OsteoRemedies®
ADVANCED MEDICAL TECHNOLOGIES

SURGEON INFORMATION

INTERSPACE® STANDARD STEM & INTERSPACE® TAPERED WEDGE STEM

TEMPORARY HIP SPACER WITH GENTAMICIN

INDICATIONS FOR USE:

InterSpace is indicated for temporary use (maximum 180 days) as a total hip replacement (THR) in skeletally mature patients undergoing a two-stage procedure due to a septic process.

The device is inserted into the femoral medullary canal and acetabular cavity 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 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:

InterSpace 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-hip” prosthesis and includes a head, neck and distal region. *Note for Interspace Tapered Wedge Stem: the distal region (stem) has a rectangular profile.*

The design allows for motion of the leg in relation to the hip for basic mobility (sitting, standing, walking) under limited weight bearing conditions (e.g. crutches, walkers, canes). The outer coating of Interspace is made with bone cement containing 1.87% gentamicin base.

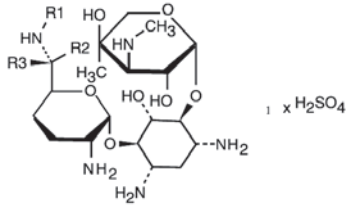
CONTRAINDICATIONS:

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 femur or acetabular region.
- 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 THR cannot be confirmed.
- The infected THR 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 THR 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 hip joint.
- The patient's weight, age or activity level would cause the surgeon to expect early failure of the system.
- The patient is unwilling or unable to use protected weight bearing mobility thoroughout the implantation period (e.g. crutches, canes, walkers etc).
- 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						
	SPC0022	**SPC0122**	**SPC0222**	**SPC0322**	**SPC0422**	**SPC0522**
Day 1	39.9	46.7	53.5	42.6	48.8	55.0
Day 2	4.7	5.5	6.4	5.3	6.2	7.0
Day 3	5.2	13.5	15.6	6.0	11.0	12.5
Day 4-7	12.8	17.0	19.6	14.8	23.5	26.6
Total	62.6 mg	82.7 mg	95.1 mg	68.7 mg	89.5 mg	101.1 mg

**In vitro* elution profile over 7 days						
	SPC0023	**SPC0123**	**SPC0223**	**SPC0323**	**SPC0423**	**SPC0523**
Day 1	33.9	39.6	45.3	34.5	39.5	44.5
Day 2	4.7	5.6	6.4	4.9	5.6	6.4
Day 3	5.4	6.3	7.3	5.6	6.4	7.3
Day 4-7	6.1	7.2	8.3	10.2	11.8	13.3
Total	50.1 mg	58.7 mg	67.3 mg	55.2 mg	63.3 mg	71.5 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 33.9 to 55.0 mg. Elution studies indicate a gentamicin release rate of 50.1 to 101.0 mg over seven days (7.2 – 14.4 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 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

THR Surgery Risks

- damage to femur or acetabulum
- 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
- difficulty in removing the device from its femoral attachments or acetabular bed
- foreign body reaction
- device loosening
- debris release
- dislocation of the device

ATTENTION: Since the device must 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. crutches, canes, walkers etc).
- 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 respect to thigh and acetabulum anatomic conditions, 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. Hip 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 hip 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 and modular interfaces. The expected useful life of the InterSpace component may be compromised in a very large or overweight individual and/or one who does not adequately protect the amount of activity and weight placed on the hip. It is recommended to always use the largest component size possible. It is essential that the patient use mobility assist devices (e.g. crutches, walker) during the implantation period.

During the implantation procedure care should be taken in placing the spacer to preserve the greater trochanter and other remaining bony tissue. 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 stikes) that could cause damage. 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. Post-operative 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. Do not allow the component to remain implanted for more than 180 days. 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. After removal of the InterSpace device, the wound site should be thoroughly irrigated to remove all bone cement debris prior to implantation of a definitive prosthesis or alternative surgical procedures (e.g. resection arthroplasty, fusion etc.). Failure to remove cement and/or bone debris may shorten the survival of the revision implant. 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. Resterilization 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, IMPLANTATION AND EXPLANTATION:

Clinical study data demonstrate the need to maintain strictly aseptic surgical techniques. Avoid washing with aqueous solutions the spacer before or after implantation in order to maintain optimal levels of antibiotic release. Selection of the proper size InterSpace component depends on the judgement of the surgeon with relationship to the requirements of the patient. 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 hip arthroplasty revision surgery, and (3) reviewing information regarding use of instrumentation for sizing and implantation and explantation of the component. For the selection of the size transparent radiograph overlays and Interspace Trial devices are available.

