Summary of Safety and Clinical Performance

PALACOS® fast R+G

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English

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2 Abbreviations / Explanations

ALBC	Antibiotic-loaded bone cement
AUS	Australia
BCIS	Bone cement implantation syndrome
BfArM	Federal Institute for Drugs and Medical Devices (Germany) *[Bundesinstitut für Arzneimittel und Medizinprodukte]*
CAN	Canada
CE	Conformité Européenne
CER	Clinical Evaluation Report
CH	Switzerland
CND	*Classificazione Nazionale dei Dispositivi medici* [National Classification of Medical Devices]
CT	Computed tomography
CS	common specifications as defined in the MDR
DIN	German standard *[Deutsches Institut für Normung]*
EMDN	European Medical Device Nomenclature
EN	European Standard *[Europäische Norm]*
EU	European Union
FDA	Food and Drug Organization (USA)
GER	Germany
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 2017/45 (2020/561 and 2023/607)
MHRA	Medicines and Healthcare Products Regulatory Agency in the UK
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
SRN	single registration number for an economic operator
SSCP	Summary of Safety and Clinical Performance
Swissmedic	Swiss Agency for Therapeutic Products (Switzerland)
TGA	Therapeutic Goods Administration (Australia)
TPLC	FDA Total Product Life Cycle (TPLC)
UDI-DI	Unique Device Identification - device identifier
UK	United Kingdom
US/USA	United States of America

3 General Information

This document applies to implantable class IIb, and class III medical devices developed by Heraeus Medical GmbH and is established to comply with the Medical Device Regulation (MDR) 2017/745 (EU) of 5th April 2017, valid from May 2021.
The Summary of Safety and Clinical Performance (SSCP) is intended to provide a summary of clinical data pertinent to the safety and clinical performance of the medical device. The SSCP is an important source of information for intended users – both healthcare professionals and if relevant for patients. It is one of several means intended to fulfil the MDR objectives, to enhance transparency and provide adequate access to information.

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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 product PALACOS® fast R+G.

PALACOS® fast R+G is part of the PALACOS® +G product family, which consists of PALACOS® R+G, PALACOS® MV+G, PALACOS® LV+G and PALACOS® fast R+G. In case that all product variants are concerned in this document, the term "PALACOS® +G bone cements" is used.

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

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

Single registration number (SRN): DE-MF-000008199

3.1.1.3 Basic UDI-DI

Product	Basic UDI-DI
PALACOS® fast R+G	426010213010101000 2AL

3.1.1.4 Medical device nomenclature (according to MDR, article 26)

The EMDN code, based on CND for PALACOS® fast R+G is P099001 (orthopaedic prostheses cements and accessories for mixing).

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

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

The device incorporates gentamicin as an integral part. If used separately, it would be considered as a medicinal product as defined in point 2 of Article 1 of Directive 2001/83/EC and it has an action ancillary to that of the bone cement (Article 1(8) of MDR).

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
PALACOS® fast R+G	2022	2013

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 (l))

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

PALACOS® fast R+G is a PMMA bone cement intended for stable anchoring of total or partial joint endoprostheses in living bone as well as for reconstruction of bone.

3.1.2.2 Indications

PALACOS® fast R+G is indicated for surgical treatment such as

- anchoring of endoprosthesis in primary and revision arthroplasty procedures of
  - hip
  - knee
  - ankle
  - shoulder
  - elbow
- reconstruction of bone via induced membrane technique after tumor surgery and / or trauma

3.1.2.3 Target Population

Adult population, predominantly elderly patients with osteoarthritis and patients with trauma.

3.1.2.4 Contraindications

PALACOS® fast R+G must not be used in the following cases:

- suspected or proven hypersensitivity to components of the bone cement including gentamicin or other aminoglycoside antibiotics
- 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 non-sensitive strains
- reconstruction of skull bone defects
- spinal surgery
- children

3.1.2.5 Lifetime of the device

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

3.1.3 Device description

3.1.3.1 Description of the device

PALACOS® fast R+G is a fast-setting, high-viscosity, radiopaque, poly (methyl methacrylate) (PMMA) bone cement.

PALACOS® fast R+G contains the aminoglycoside antibiotic gentamicin to protect the cured bone cement and surrounding tissue from colonization by bacteria that are sensitive to gentamicin. The product contains the X-ray contrast medium zirconium dioxide. To improve visibility in the surgical field, it has been colored with chlorophyll-copper-complex (E141). The bone cement consists of two components and is prepared immediately before use by mixing the polymer powder (= powder) with the monomer liquid (= liquid). A ductile dough forms that sets within a few minutes.
PALACOS® fast R+G is intended for single-use and is supplied sterile.

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Table 1: Composition of PALACOS® fast R+G

Powder		**Liquid**	
Constituent	**Primary Function**	**Constituent**	**Primary Function**
PMMA copolymer	*Polymer*	Methyl methacrylate	*Monomer*
Zirconium dioxide	*Radio-opacifier*	*N,N*-dimethyl-p-toluidine	*Accelerator*
Benzoyl peroxide	*Initiator*	Hydroquinone	*Stabilizer*
Gentamicin sulfate	*Antibiotic*	-	-
Chlorophyll-copper-complex (E141)	*Colorant; visibility in the surgical field*	Chlorophyll-copper-complex (E141)	*Colorant; visibility in the surgical field*

PALACOS® fast R+G contains:

Table 2: Composition in percentage

	PALACOS® fast R+G
Powder:	
PMMA copolymer	81 %
zirconium dioxide	15 %
benzoyl peroxide	2 %
gentamicin sulfate	2 %
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

Traces of histamine may be present in the bone cement. PALACOS® fast R+G does not contain a radiation source. No manufacturing residuals that could pose a risk to the patient have been found. Be aware that the composition table shows the constituents before mixture of the bone cement components. The methyl methacrylate will be consumed during setting of the bone cement.

