InterSpace® Temporary Shoulder Spacer with Gentamicin

INDICATIONS FOR USE:

Interspace Shoulder is indicated for temporary use (max.180 days) as an adjunct to shoulder replacement (SR) in skeletally mature patients undergoing a two-stage procedure due to a septic process.

The head and stem are inserted into the glenoideal cavity and the humeral medullary canal, respectively, following removal of the existing implant and radical debridement. The device is intended for use in conjunction with systemic antimicrobial antibiotic therapy (standard treatment approach to an infection).

Interspace Shoulder 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.).

PRODUCT DESCRIPTION:

Spacer-S is composed of fully formed gentamicin/polymethylmethacrylate (PMMA) radiopaque bone cement coated onto a stainless steel reinforcing structure. The one piece design mimics a hemi-shoulder prosthesis. The design allows for limited joint mobility, depending on the specific clinical situation.

The outer coating of InterSpace (SPS0021) is made with bone cement containing 1.87% gentamicin base corresponding to 0.8 g expressed as absolute amount. The outer coating of InterSpace small (SPS0121) is made with bone cement containing 1.87% gentamicin base (corresponding to 0.4 g expressed as absolute amount).

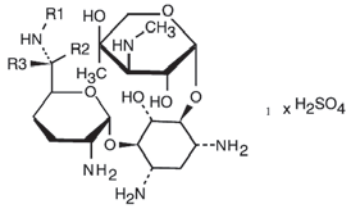
CONTRAINDICATIONS:

Use of InterSpace is contraindicated in the following situations:

- The patient's condition is such that a two-stage arthroplasty procedure is contraindicated due to decreased immune response or other relevant systemic clinical conditions.
- Lack of adequate bone structure precludes adequate support of the prosthesis in the proximal humerus and glenoid.
- The procedure is unjustified due to deficiencies in the patient's muscular, nervous or vascular systems.
- Poor bone quality (as in osteoporosis) could cause the prosthesis to migrate or to fracture host bone.
- Infection of the shoulder joint cannot be confirmed.
- The infected shoulder joint replacement devices cannot be removed.
- The infecting pathogens are resistant to gentamicin.
- The patient is sensitive (allergic) to gentamicin, aminoglycosides or PMMA bone cement.
- A systemic or secondary remote infection is suspected or confirmed.
- The patient does not have a shoulder joint replacement prosthesis and the infection is secondary to trauma, septic arthritis or other surgical procedures.
- The patient does not have sufficient bone stock to allow insertion and fixation of the prosthesis.
- The patient has neuromuscular disorders that do not allow control of the shoulder joint.
- The patient is unwilling or unable to use protected weight bearing mobility throughout the implantation period (brace).
- Myasthenia gravis.

MICROBIOLOGY:

Gentamicin sulphate is an aminoglycoside antibiotic derived from the actinomycete Micromonospora purpurea. The molecular weight is 449.55. The product contains no preservative or sodium bisulfite. Gentamicin sulphate is a complex of the gentamicins C1, C1a and C2, which illustrated below:



Gentamicin	Mol. Formula	R1	R2	R3
C1	$C_{21}H_{43}N_5O_7$	CH_3	CH_3	H
C1a	$C_{19}H_{39}N_5O_7$	H	H	H
C2	$C_{20}H_{41}N_5O_7$	H	CH_3	H

INFORMATION REGARDING 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 sensitive 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.

Most common susceptible pathogens

Gram positive bacteria

Staòhylococcus aureus; Streptococcus pyogenes; Streptococcus pneumoniae; Streptococcus 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

***In vitro* elution profile over 7 days**

	SPS0021	SPS0121
Day 1	24.8	25.5
Day 2	6.4	1.9
Day 3	8.0	2.2
Day 4-7	10.1	4.7
Total	49.3 mg	34.3 mg

**Lab data subject to SD (microbiological method)*

Testing bacteria B. subtilis. Variation range ± 20%. Data expressed in milligrams (mg)

Bibliography

Goodman & Gilman's The Pharmacological Basis of Therapeutics 12th Edition, March 2011, Chapter 54 (McDougall C, Chambers) - McGraw Hill, New York

PHARMACOLOGICAL WARNINGS:

In vitro elution studies (microbiological method) of all sizes of the InterSpace device showed that the amount of gentamicin released in the first 24 hours ranged from 24.8 mg to 25.5 mg. Elution studies indicate a gentamicin release rate of 34.3 to 49.3 mg over seven days (4.90 – 7.04 mg per day) which is well below the recommended adult dose of 3-5 mg/kg/day (or 1.0 -1.7 mg/Kg/8 hours) according to Goodman & Gilman's The Pharmacological Basis of Therapeutics 12th Edition, March 2011, Chapter 54 (McDougall C, Chambers) - McGraw Hill, New York. It is therefore unlikely that the amount of gentamicin absorbed locally from the InterSpace device will result in levels in the toxic range. Nonetheless trough concentrations which exceed 2µg/ml for longer than 10 days have been associated with toxicity (systemic administration). InterSpace should be used with caution (mainly in the first day of implantation of the spacer) in conjunction with other nephrotoxic or ototoxic drugs. The use of antibiotic loaded bone cement for fixation of the InterSpace device may increase the potential of toxic drug reactions. The InterSpace device should be used with caution in patients who are predisposed to or who have preexisting clinical conditions that would put them at risk for gentamicin toxicity (e.g. renal dysfunction, dehydration, 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 important in elderly subjects and in those receiving other nephrotoxic and/or ototoxic drugs.

POTENTIAL ADVERSE EVENTS:

The following serious and frequent adverse effects may be associated with use of the InterSpace device. Although some effects are not directly attributable to the device itself, the surgeon should be aware of these potential complications and be ready to treat the patient accordingly.

General Surgical Risks
- venous thrombosis
- transitory hypotension
- myocardical infarction
- pulmonary embolism
- arrhythmias
- sudden death

SR Surgery Risks
- damage to humerus or glenoid
- damage to blood vessels
- nerve damage, bone bed damage
- arthrofibrosis
- limb length discrepancy
- phlebitis, thrombophlebitis
- hematoma
- wound healing problems
- extensive blood loss

InterSpace Device Risks
- gentamicin toxicity: ototoxicity; nephrotoxicitys
- PMMA sensitivity
- recurrent infection
- device breakage
- device dislocation
- device loosening
- debris release
- foreign body reaction
- difficulty in removing the device

NOTE: Since the device may be fixed with antibiotic bone cement, the surgeon must be aware of its negative effects. Recurrences of infections, although rare, have been known to recur even with IV antibiotic use.

All aminoglycosides have the potential to produce reversible and irreversible vestibular, cochlear and renal toxicity. Adverse reactions to Gentamicin Sulphate are not expected at the low levels used within InterSpace. However the following adverse reactions have been associated with larger doses, typical of prescribed dosages of Gentamicin Sulphate for systemic parenteral administration.

High serum peaks of aminoglycoside caused by once-daily drug administration are well tolerated; the once-daily regimens are just as safe as or safer than multiple-dose regimens.

Neurotoxicity

- Manifested as both auditory and vestibular ototoxicity, including irreversible hearing loss
- Numbness
- Skin tingling
- Muscle twitching
- Convulsions

Neurotoxicity - Adverse effects on both the vestibular and auditory branches of the eighth nerve have been noted, especially in patients receiving high doses or prolonged therapy, in those given previous courses of therapy with an ototoxic drug, and those suffering from dehydration.

Symptoms include dizziness, vertigo, tinnitus, roaring the ears and hearing loss. Hearing loss is usually irreversible and is manifested initially by diminution of high-tone acuity. Gentamicin and tobramycin closely parallel each other in regard to ototoxic potential.

Nephrotoxicity

- Usually in patients with pre-existing renal damage
- Also in patients with normal renal function to whom aminoglycosides and administered for longer periods or in higher doses than recommended
- The symptoms of which may manifest after cessation of therapy

Nephrotoxicity - Renal function changes, as shown by rising BUN, NPN, and serum creatinine and by oliguria, cylindruria, and increased proteinuria, have been reported, especially in patients with a hystory of renal impairment who are treated for longer periods or with higher doses than those recommended. Adverse renal effects can occur in patients with initally normal renal function. Clinical studies and studies in experimental animals have been conducted to compare the nephrotoxic potential of gentamicin and tobramycin. In some of the clinical studies and in the animal studies, tobramycin caused nephrotoxicity significantly less frequently than gentamicin. In some other clinical studies, no significant difference in the incidence of nephrotoxicity between tobramycin and gentamicin was found. Neuromuscular blockage or respiratory paralysis, more commonly in patients with myasthenia gravis or Parkinson's Disease. In general aminoglycosides have little allergenic potential; both anaphylaxis and rash are unusual. Rare hypersensitivity reaction - including skin-rashes, eosinophilia, fever, etc. – have been reported. Other reported adverse events possibly related to gentamicin include: anemia/granulocytopenia, thrombocytopenia, fever, rash, exfoliative dermatitis, itching, urticaria, nausea, vomiting, diarrhea, headache, lethargy, mental confusion and disorientation. Laboratory adnormalities possibly related to gentamicin include increased serum transaminases including AST and ALT, increased serum LDH and bilirubin, decreased serum calcium, magnesium, sodium and potassium; and leukopenia, leukocytosis, and eosinophilia.

