SUMMARY of SAFETY and CLINICAL PERFORMANCE

SSCP

GENTAFIX®

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

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): GENTAFIX®1, GENTAFIX® 3, GENTAFIX® 3MV

The medical devices have also the following private labels:
AMPLIFIX 1 , AMPLIFIX 3 / BIOCEMIUM I , BIOCEMIUM III / IMPLABOND 1 , IMPLABOND 3 / OPTICEM 1 , OPTICEM 3 / ORCEM 1 , ORCEM 3 / PALAFOM 1 / SINPLUS 1 , SINPLUS 3 / ORTHOCEM 1 , ORTHOCEM 3 , ORTHOCEM 3G MV / EVOCEM 1 ET EVOCEM 3 / NexCem 1 , NexCem 3 , NexCem 3G MV / SIGNATURE Cement SV , SIGNATURE Cement LV , SIGNATURE /x Cement MV / ProstheSet 10 , ProstheSet 11 , ProstheSet 12 / PERFIX PLUS 1 , PERFIX PLUS 3 / Synth/X OH , Synth/X OL , Synth/X OM+ / BezCem® 1 , BezCem® 3 , BezGen®3MV / CM/PX 1 , CM/PX 3 , CM/PX 3G MV / DYNABONE 1 , DYNABONE 3 , DYNABONE 3G MV / TEKCEM 1 , TEKCEM 3 , TEKCEM 3G MV / C/fix 1 , C/fix 3 , C/fix 3G MV / ArthroCem 1 , ArthroCem 3 , ArthroCem 3G MV / Jointfix 1 , Jointfix 3 , Jointfix 3G MV / Prosthefix 1 , Prosthefix 3 , Prosthefix 3G MV / C/Cem 1 , C/Cem 3 , GentaCem 3 MV.

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: 376017704B01CS

1.5. Medical device nomenclature description: EMDN nomenclature: P099001 - orthopaedic cements

1.6. Class of device: III

1.7. Year when the first certificate (CE) was issued covering the device: The medical device has been introduced for the first time in the following countries:

Countries	Year of introduction		
	GENTAFIX® 1	GENTAFIX® 3	GENTAFIX® 3MV
Europe	2000	2000	2012
Colombia	2006	2006	/
Russia	2008	/	/
Egypt	2011	2011	/
Serbia	2013	/	/
Ukraine	2016	2016	2016

Philippines	2014	2014	/
Brazil	2018	2018	/
Korea	2015	2015	2015
Costa Rica	2015	2015	/
India	2016	2019	2016
Morocco	2016	2017	2017
Venezuela	2016	2018	2018
Uruguay	2016	2016	/
Kazakhstan	2016	2016	/
Macedonia	2017	2017	2017
Vietnam	2016	2016	2016
Malaysia	2018	2018	2018
Ecuador	2018	2018	/
Indonesia	2018	2018	/
Iran	2019	2019	/
Saudi Arabia	2019	2019	2019
Soudan	2015	2015	2015
Montenegro	2019	2019	2019
Lebanon	2019	2019	2019
United Arab Emirates	2020	2020	2020
Thailand	2020	2020	2020
Guatemala	2020	/	/

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

GENTAFIX® bone cements with gentamicin are intended for fixation of prosthetic components into bone medullar cavity in arthroplasty procedures.

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

- *Indications*

GENTAFIX® bone cements are intended for use in cemented arthroplasty procedures.

- GENTAFIX® 1 is indicated for primary (shoulder, hip, knee) and revision (knee) surgeries.
- GENTAFIX® 3 & 3MV are indicated for primary (hip) and revision (hip, knee) surgeries.

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- *Target population*

GENTAFIX® bone cements are to be used in patients for whom a cemented arthroplasty surgery is indicated.

2.3. Contraindications or restriction for use

- Procedures other than those stated in the INDICATIONS section.
- Presence of an active or incompletely treated infection at the bone site caused by gentamicin non sensitive strains.
- Use in patients with a history of serious neuromuscular disease.
- Hypersensitivity to gentamicin or to other constituents of the bone cement. A history of hypersensitivity or serious toxic reactions to other aminoglycosides may contraindicate use of gentamicin because of known cross-sensitivity of patients to drugs in this class.
- Severe renal impairment.
- Pre-existing calcium metabolism disorder.

- Due to non-sufficient available clinical evidence, GENTAFIX® bone cements are contraindicated in paediatric, adolescent, and skeletally immature patients, and pregnant or breast-feeding women.

3. Device description

3.1. Description of the device

GENTAFIX®1, GENTAFIX®3 and GENTAFIX®3 MV are radiopaque acrylic bone cements. They allow an immediate and long-term fixation of prosthetic implants into the medullar cavity of living bone. They contain an antibiotic issued from the family of aminoglycosides: gentamicin.

GENTAFIX® cements, like all acrylic bone cements, are presented as a powder (in a pouch) and a liquid (in an ampoule) which must be mixed extemporaneously, during the surgery.

They are single use products. The powder is sterilised by gamma radiation and the liquid by ultrafiltration.

These cements are available in 3 viscosities to correspond to the needs of surgeons: low, medium and high.

COMPOSITION	Concentration (% w/w)		
	GENTAFIX®1 High viscosity	**GENTAFIX®3** Low viscosity	**GENTAFIX® 3 MV** Medium viscosity
Powder phase	41.6g	41.6g	41.6g
Polymethylmethacrylate	84.3	84.3	85.1
Benzoyl peroxide	2.3	2.3	1.5
Barium sulphate	9.6	9.6	9.6
Gentamicin sulfate (corresponding to 1g of gentamicin base)	3.8	3.8	3.8
Liquid phase	14.4g	16.4g	18.8g
Methylmethacrylate	84.4	84.4	84.4
Butylmethacrylate	13.2	13.2	13.2
Dimethyl paratoluidine	2.4	2.4	2.4
Hydroquinone	20ppm	20ppm	20ppm

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

GENTAFIX® cements are not issued from any previous generation.

Teknimed range of GENTAFIX® cements comprises 3 variants: GENTAFIX® 1, GENTAFIX® 3, GENTAFIX® 3MV.

- GENTAFIX®1, high viscosity bone cement, recommended for manual applications.
- GENTAFIX®3, low viscosity bone cement which viscosity has been optimized to facilitate application with a syringe or an injection gun.
- GENTAFIX®3 MV, medium viscosity bone cement, for syringe or injection gun

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

No accessories are intended to be used with the bone cements.

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

Bone cements are intended to be used in combination with a bone cement restrictor, such as Teknimed CEMSTOP®. CEMSTOP® bioabsorbable cement restrictor is a diaphyseal plug for orthopaedic use. It is designed to occlude the medullary cavity before the introduction of acrylic cement during hip joint replacement.

