. Tricalcium phosphate (TCP) is more soluble than HA and improves the resorption kinetics of CERAFORM®.

Chemical Composition	
Hydroxyapatite: $Ca_{10}(PO_4)_6(OH)_2$	65%
Tricalcium phosphate: $Ca_3(PO_4)_2$	35%

CERAFORM® chemical composition

CERAFORM® and HYDROSUB® are available in various sizes (granules, sticks, wedges…) to adapt to the volume and specificities of each defect.



Pictures of CERAFORM® or HYDROSUB®. From left to right: granules, sticks, wedges

Lifetime: CERAFORM® is an implantable device, intended to be totally absorbed after a minimum of 2 years. The lifetime period may vary depending on the size of the defect, the indication and the physiological condition of the patient. It is not intended to be removed and does not need any maintenance, unless a medical complication would require a surgery.

Sterilisation: CERAFORM® is delivered sterile under double packaging, ready to use in the operating room. The product is sterilized by gamma sterilisation at 25kGy. Sterility is guaranteed until the expiry date if the packaging has not been opened or damaged.

Single use product.

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

CERAFORM® 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

No accessories are intended to be used in combination with CERAFORM®.

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

No specific other devices are intended to be used in combination with CERAFORM®. Yet, CERAFORM® has no mechanical properties. So, 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

- In some cases of wide defects close to a joint, limited range of motion of the joint has been reported.
- In some cases of tibial osteotomy, internal fractures of wedges have been reported, without any impact on the bone consolidation.
- Some cases of incomplete bone reconstruction have been observed, without impact to the patient
- Secondary fracture due to implantation in a load bearing site without mechanical stabilisation system.

Even if no cases of pain, infection or inflammation related to CERAFORM® have been reported in the literature or during PMCF studies, these complications represent nonetheless inherent risks to any surgical procedure. Indeed, some cases of infection, chronic fistulized osteitis, pain, osteolysis or fusiform finger swelling, not related to CERAFORM® but to the surgical procedure, have been reported in PMCF studies (see section 5 below).

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 CERAFORM®, 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 should preferably be done in a spongy bone site
- The ceramics cannot be resized nor support the screwing of osteosynthesis material

- The filling must be complete with a slight impaction (no overfilling)
- The covering must be complete and hermetic by suture of the deep plane.

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

No FSCA have been issued for this product.

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

NA. No devices are claimed to be equivalent to CERAFORM®.

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 CERAFORM® have been published in the scientific literature. Altogether, these publications report outcomes of 129 patients having beneficiated from a bone void filling with CERAFORM®.

Article	Nb of patients	Indication	Follow-up	CERAFORM sizes	Radiological outcomes	Clinical outcomes	Safety outcomes
#1	32	Cavitary bone lesions: 13 simple bone cysts, 6 benign tumours, 6 aneurysmal bone cysts, 3 giant cell tumours, 2 dysplasia, 2 fibromas	3 years	Not detailed	72 to 85% bone regeneration	Not reported	No inflammatory reaction and no infection minimal limited range of motion (shoulder)
#2	43	Various conditions: 4 benign tumours, 1 malignant tumour, 14 spinal fusions, 2 hip revisions, 4 joint fusions, 6 non-unions, 4 fractures, 1 osteitis	5 years	Grains, rods, blocks*	Bone regeneration in all analysed samples	Not reported	No inflammatory reaction, no infection 6 patients with minimal limited range of motion (not related to bone substitute)
#3	34	Various conditions: 13 benign cysts, 9 aneurysmal cysts, 5 osteomyelitis, 2 benign tumours, 4 fibromas, 1 fibrous dysplasia	3 years	"powder, granules, sticks, blocks, cylinders"	100% osteo-integration	90% satisfied patients, able to carry out all their daily occupation-nal activities without any limitation	No complications related to the substitute
#4	20	Humeral aneurysmal bone cysts	3.5 years	Not detailed	100% osteo-integration	95% satisfied patients who had resumed their daily activities without pain and with a good range of motion	no deep infection, nerve deficit or pathological fracture.