PATIENT PRECAUTIONS:

The physician must instruct the patient as follows:

- Protected weight bearing mobility must be used throughout the implantation period (e.g. brace).
- Any condition that tends to impose severe loading on the InterSpace device should be avoided (e.g. participation in active sports, unprotected weight bearing, likelihood of falls etc.). Report any pain, discomfort or trauma with the affected limb.
- The InterSpace product must be explanted after the temporary use.

Because the InterSpace device was designed for temporary implantation under protected load bearing conditions, the patient should be periodically evaluated with X–ray with respect to the condition of the interface fixation between bone and device, bone trophism and other relevant clinical conditions during the rehabilitation phase.

USE DURING PREGNANCY AND BREAST-FEEDING:

There are no tests that demonstrate the utilization safety of InterSpace during pregnancy, breast-feeding. Shoulder revision surgery should be avoided during the first three months of pregnancy. This product is indicated for applications in the remaining gestation period only when it is believed impossible to save the joint or preserve the patient's life through other forms of intervention.

USE IN CHILDREN:

There are no tests that demonstrate the InterSpace is safe to use in children. The device should only be used in skeletally mature individuals.

PRECAUTIONS FOR USE:

Familiarity with and attention to appropriate surgical techniques for shoulder arthroplasty revision surgery and familiarity with proper use of the InterSpace device is essential for successful use of the device. Only surgeons who have reviewed the surgical technique regarding InterSpace implantation and are aware of the limitations of its application should utilize the device.

The user must not modify the device in any way, including not adding other antibiotics as the effects pharmacologically and structurally cannot be predicted. The user must not allow damage to the device. Any alteration or damage to the component may reduce fatigue strength and may result in failure under load. The wear rate of prosthesis component contact surfaces is greatly accelerated if loose fragments of bone, bone cement, or other particulate debris become detached and act as an abrasive in the articular interfaces. The expected useful life of the InterSpace component may be compromised if the patient does not adequately limit the amount of activity and loads placed on the shoulder. It is recommended to always check before the operation if the device fits the anatomy of the patient. For doing so templates are available. It is essential that the patient use mobility assist devices (e.g. brace) during the implantation period.

Aggressive assembly methods are not required for proper implantation of the device. During the application do not subject the device to excessive forces (e.g. hammer strikes) that could cause damage. Altering the structural identity of the device can cause damages to the same (creation of cracks or fragments and risk of sterility loss leading to infection risks for the patient). Any damage to the device may affect the fatigue strength and lead to failure under load.

A fine needle aspiration from the joint site and antibiotic susceptibility testing should be performed prior to implantation of InterSpace. All patients should be instructed on the limitations of the prosthesis and the need for a subsequent surgery to implant a definitive prosthesis. Patients should be taught to govern their activities accordingly. Postoperative care is important. Implants must not be reused. Any implant, once used, should be discarded even though it may appear undamaged. Failure to adhere to these recommendations will result in increased probability of poor function, loosening, wear, fracture or premature failure. Do not use the InterSpace device in cases where the existing implant components cannot be completely explanted. Do not use the InterSpace implant in joints that contain osteosynthesis devices that could mechanically interfere with its function. Using InterSpace under conditions other than the indicated use is unlikely to provide benefit to the patient and increases the risk of the development of drug-resistant bacteria.

Warning: Do not re-sterilize and/or re-use the device. It is designed for single-use on a single patient. Re-sterilization should not be carried out since it can cause infection risks for the patient. Re-sterilization can also alter the morphology, the efficiency of the antibiotics and the mechanical features of the device, causing a malfunction of the same with serious risks for the patient's health. Re-using the device after its extraction must by all means be avoided since it can cause contamination and worsening of the patient's infection. During the extraction, the spacer can also be damaged or residues of cement can be left on the device.