PALACOS® fast R+G is available in the following pack sizes:

PALACOS® fast R+G
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It is safe to have magnetic resonance tests with PALACOS® +G bone cements. However, your ability to have magnetic resonance tests may be affected by the composition of the prosthesis you receive together with the bone cement.

3.1.3.2 Reference to previous generation(s) or variants

PALACOS® +G bone cements have been marketed before 2022. There is no difference to these earlier products marketed under the regulations of the Medical Device Directive. A description of the product history of PALACOS® R+G and PALACOS® fast R+G is given in the following section.

PALACOS® R+G

The precursor of PALACOS® R+G was Refobacin®-Palacos® which was marketed in Germany and Austria by E. Merck starting in 1972 in cooperation with Heraeus Kulzer. For other European markets Heraeus Kulzer initiated another cooperation with Schering-Plough which led to the introduction of Palacos® R with Gentamicin in 1973. The cooperation with E. Merck and Schering-Plough continued until Heraeus Kulzer established Heraeus Medical in

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the year 2004/2005 as orthopedic division (later as own legal entity Heraeus Medical GmbH) with the intention to serve the arthroplasty market worldwide through a direct sales channel. In 2005 the product received the CE mark for the first time with Heraeus Kulzer as manufacturer, which was changed to Heraeus Medical GmbH in 2008. The cooperations with Merck (Biomet Merck Biomaterials, later Biomet) and Schering-Plough were terminated. The former Refobacin®-Palacos® R and Palacos® R with Gentamicin are sold since 2006 directly by Heraeus Medical under the brand name PALACOS® R+G.

PALACOS® fast R+G
PALACOS® fast R+G is the latest gentamicin-containing PMMA bone cement introduced as CE-certified medical device by Heraeus Medical GmbH in 2013. Once again coming from the well-known PALACOS® R+G, the PALACOS® fast R+G was developed by Heraeus Medical GmbH to offer a high-viscosity and fast setting PALACOS® R+G variant.

3.1.3.3 Accessories intended to be used in combination with the device

Not applicable

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

Mixing equipment is necessary to mix the two components of PALACOS® +G bone cements to prepare the PMMA bone cement. Heraeus Medical GmbH offers various suitable mixing and application systems. An overview can be found in the product brochures (www.heraeus-medical.com).

Performance and safety testing of PALACOS® fast R+G was performed using the following application devices:

- Mixing Bowl with Spatula

PALACOS® +G bone cement can be used in combination with all cementable joint endoprostheses suitable for the anatomic locations listed in the indications.

3.1.4 Risks and warnings

3.1.4.1 Side effects and residual risks

Side effects

Frequencies are taken from literature, < 0.0001% can include potential risks not reported in literature so far.

Table 3: Frequencies of side effects

Frequency	Side effect
Immune system	
4.79%*	• hypersensitivity / allergic reaction and local reaction which may include inflammation, induration, erythema, pruritus, or pain
< 0.0001%	• anaphylactic shock
Kidney and Urinary Tract	
< 0.0001%	• renal impairment
Musculoskeletal System	
36.65%*	• ossification
22.78%*	• osteolysis due to bone cement fragments
Skin and Subcutaneous Tissue	
< 0.0001%	• rash
< 0.0001%	• urticaria

*cases reported to Heraeus Medical GmbH with frequencies lower than from literature

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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, < 0.0001% can include potential risks not reported in literature so far.

Table 4: Frequencies of residual risks

Frequency	Residual Risk
Vascular System, Heart, Respiratory System, Blood and Lymphatic System, Nervous System	
Bone Cement Implantation Syndrome (BCIS): 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. 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. 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.	
25.48%*	BCIS grade 1 moderate hypoxia (SpO2 < 94%) or hypotension [fall in systolic blood pressure > 20%]
8.17%*	BCIS grade 2 severe hypoxia (SpO2 < 88%) or hypotension [fall in systolic blood pressure > 40%] or unexpected loss of consciousness.
3.37%*	BCIS grade 3 cardiovascular collapse, requiring CPR
Nervous System	
< 0.0001%	• numbness
Blood and Lymphatic System	
< 0.0001%	• hypovolemia
Musculoskeletal System	
15.22%*	• aseptic loosening
< 0.0001%	• unequal limb length
0.27%*	• loss of range of motion
< 0.0001%	• ambulation difficulties
Infection	
3.58%*	• bacterial infection including cellulitis, and / or osteomyelitis
Generalized Disorders	
2,56%	• inflammation
< 0.0001%	• swelling / edema
0.94%*	• fibrosis
< 0.0001%	• heat necrosis

*cases reported to Heraeus Medical GmbH with frequencies lower than from literature

3.1.4.2 Warnings and precautions

Warnings

Regarding intended users

Caution should be exercised during the mixing of the two components of PALACOS® fast R+G to prevent excessive exposure to the concentrated monomer vapors, which may produce irritation of the respiratory tract, eyes, and

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possibly the liver. Personnel wearing contact lenses should not be near or involved in mixing this bone cement. Manufacturers of soft contact lenses recommend removing the lenses in the presence of damaging or irritant vapors. Since soft contact lenses are permeable to liquids and gases, they should not be worn in the operating room if methyl methacrylate is being used. Eye protection is recommended when opening the ampoule during the sterile preparation steps of the bone cement to protect the eye from any glass fragments or monomer liquid.