** "The shape of the substitute (grains, rods, blocks) was dictated by the configuration of the defect to be filled and predictable level of mechanical loading after implantation." Botez et al. 2009. We can suppose that grains = granules, rods = sticks, and blocks = wedges.*

El Adl et al [#3][1] evaluated outcomes from 34 patients. Indications were: 13 simple bone cysts, 9 aneurysmal bone cysts, 5 osteomyelitis, 2 enchondroma, 4 non-ossifying fibromas, 1 fibrous dysplasia. 29 lesions concerned the lower limb, 3 the upper limb, and 2 an extremity. At follow-up (24 – 60 months), all patients but 1 were able to carry out all their daily occupational activities without any limitation. 2 patients reported occasional mild pain after sporting activities but did not require analgesics. Radiologically, all defects resulting from the lesion itself or from surgical curettage and debridement healed with gradual replacement or disappearance of the graft during the follow-up period. In cystic lesions, healing followed a centripetal pattern. All reported complications in this study were minor and unrelated to the substitute itself. Authors conclude that CERAFORM®, soaked with autogenous bone marrow aspirate, appears as a safe and effective bone graft substitute in the treatment of benign bone defects, with similar or higher success rate than autografts, while avoiding any donor site morbidity.

In parallel, Botez et al **[#2][2]** reported outcomes from a series of 43 patients followed up to 5 years. Clinical indications were: 4 benign bone tumours/dystrophies, 1 malignant tumour, 14 spinal fusions for spinal deformities, 2 revisions of total hip arthroplasty, 4 joint fusions, 6 non-unions, 4 fresh fractures and 4 osteitis. Limited defects allowing bone continuity were grafted with granules, while in defects not allowing bone continuity, rods or wedges were preferred. For spinal fusion, granules were mixed with autologous bone marrow or autologous bone graft. Early and late postoperative observation showed no local inflammation, no superficial or profound sepsis. Radiological evolution was similar in every followed case: the initial clear zone (radiological gap) at material–receiver bone interface rapidly filled in and became continuous until the third month postoperatively. Granular appearance of substitute, showing high radiological density after implantation became homogenous from the 12th month postoperative, and remained stable afterwards. Although different shapes of available CERAFORM® were employed, radiological evolution was similar in all patients with perfect material compatibility, no local side effects and good bone substitute integration. Colonisation of the material by a mineralized tissue, similar to the cancellous bone architecture and cellular composition was observed. Presence of mature osteocytes, osteoblasts surrounding bone trabeculae, multinucleated cells osteoclasts-like and vascular buds were also observed, evoking an active bone turnover in the area of new bone formation. Authors concluded that, for limited amounts of bone loss, whenever a good contact between bone substitute and receiver bone could be obtained, CERAFORM® represents a valuable alternative to allografts.

Four years later, El Adl and Ali [#1][3] reported outcomes from a randomized controlled study including 32 patients at a mean 4-year follow-up: 16 patients received CERAFORM® soaked with bone marrow (group 1); 16 patients received CERAFORM® soaked with blood (group 2). Indications were: 13 simple bone cysts, 6 aneurysmal bone cysts, 1 enchondroma, 2 fibrous dysplasia, 3 giant cell tumours, 1 eosinophilic granuloma, 1 intraosseous granuloma, 1 benign fibrous histiocytoma, 1 osteoblastoma. 24 lesions concerned the lower limb, 4 the upper limb, and 4 one extremity. Radiologically, the percentage of CERAFORM® resorption increased from 31.3% at 6 months to 75.4% at 36 months for group 1 patients and from 20.9% at 6 months to 60.3% for group 2 patients. In the same way, the percentage of bone trabeculation through the cavitary defects increased from 30.3% at 6 months to 85.5% at 36 months for group 1 patients and from 18.9% at 6 months to 72.0% at 36 months for group 2 patients. The differences between the 2 groups of patients were statistically significant, due to the size of the substitute used. Some complications were reported in group 1: minimal limitation of range of motion, prolonged serous drainage, and persistent fusiform finger swelling; and in group 2: keloid scar, clinical upper limb length discrepancy, and local recurrence of one tumour of the proximal tibia. Authors conclude that the use of CERAFORM®, with or without bone marrow aspirate, in treatment of cavitary benign bone lesion can be justified on the ground of its efficacy. Yet, adding bone marrow aspirate has hastened the rate of its resorption and decreased the rate of its persistence.

