

## **Summary of Safety and Clinical Performance**

### **COPAL<sup>®</sup> G+C pro**

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English

**Titel: SSCP COPAL G+C pro**

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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<br>[Bundesinstitut für Arzneimittel und Medizinprodukte]  |
| CE               | Conformité Européenne   |
| CER              | Clinical Evaluation Report  |
| CND              | Classificazione Nazionale dei Dispositivi medici [National Classification of Medical Devices]   |
| CPR              | Cardiopulmonary Resuscitation   |
| 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              | Medical Device 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 and the amendments of 2017/745 (2020/561, 2023/607 and 2024/1860) |
| 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   |
| SpO <sub>2</sub> | Peripheral Oxygen Saturation  |
| 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 5<sup>th</sup> 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.

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**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 | 4260102130202010001BS |

**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 | 2024                            | 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

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**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 expected lifetime of COPAL® G+C pro. The actual lifetime of COPAL® G+C pro can be influenced by factors such as the medical situation and lifestyle of the patient.

Removal of the implant is not necessary unless it is clinically required. Implant removal is in the sole discretion of the responsible surgeon based on the medical condition of the patient.

**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

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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).

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### 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 |
|----------------------|---|----------|------------------|
| <b>Required:</b>     |   |          |                  |
| PALAMIX® cement gun  | Reusable cement gun                     | 1        | 66036163         |
| <b>Optional:</b>     |   |          |                  |
| 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 endoprotheses 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

Frequencies are taken from literature, < 0.001% can include potential risks not reported in literature so far.

Table 1 Frequencies of side effects

| Frequency                           | Side effect  |
|-------------------------------------|--|
| <b>Immune System</b>                |  |
| < 10%*                              | • hypersensitivity / allergic reaction and local reaction which may include inflammation, induration, erythema, pruritus or pain |
| < 0.001%                            | • anaphylactic shock   |
| <b>Kidney and Urinary Tract</b>     |  |
| < 10%*                              | • renal impairment   |
| <b>Musculoskeletal System</b>       |  |
| < 0.001%                            | • ossification   |
| < 0.001%                            | • osteolysis due to bone cement fragments  |
| <b>Skin and Subcutaneous Tissue</b> |  |
| < 0.001%                            | • rash   |
| < 0.001%                            | • urticaria  |

\* cases reported to Heraeus Medical GmbH presented with frequencies lower than in literature

#### Residual Risks

Residual risks listed below are procedure related risks which are beyond the control of the manufacturer, because they are procedure or user related. Frequencies are taken from literature, < 0.001% can include potential risks not reported in literature so far.

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Table 2 Frequencies of residual risks

| Frequency   | Residual Risk   |
|---|---|
| <b>Vascular System, Heart, Respiratory System, Blood and Lymphatic System</b>   |   |
| <p>Bone Cement Implantation Syndrome (BCIS):<br/>                     Insertion of bone cement may produce a high medullary pressure that forces bone marrow constituents into the venous vascular system, resulting in fat and marrow emboli.<br/>                     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 bone 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 case of pulmonary or cardiovascular events, it is necessary to monitor blood volume and possibly increase it. In case of acute respiratory failure, anesthesiologic measures should be taken.<br/>                     In general, adverse reactions of BCIS might include low blood pressure / hypotension, hypoxia, bradycardia, tachycardia, pulmonary hypertension, thrombosis, embolism, pulmonary embolism, myocardial infarction, cerebrovascular accident, respiratory arrest, and cardiac arrest</p> |   |
| > 10%*  | BCIS grade 1<br>moderate hypoxia (peripheral oxygen saturation < 94 %) or hypotension [fall in systolic blood pressure > 20 %]                                    |
| < 10%*  | BCIS grade 2<br>severe hypoxia (peripheral oxygen saturation < 88 %) or hypotension [fall in systolic blood pressure > 40 %] or unexpected loss of consciousness. |
| < 1%*   | BCIS grade 3<br>cardiovascular collapse, requiring cardiopulmonary resuscitation  |
| <b>Nervous System</b>   |   |
| < 0.0001%   | • numbness  |
| <b>Blood and Lymphatic System</b>   |   |
| < 0.0001%   | • hypovolemia   |
| <b>Musculoskeletal System</b>   |   |
| < 10%*  | • aseptic loosening   |
| < 0.0001%   | • unequal limb length   |
| < 1%*   | • loss of range of motion   |
| < 0.0001%   | • ambulation difficulties   |
| <b>Infection</b>  |   |
| < 10%*  | • Bacterial infection including cellulitis, and / or osteomyelitis  |
| <b>Generalized Disorders</b>  |   |
| < 0.0001%   | • inflammation  |
| < 0.0001%   | • swelling / edema  |
| < 10%*  | • fibrosis  |
| < 0.0001%   | • heat necrosis   |

\* cases reported to Heraeus Medical GmbH presented with frequencies lower than in literature

**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. However, COPAL® G+C pro minimizes the amount of free monomer in the operating room.

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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 overdose, because high local gentamicin and clindamycin concentrations only led to low ( $\leq 1 \mu\text{g/ml}$ ) and short-lived systemic concentrations.

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

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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

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**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, 18 product-specific clinical studies were published in the literature for COPAL® G+C. Thirteen of these were retrospective observational studies (Abdelaziz et al., 2019; Blersch et al., 2023; Blersch et al., 2024; Frank et al., 2021; Hamoudi et al., 2024; Jenny et al., 2021; Sanz-Ruiz et al., 2020; Savage et al., 2019; Sax & Fink, 2023; Schlechter et al., 2023; Theil et al., 2019; Tyas et al., 2018; Zhang et al., 2020). Additionally, five prospective studies were published in the literature, of these three prospective controlled studies (Agni et al., 2023; Gehrke et al., 2001; Sprowson et al., 2016) and two prospective cohort studies (Maher et al., 2024; Van Laarhoven et al., 2023).