Bone cements are intended to be prepared with mixing and injection systems adapted to their viscosity:

- For GENTAFIX® 1 (high viscosity), preparation with bowl and spatula and manual application are recommended.
- For GENTAFIX® 3 MV (medium viscosity) and GENTAFIX® 3 (low viscosity), use of a mixing and injection system is recommended, although manual preparation and application is possible.

4. Risks and warnings

4.1. Residual risks and undesirable side effects

After mitigation as far as possible of identified and expected risks, residual risks include:

Undesirable side effects of PMMA bone cements:

- Adverse reactions affecting the cardiovascular system reported in the scientific literature[1] (also known as Bone Cement Implantation Syndrome), such as transitory hypotensive reactions (up to 0.3% of cases reported in a survey conducted by Teknimed). Probably due to the risk of MMA monomer release during polymerisation and exposure to monomer fumes, they were observed between 10 to 165 seconds after application of bone cement, corresponding to the kinetic of release of monomer, and lasted from 30 seconds to 5 minutes. Some patients have progressed to cardiac arrest (up to 0.17% reported in traumatology and 0.017% reported in scheduled procedures)[2]. For this reason, patients should be monitored carefully for any change in blood pressure during and immediately following the application of bone cement. The anaesthetist should be told during the operation when the bone cement is implanted. Incidences of severe BCIS of 5% for primary total knee or total hip arthroplasty, 2% for primary total shoulder arthroplasty and 7% for revision procedure whatever the joint have been reported in the literature on bone cements[3], but none with Gentafix® cements.
- Postoperative infection due to non-gentamicin-sensitive strain or to failure of the gentamicin, with reported rates in the PMCF studies conducted by Teknimed of: 0% at 1-year after shoulder primary surgeries (GENTAFIX® 3), 0% at 7-year after hip primary surgery (GENTAFIX® 1 and 3) and 1.6% at 1-year after primary knee surgery (GENTAFIX® 1); 3.5% of recurrent infection at 5-year after knee revision surgery (GENTAFIX® 1 and 3) and 8% at 7-year after hip revision surgery (GENTAFIX® 3).
- Inadequate fixation may affect the cement/bone interface and lead to micromotion, issuing in a loosening of the prosthesis (up to 0.8% in the PMCF study conducted by Teknimed and 2.2% in a series of 183 total hip arthroplasties[3,4]). Long-term regular supervision is therefore recommended for all patients.
- Even if no cases have been reported, allergy to gentamicin or to one of the bone cement constituents remains a risk inherent to the use of bone cements.

Undesirable side effects typical of gentamicin:

- Neurotoxicity: manifested as both auditory and vestibular ototoxicity including transient or irreversible hearing loss, numbness, skin tingling, muscle twitching, and convulsions. Transient hearing impairment concerned up to 20% of a published cohort of 40 patients[5].

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[1] Donaldson AJ, Thomson HE, Harper NJ, Kenny NW, *2009. Bone cement implantation syndrome.* Br J Anaesth. 102(1):12-22. doi: 10.1093/bja/aen328

[2] Bonfait H, Delaunay C, De Thomasson E, Tracol P, 2021. *Bone cement implantation syndrome in hip arthroplasty: Frequency, severity and prevention*. Orthop Traumatol Surg Res. 108(2):103139. doi: 10.1016/j.otsr.2021.103139

[3] Rassir R, Schuiling M, Sierevelt I.N, van der Hoeven C.W.P., Nolte P.A. 2021. *What are the frequency, related mortality, and factors associated with Bone Cement Implantation Syndrome in arthroplasty surgery*? Clin Orthop Relat Res 479:755-76. Doi: 10.1097/CORR.0000000000001541

[4] Romanò, C.L., Romanò, D., Albisetti, A., Meani, E., 2012. *Preformed Antibiotic-Loaded Cement Spacers for Two-Stage Revision of Infected Total Hip Arthroplasty. Long-Term Results.* HIP International 22, 46–53. Doi: 10.5301/HIP.2012.9570

[5] Çöbden A, Çamurcu Y, Bulut Çöbden S, Sofu H, Üçpunar H, Sevencan A, Demirel H. *2019. Audiometric threshold shifts after total knee arthroplasty by using gentamicin-loaded bone cement.* Turk J Med Sci. Apr 18;49(2):514-518. doi: 10.3906/sag-1710-135.

- Nephrotoxicity: occurring usually in patients with pre-existing renal damage, and also in patients with normal renal function to whom aminoglycosides are administered for longer periods or in higher doses than recommended, the symptoms of which may manifest after cessation of therapy. Yet, no cases of nephrotoxicity due to gentamicin-loaded cements have been reported in the 5 main national materiovigilance databases during the past 5 years.
Avoid using gentamicin in combination with very active diuretics and in general with ototoxic and nephrotoxic products.
- Potential allergy to histamine impurity arising from the gentamicin manufacturing process. However, no cases have been reported in the 5 main national materiovigilance databases during the last 5 years.

Other adverse reactions associated with systemic use of Gentamicin therapy include: hypersensitivity, anaphylactic reactions, nausea, vomiting, urticaria, reversible granulocytopenia, anemia, blood dyscrasia, convulsions, central nervous toxicity, abnormal hepatic function, hypomagnesaemia, stomatitis, purpura, allergic contact sensitization and neuromuscular blockade.
The postoperative follow-up should be closely monitored by the surgeon for patients reporting a previous experience of sensitivity or allergic reaction to antibiotics, in particular of the aminoglycosides' family.

Any serious incident occurring in relation to the device GENTAFIX® 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 GENTAFIX® and its injection system carefully.
This device contains gentamicin, an aminoglycoside antibiotic. Special care should be taken for patients presenting contra-indicated conditions.
Ignoring the instructions for use may lead to potential undesirable effects.
For an optimum use of GENTAFIX®, 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.
The health professional must be experienced in GENTAFIX® cement preparation and must follow it scrupulously. It is therefore advisable to respect the recommended preparations times.

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.
- Always check the condition of the liquid before carrying out the procedure. Do not use the liquid component if it shows any sign of thickening or premature polymerization. These conditions indicate that the product has not been stored correctly.

Cement preparation

- For controlled and optimal use of the GENTAFIX® cement, the doses are to be stored at the recommended temperature of 20°C for a minimum of 24 hours before use.
- The duration of the cement working phases depends on the ambient temperature and those of the components, but also on the degree of relative humidity of the operating room. A high temperature reduces waiting, injection and hardening time. A low temperature extends these times.