[1] El-Adl G, Mostafa MF, Enan A, Ashraf M. Biphasic ceramic bone substitute mixed with autogenous bone marrow in the treatment of cavitary benign bone lesions. Acta Orthop Belg. 2009 Feb;75(1):110-8

[2] Botez P, Sirbu P, Simion L, Munteanu FI, Antoniac I. Application of a biphasic macroporous synthetic bone substitutes CERAFORM®: clinical and histological results. Eur J Orthop Surg Traumatol (2009) 19:387–395.

[3] El-Adl G, Ali AM. Does bone marrow affect the radiological outcome when added to biphasic ceramic graft in treatment of benign bone lesions? Eur J Orthop Surg Traumatol. 2013 Jan;23(1):13-20. doi: 10.1007/s00590-012-0943-x

Few years later, Mostafa et Fawzy [#4][4] reported outcomes from a series of 20 patients operated on for aneurysmal humeral bone cyst by autogenous fibular strut graft for reconstruction without internal fixation. The surgical procedure involved an extensive curettage of the bone cyst, placement of the fibula graft and filling of the void around the graft with CERAFORM®. At the time of final follow-up, all but 1 patient were satisfied. They had resumed their daily activities without pain and with a good range of shoulder movement. Radiological healing of the defect was seen at a mean time of 6.5 months (range 4–10) after surgery. Consolidation and remodelling of the implanted fibula were observed between 2 and 4 years after operation. At the final follow-up, radiographic evaluation revealed complete obliteration of the fibular strut graft in 11 patients and incomplete incorporation with blunting of the borders between the fibula and the host bone in 9 patients. Authors concluded that, despite the limited number of patients, the technique has proven to be effective to cure the lesion, improve function of the shoulder and avoid morbidities associated with the metallic implants currently used for internal fixation. This study demonstrated that CERAFORM® can be used successfully in wide voids to promote bone remodelling.

Altogether, authors' conclusions confirm:
- the bone remodelling induction performances of CERAFORM® in bone void filling procedures,
- the relevance of providing multiple sizes of ceramics (granules, sticks, wedges…),
- the huge variety of indications for CERAFORM®: bone cysts, tumours, fractures, surgical curettages or osteotomies,
- the long-term effect and viability of CERAFORM® once implanted in vivo, with patients followed up to 5-year post-implantation.

5.4. Overall summary of the clinical performance and safety

CERAFORM® is a product issued from the well-known technology of biphasic calcium phosphate ceramics which have been used in orthopaedic surgery for decades. It allows successful bone void filling, leading subsequently to clinical benefits for the patients such as pain alleviation and improvement in quality of life. Clinical performance and safety of CERAFORM® have been verified through 2 successive Post-Market Clinical Follow-up (PMCF) studies.

a) A first post-market clinical data collection has been conducted by Teknimed in 2008.
   25 patients (15 women, 10 men, mean age 47.96) who had undergone orthopaedic surgeries involving use of CERAFORM® bone graft substitute, were included. Indications were: 15 spine arthrodesis, 3 bone cysts, 2 knee arthrodeses, 1 hip revisions, 1 astragalo-calcaneal fusion, 1 subtalar fusion, 1 osteotomy, 1 scoliosis.
   12 to 16 months after the surgery, radiographic controls showed good integration of CERAFORM®, good bone reconstruction and good consolidation in all patients. None of the patients presented acute inflammatory reactions or infections.
   This study provided clinical evidence of the efficacy of the biphasic calcium phosphate CERAFORM® ceramic, in the reconstruction of not only small but also large bone defects in humans.

b) A second post-market clinical follow-up study was conducted by Teknimed in 2018.
   49 patients were included for a spine posterolateral fusion (mean age 64.5), and 52 patients for an orthopaedic surgery (mean age 55.1): 50 high tibial osteotomies (HTO), 1 ulnar distal tumour and 1 distal femur fracture.
   In the spine group, at the follow-up visit (1 – 33 months post-surgery), implant condensation and good integration of the bone substitute was observed in all patients. No resorption of the substitute and no osteolysis was observed.
   In the orthopaedic cohort, at the follow-up visit (4 – 47 months post-surgery), osteo-condensation was observed in 75% of patients. Osteolysis was seen in 5 patients (10%), of which 2 presented graft resorption.
   From surgery to the last follow-up visit, no complications or adverse event were reported in either group.