Research topics of the 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 18 studies, 16 reported favorable outcomes for COPAL® G+C.

Agni et al., 2023 reported outcomes which were classified as indifferent; a favorable outcome could not be clearly determined. Hamoudi et al., 2024 reported outcomes that were classified as unfavorable as they do not support the routine use of gentamicin and clindamycin antibiotic-loaded bone cement during revision total hip or knee arthroplasty for aseptic reasons. However, in this retrospective study, the patient number in the two cohorts was relatively small and the follow-up period was insufficient to detect very late infections and may have been insufficient for determining the long-term survival of the cement fixation.

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:

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Table 3 Clinical benefits

| Performance / Safety aspect | Intended Benefit                            | Clinical    | Outcome Parameter  | Threshold / Target values (as per SOTA)  |       |          |          |     |    |             |      |           |             |           |      |            |           |   |            |    |             |       |   |             |   |           |   |           |          |   |           |   |           |       |   |           |   |           |
|-----------------------------|---|-------------|--|--|-------|----------|----------|-----|----|-------------|------|-----------|-------------|-----------|------|------------|-----------|---|------------|----|-------------|-------|---|-------------|---|-----------|---|-----------|----------|---|-----------|---|-----------|-------|---|-----------|---|-----------|
| Stable fixation             | Low risk of revision or re-revision surgery |             | <b>Cumulative revision rate</b><br>(data from registries and the literature) comparable to or better than SOTA | <p><b>Cumulative revision rates:</b></p> <table border="1"> <thead> <tr> <th>Joint</th> <th>Year</th> <th>Rate [%]</th> </tr> </thead> <tbody> <tr> <td rowspan="3">Hip</td> <td>3</td> <td>1.1 – 3.2</td> </tr> <tr> <td>5</td> <td>1.5 – 3.8</td> </tr> <tr> <td>10</td> <td>2.8 – 5.3</td> </tr> <tr> <td rowspan="3">Knee</td> <td>3</td> <td>1.4 – 4.3</td> </tr> <tr> <td>5</td> <td>2.0 – 5.5</td> </tr> <tr> <td>10</td> <td>2.9 – 7.6</td> </tr> <tr> <td rowspan="3">Ankle</td> <td>1</td> <td>0.7 – 1.2</td> </tr> <tr> <td>3</td> <td>3.1 – 5.8</td> </tr> <tr> <td>5</td> <td>5.2 – 9.2</td> </tr> <tr> <td rowspan="2">Shoulder</td> <td>3</td> <td>3.1 – 4.7</td> </tr> <tr> <td>7</td> <td>4.9 – 6.7</td> </tr> <tr> <td rowspan="2">Elbow</td> <td>1</td> <td>1.3 - 3.6</td> </tr> <tr> <td>3</td> <td>3.6 – 7.5</td> </tr> </tbody> </table> | Joint | Year     | Rate [%] | Hip | 3  | 1.1 – 3.2   | 5    | 1.5 – 3.8 | 10          | 2.8 – 5.3 | Knee | 3          | 1.4 – 4.3 | 5 | 2.0 – 5.5  | 10 | 2.9 – 7.6   | Ankle | 1 | 0.7 – 1.2   | 3 | 3.1 – 5.8 | 5 | 5.2 – 9.2 | Shoulder | 3 | 3.1 – 4.7 | 7 | 4.9 – 6.7 | Elbow | 1 | 1.3 - 3.6 | 3 | 3.6 – 7.5 |
|                             |   |             |  | Joint  | Year  | Rate [%] |          |     |    |             |      |           |             |           |      |            |           |   |            |    |             |       |   |             |   |           |   |           |          |   |           |   |           |       |   |           |   |           |
| Hip                         | 3   | 1.1 – 3.2   |  |  |       |          |          |     |    |             |      |           |             |           |      |            |           |   |            |    |             |       |   |             |   |           |   |           |          |   |           |   |           |       |   |           |   |           |
|                             | 5   | 1.5 – 3.8   |  |  |       |          |          |     |    |             |      |           |             |           |      |            |           |   |            |    |             |       |   |             |   |           |   |           |          |   |           |   |           |       |   |           |   |           |
|                             | 10  | 2.8 – 5.3   |  |  |       |          |          |     |    |             |      |           |             |           |      |            |           |   |            |    |             |       |   |             |   |           |   |           |          |   |           |   |           |       |   |           |   |           |
| Knee                        | 3   | 1.4 – 4.3   |  |  |       |          |          |     |    |             |      |           |             |           |      |            |           |   |            |    |             |       |   |             |   |           |   |           |          |   |           |   |           |       |   |           |   |           |
|                             | 5   | 2.0 – 5.5   |  |  |       |          |          |     |    |             |      |           |             |           |      |            |           |   |            |    |             |       |   |             |   |           |   |           |          |   |           |   |           |       |   |           |   |           |
|                             | 10  | 2.9 – 7.6   |  |  |       |          |          |     |    |             |      |           |             |           |      |            |           |   |            |    |             |       |   |             |   |           |   |           |          |   |           |   |           |       |   |           |   |           |
| Ankle                       | 1   | 0.7 – 1.2   |  |  |       |          |          |     |    |             |      |           |             |           |      |            |           |   |            |    |             |       |   |             |   |           |   |           |          |   |           |   |           |       |   |           |   |           |
|                             | 3   | 3.1 – 5.8   |  |  |       |          |          |     |    |             |      |           |             |           |      |            |           |   |            |    |             |       |   |             |   |           |   |           |          |   |           |   |           |       |   |           |   |           |
|                             | 5   | 5.2 – 9.2   |  |  |       |          |          |     |    |             |      |           |             |           |      |            |           |   |            |    |             |       |   |             |   |           |   |           |          |   |           |   |           |       |   |           |   |           |
| Shoulder                    | 3   | 3.1 – 4.7   |  |  |       |          |          |     |    |             |      |           |             |           |      |            |           |   |            |    |             |       |   |             |   |           |   |           |          |   |           |   |           |       |   |           |   |           |
|                             | 7   | 4.9 – 6.7   |  |  |       |          |          |     |    |             |      |           |             |           |      |            |           |   |            |    |             |       |   |             |   |           |   |           |          |   |           |   |           |       |   |           |   |           |
| Elbow                       | 1   | 1.3 - 3.6   |  |  |       |          |          |     |    |             |      |           |             |           |      |            |           |   |            |    |             |       |   |             |   |           |   |           |          |   |           |   |           |       |   |           |   |           |
|                             | 3   | 3.6 – 7.5   |  |  |       |          |          |     |    |             |      |           |             |           |      |            |           |   |            |    |             |       |   |             |   |           |   |           |          |   |           |   |           |       |   |           |   |           |
|                             |   |             |  | <p><b>Cumulative re-revision rates:</b></p> <table border="1"> <thead> <tr> <th>Joint</th> <th>Year</th> <th>Rate [%]</th> </tr> </thead> <tbody> <tr> <td>Hip</td> <td>10</td> <td>15.3 – 18.7</td> </tr> <tr> <td>Knee</td> <td>10</td> <td>15.4 – 22.1</td> </tr> <tr> <td>Ankle</td> <td>5</td> <td>up to 23.0</td> </tr> <tr> <td rowspan="2">Shoulder</td> <td>1</td> <td>up to 16.2</td> </tr> <tr> <td>3</td> <td>16.1 – 20.4</td> </tr> <tr> <td>Elbow</td> <td>3</td> <td>13.3 – 20.0</td> </tr> </tbody> </table>   | Joint | Year     | Rate [%] | Hip | 10 | 15.3 – 18.7 | Knee | 10        | 15.4 – 22.1 | Ankle     | 5    | up to 23.0 | Shoulder  | 1 | up to 16.2 | 3  | 16.1 – 20.4 | Elbow | 3 | 13.3 – 20.0 |   |           |   |           |          |   |           |   |           |       |   |           |   |           |
| Joint                       | Year  | Rate [%]    |  |  |       |          |          |     |    |             |      |           |             |           |      |            |           |   |            |    |             |       |   |             |   |           |   |           |          |   |           |   |           |       |   |           |   |           |
| Hip                         | 10  | 15.3 – 18.7 |  |  |       |          |          |     |    |             |      |           |             |           |      |            |           |   |            |    |             |       |   |             |   |           |   |           |          |   |           |   |           |       |   |           |   |           |
| Knee                        | 10  | 15.4 – 22.1 |  |  |       |          |          |     |    |             |      |           |             |           |      |            |           |   |            |    |             |       |   |             |   |           |   |           |          |   |           |   |           |       |   |           |   |           |
| Ankle                       | 5   | up to 23.0  |  |  |       |          |          |     |    |             |      |           |             |           |      |            |           |   |            |    |             |       |   |             |   |           |   |           |          |   |           |   |           |       |   |           |   |           |
| Shoulder                    | 1   | up to 16.2  |  |  |       |          |          |     |    |             |      |           |             |           |      |            |           |   |            |    |             |       |   |             |   |           |   |           |          |   |           |   |           |       |   |           |   |           |
|                             | 3   | 16.1 – 20.4 |  |  |       |          |          |     |    |             |      |           |             |           |      |            |           |   |            |    |             |       |   |             |   |           |   |           |          |   |           |   |           |       |   |           |   |           |
| Elbow                       | 3   | 13.3 – 20.0 |  |  |       |          |          |     |    |             |      |           |             |           |      |            |           |   |            |    |             |       |   |             |   |           |   |           |          |   |           |   |           |       |   |           |   |           |