The monomer is a powerful lipid solvent and should not come into direct contact with the body. When handling PALACOS® fast R+G 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.

The monomer is not for injection.

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.

Care should be taken when anchoring the femoral component of hip joint endoprostheses due to the fast setting properties of PALACOS® fast R+G. Further advice is given in the IFU sections *Handling* and *Working times*.

Note: PALACOS® fast R+G 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
PALACOS® +G bone cements are considered most unlikely to cause gentamicin overdosage, because high local gentamicin concentrations only led to low (≤ 1 µg/ml) and short-lived systemic concentrations (1).

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 particularly 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 PALACOS® +G bone cements 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.

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Regarding the intended patient population
Like all aminoglycosides, gentamicin is potentially nephrotoxic. Independent of the total amount applied, care should be taken in patients with risk factors for the development of renal failure as well as in patients simultaneously treated with other nephrotoxic drugs, e.g., by periodically monitoring systemic levels of the antibiotic, serum electrolytes and renal function.
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 PALACOS® +G bone cements, the prepared bone should be carefully cleaned, aspirated, and dried just before the bone cement is placed.

Pregnancy and lactation
No sufficient data is available regarding the use of gentamicin in pregnant and lactating women in order to assess a possible health risk. Gentamicin is known to cross the placenta. In animals, gentamicin produced structural malformations in spite of maternal toxicity at high doses. Limited human experience does not point to an increased risk of structural malformations. Ototoxicity and nephrotoxicity in the fetus are potential hazards, but this has not been confirmed clinically. Cases of irreversible, bilateral, congenital hearing loss have been reported in children after prenatal exposure to streptomycin. Gentamicin is excreted in small amounts in human breast milk and absorbed by the nursing child. Because of enhanced intestinal permeability in neonates, accumulation and toxicity cannot be excluded. In view of this data, the benefits for the mother should be weighed against the potential risk to the child before using PALACOS® +G bone cements during pregnancy and lactation.

3.1.4.3 Other relevant aspects of safety

A comprehensive search on adverse events and recalls filed for PALACOS® fast R+G as well as for similar devices was carried out in various databases of the national regulatory authorities (Germany, United Kingdom, Australia, Swiss, Canada, and USA) from July 2023 to May 2024 to obtain an overview on potential device problems. A short summary is provided in the following.

The majority of adverse events and malfunctions identified for **PALACOS® fast R+G** or similar devices were found in the **FDA's MAUDE database**.

One malfunction was reported for PALACOS® fast R+G to the FDA, which was about prolongation of operation time. It was reported, that the initial insert didn't fit into the prosthesis, which led to a change in the insert for the prosthesis with an extension of operation time.

For **Cobalt™ G HV Bone Cement** 6 injuries and 1 malfunction were reported in the MAUDE database. Revision surgeries were reported for 2 aseptic loosening events, 1 infection, 1 case of implant pain and 1 event of pain, swelling and muscle cramps. In 1 case, no patient problem was provided for the revision surgery after 11 years. All injuries suggest a procedure-related background.

One malfunction for material integrity problem was reported where the bone cement did not bond to the implant. This is known to happen when bone cement is applied after the allowed working time.

Seven adverse events were identified for **Refobacin® Bone Cement R** in the MAUDE database. There were multiple revisions reported due to aseptic loosening and pain without any traceable reason. In 1 case a patient had suffered from synovitis, pain, and loss of range. This revision was performed 18 months after the initial surgery. The patient also had a history of falling with syncope episodes just after the initial surgery. Another report described a genicular nerve block to relieve the pain in the patient's knee. A reported infection in the knee was treated with incision, drainage, and exchange of the poly.

Of the 4 malfunctions, 2 also referred to the curing time, which was reported as too fast. As a result of a too short curing time, a stem was reported to be exchanged with a smaller sized stem which was cemented into the existing bone cement mantle. A small fracture occurred in the femur during the procedure. There are multiple reasons why bone cement can cure faster than expected and based on the provided information no causality assessment could be performed. A further malfunction referred to a damaged sterile packaging and for one only insufficient information was available.

Seventeen injuries and 3 malfunctions were reported for **Simplex® HV with Gentamicin**. Pain was the most prominent patient problem besides loosening, joint laxity, loss of range of motion and swelling which resulted in aseptic revisions. In 2 events revision was necessary due to disease progression or fibrosis. In a third case the

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patient had fallen. An infection was reported in which the patient allegedly presented with an allergy to the bone cement, however, allergy tests were negative. The surgeon reported that the revision was caused by patient behavior (was picking at the wound leading to infection). Other infection cases resulted in septic revision, liner exchange, and incision and drainage.

A further case reported parts of the bone cement mantle breaking off approximately 3 months after surgery, causing inflammation, post-operative swelling, and stiffness. The reason was stated as malrotation of the knee. For the same patient a femur fracture during the revision was reported, which required a rod. Another revision was reported due to inflammation of unknown reason. The patient stated that he suffered from an allergy to methyl methacrylate which was not reported prior to implantation. No allergy test confirmed the patient's statement.

Reported malfunctions included the optical presentation of bone cement vials and a case of insufficient information. Another reported malfunction was about a crepitus of the knee 2 years after the initial surgery. No revision was reported for this event.

