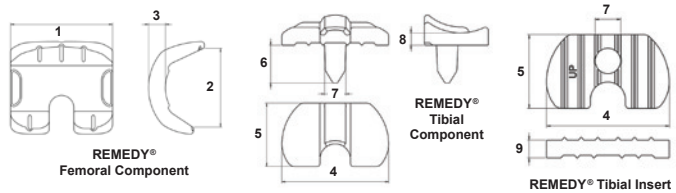
Symbols

Catalog Number	Batch Number	Consult Instruction For Use	Do Not Reuse	Use By	Do Not Use If Package Is Damaged Or Opened	Sterilized By Ethylene Oxide	Caution	Do Not Resterilize
REF	LOT					STERILE EO		



Component Description	1(mm)	2(mm)	3(mm)	4(mm)	5(mm)	6(mm)	7(mm)	8(mm)	9(mm)	Gentamicin Base (g)
REMEDY® Tibial Component 60mm				60	36	25	14	7.8		0.4
REMEDY® Tibial Component 70mm				70	42	25	14	8.2		0.6
REMEDY® Tibial Component 80mm				80	48	25	14	8.8		0.9
REMEDY® Femoral Component 54mm	54	41.6	9.5							0.5
REMEDY® Femoral Component 64mm	64	49.3	10.5							0.8
REMEDY® Femoral Component 74mm	74	56.3	11.5							1.2
REMEDY® Tibial Insert 60mm				60	36		14.5		10	0.3
REMEDY® Tibial Insert 70mm				70	42		14.5		10	0.5
REMEDY® Tibial Insert 80mm				80	48		14.5		10	0.7

OsteoRemedies®
ADVANCED MEDICAL TECHNOLOGIES

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Surgical Risks (General): pulmonary embolism, myocardial infarction, arrhythmias, venous thrombosis, transitory hypotension.

Surgery Risks (TKR): difference in limb length, wound healing issues, femur or tibia damage, blood vessel damage, nerve damage, bone bed damage, excessive blood loss, arthrofibrosis, phlebitis, thrombophlebitis, hematoma.

REMEDY® Knee Spacer Risks: recurring infection, gentamicin toxicity (ototoxicity/nephrotoxicity), implant breakage, implant loosening, PMMA sensitivity, debris release, difficult device removal, implant dislocation, foreign body reaction.

NOTES: The surgeon should be aware of the possible negative effects of bone cement, as the device must be affixed with it. Infections that recur, though rare, have been known to reappear even with IV antibiotic use. Gentamicin application may trigger negative reactions of this antibiotic following systemic use, as shown in the next paragraphs.

Gentamicin (and Aminoglycosides) Risks:
All aminoglycosides have the potential to produce reversible and irreversible vestibular, cochlear and renal toxicity when administered systemically.

Ototoxicity:
Both vestibular and auditory dysfunction can follow administration of any of the aminoglycosides. It is more likely to occur in patients with persistently elevated concentrations of drug in plasma. Ototoxicity is largely irreversible. Repeated courses of aminoglycosides can lead to deafness. Older patients may be more susceptible to ototoxicity. Drugs such as ethacrynic acid are furosemide may potentiate the ototoxic effects. Hearing loss is more likely to develop in patients with pre-existing auditory impairment following exposures to these agents. It is recommended that patients receiving high doses and /or prolonged courses of aminoglycosides be monitored carefully for ototoxicity, since initial symptoms may be reversible. However, deafness may occur several weeks after therapy is discontinued.

Nephrotoxicity:
Approximately 8-28% of patient receiving an aminoglycosides for more than several days will develop mild renal impairment, that is almost always reversible. Toxicity correlates with the total amount of drug administered. Other drugs, such as amphotericin B, vancomycin, cisplatin, cyclosporine, cephalothin, furosemide may potentiate aminoglycoside-induced nephrotoxicity. Monitoring drug concentrations in plasma is useful, particularly during prolonged and/or high dose therapy.

Neuromuscular blockade:
Episodes have occurred in association with anesthesia or administration of other neuromuscular blocking agents. Patients with myasthenia gravis are particularly susceptible to this phenomenon.

Other untoward effects:
Aminoglycosides have little allergenic potential; both anaphylaxis and rash are unusual. Rare hypersensitivity reactions, - including skin rashes, eosinophilia, fever, blood dyscrasia, angioedema, exfoliative dermatitis, and anaphylactic shock – have been reported. Allergic reaction may appear independent to dosage.

