Heraeus Medical

Summary of Safety and Clinical Performance

COPAL® G+C pro

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English

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2 Abbreviations / Explanations

ALBC	Antibiotic loaded bone cement
BCIS	Bone Cement Implantation Syndrome
BfArM	Federal Institute for Drugs and Medical Devices *[Bundesinstitut für Arzneimittel und Medizinprodukte]*
CE	Conformité Européenne
CER	Clinical Evaluation Report
CND	*Classificazione Nazionale dei Dispositivi medici* [National Classification of Medical Devices]
CS	Common Specifications as defined in the MDR
DIN	German standard *[Deutsches Institut für Normung]*
E141	chlorophyll-copper-complex (food colorant)
EMDN	European Medical Device Nomenclature
EN	European Standard *[Europäische Norm]*
EU	European Union
FSCA	Field Safety Corrective Action
FSN	Field Safety Notice
HME	Heraeus Medical GmbH
IFU	Instructions for Use
ISO	International Organization for Standardization
MDD	Medical Device Directive
MDR	REGULATION (EU) 2017/745 OF THE EUROPEAN PARLIAMENT AND OF THE COUNCIL of 5 April 2017 on medical devices, amending Directive 2001/83/EC, Regulation (EC) No 178/2002 and Regulation (EC) No 1223/2009 and repealing Council Directives 90/385/EEC and 93/42/EEC
MRI	Magnetic resonance imaging
N/A	Not applicable
NB	Notified Body
PMCF	Post-Market Clinical Follow-Up
PMMA	poly (methyl methacrylate)
PMS	Post-Market Surveillance
PSUR	Periodic Safety Update Report
SRN	Single Registration Number for an economic operator
SSCP	Summary of Safety and Clinical Performance
TD	technical documentation
Swissmedic	Swiss Agency for Therapeutic Products
UDI-DI	Unique Device Identification - device identifier
URL	Uniform Resource Locator (internet address)

3 General Information

This document applies to implantable class IIb and class III medical devices developed by Heraeus Medical GmbH and is established to comply with the Medical Device Regulation (MDR) 2017/745 (EU) of 5th April 2017, valid from May 2021.

The Summary of Safety and Clinical Performance (SSCP) is intended to provide a summary of clinical data pertinent to the safety and clinical performance of the medical device. The SSCP is an important source of information for intended users – both healthcare professionals and if relevant for patients. It is one of several means intended to fulfil the MDR objectives, to enhance transparency and provide adequate access to information.

3.1 Relevant information for Users/Healthcare Professionals

3.1.1 Device identification and general information

3.1.1.1 Device trade name(s) including all trade names the device may have on the market in different member states

This SSCP covers the products:

- COPAL® G+C pro

3.1.1.2 Manufacturer's name and address, manufacturer's single registration number (SRN)

Heraeus Medical GmbH
Philipp-Reis-Straße 8/13
61273 Wehrheim
Germany

Single Registration Number (SRN): DE-MF-000008199

3.1.1.3 Basic UDI-DI

Product	Basic UDI-DI
COPAL® G+C pro	426010213020201000 1BS

3.1.1.4 Medical device nomenclature

The EMDN code based on CND for COPAL® G+C pro is P099001 (orthopaedic prostheses cements and accessories for mixing).

3.1.1.5 Class of device (according to MDR, Annex VIII)

COPAL® G+C pro is a PMMA bone cement intended for stable anchoring of total or partial joint endoprostheses in living bone.

COPAL® G+C pro is classified as a Class III medical device as per Annex VIII of the Medical Device Regulation 2017/745 and is intended for long term use for more than 30 days.

COPAL® G+C pro incorporates gentamicin and clindamycin as integral parts, substances which, if used separately, can be considered to be medicinal products, as defined in point 2 of Article 1 of Directive 2001/83/EC. Therefore, it is classified as class III device (Rule 14). COPAL® G+C pro does not include a medicinal product derived from human blood or human plasma, as defined in point 10 of Article 1 of that Directive.

3.1.1.6 Year when the first certificate (CE) was issued covering the device

Product	Year of first CE-mark under MDR	Year of first CE-mark prior to MDR
COPAL® G+C pro	2023	n/a

3.1.1.7 Authorized representative if applicable; name and the SRN

Not applicable

3.1.1.8 Notified Body's (NB) name (the NB that will validate the SSCP) and the NB's single identification number (according to MDR, article 43 (I))

Notified Body name: TÜV SÜD Product Service GmbH
Notified Body single identification number: 0123

3.1.2 Intended use of the device

3.1.2.1 Intended purpose

COPAL® G+C pro is a PMMA bone cement intended for stable anchoring of total or partial joint endoprostheses in living bone.

3.1.2.2 Indications

COPAL® G+C pro is indicated for surgical treatment such as

- anchoring of endoprosthesis in primary and revision arthroplasty procedures of
  - hip
  - knee
  - ankle
  - shoulder
  - elbow

3.1.2.3 Target Population

Adult population, predominantly elderly patients with risk factors for periprosthetic joint infection and patients with trauma.

3.1.2.4 Contraindications

COPAL® G+C pro must not be used in the following cases:

- suspected or proven hypersensitivity to components of the bone cement including gentamicin, other aminoglycoside antibiotics, clindamycin, or lincomycin
- patients with renal impairment
- for permanent fixation purposes in the presence of an active or incompletely treated infection at the bone site caused by gentamicin and clindamycin non-sensitive strains
- spinal surgery
- during pregnancy or breast-feeding
- children

The safety of the bone cement in pregnant women or in children has not been established. Bone cement may adversely affect bone growth and fetal health.

3.1.2.5 Lifetime of the device

There is no general factor influencing the lifetime of COPAL® bone cements. The general provisions for the endoprostheses they are used to anchor also apply to bone cements. The actual lifetime of these bone cements can be influenced by factors such as the medical situation and lifestyle of the treated patients.

3.1.3 Device description

3.1.3.1 Description of the device

COPAL® G+C pro is a standard-setting, high-viscosity, radiopaque, poly (methyl methacrylate)-based (PMMA) bone cement, pre-filled into a mixing and application system, suitable for use with or without vacuum (ready to mix). It contains the aminoglycoside antibiotic gentamicin and the lincosamide antibiotic clindamycin to protect the cured bone cement and surrounding tissue from colonization by bacteria that are sensitive to gentamicin and/or clindamycin. It contains the X-ray contrast medium zirconium dioxide. To improve visibility in the surgical field, it has been colored with chlorophyll-copper-complex (E141). The bone cement consists of two components and is prepared immediately before use by mixing the polymer powder (= powder) with the monomer liquid (= liquid). A ductile dough forms that sets within a few minutes.

COPAL® G+C pro is intended for single-use and is supplied sterile.

Composition of COPAL® G+C pro

Powder	
PMMA copolymer	82 %
zirconium dioxide	10 %
benzoyl peroxide	1 %
gentamicin sulfate	4 %
clindamycin hydrochloride	3 %
Liquid	
methyl methacrylate	98 %
N, N-dimethyl-p-toluidine	2 %

The data is rounded

Other constituents:

- Powder: chlorophyll-copper-complex (E141)
- Liquid: chlorophyll-copper-complex (E141), hydroquinone

It cannot be excluded that COPAL® G+C pro contains traces of histamine. COPAL® G+C pro does not contain a radiation source.