- Prechilling of bone cement and accessories for at least 24 hours is recommended if a lower viscosity or a prolonged handling time is required. Mixing time is the same as for non-prechilled cement, however application time and hardening time are prolonged.
- The application phases of GENTAFIX® 3 and GENTAFIX® 3MV cements have been determined using injection systems recommended by TEKNIMED (VACUUKIT®) without vacuum. They may vary if different systems are used. Setting time can be reduced if mixing is performed under vacuum.
- Mixing of two units of bone cement together is not recommended as handling and hardening times can significantly differ from those validated by manufacturer.
- Additives (such as liquid antibiotics) are not to be mixed with the bone cement, as this will alter cement properties.
- Prior to the application of bone cement to the bone, the cavity should be thoroughly cleaned, washed and dried to prevent contamination by blood or marrow.
- The manufacturer does not recommend any surgical technique in particular: it is the responsibility of the physician to determine the appropriateness of the GENTAFIX® cement and specific technique for each patient.

Personnel safety

- The liquid component is a powerful lipid solvent. Do not allow the liquid to come into contact with rubber or latex gloves. Should contact occur, the gloves might dissolve and tissue damage may occur. Wearing a second pair of gloves may diminish the possibility of hypersensitivity reactions.
- The liquid monomer is highly volatile and flammable.
- Make sure the operating room is properly ventilated to eliminate monomer fumes as much as possible.
- Make sure electrocautery devices are not used near freshly implanted bone cements as that could cause the ignition of monomer fumes.
- Caution should be exercised to prevent excessive exposure to the concentrated fumes of the monomer, which may cause drowsiness, irritate the respiratory tract, eyes and even the liver.
- Do not allow personnel wearing contact lenses to be near or be involved in mixing of the bone cement.

Monitoring during application

- The final polymerization stage occurs in situ and is an exothermic reaction with considerable liberation of heat. According to ISO 5833 standard, the temperature can reach up to 95°C. The heat produced in situ during polymerisation can lead in rare cases to modification of structure of the bone[2].
- Maintain the positioning of the prosthetic component until the polymerization process has been completed, so as to obtain proper fixation.

Drug interactions and population at risk

Patients who are predisposed to or who have pre-existing clinical conditions that would put them at risk for gentamicin toxicity (e.g.: renal dysfunction, hearing difficulties, dehydration, advanced age, taking drugs which may affects kidneys, undergoing general anaesthesia, etc) should be monitored for toxic blood levels of gentamicin (before, during and in the first days following implantation) as well as for renal function.

In cases of significant obesity, gentamicin serum concentrations should be closely monitored.

To avoid the risk of adverse events, continuous monitoring (after) of renal function (serum creatinine, creatinine clearance), hepatic and laboratory parameters are recommended.

Concurrent use of other neurotoxic and/or nephrotoxic drugs can increase the possibility of Gentamicin toxicity. Co-administration with the following agents should be avoided:

- Curare-type muscular relaxants during anaesthesia: risk of neuromuscular blockade and respiratory paralysis
- Neuromuscular blocking agents such as succinylcholine, botulinum toxin: risk of toxicity due to enhanced neuromuscular block
- Other potentially nephrotoxic or ototoxic drugs such as cephalosporins and methicillin.
- Loop Diuretics such as furosemide: increased risk of ototoxicity
- Other aminoglycosides
- Anticoagulants such as warfarin and phenindione, as Gentamicin has been known to potentiate them
- Antifungals such as amphotericin: increased risk of nephrotoxicity.
- Cholinergic: antagonism of effect of neostigmine and pyridostigmine.

- Cyclosporin: increased risk of nephrotoxicity
- Cisplatin: increased risk of nephrotoxicity and possible risk of ototoxicity
- Bisphosphonates: increased risk of hypocalcaemia
- Sulphites in susceptible people, especially those with a history of asthma or allergy: risk of allergic-type reactions including anaphylactic symptoms and bronchospasm.

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

No FSCA concerning GENTAFIX® were issued during the last 5 years.

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

At the time of its first CE-marking in 1998, GENTAFIX® bone cement was assessed and endorsed by the Notified Body (SNCH) on the basis of its equivalence with CMW bone cement, manufactured by Depuy Inc. Since the EU MDR 2017/745 entry in force in 2021, no equivalence with other bone cements is claimed anymore.

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

A. PMCF study performed in 2018 by Teknimed

PMCF STUDY PROTOCOL

Title: GENTAFIX®1 and GENTAFIX®3 Outcomes Study - A retrospective clinical study

Identity of the device: GENTAFIX®1, GENTAFIX®3

Objectives of the study: The objective of this study was to confirm the clinical performance and safety of the bone cements GENTAFIX®1 and GENTAFIX®3 used for prosthesis fixation in arthroplasty surgeries in a “real life” setting.

Indication: GENTAFIX®1 and GENTAFIX®3 are indicated for prosthesis stabilisation in joint replacement surgeries.

Study design: Retrospective, non-controlled, observational post-market clinical follow-up. Clinical data were collected from patients’ medical records from baseline visit, surgery and immediate post-surgery follow-up visit, according to the standard care of patient’s visits in the investigational centres.

Endpoints: Clinical outcomes: Prosthesis stability – Safety outcomes: Evaluation of complications, adverse events

Inclusion criteria: - Patient 18 years of age or over**; -** Patient having a surgical indication for an arthroplasty; - Patient able to be followed according to the protocol; - Patient aware of the examination of their clinical data

Exclusion criteria: Patient hypersensitive or allergic to gentamicin; - Patient with metabolic bone disease; - Infection at the operative site

Statistical Analysis: Statistics analyses were descriptive as the study was an observational follow-up with no comparison. As required by statistical guideline for a small number of patients, data will be presented as follow: median (minimal value; maximal value), except for the variable Age: mean ±SD.

PMCF STUDY OUTCOMES

Description of population	99 patients were included: 50 patients with a shoulder arthroplasty (47 women, 3 men, mean age 74.6±7.4) and 49 patients with a hip arthroplasty (43 women, 6 men, mean age 74.6 ±7.4).
Perioperative outcomes	In all surgeries, quality of cement was reported as ‘cohesive’ by investigators, allowing a ‘stable’ fixation of the prosthesis. No complications or adverse events were reported during surgery and immediate post-surgery follow-up.
Postoperative performance outcomes	Postoperative data were available for patients in the shoulder cohort only. Before surgery, levels of mobility, usual activities and pain were defined as ‘severe’ by 60% and ‘mild’ for 34% of patients. At follow-up visit (median 5.5-month, min 1 - max 22), more than 70% of patients defined the levels of quality-of-life domains as “normal”.
Postoperative safety outcomes	No complications or adverse event were reported for the shoulder cohort.

Conclusion	This short-term outcome study demonstrated that GENTAFIX®1 and 3, are effective and safe bone cements relevant to be used for shoulder cemented arthroplasty.

B. PMCF study, initiated in 2019 and still currently conducted by Teknimed

PMCF STUDY PROTOCOL

Title: Safety and Clinical Performance Assessment of Bone Cements and Cement Restrictor used in Arthroplasty

Justification/Context: TEKNIMED has developed several bone cements currently used in arthroplasty procedures. With the increasing volume of these procedures, there is a need for real-life long-term safety and efficacy data on these products.