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

[4] Mostafa MF, Fawzy SI. Fibular strut graft for humeral aneurysmal bone cyst with varus deformity. Int Orthop. 2015 Jul;39(7):1391-8. doi: 10.1007/s00264-015-2746-2

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 575 patients will be included for CERAFORM®.
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.
Patients and procedures:
Results: A first interim analysis was performed in July 2021. At that time, 38 patients (mean age 52.3-year, min 17 – max 82) had been retrospectively enrolled. Aetiologies were: 21 fractures, 9 arthroses, 3 surgeries for material removal, 2 bone callus, 1 scoliosis, 1 fracture/dislocation, 1 lack of healing), of 26 traumatic, 8 degenerative, 1 degenerative / traumatic, 1 tumoral, 2 dysplasia origin. Bone injuries localisation were multiple: knee (n=17), shoulder (n=8), hip (n=3), wrist (n=3), ankle (n=3), spine (n=2), arm (n=1), elbow (n=1) and foot (n=1).
Perioperatively, CERAFORM® was used alone, and was directly applied in the bone defect. The filling phase was qualified as 'easy' and the device handling/usability as 'good' in 100% (n=38) of the procedures. No perioperative complications were reported.
Postoperative outcomes:
On pain: Before surgery, all subjects reported pain, with a mean level of 6.9 ±2.96 on a VAS scale of 0 to 10. At short-term FU (1.7 months ±1.24), pain level decreases to a mean 1.2 ±1.16. At mid-term FU (13.2 months ±6.17), pain level decreased down to a mean 0.2 ±0.6.
On well-being: Patients were globally satisfied (95%) of their surgery and mainly reported improvement (89%) or stability (5%) of their health condition at medium-term FU.
On X-Rays images: X-Rays showed that, at mid-term FU, bone regeneration was complete in all patients and no images of osteolysis were observed (except for 1 patient experiencing bone necrosis near the grafted zone but not related to CERAFORM®).
Safety: 5 "serious" adverse events were reported, all of them due to infection, suspected or definite. All patients were hospitalized. 3 patients required re-operation for: either infection site "washing", or prosthesis removal, or removal of surgical material. 1 patient was managed with local medication. 1 patient presenting a non-confirmed suspected infection was returned home.
2 "non serious" adverse events were reported: 1 patient with chronic fistulized osteitis was treated with medication and 1 patient experiencing occasional post-operative pain didn't require any additional management.
All adverse events were qualified as "not related" to CERAFORM®. The relatedness to the procedure was qualified as "possible" in 4 cases and as "probable" in 3 cases.
Conclusion: this mid-term outcomes analysis demonstrates that CERAFORM® is an effective and safe device relevant to be used in procedures requiring filling with a bone substitute.

6. Possible 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, material sources, and origins, such as:

- Autografts (58% of the 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 common available xenografts are derived from coral, porcine, or bovine source.

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 site of collection 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 Good osteoinduction properties	High risk of complications at harvesting site
Allografts	Low risk of immune reaction No morbidity at harvesting site	Low osteoinduction properties
Xenograft	No risk of complications at harvesting site	Risk of immune reaction Poor osteoinduction properties
Synthetic bone substitute		
Biphasic calcium phosphate	No risk of inflammatory reaction Good osteoconduction properties	No osteoinduction properties No mechanical properties
Hydroxyapatite	Biocompatibility, no toxicity, no antigenicity, osteoconduction	No osteoinduction properties No mechanical properties
Tricalcium phosphate	No risk of inflammatory reaction Good osteoconduction properties	No osteoinduction properties No mechanical properties
Calcium sulphate	No risk of inflammatory reaction Good osteoconduction properties	No osteoinduction properties 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

Medical devices should only be used in an adapted environment and by qualified clinicians having a sound knowledge and full mastery in the use and preparation techniques of biphasic synthetic bone substitutes such as CERAFORM®. This product is a ready-to-use device. Its preparation technique is detailed in the accompanying Instruction For Use. Qualified distributors can also provide advises on its use. The clinician 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 manufacturer nor qualified distributor 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 ISO 14155	2021	Clinical investigation of medical devices for human subjects — Good clinical practice	Fully whenever applicable
EN 62366	2015 A1:2020	Medical devices – Application of usability engineering to medical devices	Fully whenever applicable
> Product			