COPAL® G+C pro is available in the following pack sizes:

COPAL® G+C pro
40, 80

Package design and method of sterilization

The bone cement is triple packaged: The powder is located inside the cartridge and the sterile-filtered liquid in (a) brown glass ampoule(s) within the ampoule casing of the COPAL® G+C pro system. The COPAL® G+C pro system is packed in the inner blister and the protective outer blister. Both blisters are sterilized using ethylene oxide. The protective outer blister is non-sterile on the outside and sterile on the inside. Afterwards the sterilized blisters are packed in a protective aluminum pouch.

Operating principles and mode of action

Mixing the powder and liquid together produces a paste that is used to anchor the prosthesis to the bone. The hardened bone cement allows stable fixation of the prosthesis and transfers all stresses generated in a movement to the bone via the large interface. The bone cement incorporates two antibiotics, gentamicin and clindamycin, that elute from the surface of the bone cement, thereby protecting the cured bone cement and surrounding tissue from colonization by bacteria that are sensitive to gentamicin and/or clindamycin.

The bone cement can be applied as soon as the doughy bone cement no longer adheres to the gloves (doctor finger test). The application time depends on the temperature of the material and the room temperature. To ensure adequate fixation, the prosthesis should be introduced and held in position within the time window allowed for application until the bone cement has set completely. Remove any surplus bone cement while it is still soft.

3.1.3.2 Reference to previous generation(s) or variants

COPAL® G+C pro is equivalent to COPAL® G+C. COPAL® G+C has already been marketed since 1998 by Merck Biomaterial GmbH (later Biomet Merck) under the former name Copal®. There is no difference to these earlier products marketed under the regulations of the Medical Device Directive (MDD).

3.1.3.3 Accessories intended to be used in combination with the device

Not applicable.

3.1.3.4 Other devices and products intended to be used in combination with the device

For mixing and application with COPAL® G+C pro, the following products from Heraeus Medical GmbH are suitable:

Article	Description	Quantity	Reference number
Required:			
PALAGUN® *if locally available*	Single-use cement gun	1	5082371
or			
PALAMIX® cement gun	Reusable cement gun	1	66036163
Optional:			
PALAMIX® vacuum pump	Reusable vacuum pump with one-way valve	1	66036748
pro nozzle medium	Single-use, flexible, conical nozzle	10	66054436

COPAL® G+C pro can be used in combination with all cementable joint endoprostheses suitable for the anatomic locations listed in the indications.
The instructions for use of the supporting equipment must be followed.

Note: Heraeus Medical GmbH has not tested the compatibility of COPAL® G+C pro with devices of other manufacturers and does not assume any liability for this. The use of mixing equipment of other manufacturers is done in the sole discretion and responsibility of the user.

3.1.4 Risks and warnings

3.1.4.1 Side effects and residual risks

Side Effects

The assessment of side-effects is based on the following frequencies:
Frequent: > 1:1,000
Probable: 1:10,000 to 1:1,000
Occasional: 1:100,000 to 1:10,000
Remote: 1:1,000,000 to 1:100,000
Improbable: < 1:1,000,000

Frequency	Side effect
Immune System	
Improbable	• hypersensitivity / allergic reaction and local reaction which may include inflammation, induration, erythema, pruritus or pain • anaphylactic shock
Kidney and Urinary Tract	
Improbable +	• renal impairment
Musculoskeletal System	
Improbable +	• ossification • osteolysis due to bone cement fragments
Skin and Subcutaneous Tissue	
Improbable	• rash • urticaria

+ not reported to Heraeus Medical GmbH; only identified from literature / state-of-the-art

Residual Risks

Residual risks listed below are risks which are beyond the control of the manufacturer, because they are procedure or user related.

Frequency	Residual Risk
Vascular System, Heart, Respiratory System, Blood and Lymphatic System, Nervous System	
Remote	*****bone cement implantation syndrome (BCIS) due to insertion of bone cement and prosthesis may produce a high medullary pressure that forces bone marrow constituents into the venous vascular system resulting in fat and marrow emboli. This might include: o low blood pressure / hypotension o hypoxia o bradycardia o tachycardia o pulmonary hypertension o thrombosis o embolism o pulmonary embolism o myocardial infarction o cerebrovascular accident o respiratory arrest o cardiac arrest
Nervous System	
Improbable +	• numbness
Blood and Lymphatic System	
Improbable +	• hypovolemia
Musculoskeletal System	
Frequent**	• aseptic loosening
Improbable	• unequal limb length • loss of range of motion • ambulation difficulties
Infection	
Frequent**	• Bacterial infection including cellulitis, and / or osteomyelitis
Generalized Disorders	
Improbable	• inflammation • swelling / edema

Frequency	Residual Risk
	• fibrosis
Improbable +	• heat necrosis

*To avoid BCIS, it is recommended that the implantation site is cleaned thoroughly with pulsatile, high pressure, high-volume lavage using an isotonic solution and dried before the bone cement is introduced. The cement should be applied retrogradely under sustained low pressure into the medullary canal. Subsequently, the prosthesis should be introduced slowly into the cemented medullary canal.
In the event of pulmonary or cardiovascular side effects, it is necessary to monitor blood volume and possibly increase it. In the case of acute respiratory failure, anesthesiologic measures should be taken.
** As determined by registry data (National Joint Registry of England, Wales, Northern Ireland, the Isle of Man and the States of Guernsey)
+ not reported to Heraeus Medical GmbH; only identified from literature / state-of-the-art

The following adverse reactions have been observed with the use of poly (methyl methacrylate) bone cements: thrombophlebitis, hemorrhage, trochanteric bursitis.

3.1.4.2 Warnings and precautions

Warnings

Regarding intended users

Caution should be exercised during the mixing of the two components of COPAL® G+C pro to prevent excessive exposure to the concentrated monomer vapors, which may produce irritation of the respiratory tract, eyes, and possibly the liver. Personnel wearing contact lenses should not be near or involved in mixing this bone cement. Manufacturers of soft contact lenses recommend removing the lenses in the presence of damaging or irritant vapors. Since soft contact lenses are permeable to liquids and gases, they should not be worn in the operating room if methyl methacrylate is being used. Eye protection is recommended while mixing the bone cement to protect the eye from any glass fragments or monomer liquid when opening the ampoule. However, COPAL® G+C pro minimizes the amount of free monomer in the operating room.

The monomer is a powerful lipid solvent and should not come into direct contact with the body. When handling COPAL® G+C pro it is essential to wear gloves that provide the necessary protection against penetration of the monomer into the skin. Three-layered PVP gloves (polyethylene, ethylene vinyl alcohol copolymer, and polyethylene) and Viton®/butyl gloves have proved to provide good protection over an extended period. It is recommended that two pairs of gloves be worn over one another, e.g., a polyethylene surgical glove over an inner pair of standard latex surgical gloves. Do not allow the monomer to contact latex or polystyrene–butadiene gloves. Request confirmation from your glove supplier that the respective gloves are suitable for use with this bone cement.

Polymerization of the bone cement is an exothermic reaction, which occurs while the bone cement is hardening in situ. The released heat may damage bone or other tissues surrounding the implant.

Avoid over-pressurizing the bone cement because this may lead to extrusion of the bone cement beyond the site of its intended application and damage to the surrounding tissue.

Inadequate fixation or unanticipated postoperative events may affect the cement–bone interface and lead to micro motion of bone cement against bone surface. A fibrous tissue layer may develop between the bone cement and the bone and loosening of the prosthesis may occur leading to implant failure. Long-term follow-up is advised for all patients on a regularly scheduled basis.

Note: COPAL® G+C pro is a single-use device and must never be re-used! Re-use may result in diminished safety, performance, and compliance with relevant specifications.