Four injuries were identified in the **TGA DAEN** for similar devices which were about aseptic revisions due to pain and loosening.

In summary, there were no unknown malfunctions or adverse events identified. No Field Safety Corrective Actions (FSCAs), including recalls, alerts, or other safety information, were published in the databases of the national regulatory authorities. Based on the review and analysis of the data available in this Adverse Event and Recall Analysis, no new risks or hazards related to PALACOS® fast R+G were identified.

3.1.5 Summary of clinical evaluation and relevant information on Post-Market Clinical Follow-Up (PMCF)

3.1.5.1 Related to equivalent device

PALACOS® fast R+G is equivalent to PALACOS® R+G. Therefore, clinical data for PALACOS® R+G also applies to PALACOS® fast R+G and will be considered for some indications.

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

Not applicable

3.1.5.3 From other sources

The Clinical Evaluation Report (CER) of PALACOS® fast R+G identified a total of 77 publications which were considered relevant for the evaluation of safety and performance of the device under evaluation.
Seven out of these publications are related to registry data which are described in detail in section 3.1.5.4 and were therefore not considered in this section. The remaining 70 publications evaluated the indications of anchoring of endoprosthesis in hip, knee, ankle, shoulder, elbow, as well as reconstruction of bone. In summary, 64 references were considered relevant for demonstration of performance and 38 references were regarded as pertinent for discussion of clinical safety.
The publications regarding hip replacement procedures covered the aspects of arthroplasties (2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 55, 58, 59, 64, 75, 83, 86, 87) as well as infection reduction, revision, resistance development, induced membrane technique, and related economic aspects (15, 16, 17, 18, 19, 20, 21, 22, 54, 61, 79, 80, 81, 82). All publications presented favorable results in terms of safety and performance regarding PALACOS® R+G for the mentioned aspects, only Tyas *et al.* (11) described better results for COPAL® G+C in terms of infection rates after hemiarthroplasty when compared to PALACOS® R+G.

The publications regarding knee replacement procedures covered the aspects of arthroplasties (23, 24, 25, 26, 57, 65, 79, 80, 82). In addition, infection reduction, revision and related economic aspects were further topics (15, 27, 28, 29, 30, 31, 32, 33, 60, 63,70). All publications presented favorable results in terms of safety and performance regarding PALACOS® R+G.

For the evaluation of clinical data regarding the topic ankle replacement registry data were chosen, which are evaluated in detail in section 3.1.5.4. The publications regarding replacement procedures for the shoulder (34, 56,

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65) showed favorable results for PALACOS® R+G in a limited number of patients. Elbow replacement procedures in patients suffering from a hemophilic arthropathy resulted in a substantial complication and revision rate; however, even after revision without implant removal, total elbow arthroplasty with PALACOS® R+G provided good functional and subjective long-term results (35).
The publications regarding reconstruction of bone procedures covered patients either after trauma or tumor surgery showing positive outcomes in terms of safety and performance when using the induced-membrane technique leading to successful bone union (36, 37, 38, 39, 40, 41, 42, 54, 76, 77,85, 88, 89).

In summary, the clinical data from scientific publications for PALACOS® R+G showed convincing results for the confirmation of safety and performance, which can be transferred to PALACOS® fast R+G as an equivalent device.

3.1.5.4 An overall summary of the clinical performance and safety

PMMA bone cements and gentamicin are very well-studied and no additional product-specific safety concerns exist for the PALACOS® +G bone cements. 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, risks and the acceptability of the benefit-risk profile were assessed in relation to the state-of-the-art and according to the following indicative list of benchmark parameters for PALACOS® fast R+G:

Table 5: Clinical benefits

Performance / Safety aspect	**Benefit**	**Outcome Parameter**	**Threshold / Target values (as per state of the art)**
Stable fixation	Low risk of revision or re-revision surgery	Cumulative revision rate (data from registries and literature) comparable to or better than state of the art	**Cumulative (re-)revision rates:** **Primary procedures:** Hip: 2.0 – 3.8 % after 5 years Knee: 2.4 – 5.5 % after 5 years **Revision procedures:** Hip: 11.5 – 14.7 % after 5 years Knee: 11.6 – 15.6 % after 5 years
Indirect: Improvement of impaired body function	High patient satisfaction	Oxford Hip / Knee / Shoulder Score at 6 months (data from NJR reports and registries)	**Oxford Hip / Knee / Shoulder Score at 6 months:** Hip primary: 40 Knee primary: 35 Shoulder primary: 31 – 36 Hip revision: 35 Knee revision: 29
Indirect: Relief of symptoms	High patient success		
Reconstruction of bone	Preservation of function and / or limb	Union of bone defects following tumor surgery and / or trauma	**Bone union after two-stage reconstruction using induced membrane technique:** 53 – 100 %

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Performance / Safety aspect	Benefit	Outcome Parameter	Threshold / Target values (as per state of the art)
Application of ALBC	Low risk of infection	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 literature)	**Infection rates:** **Primary procedures:** Hip: 0.1 – 0.8 % Knee: 0.2 – 1.1 % Shoulder: 1.0 – 1.4 % **Revision procedures:** Hip: 2.5 – 6.1 % Knee: 2.7 – 5.8 %
Local use of antibiotic at the surgery site	Reduction of risk for systemic toxicity	Low frequency of hypersensitivity reactions to gentamicin (vigilance data, adverse event and recall database data, biologic risk assessment regarding systemic toxicity)	**Gentamicin serum concentration to not exceed persistent levels which lead to oto- or nephrotoxicity:** c(gentamicin): < 10 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 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 for primary hip and knee arthroplasty performed with PALACOS® fast R+G were 1.4% and 1.7% at 5 years, respectively, which is slightly better compared to the benchmark standards (range for hip: 2.0% - 3.8%; range for knee: 2.4 – 5.5% at 5 years). Cumulative revision rates for primary shoulder, elbow and ankle procedures were all comparable or better for the equivalent device PALACOS® R+G than benchmark standards at 10 years for shoulder and elbow and 5 years for ankle (4.6%, 8.6%, and 5.6%, respectively, with the following benchmark standards: shoulder: 4.8 – 12.7%; elbow: 6.6 – 9.6% at 10 years; ankle: 5.5 – 8.7% at 5 years).