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| Performance / Safety aspect                     | Intended Benefit                      | Clinical | Outcome Parameter  | Threshold / Target values (as per SOTA)  |                   |                   |             |             |              |               |              |             |               |               |                  |             |       |          |     |           |      |           |       |            |          |           |       |           |
|---|---------------------------------------|----------|--|--|-------------------|-------------------|-------------|-------------|--------------|---------------|--------------|-------------|---------------|---------------|------------------|-------------|-------|----------|-----|-----------|------|-----------|-------|------------|----------|-----------|-------|-----------|
|   |                                       |          | Rate of aseptic loosening (data from NJR registries and literature) comparable to or better than SOTA  | <p><b>Aseptic loosening rates:</b></p> <p>Primary procedures</p> <table border="1"> <thead> <tr> <th>Joint</th> <th>Rate [%]</th> </tr> </thead> <tbody> <tr> <td>Hip</td> <td>0.5 – 1.4</td> </tr> <tr> <td>Knee</td> <td>0.5 – 1.2</td> </tr> <tr> <td>Ankle</td> <td>0.3 – 2.3</td> </tr> <tr> <td>Shoulder</td> <td>0.5 – 1.1</td> </tr> <tr> <td>Elbow</td> <td>0.5 – 1.8</td> </tr> </tbody> </table> <p>Revision procedures</p> <table border="1"> <thead> <tr> <th>Joint</th> <th>Rate [%]</th> </tr> </thead> <tbody> <tr> <td>Hip</td> <td>4.8 – 6.7</td> </tr> <tr> <td>Knee</td> <td>3.8 – 5.3</td> </tr> <tr> <td>Ankle</td> <td>9.9 – 14.6</td> </tr> <tr> <td>Shoulder</td> <td>2.8 – 3.5</td> </tr> <tr> <td>Elbow</td> <td>4.9 – 7.4</td> </tr> </tbody> </table> | Joint             | Rate [%]          | Hip         | 0.5 – 1.4   | Knee         | 0.5 – 1.2     | Ankle        | 0.3 – 2.3   | Shoulder      | 0.5 – 1.1     | Elbow            | 0.5 – 1.8   | Joint | Rate [%] | Hip | 4.8 – 6.7 | Knee | 3.8 – 5.3 | Ankle | 9.9 – 14.6 | Shoulder | 2.8 – 3.5 | Elbow | 4.9 – 7.4 |
| Joint   | Rate [%]                              |          |  |  |                   |                   |             |             |              |               |              |             |               |               |                  |             |       |          |     |           |      |           |       |            |          |           |       |           |
| Hip   | 0.5 – 1.4                             |          |  |  |                   |                   |             |             |              |               |              |             |               |               |                  |             |       |          |     |           |      |           |       |            |          |           |       |           |
| Knee  | 0.5 – 1.2                             |          |  |  |                   |                   |             |             |              |               |              |             |               |               |                  |             |       |          |     |           |      |           |       |            |          |           |       |           |
| Ankle   | 0.3 – 2.3                             |          |  |  |                   |                   |             |             |              |               |              |             |               |               |                  |             |       |          |     |           |      |           |       |            |          |           |       |           |
| Shoulder  | 0.5 – 1.1                             |          |  |  |                   |                   |             |             |              |               |              |             |               |               |                  |             |       |          |     |           |      |           |       |            |          |           |       |           |
| Elbow   | 0.5 – 1.8                             |          |  |  |                   |                   |             |             |              |               |              |             |               |               |                  |             |       |          |     |           |      |           |       |            |          |           |       |           |
| Joint   | Rate [%]                              |          |  |  |                   |                   |             |             |              |               |              |             |               |               |                  |             |       |          |     |           |      |           |       |            |          |           |       |           |
| Hip   | 4.8 – 6.7                             |          |  |  |                   |                   |             |             |              |               |              |             |               |               |                  |             |       |          |     |           |      |           |       |            |          |           |       |           |
| Knee  | 3.8 – 5.3                             |          |  |  |                   |                   |             |             |              |               |              |             |               |               |                  |             |       |          |     |           |      |           |       |            |          |           |       |           |
| Ankle   | 9.9 – 14.6                            |          |  |  |                   |                   |             |             |              |               |              |             |               |               |                  |             |       |          |     |           |      |           |       |            |          |           |       |           |
| Shoulder  | 2.8 – 3.5                             |          |  |  |                   |                   |             |             |              |               |              |             |               |               |                  |             |       |          |     |           |      |           |       |            |          |           |       |           |
| Elbow   | 4.9 – 7.4                             |          |  |  |                   |                   |             |             |              |               |              |             |               |               |                  |             |       |          |     |           |      |           |       |            |          |           |       |           |
| Indirect: improvement of impaired body function | Improvement of impaired body function |          | Adjusted health gain as per Oxford hip/knee/shoulder score (data from NJR reports)   | <p><b>Oxford hip/knee/shoulder score at 6 months:</b></p> <table border="1"> <thead> <tr> <th>Joint (procedure)</th> <th>Score at 6 months</th> </tr> </thead> <tbody> <tr> <td>Hip primary</td> <td>39.5 – 41.7</td> </tr> <tr> <td>Hip revision</td> <td>At least 34.7</td> </tr> <tr> <td>Knee primary</td> <td>35.4 – 37.6</td> </tr> <tr> <td>Knee revision</td> <td>At least 29.0</td> </tr> <tr> <td>Shoulder primary</td> <td>35.9 – 38.9</td> </tr> </tbody> </table>   | Joint (procedure) | Score at 6 months | Hip primary | 39.5 – 41.7 | Hip revision | At least 34.7 | Knee primary | 35.4 – 37.6 | Knee revision | At least 29.0 | Shoulder primary | 35.9 – 38.9 |       |          |     |           |      |           |       |            |          |           |       |           |
| Joint (procedure)                               | Score at 6 months                     |          |  |  |                   |                   |             |             |              |               |              |             |               |               |                  |             |       |          |     |           |      |           |       |            |          |           |       |           |
| Hip primary                                     | 39.5 – 41.7                           |          |  |  |                   |                   |             |             |              |               |              |             |               |               |                  |             |       |          |     |           |      |           |       |            |          |           |       |           |
| Hip revision                                    | At least 34.7                         |          |  |  |                   |                   |             |             |              |               |              |             |               |               |                  |             |       |          |     |           |      |           |       |            |          |           |       |           |
| Knee primary                                    | 35.4 – 37.6                           |          |  |  |                   |                   |             |             |              |               |              |             |               |               |                  |             |       |          |     |           |      |           |       |            |          |           |       |           |
| Knee revision                                   | At least 29.0                         |          |  |  |                   |                   |             |             |              |               |              |             |               |               |                  |             |       |          |     |           |      |           |       |            |          |           |       |           |
| Shoulder primary                                | 35.9 – 38.9                           |          |  |  |                   |                   |             |             |              |               |              |             |               |               |                  |             |       |          |     |           |      |           |       |            |          |           |       |           |
| 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) | <p><b>Reinfection rates:</b></p> <p>Primary procedures</p> <table border="1"> <thead> <tr> <th>Joint</th> <th>Rate [%]</th> </tr> </thead> <tbody> <tr> <td>Hip</td> <td>0.1 – 1.2</td> </tr> <tr> <td>Knee</td> <td>0.2 – 2.3</td> </tr> <tr> <td>Ankle</td> <td>0.2 – 1.5</td> </tr> <tr> <td>Shoulder</td> <td>0.8 – 1.6</td> </tr> <tr> <td>Elbow</td> <td>0.2 – 1.3</td> </tr> </tbody> </table> <p>Revision procedures</p>   | Joint             | Rate [%]          | Hip         | 0.1 – 1.2   | Knee         | 0.2 – 2.3     | Ankle        | 0.2 – 1.5   | Shoulder      | 0.8 – 1.6     | Elbow            | 0.2 – 1.3   |       |          |     |           |      |           |       |            |          |           |       |           |
| Joint   | Rate [%]                              |          |  |  |                   |                   |             |             |              |               |              |             |               |               |                  |             |       |          |     |           |      |           |       |            |          |           |       |           |
| Hip   | 0.1 – 1.2                             |          |  |  |                   |                   |             |             |              |               |              |             |               |               |                  |             |       |          |     |           |      |           |       |            |          |           |       |           |
| Knee  | 0.2 – 2.3                             |          |  |  |                   |                   |             |             |              |               |              |             |               |               |                  |             |       |          |     |           |      |           |       |            |          |           |       |           |
| Ankle   | 0.2 – 1.5                             |          |  |  |                   |                   |             |             |              |               |              |             |               |               |                  |             |       |          |     |           |      |           |       |            |          |           |       |           |
| Shoulder  | 0.8 – 1.6                             |          |  |  |                   |                   |             |             |              |               |              |             |               |               |                  |             |       |          |     |           |      |           |       |            |          |           |       |           |
| Elbow   | 0.2 – 1.3                             |          |  |  |                   |                   |             |             |              |               |              |             |               |               |                  |             |       |          |     |           |      |           |       |            |          |           |       |           |