Regarding the intended patient population

COPAL® G+C pro is considered most unlikely to cause gentamicin and/or clindamycin overdosage, because high local gentamicin and clindamycin concentrations only led to low (≤ 1 µg/ml) and short-lived systemic concentrations (Gehrke et al. 2001).

Monitor patients carefully for any change in blood pressure during and immediately after the application of bone cement. Adverse patient reactions involving the cardiovascular system are in particular linked to the pressurization of bone cement and the subsequent implantation of the cemented stem. Hypotensive reactions have occurred shortly after application of bone cement. However, consequences such as cardiac arrest are only reported in very few cases.

Precautions

Regarding intended users

Do not use COPAL® G+C pro after the expiration date printed on the folding box. This device may not be safe or effective beyond its expiration date.

Follow the handling and mixing instructions to avoid contact dermatitis. Strict adherence to the instructions for mixing the powder and liquid components may reduce the incidence of this complication.

Adequately ventilate the operating room to eliminate as much monomer vapor as possible.

The liquid is highly volatile and flammable. Ignition of monomer fumes caused by use of electrocautery devices in surgical sites near freshly implanted bone cements has been reported.

Do not use the bone cement after the application phase. This may require removal of the already applied bone cement from the bone. It can lead to unequal leg length when correct positioning of the prosthetic implant is hindered, or it can lead to early loosening of the implant.

Do not use the bone cement if its consistency is inhomogeneous as this can lead to early loosening of the implant.

Regarding the intended patient population

Like all aminoglycosides, gentamicin is potentially nephrotoxic. Independent of the total amount applied, care should be taken in patients with risk factors for the development of renal failure as well as in patients simultaneously treated with other nephrotoxic drugs, e.g., by periodically monitoring systemic levels of the antibiotic, serum electrolytes and renal function.

Gentamicin and clindamycin can potentially enhance the effect of neuromuscular blocking substances. They should therefore be used with caution in patients receiving such drugs.

A clinically significant antagonistic effect between clindamycin and erythromycin is possible. Therefore, joint use should be avoided. When used together with vitamin K antagonists such as warfarin, increased blood coagulation values and bleeding have been observed. In patients treated with these drugs, the blood coagulation values should therefore be monitored closely in the period after implantation. Clindamycin can transiently cause deviation in liver function test results.

Blood pressure, pulse, and breathing must be monitored carefully during and immediately after introduction of the bone cement. Any significant change in these vital signs must be resolved without delay by taking appropriate action. When using COPAL® G+C pro, the prepared bone should be carefully cleaned, aspirated, and dried just before the bone cement is placed.

3.1.4.3 Other relevant aspects of safety

On 24 July 2017, Heraeus Medical GmbH released an Urgent Field Safety Notice which addressed general information on handling of standard Heraeus Medical GmbH bone cement packaging, which consists of cement powder bags and liquid ampoules in one box. The Urgent Field Safety Notice was applicable for all pouched PALACOS® bone cements with and without gentamicin, COPAL® G+C, and COPAL® G+V. It described that in individual cases, the secondary bag (polyethylene paper bag) of the bone cement products might tear on opening, making sterile removal of the primary bag (cement powder bag) difficult. The reduced ability of the secondary bag to be torn open occurred due to excessive tensile strength of the sealed seam. Given identical sealing parameters, affected batches of packaging material exhibited higher tensile strength of sealed seams, which, however, conformed with applicable standards. Sterility of the cement was not affected by these problems. If the bag tears on opening, this will impair sterile removal of the primary bag and the product may have to be discarded. A slight delay in operating time caused by the time required to procure a replacement product may be a consequence for patients. Heraeus Medical GmbH reported a worldwide rate/ incidence below 0.02 %. On 04 July 2018, Heraeus Medical GmbH expanded this Urgent Field Safety Notice to inform users outside Germany on this issue. Furthermore, PALAMED® (G), which was not explicitly mentioned in the previous notice, was included.

In summary, the described issue did not result in a potential for mortality or serious deterioration in health of patients, users, or other persons since the deficiency would occur prior to using the device. Except for a slight delay in operating time, no further safety issues were connected with this effect. Nevertheless, as a precautionary measure, a detailed description of correct opening procedure of the secondary bag was included in all subsequent IFU versions.

The information from this Urgent Field Safety Notices has also been entered into national safety databases, e.g., of BfArM, Swissmedic, and MHRA.

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

3.1.5.1 Related to equivalent device, if applicable

COPAL® G+C pro is equivalent to COPAL® G+C (Basic UDI-DI: 4260102130102010002B5). Therefore, all clinical experience described below for COPAL® G+C also applies to COPAL® G+C pro.

For information on literature on the equivalent device, refer to section 3.1.5.3. For an overall summary of the clinical performance and safety of the equivalent device, including data from registries, refer to section 3.1.5.4.

3.1.5.2 From conducted investigations of the device before CE-marking, if applicable

Not applicable

3.1.5.3 From other sources, if applicable

A systematic literature review yielding articles in which the device in question was used is performed at least annually. A summary of the results is provided in this section. Additionally, clinical data from medical device registries is considered. For the analysis of clinical data from medical device registries, refer to the next section of this document.

In total, ten product-specific clinical studies were published in the literature for COPAL® G+C. Five of these were retrospective observational studies (Sanz-Ruiz et al., 2020, Anagnostakos & Sahan, 2021, Jenny et al., 2021, Tyas et al., 2018, Savage et al., 2019), while 3 were retrospective observational studies (Abdelaziz et al., 2019, Ortola et al., 2017, Fink et al., 2011). Additionally, two prospective controlled studies (Gehrke et al., 2001, Sprowson et al., 2016) were performed and the results published.

Research topics of all publications included safety and performance outcome parameter, such as aseptic and septic revision rates, prevalence of deep surgical site infections, and determination of antibiotic release pattern and concentration. Of the 10 studies, 9 reported favorable outcomes for COPAL® G+C. Anagnostakos & Sahan reported

outcomes which were classified as indifferent; a favorable outcome could not be clearly determined, because only descriptive statistics were provided due to limited patient number per group and small sample size.
In conclusion, available published clinical data on COPAL® G+C has been thoroughly evaluated. In conjunction with the successful clinical use of COPAL® G+C for more than 20 years it can be concluded that the benefit / risk ratio is favorable.

A comprehensive summary on registry data is included in the following section '3.1.5.4 An overall summary of the clinical performance and safety'.

3.1.5.4 An overall summary of the clinical performance and safety

PMMA bone cements, gentamicin and clindamycin are very well-studied and no additional product-specific safety concerns exist for COPAL® G+C pro. Nonetheless, post-market clinical follow-up (PMCF) activities are performed within the scope of post-market surveillance (PMS).

As the devices under evaluation are not expected to carry significant risks when used as intended and bone cements are well-established, the clinical evaluation will be updated when new data concerning the products arise or on an annual basis, respectively.