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 materials	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	20209	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 dosimetry aspects	Fully whenever applicable

9. Revision history

Revision	Date issued	Change description	Revision validated by the Notified Body
1.0	22 JUL 2021	Creation	☐ Yes ☒ No
1.1	SEP 2021	Corrections following Round 1 of Clinical Review of MDR file (SMO: 3090169)	☐ Yes, language: English ☒ No
1.2	JAN 2022	Corrections following Round 2 of Clinical Review of MDR file (SMO: 3090169)	☐ Yes, language: English ☒ No
1.3	FEB 2022	Corrections following Round 3 of Clinical Review of MDR file (SMO: 3090169)	☐ Yes, language: English ☒ No
1.4	MAY 2022	Corrections following Round 1 of Clinical Oversight Review of MDR file (SMO: 3090169)	☒ Yes, language: English ☐ No
1.5	JUL 2022	Addition of references for HYDROSUB®	☐ Yes, language: English ☒ No
1.6	JUL 2022	Addition of the volume (2.5 cc) for the Sticks reference	☐ Yes, language: English ☐ 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 LAY-PERSONS

CERAFORM®

and its Private Label HYDROSUB®

SUMMARY of SAFETY and CLINICAL PERFORMANCE (SSCP)
for PATIENTS

CERAFORM®
and its Private Label HYDROSUB®

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: **CERAFORM®**

The medical device has also the following private labels:

Name of the company	Name of the private label
TEKNIMED	HYDROSUB

1.2. Manufacturer name and address(es):

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

1.3. Basic UDI-DI: **376017704B08D8**

1.4. Year when the device was first CE-marked: **1998**

			References	
Designation	**Size**	**Quantity**	**CERAFORM®**	**HYDROSUB®**
Granules	3 x 3 x 3 mm	5 cc	T804402	HS804402
		10 cc	T804405	HS804405
		15 cc	T804407	HS804407
		20 cc	T804410	HS804410
		30 cc	T804415	HS804415
	6 x 6 x 6 mm	15 cc	T804507	HS804507
		30 cc	T804515	HS804515
Stick	5 x 5 x 20 mm	2.5 cc	T807104	HS807104
Wedges	8°	1	T803008	HS803008
	10°	1	T803010	HS803010
	12°	1	T803012	HS803012

2. Intended use of the device

2.1. Intended purpose

CERAFORM® is an artificial material which mimics the natural bone mineral composition and structure. It is intended to be used for filling bone gaps or defects and support bone regeneration, in orthopaedic or spine surgery.

2.2. Indication(s) and intended patient groups

CERAFORM® is indicated for the filling of bone cavities or defects. These defects can be created surgically, after the curettage of a bone tumour or a cyst, or after the fusion of two bones together by example; or traumatically, after the accidental fracture of a limb by example. CERAFORM® exists in different sizes which can be adapted to the size of the cavity to fill. By example, granules can be used in tumoral or benign bone cysts (shoulder, hip, knee, foot), or fractures (shoulder, knee), or osteotomies (knee), and in spine fusion procedures. Sticks and wedges can be used in knee or shoulder fractures.

CERAFORM® offers no mechanical resistance and cannot be used to assure the stability of the bone structure. In case of large defects, additional materials, such as plates or screws, should be used to support the load-bearing of the bone.

No enough clinical evidence being available for these populations, CERAFORM® cannot be indicated in paediatric patients, and breast-feeding or pregnant women

2.3. Contraindications

- Procedures other than those stated in the INDICATIONS section
- Treatment of large bone defects which could impact the stability of the bone structure without implementing a mechanical stabilization system (such as plate(s), screw(s), nail(s), cage(s))
- Patients susceptible to allergic reactions to one of the product components

Due to non-sufficient available clinical evidence, CERAFORM® is contraindicated in paediatric patients, and breast-feeding or pregnant women.

3. Device description

CERAFORM® is a solid sponge-like implant presenting large pores to allow colonisation by bone cells. It is made from synthetic components similar to those constitutive of bone: beta tricalcium phosphate and hydroxyapatite. Its pores form an internal network, reproducing the structure of human cancellous bone.
Following its placement into the bone void or gap, CERAFORM® will resorb during the natural bone repair process (bone remodelling) and will progressively by replaced with native bone.