Objective: The objective is to collect immediate, medium and long-term data after arthroplasty surgery, on the related clinical functional and complications outcomes of market-approved TEKNIMED arthroplasty products to assess their performance and safety in a real-world setting.

Study design: global, single arm, non-controlled, multi-centric, ambispective observational study. Patients are followed as per local standard medical practices of the investigational sites. Data are collected pre-operatively, at surgery and at standard of care follow-up (FU) visits.

Primary endpoint: (i) Prosthesis survival defined as time from implantation to revision surgery due to a cement failure; (ii) In the case of cements with gentamicin, superficial and/or deep postoperative infection rate.

Performance endpoints: (i) clinical endpoints: evaluation of pain, patients' satisfaction, joints functional scores; (ii) radiological endpoints: Sedel score, quality of the cement mantle, prostheses stability, implant migration, radiolucent lines

Safety endpoints: All adverse events (such as prosthesis loosening, dislocation, deep infection …) are collected and documented during the study and categorized as whether they are serious and whether they are related to the TEKNIMED device.

Statistical Analysis: Statistical analyses are primarily descriptive as no hypotheses are enunciated to be demonstrated. Each outcome is reported for each product separately, however, some products may be grouped and summarized if the products are related and if needed (e.g. cement + injection system). There are no intentions to compare or test data across products unless requested for a publication or other clinical evidence need. When needed, Kaplan-Meier survivorship analyses will be performed for several endpoints such as implant revision or aseptic loosening.

PMCF STUDY OUTCOMES (interim analysis performed 10 March 2021 - mean FU was 12,34 ±6,41 months post-surgery)

Description of population	125 patients were included (46 males and 79 women, mean age 70.82 ±10.55): 3 primary shoulder arthroplasties, 24 primary hip arthroplasties, 61 primary knee arthroplasties, 11 revision hip arthroplasties and 26 revision knee arthroplasties.
Primary endpoint	✓ A total of 4 revision surgeries, whatever the reason for revision, were performed, providing a global 96,8% survival rate at 1-year follow-up – of which no revisions were due to a cement failure. ✓ 3 postoperative infections were reported: 1 following a primary knee arthroplasty with GENTAFIX®1, 1 following a knee revision arthroplasty with GENTAFIX® 3, and 1 following a hip revision surgery with GENTAFIX®1. The overall postoperative infection rate following primary surgery is 1.3%, which is consistent with the expected acceptable infection rate reported in the literature for knee (2-3%) and hip (1-2%) joints. The overall postoperative infection rate following revision surgery (5.26%) is slightly exceeding acceptable infection rate (5%). However due to the small number of cases, it shouldn't be considered as significant in this interim analysis.
Clinical outcomes	✓ 100% of patients reported an alleviation of pain and an improvement of their well-being at short and mid-term FU, in both primary and revision indications. No significant differences in outcomes were observed between primary surgery and revision surgery cohorts, whatever the joint concerned.
Radiological outcomes	✓ 0% radiolucent lines at short-term FU, 2.5% at mid-term FU ✓ 0% osteolytic zone at short-term FU, 2.5% at mid-term FU

	These radiological outcomes are consistent with the literature and confirm the performance of the GENTAFIX® cements to ensure the anchorage of the prostheses into the bone cavity.
Complications and adverse events	✓ Shoulder cohort: No adverse events were reported. ✓ Hip cohort: - 4 adverse events were reported for GENTAFIX®1 (of which 2 serious: 1 prosthetic dislocation and 1 superficial infection). None of them were related to the cement and both were resolved without sequelae. - 2 adverse events were reported for GENTAFIX®3 (of which 1 serious: 1 prosthetic femur fracture, not related to the cement). 1 non-serious event was related to the cement: painful and clicking phenomenon when getting up which spontaneously resolved without sequelae. ✓ Knee cohort: - 1 serious adverse event was reported for GENTAFIX®1 (infection), not related to the cement but requiring revision surgery. - 1 serious adverse event was reported for GENTAFIX®3 (infection), not related to the cement and treated without sequelae by surgical site cleaning and medication.

C. Data collected from the CliniRecord database

AMPLITUDE is a French Manufacturer of prosthetic implants for hip and knee joints replacement. They provide a private label of the Teknimed GENTAFIX® cements: AMPLIFIX® 1G & 3G cements to the surgeons using their cemented implants. As part of their Post-Market Surveillance, AMPLITUDE devised a tool to monitor clinical cases on its hip and knee implants once they have been placed on the market: CliniRecord. This database is a registry-like centralized web-accessible data collection system when each surgeon can enter data on her/his patients and implanted prostheses. This data collection system allows specific and structured clinical information to be gathered in a systematic fashion, subsequently enabling data analysis to be performed (Cf. CliniRecord_Summary).

An extract of data related to prostheses cemented with AMPLIFIX® cements was performed on 27 October 2021. Outcomes are summarised below:

4 main cohorts of patients have been identified for analysis, according to the type of surgery and the joint concerned: 125 patients with a knee revision surgery (55 with AMPLIFIX® 3G and 60 with AMPLIFIX® 1G), 104 patients with a hip primary surgery, 30 patients with a hip revision surgery.

- In the Knee / revision / 3G cohort, 85% of patients reported 'no' or 'low and rare' pain, and 89% of them were 'satisfied' or 'very satisfied' at a median follow-up of 60-month (range 1-173). 2 sepsis were reported, representing an infection rate of 3.6%. 1 revision surgery was performed (loosening of tibial component), representing a survival rate of 98.1% at 5-year FU.

- In the Hip / primary / 3G cohort, 95% of patients reported 'no' or 'low' pain, and 98% of them were 'satisfied' or 'very satisfied' with their surgery at a median follow-up of 26.5-month (range 1-136). No sepsis were reported in this cohort, representing an infection rate of 0%. 3 femoral stems were revised (2 femoral fractures and 1 stem loosening), representing a survival rate of 97.1% at 7-year FU.

- In the Hip / revision / 3G cohort, 84% of patients reported 'no' or 'low' pain, and 86% of them were 'satisfied' or 'very satisfied' with their surgery at a median follow-up of 60.5-month (range 1-133). 2 sepsis were reported, representing an infection rate of 6.7%. 4 femoral stems were revised (1 femoral fracture, 1 sepsis and 2 stems loosening), representing a survival rate of 86% at 5-year FU.

- In the Knee / revision/ 1G cohort, 86% of the cohort reported 'no' or 'low and rare' pain, and 88% of them were 'satisfied' or even 'very satisfied' at a median follow-up of 71-month (range 1-177). 2 sepsis were reported, representing an infection rate of 3.3%. 1 tibial component was revised, representing a survival rate of 98.3% at 6-year FU.

D. Data collected from a PMCF survey conducted in 2021

Teknimed launched a PMCF survey to collect information, directly from the users of its cements, on their satisfaction and their evaluation of the usability, clinical performance and safety of use of the products.