For revision arthroplasty, the cumulative re-revision rates for PALACOS® fast R+G were better in hip (5.5% at 5 years) and knee joints (3.8% at 5 years) compared to reported benchmark standards (hip: 11.5 – 14.7%; knee: 11.6 – 15.6%; all values at 5 years). Similar results were reported for shoulder, elbow and ankle joints in revision arthroplasty for PALACOS® R+G.

The analysis outcomes of the benefits of **improvement of impaired body function** as well as the **relief of symptoms** showed comparable results between PALACOS® fast R+G are other bone cements (statistically insignificant differences, all values rounded): the functional Oxford Hip Score at 6 months in primary arthroplasty was 40 for the benchmark standard and 39.9 for PALACOS® R+G. In revision arthroplasty the values are 35 for the benchmark standard and 35.7 for PALACOS® fast R+G. Similarly, the Oxford Knee Scores at 6 months are comparable: the score was reported to be 35 for the benchmark standard and 36.2 for PALACOS® fast R+G in primary arthroplasty. For revision arthroplasty, no scores are available yet for PALACOS® fast R+G.

Infection rates obtained for PALACOS® fast R+G in primary hip (0.4%), knee (0.4%) and shoulder (0.4%), arthroplasty were comparable to the reported benchmark rates (hip: 0.1 – 0.8%; knee: 0.2 – 1.1%; shoulder: 1.0-1.4%). Rates for elbow (1.6%) and ankle (1.7%) procedures were also comparable between PALACOS® R+G and the comparator group (elbow: 3.3%; ankle: 0.8%).

Infection rates for primary ankle procedures rates were calculated compared to benchmark values (1.7% for PALACOS® R+G; 0.8% for competitors). No significant differences were observed when compared to the expected

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numbers of revisions due to infection. It is important to point out that patients in the PALACOS® R+G group had a general worse health status and were chosen for cemented ankle replacement due to their very special needs. Thus, this higher rate is considered acceptable. Furthermore, no re-revisions due to infection were reported in patients undergoing re-revision with PALACOS® R+G up to now.

Infection rates obtained for PALACOS® fast R+G in revision hip (0.6%), knee (3.2%) were comparable to or better than the reported benchmark rates (hip: 2.5 – 6.1 %%; knee: 2.7 – 5.8%). Infection rates of PALACOS® R+G for revision shoulder (2.7%), elbow (4.7%) and ankle (0%) arthroplasty were comparable to or better than the reported benchmark rates (shoulder: 2.9%; elbow: 3.6 – 7.7%; ankle: 5%). Comparability to benchmark standard is reported for PALACOS® R+G in ankle revision procedures (0.0% versus 5%).

With regards to the risk of **systemic toxicity**, *in vivo* and *in vitro* (50, 51, 52) data support the claim of high local antibiotic concentration at the surgery site, while serum levels of 3.8 µg/ml for gentamicin remain well below toxic levels of 10 µg/ml (53, 53). 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.

In **reconstruction of bone**, the benchmark for successful union of bone when using the induced membrane technique was determined to be in a range between 53 – 100%. When PALACOS® R+G was used as bone cement spacer during the first surgical stage of a procedure for reconstruction of bone defects by means of the induced membrane technique, bone fusion rates were in a range between 69.6 – 100%.

In summary, this evaluation of PALACOS® fast R+G confirmed the fulfillment of the expected clinical benefits i.e., showing the success in relation to the specified clinical outcome parameters.

For PALACOS® fast R+G it can be concluded that the benefits considerably outweigh the risks for the indications

- anchoring of endoprosthesis in primary and revision arthroplasty procedures of
    - hip
    - knee
    - ankle
    - shoulder
    - elbow
- reconstruction of bone via induced membrane technique after tumor surgery and / or trauma

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.
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 the PALACOS® +G bone cements.

The following PMCF measures are planned for PALACOS® +G bone cements:

<u>Device Registry Analysis</u>
The analysis of device registry data will primarily consider NJR as the largest register in the world covering more than 3 million records and long follow-up periods. 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 register. Clinical data for the PALACOS® +G bone cements are available on a large scale and will be analyzed during the annual update of the CER.

<u>Screening of Scientific Literature</u>
The screening of scientific literature provides up-to-date information about the devices 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.

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Adverse Event and Recall Databases
Adverse events and recalls reported in databases are an important source of information about the safety of the devices under evaluation. They represent relevant information in terms of quantitative and qualitative data. The databases of FDA (USA), BfArM (GER), TGA (AUS), SwissMedic (CH), MHRA (UK), and Public Health Agency of Canada (CAN) will be evaluated periodically as part of the preparation for CER-updates and the results will be described in a Safety and Recall Database Report.
The results of the mentioned PMCF measures will be summarized in the corresponding PMCF reports. These activities will be conducted on an annual basis in connection with the continuous updates of the clinical evaluations.