Clinical benefits

The expected clinical benefits in primary and revision arthroplasty, respectively, risks and the acceptability of the benefit-risk profile will be assessed in relation to the State-of-the-Art (SOTA) and according to the following indicative list of benchmark parameters:

Performance/ Safety aspect	**Benefit**	**Outcome Parameter**	**Threshold / Target values (as per state-of-the-art)**
Stable fixation	Low risk of revision or re-revision surgery *	Cumulative revision rate and rate of aseptic loosening (data from registries and the literature) comparable to or better than state-of-the-art	**Cumulative (re-)revision rates:** Hip primary: 1.1 – 3.2% after 3y Hip primary: 2.9 – 4.8% after 10y Knee primary: 1.5 – 4.3% after 3y Knee primary: 3.2 – 5.8% after 10y Ankle primary: 5.8% after 5y Shoulder primary: 3.8% after 4y Elbow primary: 1.3 – 3.3% after 1y Hip revision: 15.9 – 25.4% after 10y Knee revision: 15.9 – 44.9% after 10y Ankle revision: 13% after 4y Shoulder revision: 16.2% after 1y Elbow revision: 13.3 – 20% after 3y **Aseptic loosening rates:** Hip primary: 0.5 – 1.4% Knee primary: 0.6 – 1.2% Ankle primary: 2.7% Shoulder primary: 0.5% Elbow primary: 1.7% Hip revision: 6.7% Knee revision: 5.3% Ankle revision: 4.9% Shoulder revision: 2.4 – 3.6% Elbow revision: 2.9 – 4.4%

Performance/ Safety aspect	Benefit	Outcome Parameter	Threshold / Target values (as per state-of-the-art)
Indirect: improvement of impaired body function	Improvement of impaired body function	Adjusted health gain as per Oxford hip/knee score (data from NJR reports)	**Oxford hip/knee score at 6 months:** Hip primary: 40 Knee primary: 36 Hip revision: 34 Knee revision: 29
Indirect: Relief of symptoms	Relief of symptoms		
Application of ALBC	Low risk of reinfection	Revisions or re-revisions caused by infections relative to the overall number of procedures, taking into account ASA-grading and indications (data from registries and the literature)	**Reinfection rates:** Hip primary: 0.1 – 1.2% Knee primary: 0.2 – 2.3% Ankle primary: 1.6% Shoulder primary: 0.5% Elbow primary: 0.2% Hip revision: 2.8% Knee revision: 3.7% Ankle revision: 0.7% Shoulder revision: 1.8% Elbow revision: 2.9 – 4.3%
Local use of antibiotic at the surgery site	Low risk for systemic toxicity	Low frequency of hypersensitivity reactions to gentamicin and/or clindamycin (vigilance data, adverse event and recall database data, biologic risk assessment regarding systemic toxicity).	Gentamicin serum concentration to not exceed levels which lead to oto- or nephrotoxicity: c(gentamicin): < 2 µg/ml Clindamycin serum concentration to not exceed concentrations of intravenous application which can lead to side effects: c(clindamycin): < 29 µg/ml

The clinical benefits and clinical outcome parameters describe relevant aspects which are important for evaluation of the benefit/risk ratio. The manufacturer has performed the analysis of clinical data of the equivalent device COPAL® G+C e.g., from endoprosthesis registries, scientific publications, complaints, and clinical data from adverse event and recall databases.

With regards to the benefit of a low risk of revision, the analysis revealed that the cumulative revision rates at 3 years for primary hip and knee arthroplasty performed with COPAL® G+C were 2.3% and 2.5%, respectively, which is comparable to benchmark standards (range for hip: 1.1 - 3.2%; range for knee: 1.5 - 4.3%) when ASA and BMI were adjusted and matched between the two groups. Similar results were obtained for primary shoulder, elbow and ankle procedures performed with COPAL® G+C: 3.9% for shoulder (benchmark standard: 3.9%, both at 4 years), 3.2% for elbow (benchmark standard: 1.3 - 3.3%, both at 1 year) and 0.0% for ankle (benchmark standard: 5.8% at 5 years).

For revision arthroplasty, the cumulative re-revision rates for COPAL® G+C in hip and knee joint were 13.2% and 11.7% (both at 10 years), respectively, which was better than reported benchmark values (hip: 15.9 - 25.4%; knee: 15.9 - 44.9%, both at 10 years). For revision shoulder, elbow and ankle procedures, the rates for COPAL® G+C were 2% (at 1 year), 15.7% (at 3 years) and 0.0% (at 1 year), respectively, thus comparable or slightly better than the benchmark standard (shoulder at 1 year: 16.2%; elbow at 3 years: 13.3 - 20%; ankle at 4 years: 13%).
Benchmark standards for the rate of aseptic loosening of primary hip and knee arthroplasty were in the range of 0.5 - 1.4%. COPAL® G+C performed better than expected, with a rate of 0.1 – 0.2% for primary hip, and 0.2 – 0.4% for primary knee arthroplasty. The rate of primary shoulder arthroplasty was comparable to benchmark (COPAL® G+C: 0%; benchmark: 0.5%), whereas the rate for primary elbow procedures was reported to be worse for COPAL® G+C compared to benchmark (COPAL® G+C: 5%; benchmark: 1.7%). There were no cases of aseptic

loosening reported for primary or revision ankle procedures with COPAL® G+C. For revision arthroplasties of other joints, the reported rates of the benchmark standard for aseptic loosening were 5 - 7% for hip and knee, and 2 – 9% for shoulder and elbow. Revision arthroplasties performed with COPAL® G+C had considerably better rates for hip and knee, with 1 – 1.5% in hip and 1 – 2.3% in knee. Again, a revision rate of 0% was reported for aseptic loosening in shoulder joints, indicating that COPAL® G+C performed better than expected. Revision elbow procedures performed worse than benchmark standard (9.3%). It should be noted that the rate of aseptic loosening was comparable to the expected revision rates by NJR. This means that when the rate of aseptic loosening was adjusted for age group, gender, indications, and implantation year, COPAL® G+C performed as expected compared to the benchmark standard for revision procedures, without a significant difference between COPAL® G+C and non-Heraeus ALBC ($p = 0.827$).

With regards to the benefit of a low risk of reinfection, the analysis revealed similar results as those for aseptic loosening: infection rates obtained for COPAL® G+C in primary hip (0.6%), knee (1.1%) and shoulder arthroplasty (0.3%) were comparable to the reported benchmark rates of 0.1 – 2.3%. NJR data on revision of the initial prosthesis due to infection showed higher values for elbow procedures with COPAL® G+C compared to benchmark standard (2.5% versus 0.2%). This is supposedly due to differences the patient populations, as COPAL® G+C is more often used in patients with a higher ASA grade and/or higher BMI. Both are well known risk-factors for an increased risk of infections. This is supported by the fact that the infection rate was comparable to the expected revision rates by NJR, meaning that when the infection rate was adjusted for age group, gender, indications, and implantation year, COPAL® G+C performed as expected compared to the benchmark standard for revision procedures, without a significant difference between COPAL® G+C and non-Heraeus ALBC ($p = 0.649$). There were no cases of infection reported for primary ankle procedures with COPAL® G+C. For the benefit of a low risk of reinfection of an already revised prosthesis, infection rates were similar to benchmark standards in all joints.

The analysis of the outcomes for the benefits of improvement of impaired body function as well as relief of symptoms revealed comparable results between COPAL® G+C and expected values (statistically insignificant differences, all values rounded): the benchmark for the functional Oxford Hip Score at 6 months in primary arthroplasty is 40 compared to a slightly higher 41 for COPAL® G+C. In revision arthroplasty the values are 34 for both the benchmark standard and COPAL® G+C. Similarly, the Oxford Knee Scores at 6 months are comparable: 36 for the benchmark standard in primary arthroplasty compared to 35 for COPAL® G+C. In revision arthroplasty, COPAL® G+C reaches slightly higher values with 30 compared to 29 of the benchmark standard.