CERAFORM® allows restoring bone integrity, resulting in pain alleviation and improvement of quality of life for the patients. CERAFORM® is available in multiple sizes to adapt to the specificities of each defect.



Pictures of CERAFORM®. From left to right: granules, sticks, wedges

CERAFORM® is intended to be totally absorbed after a minimum of 2 years. The lifetime period may vary depending on the size of the defect, the indication and the physiological condition of the patient. It 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

- In some cases of wide defects close to a joint, a temporary limited range of motion of the joint has been experienced.
- In some cases of tibial augmentation procedure (osteotomy), internal fractures of wedges have been reported, without any impact on the bone consolidation.
- Some cases of incomplete bone reconstruction have been observed, without impact to the patient.
- Post-surgery fracture, due to the implantation of the product in a load-bearing site of the body (in the knee by example), without any mechanical stabilisation system (plate, screw, or nail) to support the loading, potentially necessitating a second surgery.
- Even if no cases of pain, infection or inflammation related to CERAFORM® have been reported in the literature or during clinical studies, these complications represent nonetheless inherent risks to any surgical procedure. Indeed, some cases of infection, chronic fistulized osteitis, pain, osteolysis or fusiform finger swelling, not related to CERAFORM® but to the surgical procedure, have been reported in clinical studies.

4.2. Warnings and Precautions

No warning and precautions are applicable for patients as this device is intended to be used only by healthcare professionals.

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

No FSCA have been issued since the release of CERAFORM® 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 to propose an alternative to the bone grafts of human or animal origins which could induce infection or inflammatory reactions. CERAFORM® is a well-known legacy device which has been sold for more than 22 years. A long history of surveillance of its safety since its release on the market has proved that it carries no significant risks.

4 articles reporting clinical and radiological outcomes of CERAFORM® have been published in the scientific literature. Altogether, these publications report outcomes of 129 patients having beneficiated from a bone void filling with CERAFORM®.

In the first series, 24 to 60 months after the surgery, all included patients but 1 (i.e.: 33 patients) were able to carry out all their daily occupational activities without any limitation. 2 patients reported occasional mild pain after sporting activities but did not require analgesics. On X-ray images, all bone defects healed gradually. All reported complications in this study were minor and unrelated to the substitute itself.

In another study of 43 patients followed up to 5 years, radiological evolution was similar in all patients with perfect material compatibility, no local side effects and good bone substitute integration. No local inflammation, no superficial or profound sepsis were observed.

Four years later, another study reported outcomes of 32 patients at an average of 4-year follow-up. Radiological follow-up showed CERAFORM® incorporation increasing steadily with time after its implantation. Some complications were reported: minimal limitation of range of motion, prolonged serous drainage, persistent fusiform finger swelling, keloid scar, clinical upper limb length discrepancy, and local recurrence of one tumour of the proximal tibia.

Few years later, another article reported outcomes from a series of 20 patients. At the time of final follow-up, all but 1 patient were satisfied. They had resumed their daily activities without pain and with a good range of shoulder movement. Radiological healing of the defect was seen between 4 and 10 months after surgery.

Authors' conclusions of these articles confirm the clinical and radiological performance and safety of use of CERAFORM® in bone void filling procedures.

5.2. Clinical evidence for CE marking

CERAFORM® was first CE marked and placed on the market in 1998. At that time, the clinical evidence was based on the equivalence of CERAFORM® with another device already placed on the market. Since then, Teknimed conducted 3 clinical studies to first assess, then to confirm the efficacy and safety of using CERAFORM®.

a) A first clinical data collection has been conducted in 2008.

25 patients (15 women, 10 men, mean age 47.96) who had undergone an orthopaedic surgery involving the use of CERAFORM® were included. Indications were: 15 spine arthrodesis, 3 bone cysts, 2 knee arthrodeses, 1 hip revision, 1 astragalo-calcaneal fusion, 1 subtalar fusion, 1 osteotomy, 1 scoliosis.

12 to 16 months after the surgery, radiographic controls showed a good integration of CERAFORM®, a good bone reconstruction and consolidation in all patients. No patient presented any inflammatory reaction or infection.

This study provided clinical evidence of the efficacy of CERAFORM® in the reconstruction of bone defects in humans.

b) A second clinical follow-up study was conducted in 2018.