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| Performance / Safety aspect                 | Intended Benefit               | Clinical   | Outcome Parameter  | Threshold / Target values (as per SOTA) |           |
|---|--------------------------------|--|--|---|-----------|
|   |                                |  |  | Joint                                   | Rate [%]  |
|   |                                |  |  | Hip                                     | 1.7 – 2.8 |
|   |                                |  |  | Knee                                    | 2.8 – 3.7 |
|   |                                |  |  | Ankle                                   | 6.7 – 9.9 |
|   |                                |  |  | Shoulder                                | 4.2 – 5.3 |
|   |                                |  |  | Elbow                                   | 3.7 – 5.6 |
| 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:<br>c(gentamicin): < 2 µg/ml<br><br>Clindamycin serum concentration to not exceed concentrations of intravenous application which can lead to side effects:<br>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 2.2% and 2.5%, respectively. When considering only patients with ASA grade > P2 and BMI > 35 kg/m<sup>2</sup>, the cumulative revision rates at 3 years were 2.8% and 1.6%, respectively. The cumulative revision rates for primary hip and knee arthroplasty at 3 years are therefore comparable to benchmark standards (range for hip: 1.1 - 3.2%; range for knee: 1.4 - 4.3%). The cumulative revision rates at 5 years for primary hip and knee arthroplasty with COPAL® G+C are 2.8% (hip) and 3.0% (knee) or 2.8% (hip) and 3.7% (knee) when considering only patients with ASA grade > P2 and BMI > 35 kg/m<sup>2</sup> which are comparable to benchmark standards (range for hip: 1.5 – 3.8%; range for knee: 2.0 – 5.5%). Also, the cumulative revision rates at 10 years for primary hip and knee arthroplasty performed with COPAL® G+C (hip: 4.8%; knee 3.7%) were comparable to benchmark standards (range for hip: 2.8 – 5.3%; range for knee: 2.9 – 7.6%). Similar results were obtained for primary shoulder, elbow and ankle procedures performed with COPAL® G+C: 2.4% (at 3 years) and 4.2% (at 7 years) for shoulder (benchmark standard: 3.1 – 4.7% at 3 years; 4.9 – 6.7% at 7 years), 3.4% (at 1 year) for elbow (benchmark standard: 1.3 - 3.6% at 1 year). For primary elbow procedures, the cumulative revision rate at 3 years was higher when using COPAL® G+C (11.4%) compared to the benchmark standard (range: 3.6 – 7.5%). However, this does not take into consideration the fact that COPAL® G+C is more often used in patients with a higher ASA level and / or higher BMI. Both are risk-factors for complications during arthroplasties such as revisions. Available data from 2022 for primary ankle arthroplasty showed a cumulative revision rate of 0.0% at 1 year (benchmark standard: 0.7 – 1.2).