With regards to the risk of systemic toxicity, *in vivo* (Gehrke et al. 2001) and *in vitro* (Boelch et al. 2017, Karaglani et al. 2020) data support the claim of high local antibiotic concentration at the surgery site, while serum levels of 0.96 µg/ml for gentamicin and 0.18 µg/ml for clindamycin remain well below toxic levels (2 µg/ml and 0,18 µg/ml, respectively). In line with these results, no reports on adverse antibiotics levels (cases without additional systemic treatment of the same antibiotic) have been obtained from vigilance data or adverse event and recall databases.

For all presented data on ankle procedures, it should generally be noted that more clinical data is necessary to obtain statistically relevant results. PMCF measures are planned to gather more information on outcome parameters for ankle primary and revision procedures.

In summary, this evaluation of COPAL® G+C, which is equivalent to COPAL® G+C pro, confirmed the fulfillment of the expected clinical benefits i.e., showing the success in relation to the specified clinical outcome parameters.

For COPAL® G+C pro it can be concluded that the benefits considerably outweigh the risks for the indications

- anchoring of endoprosthesis in primary and revision arthroplasty procedures of
    - hip
    - knee
    - ankle
    - shoulder
    - elbow

3.1.5.5 Ongoing or planned post-market clinical follow-up

Some data gaps exist for small joints which will be addressed by the collection of further data from registries. Furthermore, a Post-Market Clinical Follow-up (PMCF) study is planned for COPAL® G+C pro to obtain clinical data, details of which can be found below.

The strategy and methodology to systematically collect and assess qualitative and quantitative aspects of clinical safety with clear reference to the determination of residual risks and side-effects of the device under evaluation will be described in the latest version of the Post-Market Surveillance Plan for COPAL® G+C pro.

The following PMCF measures are planned for COPAL® G+C pro:

PMCF Study
A prospective, open, non-controlled, observational, multi-center, multi-national PMCF study is planned for COPAL® G+C pro to verify the presumption that there will be no clinically significant difference in the safety and clinical performance of the device under evaluation (COPAL® G+C pro) compared with the equivalent device (COPAL® G+C). As the only difference between COPAL® G+C and COPAL® G+C pro is that COPAL® G+C is pre-filled into the mixing and application system of COPAL® G+C pro, potential occurrence of clinically significant differences is, if at all, expected to arise during the preparation steps and application of the bone cement. Therefore, data from individual treatments will be collected to assess (short-term) safety and performance aspects of the device. Detection of possible long-term clinical differences will be covered by registry analysis (see below).

Device Registry Analysis
The analysis of device registry data will primarily consider NJR as the largest register in the world, covering more than 3 million records. The registry presents data on joint replacement up to 15 years of follow-up, with data on hips, knees, shoulders, elbows, and ankle replacements. A representative patient population, a sufficient sample size, and an adequate follow-up are provided by this registry. Clinical data for COPAL® G+C is available and will be analyzed during the annual update of the CER. Clinical data for COPAL® G+C pro will be analyzed during the annual update of the CER upon data availability.

Screening of Scientific Literature
The screening of scientific literature provides up-to-date information about the device under evaluation and is an important source of new clinical data to update the clinical evaluation. It covers both favorable and unfavorable data with different levels of data quality, including data on possible misuse or off-label use.

Adverse Event and Recall Databases
Adverse events and recalls reported in databases are an important source of information about the safety of the device under evaluation. They represent relevant information in terms of quantitative and qualitative data. Databases of authorities will be evaluated periodically as part of the preparation for CER-updates and the results will be described in a Safety and Recall Database Report.

The results will be summarized in the corresponding PMCF reports. These activities will be conducted on an annual basis in connection with the continuous updates of the clinical evaluations.

3.1.6 Possible diagnostic or therapeutic alternatives

Primary arthroplasty operations and endoprosthesis revision operation as well as the use of PMMA bone cements are very well-established procedures in joint replacement surgery.

PMMA has been widely used for the fixation of various endoprostheses in orthopedic surgery since decades. At present, PMMA is still the most commonly used filling material in primary arthroplasty operations. Uncemented procedures have also been used in primary arthroplasty operations. Furthermore, hybrid techniques have been developed during the past decades. The review of the literature indicates that there is no evidence to prove the superiority of cementless over cemented total joint arthroplasties. Hence, the use of PMMA bone cement can be considered state-of-the-art in primary arthroplasty operations.

In addition to the well-known characteristics and safety profile, a great advantage of PMMA is the long-term experience with this material and the familiarity of the majority of orthopedic surgeons.

If conservative treatments fail, a reconstructive surgical procedure such as resurfacing, or replacement of the diseased joint may be necessary. In primary arthroplasty operations of different etiologies, it is generally agreed that clinicians should attempt the core non-surgical therapies prior to referral for surgery. In patients with suspected or confirmed prosthetic joint infections, however, there is no conservative treatment option and hence, those patients have to undergo one-stage or two-stage revision surgery.

Internal fixation treatment is a well-established clinical procedure to stabilize fractured bone or bone defects. The ability of fractured or defect bone to support the internal fixation devices is often deteriorated in the aging population and by various medical conditions. Thus, filling and stabilizing the bone structure with (antibiotic) bone cement to improve the pullout strength of implants and to reduce cut outs and failures is a state-of-the-art procedure within the scope of internal fixation treatment.

The use of ALBC for the stable anchoring of joint prostheses in primary arthroplasty operations as well as in revision operations resulting from the aseptic loosening of the prosthesis and periprosthetic infection can also be considered state-of-the-art. Selection of the appropriate antimicrobial substance(s) in the bone cement has to be based on the isolated microorganisms that should be sensitive to the antibiotic(s).

Implantation of ALBC is contraindicated in patients with known hypersensitivity to the antibiotic(s) or other components of the bone cement. In patients with severe renal insufficiency, a bone cement loaded with an aminoglycoside antibiotic should not be applied because of potential nephrotoxicity caused by an aminoglycoside. As there is insufficient data on the use of gentamicin and clindamycin in pregnant and breast-feeding women to evaluate any possible risk the use of ALBC containing gentamicin and clindamycin during pregnancy and lactation is generally not advised, unless the benefits for the mother outweigh the potential risk to the child.

Furthermore, the usage of vacuum mixing systems is well-established in the clinical setting.

Based on a comprehensive literature search, it can be concluded that the use of PMMA bone cement or ALBC in joint replacement and revision surgery procedures as well as reconstruction of bone indicated in various medical conditions complies with the current state-of-the-art.

3.1.7 Suggested profile and training for user

The surgeon must be thoroughly familiar with the properties and handling characteristics of COPAL® G+C pro. As the handling of the products varies with temperature, humidity, and mixing technique, a test mix should be performed to ensure familiarity with its characteristics.

3.1.8 Reference to any harmonized standards and CS applied

List of common specification

Not applicable – There are currently no common specifications for this product.