49 patients were included for a spine posterolateral fusion (mean age 64.5), and 52 patients for an orthopaedic surgery (mean age 55.1): 50 tibial osteotomies, 1 ulnar distal tumour and 1 distal femur fracture.

In the spine group, at the follow-up visit (1 – 33 months post-surgery), implant condensation and good integration of the bone substitute was observed in all patients. No resorption of the substitute and no osteolysis was observed.

In the orthopaedic group, at the follow-up visit (4 – 47 months post-surgery), bone consolidation was observed in 75% of patients. Bone destruction was observed in 5 patients (10%), of which 2 presented destruction of the graft.

From the surgery to the last follow-up visit, no complications or adverse event were reported in either group.

c) Since 2020, Teknimed is currently conducting a third clinical follow-up study on CERAFORM®.

A first analysis of the collected data was performed in July 2021. At that time, 38 patients (mean age 52-year) had been included. Aetiologies were: 21 fractures, 9 arthroses, 3 surgeries for material removal, 2 bone callus, 1 scoliosis, 1 fracture/dislocation, 1 lack of healing. Bone injuries localisation were multiple: knee (n=17), shoulder (n=8), hip (n=3), wrist (n=3), ankle (n=3), spine (n=2), arm (n=1), elbow (n=1) and foot (n=1).

During the surgery, CERAFORM® was used alone, and was directly applied in the bone defect. The filling phase was qualified as 'easy' and the device handling/usability as 'good' by the clinician, in 100% of the procedures. No complications were reported during the surgeries.

Postoperative outcomes:

On pain: Before surgery, all subjects reported pain, with an average level of 7 on a scale of 10 (0 = no pain, 10 = the highest level of pain). 2-month after the surgery, the level of pain decreases to an average of 1.2/10. After about 1 year, the level of pain level still decreased down to an average of 0.2/10.

On well-being: 95% of patients were satisfied of their surgery and 89% of them reported an improvement of their health condition at medium-term FU.

On X-Rays images, 1 month after the surgery, the bone regeneration was complete in all patients and no image of bone destruction (osteolysis) were observed (except for 1 patient experiencing bone necrosis near the grafted zone but not related to CERAFORM®).

Safety: 5 "serious" adverse events were reported, all of them due to suspected or definite infection. All patients were reoperated: 3 for a site "washing" and prosthetic material removal; 1 for a site "washing" without additional procedure; 1 patient presenting a non-confirmed suspected infection was returned home.

2 "non serious" adverse events were reported: 1 patient with a chronic bone inflammation (fistulized osteitis) was treated with medication and 1 patient experiencing occasional post-operative pain didn't require any additional management.

All adverse events were not related to CERAFORM® but were related possibly (in 4 cases) or probably (in 3 cases) to the surgical procedure itself.

Conclusion: this mid-term outcomes analysis demonstrates that CERAFORM® is an effective and safe device relevant to be used in procedures requiring filling with a bone substitute.

5.3 Safety

Teknimed is continuously conducting Post-Market Surveillance and Clinical Follow-up to document and evaluate the benefits and risks of using CERAFORM®.

Benefits for the patients are a pain alleviation and an improvement of their health status.

Regarding risks, the two identified residual risks are a secondary fracture due to an implementation in a load-bearing site or an allergy to one CERAFORM® component. Patients who are at risk of allergy to calcium phosphate or to hydroxyapatite should discuss this with their surgeon.

Considering the clinical benefits on quality of life, versus the low associated level of risks, the overall benefit-risk balance of using CERAFORM® for patients is considered acceptable.

6. Possible therapeutic alternatives

Bone grafting is required when the size of the zone 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, such as:

- Autografts (58% of the 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 common available xenografts are derived from coral, porcine, or bovine source.

All these grafts give good clinical results but they remain at risk of immune reaction which can result in 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.

Finally, the choice of the 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) of the graft.

7. Suggested profile and training for users

Medical devices should only be used in an adapted environment and by qualified clinicians having a sound knowledge and full mastery in the use and preparation techniques of biphasic synthetic bone substitute such as CERAFORM®. This product is a ready-to-use. Its preparation technique is detailed in the accompanying Instruction for use. Qualified distributors can also provide advises on its use. The clinician 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 manufacturer nor qualified distributor can be held responsible for these complications.