Pregnancy and Breast-feeding
There are no existing data that illustrates the usage safety of the REMEDY® Knee Spacer during pregnancy and breast-feeding. It is recommended that knee revision surgery be avoided during the first three months of pregnancy. The REMEDY® Knee Spacer can be used in the remaining gestation time only when it is determined that it is impossible to save the joint or preserve the patient's life by other means of intervention.

REMEDY® Tibial Insert
The REMEDY® Tibial Insert must be used in combination with the REMEDY® Tibial Component in the event of lack of a significant part of bone. The REMEDY® Tibial Insert contains a hole that allows coupling to its REMEDY® Tibial Component. This component (Tibial Component + Tibial Insert) must be combined with the REMEDY® Femoral Component. These two independent articulating components resemble an anatomically correct knee prosthesis. The final device is a temporary, implantable REMEDY® Knee Spacer.

REMEDY® Knee Spacer Indications
The REMEDY® Knee Spacer, which consists of a Femoral Component, a Tibial Component and a Tibial Insert, is indicated for temporary use (maximum 180 days) as an adjunct to total knee replacement (TKR) in patients undergoing a two-stage procedure due to a septic process and where gentamicin is the most appropriate antibiotic based on the susceptibility pattern of the infecting micro-organisms.

The REMEDY® Knee Spacer is applied on the femoral condyles (Femoral component) and on the tibial plate (Tibial component) following removal of the existing implant and radical debridement. The use of the Tibial insert is optional, when a large tibial defect is present. The device is intended for use in conjunction with systemic antimicrobial antibiotic therapy (standard treatment approach to an infection).

The REMEDY® Knee Spacer is not intended for use for more than 180 days, at which time it must be explanted and a permanent device implanted or another appropriate treatment performed (e.g. resection arthroplasty, fusion etc.). Because of the inherent mechanical limitations of the device materials (gentamicin/polymethylmethacrylate), the device is only indicated for patients who will consistently use traditional mobility assist devices (e.g., crutches, walkers, canes) throughout the implantation period.

REMEDY® Knee Spacer Contraindications
- Deficiencies in the patient's vascular, nervous or muscular systems.
- Osteoporosis or poor bone quality may cause the implant to fracture existing bone or migrate.
- Sufficient bone not available to allow insertion and fixation of the knee spacer.
- Patient's two-stage arthroplasty procedure is contraindicated based on decreased immune response or systemic clinical conditions.
- The infected TKR devices cannot be removed.
- Patient exhibits hypersensitivity (allergy) to PMMA bone cement, aminoglycosides or gentamicin.
- Lack of adequate bone structure which precludes adequate support of the spacer.
- Lack of adequate competence (anatomical and functional) of peripheral ligamentous apparatus and extensor mechanism.
- Infection of the TKR cannot be confirmed.
- Infecting bacterium/pathogens resistant to gentamicin.
- Infecting bacterium/pathogens are not susceptible to gentamicin.
- A remote infection (systemic/secondary) is suspected or verified.
- Myasthenia gravis.
- The patient does not have a TKR and the infection is secondary to trauma, septic arthritis or other surgical procedures.
- The patient has neuromuscular disorders that do not allow control of the knee joint.
- Patient is unable or rejecting the use of protected weight bearing devices throughout the implantation period (canes, walkers, crutches, etc.).
- Age, weight or activity level, may cause the surgeon to expect possible, early failure of the knee spacer.

Possible Adverse Events
The list provided below addresses frequent and serious adverse effects which may be associated with the use of the REMEDY® Knee Spacer. *Note that some effects are not directly associated with the device itself, however the surgeon should be aware of these possible issues, and ready to treat them accordingly.*

OsteoRemedies®
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SURGEON INFORMATION

REMEDY® KNEE SPACER
Temporary REMEDY® Knee Spacer with Gentamicin

REMEDY® Femoral Component | REMEDY® Tibial Component | REMEDY® Tibial Insert

Overview
The REMEDY® Knee Spacer is part of the treatment foreseen in a two-stage procedure performed in the event of permanent prosthesis infection. The REMEDY® Knee Spacer implant is intended for temporary use only (180 days or less). It allows basic joint mobility and releases antibiotic into the joint area to protect the implant from bacterial colonization. A second surgery will be required at a later date to remove the REMEDY® Knee Spacer and replace it with a permanent knee joint implant.