3.1.6 Possible diagnostic or therapeutic alternatives

Primary arthroplasty operations and endoprosthesis revision operation as well as the use of PMMA bone cements are very well-established procedures in joint replacement surgery.
PMMA has been widely used for the fixation of various endoprostheses in orthopedic surgery since decades. At present, PMMA is still the most commonly used filling material in primary arthroplasty operations. Uncemented procedures have also been used in primary arthroplasty operations. Furthermore, hybrid techniques have been developed during the past decades. The review of the literature indicates that there is no evidence to prove the superiority of cementless over cemented total joint arthroplasties. Hence, the use of PMMA bone cement can be considered state-of-the-art in primary arthroplasty operations.
In addition to the well-known characteristics and safety profile, a great advantage of PMMA is the long-term experience with this material and the familiarity of the majority of orthopedic surgeons.
If conservative treatments fail, a reconstructive surgical procedure such as resurfacing, or replacement of the diseased joint may be necessary. In primary arthroplasty operations of different etiologies, it is generally agreed that clinicians should attempt the core non-surgical therapies prior to referral for surgery. In patients with suspected or confirmed prosthetic joint infections, however, there is no conservative treatment option and hence, those patients have to undergo one-stage or two-stage revision surgery.
Furthermore, PMMA bone cements play an important role in the induced membrane technique for plastic reconstruction of bone defects.
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 in pregnant and breast-feeding women to evaluate any possible risk the use of ALBC containing gentamicin during pregnancy and lactation is generally not advised unless the benefits for the mother outweigh the potential risk to the child.
Differences in early polymerization behavior especially of the PALACOS® +G bone cements do not have any consequences for the clinical outcome.
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

Healthcare professionals in a clinical context and experienced in the handling of the product.
The surgeon and nurse must be thoroughly familiar with the properties and handling characteristics of PALACOS® +G bone cements. 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.

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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.

Table 6: List of harmonized standards

Number	Title	Issue Date	Application
DIN EN ISO 13485	Medical devices - Quality management systems - Requirements for regulatory purposes (ISO 13485:2016); German version EN ISO 13485:2016 + AC:2018 + A11:2021	2021	partially, clause 7.5.3 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 + A11:2021	2022	full
DIN EN ISO 15223-1	Medical devices - Symbols to be used with medical device labels, labelling and information to be supplied - Part 1: General requirements (ISO 15223-1:2021); German version EN ISO 15223-1:2021	2022	full
DIN EN ISO 14155	Clinical investigation of medical devices for human subjects - Good clinical practice (ISO 14155:2020); German version EN ISO 14155:2020	2021	partially, clause 6.3
DIN EN ISO 14602	Non-active surgical implants - Implants for osteosynthesis - Particular requirements (ISO 14602:2010); German version EN ISO 14602:2011	2012	full
DIN EN ISO 11607-1	Packaging for terminally sterilized medical devices - Part 1: Requirements for materials, sterile barrier systems and packaging systems (ISO 11607-1:2019); German version EN ISO 11607-1:2020	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); German version EN ISO 11607-2:2020	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	2002	full
DIN EN 556-1 Cor 1	Sterilization of medical devices - Requirements for medical devices to be designated "STERILE" - Part 1: Requirements for terminally sterilized medical devices; German version EN 556-1:2001, Corrigenda to DIN EN 556-1:2002-03; German version EN 556-1:2001/AC:2006	2006	full
DIN EN 556-2	Sterilization of medical devices - Requirements for medical devices to be designated "STERILE" - Part 2: Requirements for aseptically processed medical devices; German version EN 556-2:2015	2015	full
DIN EN ISO 14937	Sterilization of health care products - General requirements for characterization of a sterilizing agent and the development, validation and routine control of a sterilization process for medical devices	2010	full

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Number	Title	Issue Date	Application
	(ISO 14937:2009); German version EN ISO 14937:2009		
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 health care products - Microbiological methods - Part 2: Tests of sterility performed in the definition, validation and maintenance of a sterilization process (ISO 11737-2:2019); German version EN ISO 11737-2:2020	2020	full
DIN EN ISO 13408-1	Aseptic processing of health care products - Part 1: General requirements (ISO 13408-1:2008, including Amd 1:2013); German version EN ISO 13408-1:2015	2015	full
DIN EN ISO 13408-2	Aseptic processing of health care products - Part 2: Sterilizing filtration (ISO 13408-2:2018); German version EN ISO 13408-2:2018	2018	full
DIN EN ISO 13408-4	Aseptic processing of health care products - Part 4: Clean-in-place technologies (ISO 13408-4:2005); German version EN ISO 13408-4:2011	2011	full
DIN EN ISO 17665-1	Sterilization of health care products - Moist heat - Part 1: Requirements for the development, validation and routine control of a sterilization process for medical devices (ISO 17665-1:2006); German version EN ISO 17665-1:2006	2006	full
DIN EN ISO 10993-7	Biological evaluation of medical devices - Part 7: Ethylene oxide sterilization residuals (ISO 10993-7:2008); German version EN ISO 10993-7:2008	2022	full

Relevant adopted monographs of the European Pharmacopoeia

European Pharmacopoeia	Monograph 0331 – Gentamicin sulfate
	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

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3.1.9 Revision history

Table 7: Document history

SSCP Revision number	Date issued	Change description	Revision validated by the Notified Body
4	Dec 2024	Section 3.1.4.1: Update of wording for BCIS and residual risk frequencies Section 3.1.4.2: Update of current information on aspects of safety Section 3.1.5.3: Update of current clinical evidence Section 3.1.5.4: Update of benchmarks for clinical performance and safety and of performance of the product Section 3.1.7: Wording completed from instructions for use Section 3.2.5: Update of wording for BCIS and residual risk frequencies Section 3.2.6: Summary of product performance updated Correction of wording and layout errors throughout the document.	☒Yes Validation language: English ☐No (only applicable for class IIa or some IIb implantable devices (MDR, Article 52 (4) 2nd paragraph) for which the SSCP is not yet validated by the NB)

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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 Instruction for Use (IFU) to provide information on the safe use of the device.