About 50 distributors or surgeons answered the questionnaire, covering 1934 patients with GENTAFIX® 1, 344 patients with GENTAFIX® 3 and 119 patients with GENTAFIX® 3MV, for primary (90%) or revision (10%) surgeries, in shoulder, hip

and knee. These numbers demonstrated that all 3 GENTAFIX® cements (1, 3 & 3MV) are actually used worldwide, in all types of surgeries and in all joints. Distribution of surgery type (primary vs revision) corresponds to the respective numbers of these surgeries in the nowadays practices in orthopaedic surgery.

According to the collected answers, a great majority of patients reported an improved health status after the surgery, consisting in alleviation of their pain (81.5% of improved level of pain), or an improved quality of life (79%). Overall, 92.3% of patients were satisfied of their surgery.
No (0%) postoperative adverse events were reported and all (100%) prostheses fixation were reported stable. Only 1 user reported a transient hypotension in 30% of his patients (representing 0.3% of the whole cohort).

E. Safety findings from continuous post-market surveillance (PMS)

During the 5 years period from 2016 to 2020, no complaints with a patient impact involving GENTAFIX® 3 or 3MV were recorded. 2 complaints with a patient impact have been reported for GENTAFIX® 1:

- A patient presented nickel and cobalt allergies following implantation of 2 knee prothesis. Since GENTAFIX® cement contains neither nickel nor cobalt, Teknimed product is not responsible for the allergies.
- A loosening of the acetabular component, due to a bad adhesion of the cement, led to a new surgery 6 months after the initial one. After investigation, it was concluded that the too high temperature in the surgery room led to a cement of poor quality after mixing.

No materiovigilance reports or batch recalls were registered for competing products in the main public materiovigilance online databases during the same period.

No trend for device malfunction leading to patient harm and no new risks were identified during this 5-year period. The rate of complaints in proportion to the number of sold units for the same period is significantly low and confirms the expected long-term safety of the device.

5.4. Overall summary of the clinical performance and safety

GENTAFIX® is a product issued from a well-known technology which has been used in orthopaedic surgeries for more than 50 years. It allows successful fixation of prosthetic implants into living bone cavity, leading to clinical benefits for the patients such as pain alleviation and improvement in quality of life.
Performance and safety of GENTAFIX® cement have been verified and confirmed through 2 PMCF studies (short-term performance), the CliniRecord register-like web database (long-term performance and safety), continuous PMS activity (long-term safety) and clinical evaluation (literature review and benchmarking):

SHOULDER	**Claimed performance**	**Claimed benefits**	**Literature benchmark rates** (13 834 patients)	**Reported rates from PMCF studies** (n=273 patients)	**Reported rates from CliniRecord** (n=249 patients)	**Reported rates from PMS** (400 000 units)
Primary surgery	Efficient antibiotic release	Efficient prophylactic and curing effect	infection rate < 2%	0% at 5.5-month for Gentafix®1 (n=52)	-	0%
	Efficient prosthesis fixation	Long-term survival	survival rate > 90% at 10-year FU	100% survival rate at 5.5-m FU for Gentafix®1 (n=52)	-	NA

HIP	**Claimed performance**	**Claimed benefits**	**Literature benchmark rates** (13 834 patients)	**Reported rates from PMCF studies** (n=273 patients)	**Reported rates from CliniRecord** (n=249 patients)	**Reported rates from PMS** (400 000 units)
Primary surgery	Efficient antibiotic release	Efficient prophylactic and curing effect	infection rate < 2%	0% at 1-y FU for Gentafix®1 (n=61) & 3 (n=61)	0% at 7-y FU for Gentafix®3 (n=104)	0.003%
	Efficient prosthesis fixation	Long-term survival	survival rate > 95% at 10-year FU	97,1% for Gentafix®1(n=61) 94,7% for Gentafix®3 (n=61) at 1-y FU*	97.1% at 7-year FU for Gentafix®3 (n=104)	NA

Revision surgery	Efficient antibiotic release	Efficient prophylactic and curing effect	recurrent sepsis rate < 10% at 5-y FU	9% at 1-y FU for Gentafix®1 (n=7)*	6.7% at 7-y for Gentafix®3 (n=30)	0%
		Long-term survival	survival rate < 87% at 5-y FU	100% at 1-y FU for Gentafix®1 (n=7)*	86% at 5-y for Gentafix®3 (n=30)	0%

KNEE	**Claimed performance**	**Claimed benefits**	**Literature benchmark rates** (13 834 patients)	**Reported rates from PMCF studies** (n=273 patients)	**Reported rates from CliniRecord** (249 patients)	**Reported rates from PMS** (400 000 units)
Primary surgery	Efficient antibiotic release	Efficient prophylactic and curing effect	infection rate < 2%	1.7% at 1-y for Gentafix®1 (n=57)	-	0%
	Efficient prosthesis fixation	Long-term survival	survival rate > 90% at 10-year FU	98,25% for Gentafix®1 (n=57)	-	NA
Revision surgery	Efficient antibiotic release	Efficient prophylactic and curing effect	recurrent sepsis rate < 10% at 5-y FU	3.8% at 1-y FU for Gentafix®1 (n=27)	3.3% for Gentafix®1 (n=60) 3.6% for Gentafix®3 (n=55) at 5-y FU	0%
		Long-term survival	survival rate < 86% at 5-y FU	100% at 1-y FU for Gentafix®1 (n=27)	98.3% for Gentafix®1 (n=60) 98.1% for Gentafix®3 (n=55) at 5-y FU	O%

*: *Not significative due to too small cohorts of patients*

Through literature review, the very long usage, for more than 50 years, of PMMA cements and antibiotic-loaded bone cements in primary and revision arthroplasty procedures was demonstrated and confirmed that they can be considered as efficient and safe well-known technologies. Post-market surveillance showed that no new and/or unexpected risks were identified during the last 10 years, in any relevant European Member State. Benefits-risks analysis demonstrated that all claims are supported by benefices responding to quantified benchmark criteria. The benefits-risks ratio of a cemented arthroplasty using GENTAFIX® bone cements for the patients can safely be considered positive.
To conclude, no critical risks have been identified versus a clear benefit of prophylaxis in primary arthroplasty for patients at risk of infection or curing in revision arthroplasty following joint infection.

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

The PMCF study described in section 5.3.B. above is on-going and continues to be currently conducted by Teknimed.

6. Possible diagnostic or therapeutic alternatives

Once the indication for an arthroplasty procedure has been clearly identified and the patient has agreed to be operated on, the surgeon will have to choose between 2 types of prostheses: cemented and uncemented.
No significant difference in the benefit-risk balance for these 2 types of prostheses have been clearly demonstrated in the medical literature. Their respective benefits and risks are still controversial. Consequently, the type of prosthesis used will usually be decided upon by the surgeon, based on the patient age, lifestyle, and the surgeon's past experience.