The REMEDY® Knee Spacer consists of two individual implants (femoral and tibial) which, when joined, allow to better fit the anatomy of the patient. A REMEDY® Tibial Insert Component is also available in different sizes to enable the best possible patient solutions.

Each REMEDY® Femoral Component (three sizes available) is matchable to each REMEDY® Tibial Component (three sizes available). Each REMEDY® Tibial Insert (three sizes available) is matchable only with its corresponding Tibial Component.

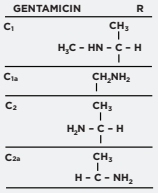
REMEDY® Knee Spacers:
- single-use medical devices/ethylene oxide sterile
- formed with bone cement (PMMA) and gentamicin
- release gentamicin

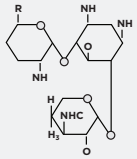
REMEDY® Femoral Component
The REMEDY® Femoral Component must be used in combination with the appropriate REMEDY® Tibial Component. When these two devices are joined, the form emulates an anatomically correct knee prosthesis. The REMEDY® Knee Spacer is temporary, implantable and composed of gentamicin bone cement.

REMEDY® Tibial Component
The REMEDY® Tibial Component must be used in combination with the REMEDY® Femoral Component. When these two devices are joined, the form emulates an anatomically correct knee prosthesis. The REMEDY® Knee Spacer is temporary, implantable and composed of gentamicin bone cement. In the event of a large tibial bone defect, a REMEDY® Tibial Insert may also be used in combination with REMEDY® Tibial Component. The REMEDY® Tibial Component presents a stem that guides the application of the insert which is a flat base with a central hole. The final device is a temporary implantable REMEDY® Knee Spacer.

Use in Children
No data or tests support that the REMEDY® Knee Spacer is safe to use in children. The REMEDY® Knee Spacer should only be used in mature adults.

Chemistry/Structure - Gentamicin Sulphate
Gentamicin is an aminoglycoside antibiotic derived from the actinomycetes Micromonospora purpurea. Gentamicin is a complex of the gentamicins C1, C1a, C2 and C2a as shown. The molecular weight is 449.55. The compound is supplied as sulphate.





GENTAMICIN SULPHATE RELEASED FROM PMMA
Mechanism of Action
Bacteria tend to adhere to surfaces where they can multiply and create a defensive barrier called a biofilm (complex structure mainly made by extracellular polysaccharides and proteins). Bacteria embedded in a biofilm are more resistant to most antibiotic therapy because the glycoprotein structure is difficult for antimicrobial agents to penetrate. PMMA, due to its surface characteristics, is one of the materials with the highest risk of bacterial colonization. It has been demonstrated *in vitro* that the presence of antibiotics in PMMA reduces bacterial adhesion.

Gentamicin activity is primarily directed against aerobic, gram negative bacilli. The action against most gram positive bacteria is limited. Gentamicin is active against susceptible strains of enterococci and streptococci at concentrations which can be achieved clinically only when combined with a penicillin. Gentamicin is active *in vitro* against more than 90% of strains of *S. aureus* and 75% of *S. epidermidis*. Gentamicin has been shown to be active against most strains of the following organisms both *in vitro* and in clinical infections.

Common susceptible pathogens
Gram positive bacteria
Staphylococcus aureus; Streptococcus pyogenes; Streptococcus pneumoniae; Streptococcus (Enterococcus) faecalis; Listeria monocytogenes

Gram negative bacteria
Citrobacter; Enterobacter; Escherichia coli Klebsiella spp.; Proteus mirabilis; Proteus vulgaris; Morganella morganii; Providencia spp.; Salmonella spp.; Serratia; Shigella spp.; Pseudomonas aeruginosa

Bibliography
Godman & Gilman's *The Pharmacological Basis of Therapeutics* 2005, XI Ed., Chapter 45 (Henry F. Chambers) pp.1155-1170; McGraw Hill, New York.