For revision arthroplasty, the cumulative re-revision rates for COPAL® G+C in the hip joint were 7.8%, 9.8%, and 13.8% at 3, 5, and 10 years, respectively, which are comparable to the corresponding benchmark standards (9.4 – 12.7% at 3 years; 11.5 – 14.9% at 5 years; 15.3 – 18.7% at 10 years). The cumulative re-revision rate for COPAL® G+C in the knee joint were 5.8%, 7.8%, and 13.0% at 3, 5, and 10 years, respectively, that are also comparable to the benchmark standards (8.5 – 13.7% at 3 years; 11.6 – 16.7% at 5 years; 15.4 – 22.1% at 10 years). For revision shoulder and elbow procedures, the rates for COPAL® G+C were 10.5% (shoulder at 1 year), 14.7% and 16.2% (shoulder and elbow at 3 years, respectively) thus comparable, or slightly better than the benchmark standard (shoulder at 1 year: up to 16.2%; shoulder at 3 years: 16.1 – 20.4%; elbow at 3 years: 13.3 -

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20%). Available data from 2022 showed a cumulative re-revision rate of COPAL® G+C in the ankle of 0.0% at 1 year.

Benchmark standards for the rate of aseptic loosening of primary hip and knee arthroplasty were in the range of 0.5 - 1.4% (hip) and 0.5 - 1.2% (knee). COPAL® G+C performed better than expected, with a rate of 0.1 – 0.2% for primary hip, and 0.2 – 0.3% for primary knee arthroplasty. The rate of primary shoulder arthroplasty was comparable to benchmark (COPAL® G+C: 0.0%; benchmark: 0.5 – 1.1%), whereas the rate for primary elbow procedures was reported to be worse for COPAL® G+C compared to benchmark (COPAL® G+C: 3.3%; benchmark: 0.5 – 1.8%). 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 4.8 – 6.7% for hip, 3.8 – 5.3% for knee, 2.8 – 3.5% for shoulder, 4.9 – 7.4% for elbow. Revision arthroplasties performed with COPAL® G+C had considerably better rates for hip and knee, with 0.7 – 1.7% in hip and 1.2 – 2.8% 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 (10.8%). 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 ( $p = 0.553$ ).