7. Suggested profile and training for users

Implantation of TEKNIMED products should only be performed in an adapted environment and by qualified operators having a sound knowledge and full mastery in bone cements preparation techniques. No specific training is required to

use Teknimed bone cements as the technique of mixing and injecting bone cements is considered basic knowledge for orthopaedic surgeons.
However, if needed, preparation techniques can be acquired from the distributors qualified by TEKNIMED.

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	2020	Clinical investigation of medical devices for human subjects — Good clinical practice	Fully whenever applicable
EN 62366-1	2015/ A1:2020	Medical devices – Application of usability engineering to medical devices	Fully whenever applicable
> Product standards			
ISO 5833	2002	Implants for surgery — Acrylic resin cements	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 10993-6	2017	Biological evaluation of medical devices — Part 6: Tests for local effects after implantation	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
ISO 10993-18	2020	Biological evaluation of medical devices — Part 18: Chemical characterization of materials	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 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 868-7	2017	Packaging for terminally sterilized medical devices - Part 7: Adhesive coated paper for low temperature sterilization processes — 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
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 556-2	2015	Sterilization of medical devices — Requirements for medical devices to be designated ''STERILE'' — Part 2: Requirements for aseptically processed medical devices	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 5276	2019	Standard Test Method for Drop Test of Loaded Containers by Free Fall	Fully whenever applicable
ASTM D 642	2020	Standard Test Method for Determining Compressive Resistance of Shipping Containers, Components, and Unit Loads 1	Fully whenever applicable
ASTM D 999	2015	Standard Test Methods for Vibration Testing of Shipping Containers	Fully whenever applicable
ASTM D 6653	2013	Standard Test Methods for Determining the Effects of High Altitude on Packaging Systems by Vacuum Method	Fully whenever applicable
ASTM D 4728	2017	Standard Test Method for Random 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

> Microbiology standards

EN ISO 11737-1	2018 / A1: 2021	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
EN ISO 11138-2	2017	Sterilization of health care products — Biological indicators — Part 2: Biological indicators for ethylene oxide sterilization processes	Fully whenever applicable

> Gamma 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

> Ethylene oxyde sterilisation standards

EN ISO 11135-1	2014 / A1:2019	Sterilization of health care products — Ethylene oxide — Part 1: Requirements for development, validation and routine control of a sterilization process for medical devices	Fully whenever applicable

EN ISO 10993-7	2008	Biological evaluation of medical devices — Part 7: Ethylene oxide sterilization residuals	Fully whenever applicable

> Aseptic processing standards

EN ISO 13408-1	2015	Aseptic processing of health care products — Part 1: General requirements	Fully whenever applicable
EN ISO 13408-2	2018	Aseptic processing of health care products — Part 2: Filtration	Fully whenever applicable

9. Revision history

Revision number	Date issued	Change description	Revision validated by the Notified Body
1.0	05 MAR 2021	Creation	☐ Yes, validation language: English ☒ No
1.1	05 MAY 2021	Update following BSI clinical review (Round 1)	☐ Yes, validation language: English ☒ No
1.2	18 NOV 2021	Update following BSI clinical review (Round 2)	☐ Yes, validation language: English ☒ No
1.3	08 FEB 2022	Update following ANSM Medicinal review and consecutive changes in IFU	☐ Yes, validation language: English ☒ No
1.4	31 MAY 2022	Update following BSI clinical review (Round 3)	☐ Yes, validation language: English ☒ No
1.5	AUG 2022	Update following BSI clinical review (Round 4)	☐ Yes, validation language: English ☒ No
1.6	SEP 2022	Update following additional questions from BSI	☒ Yes, validation 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 PATIENTS - English Version
GENTAFIX®

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: GENTAFIX®

3 different GENTAFIX® bone cements exist, with 3 different viscosities: GENTAFIX® 1, GENTAFIX® 3 and GENTAFIX® 3MV.

The medical device has also the following private labels:
AMPLIFIX 1 / AMPLIFIX 3; BIOCEMIUM I / BIOCEMIUM III;IMPLABOND 1 / IMPLABOND 3; OPTICEM 1 / OPTICEM 3; ORCEM 1 / ORCEM 3; PALAFOM 1; SINPLUS 1 / SINPLUS 3; ORTHOCEM 1 / ORTHOCEM 3 / ORTHOCEM 3G MV; EVOCEM 1 ET EVOCEM 3; NexCem 1 / NexCem 3 / NexCem 3G MV; SIGNATURE Cement SV / SIGNATURE Cement LV / SIGNATURE -x Cement MV ; ProstheSet 10 / ProstheSet 11 / ProstheSet 12; PERFIX PLUS 1 / PERFIX PLUS 3; Synth-X OH / Synth-X OL / Synth-X OM+; BezCem® 1 / BezCem® 3 / BezGen®3MV; CM-PX 1 / CM-PX 3 / CM-PX 3G MV; DYNABONE 1 / DYNABONE 3 / DYNABONE 3G MV; TEKCEM 1 / TEKCEM 3 / TEKCEM 3G MV; C-fix 1 / C-fix 3 / C-fix 3G MV; ArthroCem 1 / ArthroCem 3 / ArthroCem 3G MV; Jointfix 1 / Jointfix 3 / Jointfix 3G MV; Prosthefix 1 / Prosthefix 3 / Prosthefix 3G MV; C-Cem 1 / C-Cem 3 / GentaCem 3 MV.

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: 376017704B01CS

1.4. Year when the device was first CE-marked: 2000 for GENTAFIX® 1 and 3, 2012 for GENTAFIX® 3MV

2. Intended use of the device

2.1. Intended purpose

GENTAFIX® are used to fix prostheses into bones. These cements can be more or less viscous. They are adapted to the needs of the surgeon: type of prosthesis, joint morphologies (hip, knee or shoulder) and mode of application (manual, or with a syringe or injection gun).

2.2. Indication(s) and intended patient groups

GENTAFIX® are used in orthopaedic surgical procedures. They fix prostheses into bones. They can be used for the first fixation of a prosthesis in a joint (primary surgery). It can also be used when a prosthesis needs to be replaced by a new one (revision surgery). This happens in case of wear of the previous prosthesis or infection for example.
- GENTAFIX® 1 can be used for the first fixation of a prosthesis (primary surgery) in shoulder, hip and knee, and in replacement of a previous prosthesis (revision surgery) in the knee.
- GENTAFIX® 3 and 3MV can be used for the first fixation of a hip prosthesis (primary surgery), and in replacement of a previous prosthesis (revision surgery) in the hip and knee.