Antibiotic warnings
The release of gentamicin from *in vitro* studies has been shown to be below the recommended adult dose of 3-5 mg/kg/day (or 1.0 -1.7 mg/Kg/8 hours) according to the US Pharmacopoeia (gentamicin sulphate monograph). Toxic levels are not expected when gentamicin is released locally from the REMEDY® Knee Spacer. However trough concentrations exceeding 2 µg/ml for longer than 10 days have been associated with toxicity (systemic administration). The REMEDY® Knee Spacer should be used with caution, during the first day of implantation, when used in conjunction with ototoxic or nephrotoxic drugs. The device should be used with caution in patients predisposed to or who have preexisting medical conditions that would put them at risk for gentamicin toxicity (dehydration, renal dysfunction, advanced age, etc.). All patients should be monitored for toxic blood levels of gentamicin, nephrotoxicity and ototoxicity while the device is *in situ:* this is especially critical for elderly patients and those receiving other ototoxic and/or nephrotoxic drugs.

Precautions
Review of the OsteoRemedies® LLC surgical technique for knee arthroplasty revision surgery and familiarity with the proper use of the REMEDY® Knee Spacer is required for successful implantation of the device. Only surgeons who have studied the REMEDY® Knee Spacer surgical technique and are aware of the limitations of its application are allowed to perform the procedure. The surgeon is not allowed to adjust or modify the device in any way (do not add additional antibiotics as the effects structurally and pharmacologically cannot be known). The user must protect the device from harm as any damage to the implant may reduce fatigue strength and may result in failure under load thus possibly affecting the patient. If particulate debris becomes detached (loose fragments of bone or bone cement) the wear rate of component contact surface is greatly accelerated as debris acts as an abrasive and damaging anomaly. The REMEDY® Knee Spacer may be compromised in an overweight or obese patient and/or one who does not limit the amount of activity and weight placed on the knee. Always use the largest component size possible to ensure ideal performance. It is essential that the patient use mobility-assisted devices (e.g. crutches, walker, cane) during the implantation period.

Care should be taken in placing the spacer to preserve the bony tissue during the implantation procedure. Implantation methods which are deemed aggressive are not needed for proper placement of the spacer. Any damage to the device may affect the fatigue strength and lead to failure under load, therefore do not subject the device to excessive forces (mallet strikes). Antibiotic susceptibility testing should be performed prior to implantation of the REMEDY® Knee Spacer following a fine needle aspiration from the joint site. Patients should be informed of the limitations of the implant and the requirement for additional surgery to implant a permanent knee prosthesis. Patients should be instructed to adjust their activities and be informed that postoperative care is essential.

The REMEDY® Knee Spacer is single-use intended for an individual patient. Do not resterilize and/or reuse. Resterilization of the components can cause risk of infection to the patient and may change the morphology of the device, the effectiveness of the antibiotic component and mechanical properties of the implant, that could cause a malfunction with serious health risks for the patient.

Implants should not be reused once removed, though they may appear not damaged as this could cause contamination and aggravation of patient infection. The removal of the device may damage the implant itself, and cement residues may remain adhered as well to the device. By not following these recommendations there will be an increased likelihood of wear, loosening, poor function, fracture or premature failure. Excess material is deemed as surgical waste and must be removed/destroyed at the conclusion of the surgical procedure.

The REMEDY® Knee Spacer should not be implanted if the existing implant cannot be completely removed.

The REMEDY® Knee Spacer is comprised of two components (femoral component, tibial component) or three components (femoral component, tibial component and tibial insert). It is important not to use the individual components alone within the anatomy.

The REMEDY® Knee Spacer must not be rinsed or cleaned with liquids prior to implanting.

The REMEDY® Knee Spacer should not be used in areas that contain osteosynthesis implants that may interfere with the device and its mechanical function.

The REMEDY® Knee Spacer must not remain implanted for more than 180 days. The operative area should be rigorously irrigated and rinsed after device extraction to remove all cement debris prior to implantation of the permanent prosthesis or other surgical procedures (fusion, resection arthroplasty, etc.). Survival of the revision implant may be jeopardized if cement and/or bone debris are not thoroughly removed. The device has specific indications for use. Thus its use under conditions other than the intended ones is unlikely to provide any benefit to the patient, and increases the risk of developing drug-resistant bacteria.

Implantation/Utilization
Aseptic surgical techniques are critically important based on clinical study data. Correct sizing of the REMEDY® Knee Spacer depends on the selection and judgment of the surgeon in relation to the patient's anatomy and need. In order for the surgeon to effectively implant the device the surgeon shall: (A) study available literature, (B) properly and thoroughly train on the techniques required for the REMEDY® Knee Spacer surgery, and (C) study and become informed regarding the use of instrumentation for sizing and implantation of the devices.