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 (0.7%), knee (0.9%) and shoulder arthroplasty (0.2%) 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 (1.6% versus 0.2 – 1.3%). However, the infection rate was comparable to the expected revision rate by NJR, meaning that when the infection rate was adjusted for age group, gender, indications, and implantation year, COPAL® G+C performed as expected without a significant difference between COPAL® G+C and non-Heraeus ALBC ( $p = 1$ ). 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 hip, knee, ankle and elbow. The rate of revisions due to infection for shoulder revision procedures is higher with COPAL® G+C compared to the benchmark standard (7.9% versus 4.2 – 5.3%), but it aligns with the expected revision rates by NJR. This means that when the rate of revision caused by infection is adjusted for age group, gender, indications, and implantation year, COPAL® G+C performs as expected compared without a significant difference between COPAL® G+C and non-Heraeus ALBC ( $p = 1$ ).

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 primary and revision hip and knee procedures. The benchmark for the functional Oxford Hip Score at 6 months in primary arthroplasty is 39.5 – 41.7 compared to 39.8 for COPAL® G+C. In revision arthroplasty the values are 34.7 for the benchmark standard and 34.6 for COPAL® G+C. Similarly, the Oxford Knee Scores at 6 months are comparable: 35.4 – 37.6 for the benchmark standard in primary arthroplasty compared to 36.5 for COPAL® G+C. In revision arthroplasty, COPAL® G+C reaches similar values with 30.2 compared to 29.0 of the benchmark standards. The Oxford Shoulder Score for primary shoulder arthroplasty when using COPAL® G+C is slightly lower than the benchmark standard (31.7 versus 35.9 – 38.9). This might be due to the low number of patient records providing this information.

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 29 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

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- 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 ongoing 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 are collected to assess (short-term) safety and performance aspects of the device. The current interim analysis (cut-off date 13 AUG 2024) focusing on the description of the study status and the occurrence of safety events did not identify previously unknown side effects or risks. 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.

The results of the mentioned PMCF measures will be summarized in the corresponding PMCF reports or the CER and evaluated in the CER. 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

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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**

*Table 4 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 |

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| 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 +AMD 1:2023); German version EN ISO 11607-1:2020 + A1:2023   | 2024       | 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 +AMD 1:2023); German version EN ISO 11607-2:2020 +A1:2023  | 2024       | 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  | 2024       | 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 microorganisms on products (ISO 11737-1:2018 + Amd 1:2021); German version EN ISO 11737-1:2018 + A1:2021  | 2021       | full                  |
| DIN EN ISO 11737-2 | Sterilization of medical devices - Microbiological methods - Part 2: Tests of sterility performed in the   | 2020       | full                  |

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| Number             | Title  | Issue Date | Application |
|--------------------|--|------------|-------------|
|                    | definition, validation and maintenance of a sterilization process (ISO 11737-2:2019); German version EN ISO 11737-2:2020                               |            |             |
| 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        |

### 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

Table 5 Document history

| Revision | Date issued | Change description  | Revision validated by the Notified Body  |
|----------|-------------|---|--|
| Rev06    | 2025-03     | <p>Section 2 Abbreviations updated</p> <p>Sections 3.1.1.6 and 3.2.2.4 Information on first CE-mark updated;</p> <p>Sections 3.1.2.5 and 3.2.3.4 Wording for lifetime of the device updated;</p> <p>Section 3.1.3.4 Deletion of PALAGUN®</p> <p>Section 3.1.4.1 and 3.2.5 Update of information on frequencies of side effects and residual risks, Update of wording for BCIS;</p> <p>Section 3.1.4.2 Update of warnings;</p> <p>Section 3.1.5.3 Update of current clinical evidence;</p> <p>Section 3.1.5.4 Update of benchmarks for clinical performance and safety and of performance of the product;</p> <p>Sections 3.1.5.5 and 3.2.6 Status of PMCF-study updated;</p> <p>Section 3.1.5.5 Update in line with PMCF-plan</p> <p>Section 3.1.8 Update of list of harmonized standards</p> | <p><input checked="" type="checkbox"/> Yes</p> <p>Validation language: English</p> <p><input type="checkbox"/> No (only applicable for class IIa or some IIb implantable devices (MDR, Article 52 (4) 2<sup>nd</sup> paragraph) for which the SSCP is not yet validated by the NB)</p> |

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|  |  |   |  |
|--|--|---|--|
|  |  | Section 3.2.6 Summary of product performance updated;<br>Editorial updates and corrections of spelling throughout the document;<br>Update of reference list |  |
|--|--|---|--|

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**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).

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**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 | 4260102130202010001BS |

**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 | 2024                            | 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.

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**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 actual lifetime of the COPAL® G+C bone cement can be influenced by factors such as your medical situation and your lifestyle.

Removal of the implant is not necessary unless it is clinically required. Implant removal is in the discretion of the responsible surgeon based on your medical condition.

**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:

| <b>Powder:</b>            |      |   |
|---------------------------|------|---|
| PMMA copolymer            | 82 % | Polymer (powder component)                                    |
| Zirconium dioxide         | 10 % | X-ray contrast medium (enabling visualization with X-ray, CT) |
| Benzoyl peroxide          | 1 %  | Chemical component initiating the polymerization reaction     |
| Gentamicin sulfate        | 4 %  | Antibiotic  |
| Clindamycin hydrochloride | 3 %  | Antibiotic  |
| <b>Liquid:</b>            |      |   |
| 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)

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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. As an example, if a side effect occurs in less than 1% of cases (< 1%), the side effect will occur in less than 1 in 100 surgeries.