3.2.1 Background information

PALACOS® fast R+G is a bone cement. PALACOS® fast R+G is part of the product family PALACOS® +G bone cements. It is based on a biologically safe material called poly (methyl methacrylate) (PMMA). This material has a long history of safe use in humans. PALACOS® R+G was the basis for development of the bone cements PALACOS® MV+G, PALACOS® LV+G, and PALACOS® fast R+G. All four bone cements together comprise the product family PALACOS® +G bone cements.

PALACOS® +G bone cements are 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 movable surfaces of a joint. The healthy parts of the joint stay intact.

Bone cements can also treat cases of bone loss. For example, after severe accidents with multiple fractures in a bone. The name of this surgical technique is reconstruction of bone. It restores bone continuity mainly in patients suffering from tumor of the bone or in trauma.

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 PALACOS® +G bone cements. 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

PALACOS® fast R+G

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 with letters. It allows the unmistakable identification of a specific medical device on the market. An 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	Basic UDI-DI
PALACOS® fast R+G	4260102130101010002AL

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 different 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 under MDD
PALACOS® fast R+G	2022	2013

3.2.3 Intended use of the device

3.2.3.1 Intended purpose

PALACOS® fast R+G is intended for stable anchoring of total or partial joint replacements (endoprostheses) in living bone as well as for reconstruction of bone.

3.2.3.2 Indications and intended patient groups

PALACOS® fast R+G is indicated for surgical treatment such as

- anchoring of endoprosthesis in primary and revision arthroplasty procedures of
  - hip
  - knee
  - ankle
  - shoulder
  - elbow
- reconstruction of bone via induced membrane technique after tumor surgery and / or trauma

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These treatments are typically conducted in adults, predominantly elderly patients with osteoarthritis and patients with trauma.

3.2.3.3 Contraindications/ advice against treatment

PALACOS® fast R+G must not be used in the following cases:

- known or suspected intolerance against parts of the bone cement or against the antibiotic gentamicin
- infection at the site of the body where the surgery is planned
- patients with impaired kidney function
- reconstruction of skull bone defects
- spinal surgery
- children

3.2.3.4 Lifetime of the device

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

3.2.4 Device description

PALACOS® +G bone cements are based on a biologically safe material called poly (methyl methacrylate) (PMMA) which has a long history of safe use in humans.

Composition
The cement consists of two 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 the application of the dough to the bone. There it hardens completely. In addition, the cement contains an antibiotic (gentamicin). Your treating surgeon chose the antibiotic to prevent an infection.

PALACOS® fast R+G contains:

Table 8: Composition of PALACOS® fast R+G in percentage

Constituents	**PALACOS® fast R+G**
Powder:	
PMMA copolymer *Polymer (powder component)*	81 %
zirconium dioxide *X-ray contrast medium (enabling visualization with X-ray, CT or MRI)*	15 %
benzoyl peroxide *Chemical component initiating the polymerization reaction*	2 %
gentamicin sulfate *(Antibiotic)*	2 %
Liquid:	
methyl methacrylate *Monomer (liquid component)*	98 %
N, N-dimethyl-p-toluidine Chemical component accelerating the polymerization reaction	2 %

The data is rounded

Other constituents:
- Powder: chlorophyll-copper-complex (E141) (Food colorant. Improving visibility of the bone cement in the surgical field)

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- Liquid: chlorophyll-copper-complex (E141), hydroquinone (chemical component stabilizing the chemical reaction)
Traces of histamine may be present in these bone cements. 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. PALACOS® +G bone cements are intended for single-use and are supplied sterile.

3.2.5 Risks and warning

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 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 or to the handling of the user.
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 that complies with harmonized risk management guidelines. It ensures that the benefits of using the medical device are greater than any 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 literature, < 0.0001% can include potential risks not reported in literature so far.

Table 9: Frequencies of side effects

Frequency	Side effect
Immune system	
4.79%*	• hypersensitivity / allergic reaction and local reaction which may include inflammation, induration, erythema, pruritus, or pain
< 0.0001%	• anaphylactic shock
Kidney and Urinary Tract	
< 0.0001%	• renal impairment
Musculoskeletal System	
36.65%*	• ossification
22.78%*	• osteolysis due to bone cement fragments
Skin and Subcutaneous Tissue	
< 0.0001%	• rash
< 0.0001%	• urticaria

*cases reported to Heraeus Medical GmbH with frequencies lower than from 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, < 0.0001% can include potential risks not reported in literature so far.

