OSTEOREMEDIES®
ADVANCED MEDICAL TECHNOLOGIES

SURGEON INFORMATION

REMEDY® SHOULDER SPACER

Temporary REMEDY® Shoulder Spacer with Gentamicin

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Overview

The REMEDY® Shoulder Spacer is part of the treatment foreseen in a two-stage procedure performed in the event of permanent prosthesis infection. The REMEDY® Shoulder 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® Shoulder Spacer and replace it with a permanent shoulder joint implant.

The REMEDY® Shoulder Spacer consists of two individual implants (head and stem) which, when joined, allow to better fit the anatomy of the patient.

Each REMEDY® Modular Humeral Head can be combined with each REMEDY® Modular Humeral Stem.

Modularity is offered by selecting optional neck lengths (offset) and using a threaded connection featured on both implants. REMEDY® Modular Humeral Heads include a monomer (MMA) phial that serves as an adhesive (which binds the head and stem) and "cover cap". The liquid is sterilized by filtration.

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

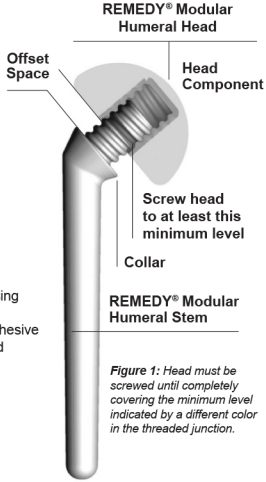


Figure 1: *Head must be screwed until completely covering the minimum level indicated by a different color in the threaded junction.*

REMEDY® Modular Humeral Head

The REMEDY® Modular Humeral Head must be used together with the appropriate REMEDY® Modular Humeral Stem. When both head and stem are joined, the shape emulates an anatomically correct shoulder prosthesis. The REMEDY® Shoulder Spacer is temporary, implantable and composed of gentamicin bone cement.

REMEDY® Modular Humeral Stem

The REMEDY® Modular Humeral Stem is made of formed bone cement (PMMA) with gentamicin applied to a stainless steel reinforcing structure, with a straight profile and an oval cross-section. The combination of a stem with a head generates a device resembling a shoulder prosthesis. The REMEDY® Shoulder Spacer is temporary, implantable and composed of gentamicin bone cement.

REMEDY® Shoulder Spacer Indications

The REMEDY® Shoulder Spacer, which consists of a modular head and stem, is indicated for temporary use (maximum 180 days) as an adjunct to total or hemi-shoulder replacement in skeletally mature 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 head and stem components are inserted into the glenoidal cavity and humeral medullary canal, respectively, following removal of the existing prosthetic components and radical debridement. The device is intended for use in conjunction with systemic antimicrobial antibiotic therapy (standard treatment approach to an infection).

The REMEDY® Shoulder 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.).

REMEDY® Shoulder 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 shoulder spacer.
- Patient's two-stage arthroplasty procedure is contraindicated based on decreased immune response or systemic clinical conditions.
- The infected shoulder joint replacement devices cannot be removed.
- Patient exhibits hypersensitivity (allergy) to PMMA bone cement, aminoglycosides or gentamicin.
- Infecting bacterium/pathogens resistant to gentamicin.
- A remote infection (systemic/secondary) is suspected or verified.
- The patient does not have a shoulder joint replacement prosthesis and the infection is secondary to trauma, septic arthritis or other surgical procedures.
- Lack of ideal bone disallows support of the prosthesis in the proximal humerus and glenoid.
- Patient has neuromuscular disorders disallowing proper control of the shoulder.
- Patient is unable or rejecting the use of protected weight bearing devices throughout the implantation period (brace).
- Age, weight or activity level, may cause the surgeon to expect possible, early failure of the shoulder spacer.
- Infecting bacterium/pathogens are not susceptible to gentamicin.
- Myasthenia gravis.

Possible Adverse Events

The list provided below addresses frequent and serious adverse effects which may be associated with the use of the REMEDY® Shoulder 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.

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

Surgery Risks (Shoulder Replacement): difference in limb length, wound healing issues, humerus or glenoid damage, blood vessel damage, nerve damage, bone bed damage, excessive blood loss, arthrofibrosis, phlebitis, thrombophlebitis, hematoma.

REMEDY® Shoulder Spacer Risks: recurring infection, gentamicin toxicity (ototoxicity/nephrotoxicity), implant breakage, head disassembling, 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 and 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, vancomcyin, cisplatin, cyclosporine, cephalotin, furosemide may potentiate aminoglycoside-induced nephrotoxicity. Monitoring drug concentrations in plasma is useful, particularly during prolonged and/or high dose therapy.