**Side effects**

Frequencies are taken from the literature, < 0.001% can include potential risks not reported in the literature so far.

*Table 6 Frequencies of side effects*

| Frequency                           | Side effect  |
|-------------------------------------|--|
| <b>Immune System</b>                |  |
| < 10%*                              | • hypersensitivity / allergic reaction and local reaction which may include inflammation, induration, reddening of skin, itching or pain |
| < 0.001%                            | • anaphylactic shock   |
| <b>Kidney and Urinary Tract</b>     |  |
| < 10%*                              | • renal impairment   |
| <b>Musculoskeletal System</b>       |  |
| < 0.001%                            | • tissue modification to bone  |
| < 0.001%                            | • dissolution of bone  |
| <b>Skin and Subcutaneous Tissue</b> |  |
| < 0.001%                            | • rash   |
| < 0.001%                            | • hives  |

\* cases reported to Heraeus Medical GmbH showed frequencies lower than in literature

**Residual risks**

Residual risks listed below are procedure related risks which are beyond the control of the manufacturer because they are procedure or user related. Frequencies are taken from literature, < 0.001% can include potential risks not reported in literature so far.

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Table 7 Frequencies of residual risks

| Frequency   | Residual Risk   |
|---|---|
| <b>Vascular System, Heart, Respiratory System, Blood and Lymphatic System</b>   |   |
| Bone Cement Implantation Syndrome (BCIS):<br>Insertion of bone cement may produce a high medullary pressure that forces bone marrow constituents into the venous vascular system, resulting in fat and marrow emboli.<br>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 bone 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 case of pulmonary or cardiovascular events, it is necessary to monitor blood volume and possibly increase it. In case of acute respiratory failure, anesthesiologic measures should be taken.<br>In general, adverse reactions of BCIS might include low blood pressure / hypotension, hypoxia, bradycardia, tachycardia, pulmonary hypertension, thrombosis, embolism, pulmonary embolism, myocardial infarction, cerebrovascular accident, respiratory arrest, and cardiac arrest. |   |
| > 10%*  | BCIS grade 1<br>moderate hypoxia (SpO <sub>2</sub> < 94 %) or hypotension [fall in systolic blood pressure > 20 %]                                    |
| < 10%*  | BCIS grade 2<br>severe hypoxia (SpO <sub>2</sub> < 88 %) or hypotension [fall in systolic blood pressure > 40 %] or unexpected loss of consciousness. |
| < 1%*   | BCIS grade 3<br>cardiovascular collapse, requiring CPR  |
| <b>Nervous System</b>   |   |
| < 0.0001%   | • numbness  |
| <b>Blood and Lymphatic System</b>   |   |
| < 0.0001%   | • hypovolemia   |
| <b>Musculoskeletal System</b>   |   |
| < 10%*  | • aseptic loosening   |
| < 0.0001%   | • unequal limb length   |
| < 1%*   | • loss of range of motion   |
| < 0.0001%   | • ambulation difficulties   |
| <b>Infection</b>  |   |
| < 10%*  | • Bacterial infection including cellulitis, and / or osteomyelitis  |
| <b>Generalized Disorders</b>  |   |
| < 0.0001%   | • inflammation  |
| < 0.0001%   | • swelling / edema  |
| < 10%*  | • fibrosis  |
| < 0.0001%   | • heat necrosis   |

\* cases reported to Heraeus Medical GmbH presented with frequencies lower than in literature

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](mailto: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 overdose 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.

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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 2.2% 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: 1.4% - 4.3%).

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- 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. Exceptions were the number of re-operations because of an infection for first-time elbow procedures and for revision shoulder procedures, where the rates were 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. Eighteen clinical studies were identified and analyzed. It can be concluded that overall, the 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. The study is currently ongoing.
- 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

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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.