List of harmonized standards

Number	Title	Issue Date	Application
DIN EN ISO 13485	Medical devices - Quality management systems - Requirements for regulatory purposes (ISO	2021	partially, clause 7.5.3

Number	Title	Issue Date	Application
	13485:2016); German version EN ISO 13485:2016 + AC:2018 + A11:2021		and 7.5.4 excluded
DIN EN ISO 14971	Medical devices – Application of risk management to medical devices (ISO 14971:2019); German version EN ISO 14971:2019	2022	full
DIN EN ISO 15223-1	Medical devices - Symbols to be used with medical device labels, labelling and information to be supplied - Part 1: General requirements (ISO 15223-1:2021); German version EN ISO 15223-1:2021	2022	full
DIN EN ISO 14155	Clinical investigation of medical devices for human subjects - Good clinical practice (ISO 14155:2020); German version EN ISO 14155:2020	2021	Partially, clause 6.3
DIN EN ISO 14602	Non-active surgical implants - Implants for osteosynthesis - Particular requirements (ISO 14602:2010); German version EN ISO 14602:2011	2012	full
DIN EN ISO 11607-1	Packaging for terminally sterilized medical devices - Part 1: Requirements for materials, sterile barrier systems and packaging systems (ISO 11607-1:2019); German version EN ISO 11607-1:2020	2020	full
DIN EN ISO 11607-2	Packaging for terminally sterilized medical devices - Part 2: Validation requirements for forming, sealing and assembly processes (ISO 11607-2:2019); German version EN ISO 11607-2:2020	2020	full
DIN EN 556-1	Sterilization of medical devices - Requirements for medical devices to be designated "STERILE" - Part 1: Requirements for terminally sterilized medical devices; German version EN 556-1:2001	2002	full
DIN EN 556-1 Cor. 1	Sterilization of medical devices - Requirements for medical devices to be designated "STERILE" - Part 1: Requirements for terminally sterilized medical devices; German version EN 556-1:2001, Corrigenda to DIN EN 556-1:2002-03; German version EN 556-1:2001/AC:2006	2006	full
DIN EN 556-2	Sterilization of medical devices - Requirements for medical devices to be designated "STERILE" - Part 2: Requirements for aseptically processed medical devices; German version EN 556-2:2015	2015	full
DIN EN ISO 14937	Sterilization of health care products - General requirements for characterization of a sterilizing agent and the development, validation and routine control of a sterilization process for medical devices (ISO 14937:2009); German version EN ISO 14937:2009	2010	full
DIN EN ISO 11135	Sterilization of health-care products - Ethylene oxide - Requirements for the development, validation and routine control of a sterilization process for medical devices (ISO 11135:2014 + Amd.1:2018); German version EN ISO 11135:2014 + A1:2019	2020	full
DIN EN ISO 11737-1	Sterilization of health care products - Microbiological methods - Part 1: Determination of a population of	2021	full

Number	Title	Issue Date	Application
	microorganisms on products (ISO 11737-1:2018 + Amd 1:2021); German version EN ISO 11737-1:2018 + A1:2021		
DIN EN ISO 11737-2	Sterilization of medical devices - Microbiological methods - Part 2: Tests of sterility performed in the definition, validation and maintenance of a sterilization process (ISO 11737-2:2019); German version EN ISO 11737-2:2020	2020	full
DIN EN ISO 13408-1	Aseptic processing of health care products - Part 1: General requirements (ISO 13408-1:2008, including Amd 1:2013); German version EN ISO 13408-1:2015	2015	full
DIN EN ISO 13408-2	Aseptic processing of health care products - Part 2: Sterilizing filtration (ISO 13408-2:2018); German version EN ISO 13408-2:2018	2018	full
DIN EN ISO 13408-4	Aseptic processing of health care products - Part 4: Clean-in-place technologies (ISO 13408-4:2005); German version EN ISO 13408-4:2011	2011	full
DIN EN ISO 17665-1	Sterilization of health care products - Moist heat - Part 1: Requirements for the development, validation and routine control of a sterilization process for medical devices (ISO 17665-1:2006); German version EN ISO 17665-1:2006	2006	full
DIN EN ISO 10993-7	Biological evaluation of medical devices - Part 7: Ethylene oxide sterilization residuals (ISO 10993-7:2008); German version EN ISO 10993-7:2008	2009	full
DIN EN ISO 10993-7 Corrigendum 1	Biological evaluation of medical devices - Part 7: Ethylene oxide sterilization residuals (ISO 10993-7:2008) Corrigendum to DIN EN ISO 10993-7:2009-02 (ISO 10993-7:2008); German version EN ISO 10993-7:2008, Corrigendum to DIN EN ISO 10993-7:2009-02, German version EN ISO 10993-7:2008/AC:2009	2011	full

Relevant adopted monographs of the European Pharmacopoeia

European Pharmacopoeia	Monograph 0331 – Gentamicin sulfate
	Monograph 0582 – Clindamycin hydrochloride
	Chapter 2.6.14 – Bacterial Endotoxins
	Chapter 2.6.1 – Sterility
	Chapter 2.6.8 – Pyrogens
	Chapter 2.6.12 – Microbiological examination of non-sterile products: microbial enumeration tests

3.1.9 Revision history

Revision	Date issued	Change description	Revision validated by the Notified Body
Rev05	2024-06	Section 3.1.3.1 listing of composition corrected	☒Yes Validation language: English ☐No (only applicable for class IIa or some IIb implantable devices (MDR, Article 52 (4) 2nd paragraph) for which the SSCP is not yet validated by the NB)

3.2 Relevant Information for patients

The following chapters provide a summary of the safety and clinical performance of the device intended for patients.

This Summary of Safety and Clinical Performance (SSCP) provides public access to an updated summary of the main aspects of the safety and clinical performance of the device. The information presented below addresses patients or lay persons. The first part of the document shows a more extensive summary of safety and clinical performance prepared for healthcare professionals.

The SSCP does not provide general advice on the treatment of a medical condition. Please contact your doctor/surgeon in case you have questions about your medical condition or about the use of the device in your situation. This SSCP does not replace an Implant Card or the Instructions for Use (IFU) to provide information on the safe use of the device.

3.2.1 Background information

COPAL® G+C is a bone cement. It is based on a biologically safe material called poly (methyl methacrylate) (PMMA). This material has a long history of safe use in humans.

COPAL® G+C pro is a mixing and application system which contains the bone cement COPAL® G+C. Your surgeon may use the COPAL® G+C pro mixing and application system to prepare and apply the bone cement to your bone. Alternatively, your surgeon will use another mixing and application system for preparation and application.

COPAL® G+C bone cement is used in adults such as elderly patients with degenerative joint disease. Osteoarthritis is an example for such a joint disease. Osteoarthritis is the most common form of arthritis and affects millions of people worldwide. It occurs when the protective cartilage that cushions the ends of the bones wears down over time. Patients with trauma after severe accidents with several fractures in a bone can also be considered for treatment with bone cements. The bone cement is used to anchor total or partial joint endoprostheses. It attaches endoprostheses firmly and stably to the bone. Endoprostheses are medical devices used to replace parts of the inside of your body. Hip, knee or shoulder joints can be replaced by an endoprostheses, for example.

Arthroplasty is a surgical procedure to restore the function of a joint. Primary arthroplasty refers to the first joint replacement. Revision arthroplasty refers to follow-up surgery on the same joint. In total joint replacement parts of a joint are removed and replaced by an implant, the endoprosthesis. In partial joint replacement artificial surfaces replace only the moveable surfaces of a joint. The healthy parts of the joint stay intact.

Your doctor/surgeon applies the bone cement during surgery. The instructions for use give directions.

Your doctor/surgeon takes care of the following aspects during your surgery:

- The bone cement is applied to your carefully cleaned, aspirated, and dried bone.
- Your prosthesis is put in place and held until the bone cement has set completely.
- During and immediately after the bone cement is applied, your doctor/surgeon will monitor your blood pressure, pulse, and breathing carefully. This ensures early detection and treatment of adverse events such as low blood pressure and cardiac arrest. Drops in blood pressure have occurred remotely and shortly after application of bone cement. However, consequences such as cardiac arrest are only reported in very few cases.

It is safe to have magnetic resonance tests (MRI) with COPAL® G+C bone cement. But the composition of the prosthesis you receive together with the bone cement may affect your ability to have magnetic resonance tests. You will receive an implant card for the bone cement that was used. Additionally, you will receive an implant card for the prosthesis. Please keep these documents and provide them in future examinations (e.g., X-ray, CT scan, MRI).