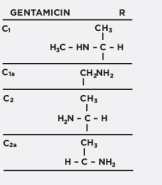
Neuromuscular blockade:
Episodes have occurred in association with anesthesia or administration of other neuromuscular blocking agents. Patients with myasthenia gravis are particularly susceptible to this phenomenon.

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® Shoulder Spacer during pregnancy and breast-feeding. It is recommended that shoulder revision surgery be avoided during the first three months of pregnancy. The REMEDY® Shoulder 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.

Use in Children
No data or tests support that the REMEDY® Shoulder Spacer is safe to use in children. The REMEDY® Shoulder 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
Goodman & Gilman's *The Pharmacological Basis of Therapeutics* 12th Edition, March 2011, Chapter 54 (McDougall C. Chambers) 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® Shoulder Spacer. However trough concentrations exceeding 2 µg/ml for longer than 10 days have been associated with toxicity (systemic administration). The REMEDY® Shoulder 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, available on the website, for th proper use of the REMEDY® Shoulder Spacer is required for successful implantation of the device. Only surgeons who have studied the REMEDY® Shoulder 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 structurally and pharmacologically effects 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® Shoulder 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 shoulder. Always use the component size which shows the best fitting to ensure ideal performance.

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® Shoulder 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 shoulder prosthesis. Patients should be instructed to adjust their activities and be informed that postoperative care is essential.

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

The REMEDY® Shoulder Spacer is comprised of two components (head and a stem). It is important not to use the individual components alone within the anatomy.

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

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

The REMEDY® Modular Humeral Head must be torqued/screwed at least to the colored line indicated on the stem neck (see Figure 1).

MMA liquid is provided within the Humeral Head packaging to affix the head to the stem. Excessive vapor inhalation of the liquid component may cause drowsiness: prolonged exposure to vapors may irritate the respiratory system and eyes. Avoid monomer contact with the mucous membranes and skin (wear a second pair of surgical gloves to reduce reactions created by hypersensitivity). Susceptible patients have been observed to experience contact dermatitis. The liquid component should not come into contact with accessories made of rubber or elastomers. The liquid component is flammable and volatile and for this reason the operating theatre must be correctly ventilated. The liquid component and/or its vapors must never be directly exposed to naked flames or heated materials.

The REMEDY® Shoulder 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
It is important to maintain strictly aseptic surgical techniques. Correct sizing of the REMEDY® Shoulder 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® Shoulder 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® Shoulder Templates). REMEDY® Shoulder Trial devices are also available to ensure the implant has been correctly sized for the patient's anatomy.

Warning: the REMEDY® Shoulder Spacer must be proximally cemented with a gentamicin-loaded cement. The use of bone cement is compulsory to avoid rotation and to limit the risk of dislocation or spacer loosening.

Head Size Selection
To limit the risk of dislocation, the largest head size should be chosen according to the anatomy of the patient. The measurement can be determined with the use of the REMEDY® Shoulder Trial or REMEDY® Shoulder Templates provided. The glenoid may be reamed in relation to the quality of the residual bone thus allowing the use of a larger diameter head. This could help the removal of any existing infected tissue and may prevent possible dislocation in the future.

Stem Selection
The choice of the stem size depends on the dimensions of the humeral canal and on the stability achieved. The measurement can be determined with the use of REMEDY® Shoulder Trial or REMEDY® Shoulder Templates provided.

Offset Selection
Screwing/torquing the head onto the threaded connection of the stem provides the proper offset size to be selected. The goal is to achieve ideal soft tissue tensioning by following the patient's anatomy to reduce the risk of dislocation. *Note: the maximum offset possible is the one achieved once the colored thread is completely covered by the head.*

Application Instructions
The common routes of access to the shoulder may be utilized for the insertion of the REMEDY® Shoulder Spacer. 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® Shoulder Spacer. Excess cement or debris from the previous device must be removed to ensure a clear operative area.

Trial Use
REMEDY® Shoulder Trials are provided to help determine the appropriate size needed. The size to be implanted is the one that is nearest to the size of the removed implant. When the appropriate sizes of the stem and head device are determined and selected, screw the head component in a clockwise motion onto the threaded junction of the stem component. Place the stem completely within the diaphysis canal of the humerus. The correct position is the following:

- The lower protrusion of the stem collar shall rest on the proximal diaphysis cortex.
- The stem shall not be obstructed by additional devices within the diaphysis canal. Position the head keeping approximately 40° of retroversion. Check the correct offset by screwing in or out the head to discover the best fit. When the correct offset has been selected, remove the trial, and count the number of threads not included in the head.