2.3. Contraindications

- Procedures other than those listed in the INDICATIONS section (paragraph 2.2).
- Presence of infection at the bone site caused by a strain resistant to the drug (gentamicin non sensitive strains).
- Use in patients with a history of serious nerves or ganglia diseases (neuromuscular diseases).
- Intolerance to constituents of the product (gentamicin or other constituents). Past intolerance to other drugs of the same family (aminoglycosides) may suggest not to use gentamicin. Cross-sensitivity of patients to drugs in this family exists.
- Use in patients having renal issues.
- Use in patients having calcium issues (calcium metabolism disorder).
- Not enough data are available on some categories of patients. GENTAFIX® cannot be used in young patients (children, adolescent and patient with immature skeleton). GENTAFIX® cannot be used in breast-feeding or pregnant women.

3. Device description

GENTAFIX® bone cements have been designed to fix prostheses (i.e., artificial joints) into bones of joints such as hip, knee or shoulder.

The bone cement is prepared just before the surgery. Liquid and powder are mixed together. The mixing is done either with a bowl and spatula or, for medium and low viscosity bone cements, with a mixing and injection kit. Right after mixing, the bone cement is applied and the prosthesis is positioned. After a delay of about a quarter of hour, the bone cement has fully hardened and the prosthesis is permanently fixed to the bone.

GENTAFIX® bone cements are made of biocompatible synthetic components (molecules of the acrylic kind). They contain an antibiotic: Gentamicin. This antibiotic helps preventing infection against a large variety of bacteria, or curing already infected joints. Their use allows a release of drug (antibiotic). This release is directly in the area where the bacterial infection might take place after a joint surgery.

GENTAFIX® bone cements contain also particles which make them visible on X-rays. They help surgeons controlling the good fixation of the prosthesis in the cement.

The full composition of the bone cement is described in the table below:

	Concentration (% w/w)		
COMPOSITION	**GENTAFIX®1** High viscosity	**GENTAFIX®3** Low viscosity	**GENTAFIX® 3 MV** Medium viscosity
Powder phase	**41.6g**	**41.6g**	**41.6g**
Polymethylmethacrylate	84.3	84.3	85.1
Benzoyl peroxide	2.3	2.3	1.5
Barium sulphate	9.6	9.6	9.6
Gentamicin sulfate (corresponding to 1g of gentamicin base)	3.8	3.8	3.8
Liquid phase	**14.4g**	**16.4g**	**18.8g**
Methylmethacrylate	84.4	84.4	84.4
Butylmethacrylate	13.2	13.2	13.2
Dimethyl paratoluidine	2.4	2.4	2.4
Hydroquinone	20ppm	20ppm	20ppm

GENTAFIX® bone cements have an expected lifetime of 15 years. At the end of this expected lifetime, the cement does not need to be removed and does not need any maintenance. The cement can remain in place all lifelong, unless a medical complication would require a new 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

Any serious incident that you presume is occurring in relation to the GENTAFIX® cement must be reported without delay to your surgeon.

All identified risks linked to the use of this device or of similar devices on the market, have been analysed and reduced as far as possible. Some residual risks still exist. They are explained in the Instruction for Use given with the medical device and are listed below.

Undesirable side effects of acrylic bone cements include:

- Low blood pressure reactions (hypotension) have been reported in the scientific literature (and up to 0.3% of cases reported to Teknimed), probably due to the release of cements components, occurring between 10 to 165 seconds following application of bone cement. These reactions have lasted from 30 seconds to 5 minutes. The Bone Cement Implantation Syndrome (BCIS) is an undesirable side effect which can impact the cardiac and circulatory system. Severe BCIS have been described in 5% of primary total knee or total hip surgeries, 2% of primary total shoulder surgeries and 7% of revision procedures of all joints, in scientific articles, but none with Gentafix® cements. Some patients have progressed to cardiac arrest (up to 0.17% reported in traumatology and 0.017% reported in scheduled procedures).
- Infection after surgery by non-gentamicin-sensitive bacteria or because of failure of the gentamicin, can occur with reported rates in the PMCF studies conducted by Teknimed of: 0% at 1-year after shoulder primary surgeries (GENTAFIX® 3), 0% at 7-year after hip primary surgery (GENTAFIX® 1 and 3) and 1.6% at 1-year after primary knee surgery (GENTAFIX® 1); 3.5% of recurrent infection at 5-year after knee revision surgery (GENTAFIX® 1 and 3) and 8% at 7-year after hip revision surgery (GENTAFIX® 3).
- Bad fixation of the prosthesis can lead to a poor liaison between the bone and the cement resulting in a detachment of the prosthesis (up to 0.8% in the PMCF study conducted by Teknimed and 2.2% in a series of 183 total hip arthroplasties).
- Even if no cases have been reported, allergy to gentamicin or to one of the bone cement constituents remains a risk inherent to the use of bone cements.

The undesirable side effects typical of gentamicin include:

- Toxicity to the nervous system (Neurotoxicity): manifested by hearing troubles (auditory and vestibular ototoxicity) including transient or irreversible hearing loss, numbness, skin tingling, muscle twitching, and convulsions. In a scientific article, transient loss in hearing, lasting from 3 days to 4 weeks after the surgery, concerned up to 20% of a series of 40 patients.
- Toxicity to the kidney (Nephrotoxicity): Usually in patients with pre-existing renal damage, and also in patients with normal renal function to whom aminoglycosides are administered for longer periods or in higher doses than recommended. The symptoms may appear after the end of the treatment. Yet, no cases of nephrotoxicity due to cements containing gentamicin have been reported in the 5 main national safety databases during the past 5 years.
- Potential allergy to impurities (histamine impurities arising from the gentamicin manufacturing process). However, no cases have been reported in the 5 main national safety databases during the last 5 years.

- Other adverse reactions associated with the drug (gentamicin) exist: hypersensitivity, allergic reactions, nausea, vomiting, urticaria, decrease in the number of white blood cells (reversible granulocytopenia), anemia, blood anomaly (blood dyscrasia), convulsions, central nervous toxicity, abnormal hepatic function, low level of magnesium in the blood (hypomagnesaemia), mouth inflammation (stomatitis), red blotches under the skin (purpura), allergic contact sensitization and neuromuscular impairment (neuromuscular blockade).

4.2. Warnings and Precautions

No warning and precautions for patients. This device is only used by healthcare professionals.
Patients having following medical history should mention it to their surgeon:

- intolerance to the drug (gentamicin),
- intolerance to bone cement components,
- renal or nervous disorder,
- treatment with drug of the same family (aminoglycoside family).

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

No field safety corrective actions have been issued for GENTAFIX® cements in the last years.

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

5.1. Clinical background

GENTAFIX® is a product issued from a very-well known technology. It has been used in orthopaedic surgery for many years. It allows successful fixation of prosthetic implants into living bone cavity, leading to clinical benefits for the patients such as pain relief and improvement in quality of life. 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

GENTAFIX® 1 & 3 were first CE marked and placed on the market in 1998. GENTAFIX® 3MV was first CE marked and placed on the market in 2012. At that time, the clinical safety was demonstrated by equivalence with another product.