3.2.2 Device identification and general information

3.2.2.1 Products (device trade names) covered by this document

- COPAL® G+C pro

3.2.2.2 Manufacturer name and address

Heraeus Medical GmbH
Philipp-Reis-Str. 8/13
61273 Wehrheim
Germany

3.2.2.3 Basic UDI-DI number of the concerned product

The unique device identification (UDI) consists of a series of numbers or numbers with letters. It allows the unmistakable identification of a specific medical device on the market. A UDI device identifier (UDI-DI) is specific to a device, connecting the product to the information on the EUDAMED database.

The following UDI-DI numbers are assigned to the different products:

Product	UDI-DI
COPAL® G+C pro	426010213020201000 1BS

3.2.2.4 Year of first CE-mark

Before a medical device is introduced on the market in the European Union, it needs to show that the product fulfills the requirements. The so-called CE-certification documents the fulfilment, and the CE-mark is placed on the product. The legal requirements for medical devices have changed in May 2021. Then, the Medical Device Regulation (MDR) replaced the Medical Device Directive (MDD).

The following table contains the detailed information about the products. The table lists the year of the first CE-mark under MDR and under MDD.

Product	Year of first CE-mark under MDR	Year of first CE-mark prior to MDR
COPAL® G+C pro	2023	n/a

3.2.3 Intended use of the device

3.2.3.1 Intended purpose

COPAL® G+C pro is a PMMA bone cement intended for stable anchoring of total or partial joint endoprostheses in living bone.

3.2.3.2 Indications and intended patient groups

COPAL® G+C pro is indicated for surgical treatment such as

- anchoring of endoprosthesis in primary and revision arthroplasty procedures of
    - hip
    - knee
    - ankle
    - shoulder
    - elbow

These treatments are typically conducted in adults, predominantly elderly patients with risk factors for periprosthetic joint infection and patients with trauma.

3.2.3.3 Contraindications / advice against treatment

COPAL® G+C pro must not be used in the following cases:

- suspected or proven hypersensitivity to components of the bone cement including gentamicin, other aminoglycoside antibiotics, clindamycin, or lincomycin
- patients with renal impairment
- for permanent fixation purposes in the presence of an active or incompletely treated infection at the bone site caused by gentamicin and clindamycin non-sensitive strains
- spinal surgery
- during pregnancy or breast-feeding
- children

The safety of the bone cement in pregnant women or in children has not been established. Bone cement may adversely affect bone growth and fetal health.

3.2.3.4 Lifetime of the device

There is no general factor influencing the lifetime of COPAL® G+C bone cement. The general provisions for the prosthesis they are used also anchor also apply to bone cements. The actual lifetime of the COPAL® G+C bone cement can be influenced by factors such as your medical situation and your lifestyle.

3.2.4 Device description

COPAL® G+C is a bone cement which is based on a biologically safe material called polymethylmethacrylate (PMMA) which has a long history of safe use in humans.

COPAL® G+C pro is a mixing and application system which contains the bone cement COPAL® G+C.

Composition

The cement consists of 2 main components, a powder and a liquid. The table below shows the composition of the components. Mixing of the components starts a chemical reaction. This so-called polymerization forms a soft dough. The dough becomes more and more solid over time. Your surgeon determines the right time for application of the dough to the bone. There it hardens completely. In addition, the cement contains two antibiotics (gentamicin and clindamycin). Your treating surgeon chose these antibiotics to prevent an infection.

COPAL® G+C pro contains:

Powder:		
PMMA copolymer	82 %	Polymer (powder component)
Zirconium dioxide	10 %	X-ray contrast medium (enabling visualization with X-ray, CT or MRI)
Benzoyl peroxide	1 %	Chemical component initiating the polymerization reaction
Gentamicin sulfate	4 %	Antibiotic
Clindamycin hydrochloride	3 %	Antibiotic
Liquid:		
Methyl methacrylate	98 %	Monomer (liquid component)
N, N-dimethyl-p-toluidine	2 %	Chemical component accelerating the polymerization reaction

Other constituents:

- Powder: chlorophyll-copper-complex (E141) (Food colorant. Improving visibility of the bone cement in the surgical field)
- Liquid: chlorophyll-copper-complex (E141), hydroquinone (chemical component stabilizing the chemical reaction)

Traces of histamine may be present in the bone cement. But no manufacturing residuals that could pose a risk to you have been found. Be aware that the composition table shows the constituents before mixture of the bone cement components. The methyl methacrylate is completely used up during setting and forms the hardened bone cement. COPAL® G+C bone cement is intended for single-use and is supplied sterile.

3.2.5 Risks and warnings

Contact your doctor/surgeon if you believe that you are experiencing side effects. This applies for side effects related to the device or its use, and also if you are concerned about risks. This document does not replace a consultation with your doctor/surgeon if needed.

Side effects are events that are known when using the device. They can be caused by the device.
Residual risks are risks which cannot be controlled by the device manufacturer. They are mostly related to the surgical procedure in general.
Adverse events are events that can occur in a clinical investigation. They have a negative impact mostly on the patient. No causal relationship with the device must be present.

Heraeus Medical GmbH has a risk management process according to harmonized risk management guidelines. It ensures that the benefits of using the medical device are greater than potential risks.

Side effects and residual risks of the device can occur with different frequencies. Following frequencies could be relevant:

Frequent: > 1:1 000
Probable: 1:10 000 to 1:1 000
Occasional: 1:100 000 to 1:10 000
Remote: 1:1 000 000 to 1:100 000
Improbable: < 1:1 000 000

By way of example, in case that a side effect is considered as improbable, the side effect will occur in less than 1 out of 1 000 000 surgeries.

Side effects

The following side effects can occur during or after the surgery.

Improbable:
Allergic reaction including local reaction and allergic shock
Renal impairment
Bone or tissue changes (dissolution of bone or tissue modification to bone)
Reddening of skin or tissue, hives

Residual risks

The following residual risks can occur during or after surgery:

Remote:
Drop or increase in blood pressure, reduced oxygen supply, heartbeat too fast or too slow, thrombosis, embolism, myocardial infarction, stroke, respiratory arrest, cardiac arrest.

Frequent:
Loss of the implant due to different reasons (for example: insufficient connection between bone cement, endoprosthesis and/or bone; falls; fracture near the endoprosthesis)

Frequent:
Bacterial infection including infection of the bone marrow and/or cellulitis

Improbable:
Numbness
Blood loss
Unequal limb length, loss of range of motion of the concerned part of the body, ambulation difficulties
Necrosis of tissue due to heat
Inflammation
Swelling / Edema
Fibrosis

Please contact your doctor/surgeon if you have any questions.

Reporting of side effects, residual risks, or adverse events

If you experience any of these side effects or residual risks, or if you notice any adverse events not listed in this document, contact your doctor/surgeon immediately. You can also contact Heraeus Medical GmbH directly using the following email- address: hm.vigilance.medical@heraeus.com

Warnings and precautions

COPAL® G+C bone cement contains gentamicin and clindamycin, two antibiotics. It is most unlikely that this bone cement causes gentamicin or clindamycin overdosage because the gentamicin and clindamycin it carries mostly stays in the area where the cement is applied. It only leads to low and short-lived levels of antibiotics in the rest of the body.

Gentamicin can potentially cause side effects in patients with impaired renal function, patients who are at risk of developing renal failure, or in patients who simultaneously receive drugs which affect the kidneys. In these cases, your doctor/surgeon may advise to monitor your blood levels of the antibiotic, electrolytes, or renal function.