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Table 10: Frequencies of Residual risks

Frequency	Residual Risk
Vascular System, Heart, Respiratory System, Blood and Lymphatic System, Nervous System	
Bone Cement Implantation Syndrome (BCIS): 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. 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. 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.	
25.48%*	BCIS grade 1 moderate hypoxia (SpO2 < 94%) or hypotension [fall in systolic blood pressure > 20%]
8.17%*	BCIS grade 2 severe hypoxia (SpO2 < 88%) or hypotension [fall in systolic blood pressure > 40%] or unexpected loss of consciousness.
3.37%*	BCIS grade 3 cardiovascular collapse, requiring CPR
Nervous System	
< 0.0001%	• numbness
Blood and Lymphatic System	
< 0.0001%	• hypovolemia
Musculoskeletal System	
15.22%*	• aseptic loosening
< 0.0001%	• unequal limb length
0.27%*	• loss of range of motion
< 0.0001%	• ambulation difficulties
Infection	
3.58%*	• bacterial infection including cellulitis, and / or osteomyelitis
Generalized Disorders	
2,56%	• inflammation
< 0.0001%	• swelling / edema
0.94%*	• fibrosis
< 0.0001%	• heat necrosis

*cases reported to Heraeus Medical GmbH with frequencies lower than from literature

Please contact your healthcare professional 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

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

PALACOS® R+G was the first bone cement with an antibiotic introduced in 1972. All further products of the PALACOS® +G product family like PALACOS® fast R+G are based on PALACOS® R+G. They own few modifications in terms of product characteristics. PALACOS® fast R+G was developed and placed on the market in 2013. PALACOS® +G bone cements treated a total of about 30 million patients worldwide so far. The product range of PALACOS® +G bone cements can be considered as state-of-the-art in the field of stable anchoring of joint endoprostheses as well as for reconstruction of bone.

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The manufacturer performs the analysis of any clinical data regularly. Sources can be endoprosthesis 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 parameters relate to the use of the bone cements:

- Stable fixation of the endoprosthesis with a low risk of revision surgery. This is evaluated based on long-term data from regional or national registries.
- Improvement of impaired body function with a high patient satisfaction. This is evaluated based on quality-of-life data from registries.
- Relief of symptoms related to the surgical procedure with high patient success. This is evaluated based on quality-of-life data from registries.
- Application of bone cements in combination with an antibiotic with a low risk of infection. This is evaluated based on 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 reduced risk for side effects compared to oral or intravenous administration of the antibiotic. This is evaluated based on complaints reported to manufacturer, evaluation of databases and data regarding the development of the medical device.
- The reconstruction of bone via induced membrane technique can result in the preservation of function of the limb or of the limb itself. This is evaluated by determination of the union of bone defects after tumor surgery and / or trauma.

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

The analysis revealed that PALACOS® fast R+G performed as expected in all aspects of the above-listed outcome parameters:

- Stable fixation was analyzed by the rate at which operations needed to be repeated (revision rate). The rate was in a range comparable with the current state-of-the-art. For example, the revision rate of PALACOS® fast R+G was reported to be 1.4% for primary hip and 1.7% for primary knee, which is better than benchmark standards (range for hip: 2.0 – 3.8% after 5 years; range for knee: 2.4 – 5.5% after 5 years).
- 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, PALACOS® fast R+G was comparable to or better than 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, PALACOS® fast R+G were comparable to the 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 PALACOS® fast R+G and for revision surgeries.
- PALACOS® fast R+G contains an antibiotic 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

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up the blood concentrations of antibiotics released from the bone cement would go after an operation with PALACOS® fast R+G. The result was that the values remained far below the levels which can lead to severe side effects.

- Reconstruction of bone via induced membrane technique was analyzed by the rate of successful bone union after two-stage reconstruction. The performance of PALACOS® R+G was comparable to the state-of-the-art.

Additionally, the scientific literature for PALACOS® R+G and PALACOS® fast R+G was thoroughly evaluated, and 77 scientific publications were identified and analyzed. It can be summarized that all data show favorable clinical results for PALACOS® R+G and PALACOS® fast R+G.

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 PALACOS® fast R+G:

- anchoring of endoprosthesis in primary and revision arthroplasty procedures of
  - hip
  - knee
  - ankle
  - shoulder
  - elbow
- reconstruction of bone via induced membrane technique after tumor surgery and / or trauma

The following activities are planned to ensure safety and performance of PALACOS® +G bone cements:

- Device Registry Analysis, to monitor the safety and performance of PALACOS® +G bone cements
- Screening of Scientific Literature, to monitor the safety and performance of PALACOS® +G bone cements
- Authority Databases (adverse events and recalls), to monitor the safety of PALACOS® +G bone cements

The same activities are performed for similar products, in order 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 surgery is possible. On the other hand, surgical treatment such as joint surgery like hip replacement surgery could be reasonable. Choice of treatment depends on your specific condition and your doctor's opinion.

Joint surgery

If possible, your doctor/surgeon will try to treat defective joints by other means. If all other treatment options fail, a reconstructive joint surgery may be necessary. This means, 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

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used in primary joint surgeries. However, current data do not allow to determine if cementless or cemented 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.

Reconstruction of bone

Oncological treatment or trauma may lead to bone loss. PMMA bone cement is able to fill certain bone defects depending on the depth and surface of the defect. The method "Induced Membrane Technique" can support new bone growth in an area where part of a bone had to be removed due to cancer or was lost due to trauma. For this approach bone cement is only placed between the ends of a defect for a short period of time. The bone cement is not fixed to the bone.

For larger defects further therapy options have to be considered. Therapy options like human tissues from donors, metal implants or custom-made protheses are available. The attending surgeon will choose the appropriate surgical approach according to the patient's situation.

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