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**References**

- Abdelaziz, H., von Förster, G., Kühn, K.-D., Gehrke, T., & Citak, M. (2019). Minimum 5 years' follow-up after gentamicin- and clindamycin-loaded PMMA cement in total joint arthroplasty. *Journal of Medical Microbiology*, 68(3), 475–479. <https://doi.org/10.1099/jmm.0.000895>
- Agni, N. R., Costa, M. L., Achten, J., Peckham, N., Dutton, S. J., Png, M. E., Reed, M. R., & WHITE 8 Investigators. (2023). High-dose dual-antibiotic loaded cement for hip hemiarthroplasty in the UK (WHITE 8): A randomised controlled trial. *Lancet (London, England)*, 402(10397), 196–202. [https://doi.org/10.1016/S0140-6736\(23\)00962-5](https://doi.org/10.1016/S0140-6736(23)00962-5)
- Blersch, B. P., Barthels, M., Schuster, P., & Fink, B. (2023). A Low Rate of Periprosthetic Infections after Aseptic Knee Prosthesis Revision Using Dual-Antibiotic-Impregnated Bone Cement. *Antibiotics (Basel, Switzerland)*, 12(9), 1368. <https://doi.org/10.3390/antibiotics12091368>
- Blersch, B. P., Sax, F. H., & Fink, B. (2024). How Useful Is Preoperative Aspiration before Revision of Unicompartamental Knee Prostheses Because of Osteoarthritis in the Other Compartments? *Antibiotics*, 13(4), 361. [doi: 10.3390/antibiotics13040361](https://doi.org/10.3390/antibiotics13040361)
- Boelch, S. P., Jordan, M. C., Arnholdt, J., Rudert, M., Luedemann, M., & Steinert, A. F. (2017). Loading with vancomycin does not decrease gentamicin elution in gentamicin premixed bone cement. *Journal of Materials Science. Materials in Medicine*, 28(7), 104. <https://doi.org/10.1007/s10856-017-5915-6>
- Frank, B. J., Aichmair, A., Simon, S., Schwarz, G. M., Dominkus, M., & Hofstaetter, J. G. (2021). Analysis of culture positive first and second stage procedures in periprosthetic knee and hip joint infections. *The Journal of Arthroplasty*, 36(6), 2158–2164. [doi: 10.1016/j.arth.2021.01.074](https://doi.org/10.1016/j.arth.2021.01.074)
- Gehrke, T., Förster, G., & Frommelt, L. (2001). Pharmacokinetic Study of a Gentamicin/Clindamycin Bone Cement Used in One-stage Revision Arthroplasty (pp. 127–134). [https://doi.org/10.1007/978-3-642-59478-6\\_11](https://doi.org/10.1007/978-3-642-59478-6_11)
- Hamoudi, C., Hamon, M., Reiter-Schatz, A., Debordes, P.-A., Gaudias, J., Rondé-Oustau, C., & Jenny, J.-Y. (2024). Cement loaded with high-dose gentamicin and clindamycin does not reduce the risk of subsequent infection after aseptic total hip or knee revision arthroplasty: A preliminary study. *Journal of Orthopaedics and Traumatology: Official Journal of the Italian Society of Orthopaedics and Traumatology*, 25(1), 37. <https://doi.org/10.1186/s10195-024-00775-1>
- Jenny, J.-Y., Hamon, M., Klein, S., Reiter-Schatz, A., Rondé-Oustau, C., Boéri, C., Wisniewski, S., & Gaudias, J. (2021). Cement Loaded With High-Dose Gentamicin and Clindamycin Reduces the Risk of Subsequent Infection After One-Stage Hip or Knee Arthroplasty Exchange for Periprosthetic Infection: A Preliminary Study. *The Journal of Arthroplasty*, 36(12), 3973–3978. <https://doi.org/10.1016/j.arth.2021.08.014>
- Karaglani, M., Tzitzikou, E., Tottas, S., Kougioumtzis, I., Arvanitidis, K., Kolios, G., Chatzaki, E., & Drosos, G. I. (2020). Gentamycin elution from polymethylmethacrylate and bone graft substitute: Comparison between commercially available and home-made preparations. *Journal of Orthopaedics*, 19, 9–13. <https://doi.org/10.1016/j.jor.2019.11.034>
- Maher, M., Ward, A., Ward, K., Robinson, K., & Mills, E. (2024). Minimizing the Risk of Surgical Site Infection Following Hip Fracture Operation. *Surgical Infections*, 25(8), 574–579. <https://doi.org/10.1089/sur.2024.019>
- Sanz-Ruiz, P., Matas-Diez, J. A., Villanueva-Martínez, M., Santos-Vaquinha Blanco, A. D., & Vaquero, J. (2020). Is Dual Antibiotic-Loaded Bone Cement More Effective and Cost-Efficient Than a Single Antibiotic-Loaded Bone Cement to Reduce the Risk of Prosthetic Joint Infection in Aseptic Revision Knee Arthroplasty? *The Journal of Arthroplasty*, 35(12), 3724–3729. <https://doi.org/10.1016/j.arth.2020.06.045>
- Savage, P., McCormick, M., & Al-Dadah, O. (2019). Arthroplasty infection rates in fractured neck of femur: Single vs dual antibiotic cement. *Annals of the Royal College of Surgeons of England*, 101(7), 514–518. <https://doi.org/10.1308/rcsann.2019.0054>
- Sax, F. H., & Fink, B. (2023). Total Knee Arthroplasty in Unrecognized Septic Arthritis-A Descriptive Case Series Study. *Antibiotics (Basel, Switzerland)*, 12(7), 1153. <https://doi.org/10.3390/antibiotics12071153>
- Schlechter, M., Theil, C., Gosheger, G., Moellenbeck, B., Schwarze, J., Puetzler, J., & Bockholt, S. (2023). Good Mid-Term Implant Survival of a Novel Single-Design Rotating-Hinge Total Knee Arthroplasty. *Journal of Clinical Medicine*, 12(19), 6113. [doi: 10.3390/jcm12196113](https://doi.org/10.3390/jcm12196113)
- Sprowson, A. P., Jensen, C., Chambers, S., Parsons, N. R., Aradhyula, N. M., Carluke, I., Inman, D., & Reed, M. R. (2016). The use of high-dose dual-impregnated antibiotic-laden cement with hemiarthroplasty for the treatment of a fracture of the hip. *The Bone & Joint Journal*, 98-B(11), 1534–1541. <https://doi.org/10.1302/0301-620X.98B11.34693>

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- Theil, C., Schmidt-Braekling, T., Gosheger, G., Moellenbeck, B., Schwarze, J., & Dieckmann, R. (2019). A single centre study of 41 cases on the use of porous tantalum metal implants in acetabular revision surgery. *BMC Musculoskeletal Disorders*, 20(1), 238. <https://doi.org/10.1186/s12891-019-2626-9>
- Tyas, B., Marsh, M., Oswald, T., Refaie, R., Molyneux, C., & Reed, M. (2018). Antibiotic resistance profiles of deep surgical site infections in hip hemiarthroplasty; comparing low dose single antibiotic versus high dose dual antibiotic impregnated cement. *Journal of Bone and Joint Infection*, 3(3), 123–129. <https://doi.org/10.7150/jbji.22192>
- Van Laarhoven, S. N., Te Molder, M. E., Van Hellemond, G. G., & Heesterbeek, P. J. (2023). Acceptable migration of a fully cemented rotating hinge-type knee revision system measured in 20 patients with model-based RSA with a 2-year follow-up. *Acta Orthopaedica*, 94, 185-190. doi: 10.2340/17453674.2023.12305
- Zhang, X., Li, Z., Wang, W., Liu, T., & Peng, W. (2020). Mid-term results of revision surgery using double-trabecular metal cups alone or combined with impaction bone grafting for complex acetabular defects. *Journal of Orthopaedic Surgery and Research*, 15(1), 301. <https://doi.org/10.1186/s13018-020-01828-x>