Proper sizing and selection of components can be determined by use of transparent radiograph overlays (REMEDY® Knee Templates). REMEDY® Knee Trial devices are also available to ensure the implant has been correctly sized for the patient's anatomy.

Application Instructions
Following the removal of the existing implant and thorough debridement, the REMEDY® Knee Spacer is typically applied using the medial para-patellar route. The size to be implanted is the one that is nearest to the size of the removed implant. Transparent radiograph overlays (REMEDY® Knee Templates) and REMEDY® Knee Trials are provided to help determine the appropriate size needed.

The operative site must be irrigated with Ringer or physiological solution while thorough debridement must be executed after removal of the prosthesis and before inserting the REMEDY® Knee Spacer. Excess cement or debris from the previous device must be removed to ensure a clear operative area.

The size is selected in relation to the dimensions of the removed implant, the type of bone defect, the condition of the ligamentous apparatus and the flexion-extension spaces. Other consideration shall be given in relation to the stability of the implant and the range of movement: the achievement of full extension and 90° flexion is important, in particular with a flexion area sufficiently close to avoid antero-posterior movement of the flexed knee.

The components must be tightly fixed with gentamicin-loaded bone cement. Apply the REMEDY® Femoral Component first, and wait for the polymerization of the cement, than proceed with the application of the REMEDY® Tibial Component (if needed the REMEDY® Tibial Insert), avoiding allowing excess cement to adhere to the joint surfaces. *Note: The REMEDY® Tibial Component and REMEDY® Tibial Insert must be affixed with gentamicin-loaded bone cement.*

It is possible to reduce the joint prior to the tibial component cement curing, performing flexion/extension movements to achieve a centering of the tibial component in relation to the femoral component. Clean the area from any debris. Following suture and extensor apparatus reconstruction, the knee must be stable, but not too tight. Joint excursion should range from 0° and 90°.

To prevent dislocation, the same measures utilized for a permanent total knee replacement should be adopted. Additional considerations include:
- instructions, techniques or guides for the spacer device.
- choice of the correct size.
- proper cement fixation of the components with gentamicin-loaded bone cement.
- placement with appropriate joint tension of the soft tissues around the knee joint.
- in cases at risk consider the use of a brace (possibly articulated) to assist in flexion to lower the risk of dislocation.
- application in at risk cases of an orthopaedic brace (possibly articulated) to assist flexion without dislocation.
- explantation of the spacer device.

Postoperative treatment
Postoperative treatment is comparable with a primary knee implant, however, weight-bearing can be only partial (use of canes, crutches, etc.). It is recommended that partial weight-bearing be assessed on an individual basis in relation to the anatomic conditions of the femur and tibia, bone trophism and the clinical conditions of the patient during rehabilitation stages. Avoid weight bearing or forced mobilization which could cause the implant to damage the biological structure. If needed, a brace (possibly articulated) to assist flexion may be suggested in cases at risk of dislocation (in relation to the stability and/or the condition of the extensor apparatus).

Explantation
The REMEDY® Knee Spacer must be removed within 180 days of implantation and is not intended for use as a permanent prosthesis. Revision instruments (mallets, osteotomes, etc.) can be used in the surgical procedure. The wound site should thoroughly be cleaned of all bone cement debris prior to implantation of a definitive implant or performing an alternative surgical procedure (e.g. resection arthroplasty, fusion, etc.). Cement or bone debris may shorten the survival of the revision implant if not removed.

Patient Precautions
Surgeon-to-patient instructions:
- Pain, discomfort or trauma with the affected limb must be communicated to the surgeon.
- Canes, crutches, walkers, etc., (protected weight-bearing mobility devices) must be used at all times while the device is implanted.
- The REMEDY® Knee Spacer must be removed after temporary implantation (not to exceed 180 days).
- Excessive loading/weight on the REMEDY® Knee Spacer must be averted (sports activity, obesity, falling, unprotected weight bearing, etc.).

The patient's anatomic conditions of the knee district, bone trophism and other relevant clinical conditions during the rehabilitation phase should be periodically reviewed as the REMEDY® Knee Spacer was designed for temporary implantation under protected load bearing conditions.

How supplied
The REMEDY® Knee Spacer implants are packaged and distributed sterile. Do not resterilize. All packages should be inspected for integrity prior to use. If a package is opened, contaminated or damaged please do not use.

Caution
Federal law restricts this device to sale by or on the order of a physician.

Information
For further product information, please contact Customer Service.