Clindamycin can potentially enhance the effect of muscle relaxants.

Other relevant aspects of safety

In 2017, Heraeus Medical GmbH officially informed users on the proper handling of the bone cement packaging. It had received complaints on issues regarding the opening of the bags. Slight delays in operating times had happened.
Heraeus Medical GmbH updated the instructions for use and included a new picture to illustrate the proper handling.
Information on this Field Safety Notice can also be found in the national safety databases of BfArM, Swissmedic, and MHRA.

3.2.6 Summary of clinical evaluation and post-market clinical follow-up

COPAL® G+C has been on the market since 1998. It is considered as state-of-the-art in the field of stable anchoring of joint endoprostheses. COPAL® G+C pro will be placed on the market in 2023. It contains the well-known bone cement COPAL® G+C.

The manufacturer performs the analysis of any clinical data regularly. Sources can be endoprostheses registries and scientific publications, for example. These activities are called post-market clinical follow-up measures. They allow the continuous proof of the benefit/risk ratio of the medical device. Registries are databases which collect long-term results after application of products in patients. These databases can be initiated by governmental authorities, medical societies, or manufacturers. In most cases they collect data from hospitals or private practices on a regional or national level.

The following clinical benefits and outcome parameter relate to the use of the bone cements:

- Stable fixation of the endoprosthesis with a low risk of revision surgery. This is evaluated on the basis of long-term data from regional or national registries.

- Improvement of impaired body function with a high patient satisfaction. This is evaluated on the basis of quality-of-life data from registries.

- Relief of symptoms related to the surgical procedure with high patient success. This is evaluated on the basis of quality-of-life data from registries.

- Application of bone cements in combination with an antibiotic with a low risk of reinfection. This is evaluated on the basis of revisions that are caused by infections, compared to the overall number of revisions (based on data from registries).

- Local use of an antibiotic within the bone cement can result in a low risk for side effects compared to oral or intravenous administration of the antibiotic. This is evaluated on the basis of complaints reported to manufacturer, evaluation of databases and data regarding the development of the medical device.

The above-mentioned clinical benefits and clinical outcome parameters are important to decide on the benefit/risk ratio of COPAL® G+C bone cement. The manufacturer evaluates the achievement of these clinical benefits.

The analysis revealed that COPAL® G+C bone cement performed as expected in all aspects of the above-listed outcome parameters:

- Stable fixation was analyzed by two aspects: the rate at which operations needed to be repeated (revision rate) and the rate at which endoprostheses loosened over time (aseptic loosening). Both rates were in a range comparable with the current state-of-the-art. For example, the revision rate of COPAL® G+C was reported to be 2.3% for primary hip and 2.5% for primary knee, which is comparable to benchmark standards (range for hip: 1.1% - 3.2%; range for knee: 1.5% - 4.3%).
- Impaired body function was evaluated through questionnaires. In these, patients have reported on how much they are impacted in their daily activities. In all cases, COPAL® G+C was comparable to current state-of-the-art.
- Relief of symptoms was evaluated through questionnaires. In these, patients have reported on how much better their joint was after the surgery. In all cases, COPAL® G+C was comparable to current state-of-the-art.
- The number of re-operations because of an infection at the site of surgery was comparable to the current state-of-the-art in patients who underwent their first operation with COPAL® G+C and for revision surgeries. The only exception was the number of re-operations because of an infection for first-time elbow procedures, where the rate was slightly higher than expected. It should be noted that many doctors use COPAL® G+C for the first operation mainly in patients with many other health issues. Because of this, their risk of infection is generally higher. As there are not many bone cements with two antibiotics like COPAL® G+C, also bone cements with only one antibiotic are considered for the state-of-the-art. But patients receiving a bone cement with only one antibiotic are typically of better health.
- COPAL® G+C bone cement contains antibiotics that can also be given directly into the veins. From this it is known that too high amounts can cause severe side effects. In a clinical study, it was measured how high up the blood concentrations of antibiotics released from the bone cement would go after an operation with COPAL® G+C. The result was that the values remained far below the levels which can lead to severe side effects.

Additionally, the scientific literature for COPAL® G+C was thoroughly evaluated. Ten clinical studies were identified and analyzed. It can be concluded that all data show favorable clinical results for COPAL® G+C.
In conclusion, the success rates of the clinical benefits were comparable to or better than the current state-of-the-art.

Therefore, the manufacturer confirms that the benefits outweigh the risks for the indications of COPAL® G+C pro:

- anchoring of endoprosthesis in primary and revision arthroplasty procedures of
  - hip
  - knee
  - ankle
  - shoulder
  - elbow

The following activities are planned to ensure safety and performance of COPAL® G+C pro:

- A post-market clinical follow-up study, where data on the mixing and application system of COPAL® G+C pro will be collected
- Device Registry Analysis, to monitor the safety and performance of COPAL® G+C pro
- Screening of Scientific Literature, to monitor the safety and performance of COPAL® G+C pro
- Authority Databases (adverse events and recalls), to monitor the safety of COPAL® G+C pro

The same activities are performed for similar products to detect potential safety or performance issues early. The results will be summarized in reports. These activities will be conducted on an annual basis in connection with the continuous updates of the clinical evaluations.

3.2.7 Possible diagnostic or therapeutic alternatives

General information

Contact your doctor/surgeon when you consider alternative treatments. Depending on your individual situation, two treatment approaches are possible. On the one hand conservative treatment such as physiotherapy or pain medication without a surgery is possible. On the other hand, surgical treatment such as joint surgery like hip replacement surgery could be reasonable. Choice of treatment depends on your specific condition and your doctor's opinion.

Joint surgery

If possible, your doctor/surgeon will try to treat defective joints by other means. If all other treatment options fail, a reconstructive joint surgery may be necessary. This means that the complete joint or only parts of the joint are replaced by an endoprosthesis. Joint surgeries and endoprosthesis revision operation as well as the use of PMMA bone cements are very well-established procedures in joint replacement surgery.

PMMA is widely and successfully used for the fixation of various endoprostheses since decades. At present, PMMA is still the most commonly used fixation material in primary joint surgeries. Uncemented procedures have also been used in primary joint surgeries. However, current data do not allow to determine if cementless or cemented procedures generally perform better in joint surgeries. The advantage of the cemented procedures using PMMA is the long-term experience with this material. Also, the majority of orthopedic surgeons is familiar with the use of PMMA. Furthermore, bone cement can apply local antibiotics. This allows for infection prevention in patients at risk for infection. In addition, bone cements generally spread the force of movement evenly into the bone. Especially in patients with poor bone substance this is an advantage. Your doctor/surgeon will decide on the procedure that fits to your specific clinical condition best.

There is no other treatment option than a surgery in patients with suspected or confirmed infection of the implanted device (so-called prosthetic joint infections). Such a revision surgery can be either a one-stage or a two-stage surgery. A so-called one-stage surgery takes place in a single surgical step. The surgeon removes the infected prosthesis and bone cement, cleans the surgical site thoroughly, and places a new prosthesis. A so-called two-

stage approach consists of two separate surgeries. During the first surgery, the surgeon removes the infected prosthesis and bone cement, cleans the surgical site thoroughly, and places a provisional spacer. This ensures proper treatment of the infection. The spacer also provides a limited range of motion during the time until the second operation. After the infection is cured, the second surgery takes place. The surgeon removes the provisional spacer and places a new permanent prosthesis. The attending surgeon will choose the appropriate surgical approach according to the patient's situation.

References

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