UTILIZATION AND IMPLANTATION:

Warning: Before the InterSpace is implanted; it is necessary to verify the device fits the anatomy of the patient by using transparent radiograph overlay (Interspace template) or trial device (Interspace trial).If the InterSpace does not fit the patient, the surgeon must not implant the device.

Clinical data demonstrate the need to maintain strictly aseptic surgical technique. Avoid washing with aqueous solutions the spacer before or after implantation in order to maintain optimal levels of antibiotic release.

The surgeon shall become thoroughly familiar with the technique of implantation of the prostheses by: (1) appropriate reading of the literature, (2) training in the operative skills and techniques required for InterSpace shoulder arthroplasty revision surgery, and (3) reviewing information regarding use of instrumentation for sizing, implantation and explanation of the component.

Note: The device is compatible with magnetic resonance (MR), however the image of the shoulder distric in proximity of the device may be blurred.

In order to prevent dislocation, the same measures taken for a permanent total or hemi shoulder replacement are advised, plus other specifics such as:

1) proximal cementation (Cemex Genta) of the stem, if necessary, to avoid spacer rotation in cases of lysis or fragmentation of the proximal humeral bone;

2) insertion with appropriate joint tension of the soft tissues around the shoulder joint;

3) application, in cases at risk, of an orthopaedic abduction brace (possibly articulated) to assist mobility without dislocation; and

4) explantation of the spacer device (see below).

InterSpace can be applied using an anterior delto-pectoral approach or a trans-deltoid approach. After removal of the prosthesis and before inserting InterSpace, the host site must be irrigated with Ringer or physiological solution. In particular, any residual cement from the previous implant must be removed. Insert the stem of the spacer and position the head keeping approximately 40° of retroversion (as for metallic prostheses). In the event the stem is unstable, proximal cementation with Cemex Genta bone cement can be performed. Then reduce the head of the spacer in the scapular glenoid cavity. Reconstruct the muscle insertions if possible, especially the “cap” of the rotators and the subscapular to ensure greater stability for the implant.

Post-operative treatment

Possibility of passive and active, total or partial movements must be assessed on an individual basis in relation to anatomic humeral conditions, bone trophism 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-ligementous 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 InterSpace is implanted.

Explantation

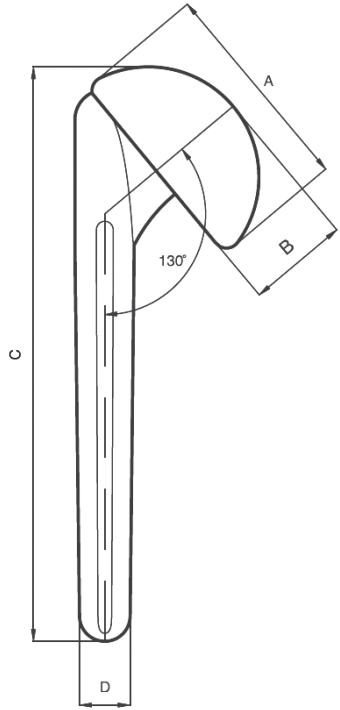
The InterSpace is not intended for use as a permanent prosthesis and must be removed within 180 days of implantation. The device was tested to be safely used for not more than 6 months. If this period is extended for too long this can lead to wearing, development of debris and eventually to breakage that can cause pain, inflammation and bone re-absorption. Osteotomes, mallets and other revision instruments may be used to aide in the explanation procedure. Care should be taken to assure that the wound site is thoroughly cleaned of all bone cement debris prior to implantation of a definitive prosthesis or performing an alternative surgical procedure (e.g. resection arthroplasty, fusion etc.). Failure to remove cement and/or bone debris may shorten the survival of the revision implant.

HOW SUPPLIED:

InterSpace implants are supplied sterile. Do not re-sterilize. Prior to use, all packages should be inspected for integrity. If a package is damaged, opened or contaminated in any way, it must not be used.

CAUTION:

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



(REF)	A (Ø mm)	B (mm)	C (mm)	D (mm)	Gentamicin base (g)
SPS0021	46	22	125	11	0.8
SPS0121	41	16	99	7	0.4

Symbols:

USE BY

STERILIZED USING ETHYLENE OXIDE

DO NOT RESTERILISE

BATCH NUMBER

CONTENTS STERILE UNLESS PACKAGE IS DAMAGED OR OPENED

CATALOGUE NUMBER

DO NOT RE-USE

CONSULT INTSRUCTIONS FOR USE

CAUTION

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