A. Summary of clinical studies conducted by Teknimed

In a study started in 2020, and still current, 125 patients are participating to date: 3 primary shoulder surgery, 24 primary hip surgeries, 61 primary knee surgeries, 11 hip revision surgeries and 26 knee revision surgeries. All (100%) of patients reported pain relief and improvement of their well-being, 1 year after their surgery. No differences were observed between primary or revision surgery, or between Gentafix®1 or 3 or 3MV, whatever the operated joint.
The CliniRecord database (Cf. description below) present outcomes from a total of 249 patients.
Most of patients (85%) having had a knee revision surgery reported no or low pain 5 years after the surgery, and 89% of them were satisfied. Likewise, 95% of patients having had a primary hip surgery reported no or low pain, and 98% of them were satisfied 2 years after the surgery. Among patients having had a hip revision surgery, 84% of them reported no or low pain, and 86% of them were satisfied 5 years after their surgery. Finally, in the group of patients having had a knee revision surgery, 86% of them reported no or low pain, and 88% of them were satisfied 5 years after the surgery.

B. Comparison to outcomes obtained with other cements

Teknimed is always checking the performance and safety of its product. Different ways are used to detect any issue related to this device:
- Literature review on the product or similar products, which allows to benchmark the outcomes usually reported for such device or surgical procedures;
- Analysis of complaints from clients, through Post-Market Surveillance (PMS) activities conducted by Teknimed which consist of collecting, recording and analysing all complaints from clients and/or surgeons;
- Clinical study with surgeons using this device, such as Post-Market Clinical Follow-up (PMCF) which are clinical studies conducted by Teknimed after the device is placed on the market or such as CliniRecord which is a clinical study conducted by another Company.

Below is a summary of the currently benchmarked and collected clinical data:

SHOULDER (Gentafix®1)	**Claimed performance**	**Claimed benefits**	**Rates found in medical literature** (13 834 patients)	**Reported rates from PMCF studies** (273 patients)	**Reported rates from CliniRecord** (249 patients)	**Reported rates from PMS** (400 000 units)
Primary surgery	Efficient antibiotic release	Efficient infection preventive effect	infection rate < 2%	0% infection after 5.5 months (52 patients with Gentafix®1)	-	0%

	Efficient prosthesis fixation	Long-stay in place	> 90% implants still in place after 10-year FU	100% implants still in place after 5.5-month (52 patients with Gentafix®1,)	-	NA

HIP	Claimed performance	Claimed benefits	Literature benchmark rates (13 834 patients)	Reported rates from PMCF studies (273 patients)	Reported rates from CliniRecord (249 patients)	Reported rates from PMS (400 000 units)
Primary surgery	Efficient antibiotic release	Efficient infection preventive effect	infection rate < 2%	0% infections after 1 year (61 patients with Gentafix®1 and 61 patients with Gentafix® 3)	0% at 7-y FU (104 patients with Gentafix®3)	0.003%
	Efficient prosthesis fixation	Long stay in place	95% implants still in place after 10 years	97,1% implants (61 patients with Gentafix®1) and 94,7% (61 patients with Gentafix®3) still in place after 1 year	97.1% implants still in place after 7 years (104 patients with Gentafix®3)	NA
Revision surgery	Efficient antibiotic release	Efficient curing effect	rate of recurrent infections < 10% after 5 years	9% recurrent infections after 1 year (7 patients with Gentafix®1)*	6.7% recurrent infections after 7 years (30 patients with Gentafix®3)	0%
		Long-term survival	87% implants still in place after 5 years	100% implants still in place after 1 year (7 patients with Gentafix®1)*	86% implants still in place after 5 years (30 patients with Gentafix®3)	0%

KNEE	Claimed performance	Claimed benefits	Literature benchmark rates (13 834 patients)	Reported rates from PMCF studies (264 patients)	Reported rates from CliniRecord (249 patients)	Reported rates from PMS (400 000 units)
Primary surgery	Efficient antibiotic release	Efficient infection preventive effect	infection rate < 2%	1.7% infections after 1 year (57 patients with Gentafix®1)	-	0%
	Efficient prosthesis fixation	Long-term survival	90% implants still in place after 10 years	98,25% implants still in place after 1 year (57 patients with Gentafix®1)		NA
Revision surgery	Efficient antibiotic release	Efficient curing effect	rate of recurrent infection < 10% after 5 years	3.8% recurrent infections after 1 year (27 patients with Gentafix®1)	3.3% recurrent infections (60 patients with Gentafix®1) and 3.6% recurrent infection (55 patients with Gentafix®3) after 5 years	0%
		Long-term survival	86% implants still in place after 5 years	100% implants still in place after 1 year (27 patients with Gentafix®1)	98.3% implants still in place for Gentafix®1 (60 patients) and 98.1% for Gentafix®3 (55 patients) after 5 years	0%

*: *Not significative due to too small cohorts of patients*

Scientific publications showed that PMMA bone cements loaded with drugs are used for more than 50 years. They are used in on first or revision prosthesis fixation with very good results.
No new and/or unexpected risks were identified during the last 5 years. It corresponds to almost 400 000 sold units.
The balance between benefit and risk with the product can be considered positive.

Conclusion: GENTAFIX® is an effective and safe product. No critical risks have been identified. A clear benefit of using a drug (gentamicin) in first or revision prosthesis fixation exists.

5.3 Safety

Teknimed is always doing clinical studies (Scientific literature reviews, Post-Market Surveillance and Clinical Follow-up). They document and evaluate the benefits and risks of GENTAFIX®.
No new or unexpected risks were identified. Benefits were confirmed by clinical studies.
Regarding risks, the main one remains the risk of allergy to one component of the product. No other risks were identified during many years of post-market surveillance. Patients who are at risks of allergy to gentamicin should discuss this with their surgeon.

6. Possible diagnostic or therapeutic alternatives

When considering other treatments, it is recommended to contact your surgeon. He/She can take into account your individual situation.
To replace a joint, the surgeon can choose between two types of prostheses: cemented and uncemented. A cemented stem will usually have a very smooth surface. Its fixation into the bone shaft will be assured by an acrylic bone cement mantle between the metal and the bone. This cement interface must be thin and regular. An uncemented stem (also called cementless or press-fit), will usually be coated with a porous substance, such as a plasma spray with hydroxyapatite. The fixation of the stem into the shaft will be assured by the induced bone ingrowth into the porous coating.
No significative difference in the balance between benefit and risk for these two procedures (cemented versus uncemented) have been clearly demonstrated in the published literature. Their respective benefits and risks are still controversial. Consequently, the type of prosthesis used will be decided by the surgeon. This decision will be based on the patient age, lifestyle, and the surgeon's past experience.

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 orthopedic surgery.