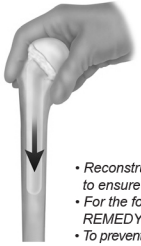
REMEDY® Shoulder Spacer Use
- Open the package of the selected REMEDY® Modular Humeral Head size
- Remove the monomer vial.
- Carefully, break the vial open and pour all the monomer into the screw opening of the humeral head.
- Seal the head with the "cover cap" and shake the head for 60 seconds.
- Remove the "cover cap" and dispose the excess MMA.


Cover Cap

- In a clockwise motion, screw the head onto the threaded portion of the stem till the reference thread chosen with the trial is reached. Make sure that the colored line is completely covered. Monomer provides fixation between the two components.

• Using a gentamicin-loaded acrylic cement, apply the cement to the proximal aspect of the stem.

Note:
• The offset space can be filled with gentamicin-loaded acrylic cement.
• Bone cement may also be applied once the stem is seated within the humeral canal.



• Place the stem within the humeral canal and check the correct positioning as done with the trials:
- The lower protrusion of the stem collar shall rest on the proximal diaphysis cortex.
- The stem shall not be obstructed by additional devices within the diaphysis canal.

Reduce the head into the scapular glenoid cavity maintaining 40° of retroversion.

• Reconstruct the muscle insertions if possible, especially the "cap" of the rotators and the subscapular to ensure greater stability for the implant.
• For the following three hours the patient must not move the limb to ensure correct fixation of the REMEDY® Modular Humeral Head.
• To prevent dislocation, the same measures utilized for a permanent shoulder replacement should be adopted.

Additional considerations include:
• instructions, techniques or guides for the spacer device.
• options for ideal head diameter and correct stem length.
• placement with appropriate joint tension of the soft tissues around the shoulder joint (offset adjustment).
• in cases at risk consider the use of a brace to assist the stability of the joint.
• proximal cementation (with gentamicin-loaded acrylic cement) of the stem.

MRI Safety Information
The REMEDY® Shoulder Spacer has not been evaluated for safety and compatibility in the MR environment. It has not been tested for heating, migration, or image artifact in the MR environment. The safety of REMEDY® Shoulder Spacer in the MR environment is unknown. Scanning a patient who has this device may result in patient injury.

Postoperative treatment
Possibility of passive and active, total or partial movements must be assessed on an individual basis in relation to anatomic humeral conditions, bone tropism and clinical conditions of the patient during the rehabilitation phase. The surgeon must warn every patient to avoid high risk behaviour activities, such as excessive mobility of the limb. The risk, due to excessive load or forced movements, that the spacer's structure inflict damage upon the host bone tissue or the teno-capsular-ligamentous structures must be avoided. The surgeon must warn the patient to avoid lifting with the operated limb. The patient must be advised to communicate any pain or discomfort as well as any other trauma suffered by the operated limb. The surgeon may prescribe a brace to assure stability of the joint while the REMEDY® Shoulder Spacer is implanted.

Explantation
The REMEDY® Shoulder 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.
• Brace must be used at all times while the device is implanted, if prescribed by the surgeon.

(Continued on page 8)

• The REMEDY® Shoulder Spacer must be removed after temporary implantation (not to exceed 180 days).
• Excessive loading/weight on the REMEDY® Shoulder Spacer must be averted (sports activity, obesity, falling, etc.).

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

How supplied
The REMEDY® Shoulder 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.

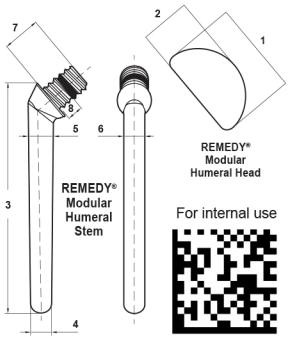
Information
For further product information, please contact Customer Service.

Symbols:

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

Additional symbols for REMEDY® Modular Head only:

STERILE — Sterile
STERILE A — Sterilized Using Aseptic Processing Techniques
Flammable Liquid



Component Description	1(mm)	2(mm)	3(mm)	4(mm)	5(mm)	6(mm)	7(mm)	8(mm)	Gentamicin Base (g)
REMEDY® Modular Humeral Head 40mm	40	25							0.5
REMEDY® Modular Humeral Head 45mm	45	25							0.5
REMEDY® Modular Humeral Head 50 mm	50	25							0.6
REMEDY® Modular Humeral Stem - Small			101	7	9.4	7.8	19	9	0.1
REMEDY® Modular Humeral Stem - Medium			116	10.5	12.6	10.5	19	9	0.3
REMEDY® Modular Humeral Stem - Large			131	14	15.8	14	19	9	0.5

OSTEOREMEDIES®
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6800 Poplar Avenue | Suite 120 | Memphis, TN 38138
901.453.3141 | info@OsteoRemedies.com | OsteoRemedies.com