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

In order to prevent dislocation, the same measures taken for a permanent total hip replacement (THR) are advised, plus other specifics such as:

1) Choice of the correct length of the stem, sufficiently long, and of proper head diameter (see below);
2) Proximal cementation (acrylic cement) of the stem (neck region), if necessary, to avoid spacer rotation in case of lysis or fragmentation of the proximal femoral bone;
3) Insertion with appropriate joint tension of the soft tissues around the hip joint;
4) Obtaining adequate head support in the case of severe acetabular bone loss;
5) Application, in cases at risk, of an orthopaedic abduction brace (possibly articulated) to assist flexion without dislocation.

Head size choice

The largest head size which articulates within the acetabulum should be chosen in order to avoid possible dislocation. The basis for measurement is the removed acetabular cup. A reaming of the remaining acetabular dome, if the residual bone quality permits, may allow the application of a larger head diameter. This may be useful both for the removal of the infected tissue, and for deepening of the spacer head that may help prevent possible dislocation.

Stem length choice

A long-stem is advised when distal anchorage is required. This is important in the absence of proximal support, in the presence of large metaphyseal defects or after a trans-femoral approach for implant removal. *Note for Interspace Tapered Wedge Stem: Interspace Tapered Wedge Stem must be proximally cemented. Cementation has to be performed with an antibiotic-loaded cement.*

Post-operative treatment

As a general rule, post-operative treatment is superimposable with a primary hip prosthesis, with the difference that the weight-bearing can be only partial (use of crutches). Partial weight-bearing must be assessed on an individual basis in relation to the anatomic conditions of the femur and acetabulum, bone trophism and the clinical conditions of the patient during rehabilitation stages. In particular, one should avoid the risk that excessive weightbearing or forced mobilisation cause the structure of the spacer to damage the biological structure. If the surgeon deems it necessary, in cases at risk of dislocation an orthopaedic abduction brace (possibly articulated) to assist flexion may be prescribed.

Explantation

The InterSpace is not intended for use as a permanent prosthesis and must be removed within 180 days of implantation. Osteotomes, mallets and other revision instruments may be used to aid in the explantation 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:

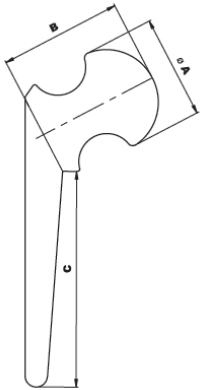
InterSpace implants are supplied sterile. Do not re-sterilize. Prior to use, all packages should be inspected for integrity. If a package is damaged, opened or contaminated in any way, it must not be used.

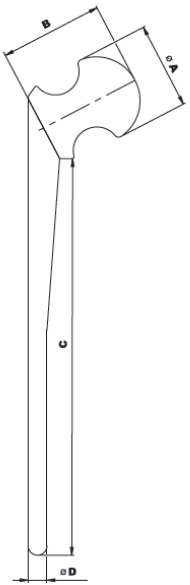
CAUTION:

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

INTERSPACE®

STANDARD PROFILE

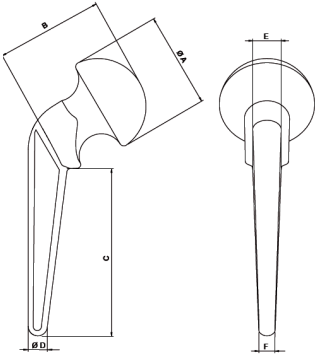


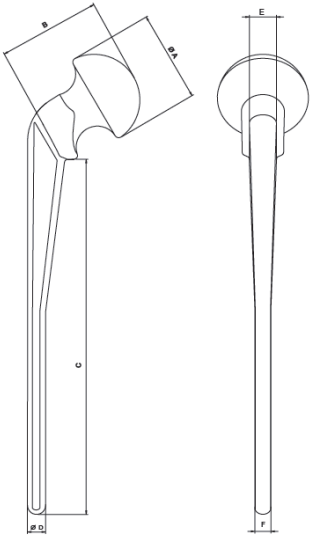


REF	A (mm)	B (mm)	C (mm)	D (mm)	Gentamicin Base
SPC0022	46	54,5	96	–	1.1 g
SPC0122	54	60	94	–	1.9 g
SPC0222	60	73	98	–	3.0 g
SPC0322	46	54.5	211	10	1.3 g
SPC0422	54	60	209	10,5	2.1 g
SPC0522	60	73	211	11	3.2 g

INTERSPACE®

TAPERED WEDGE STEM PROFILE





REF	A (mm)	B (mm)	C (mm)	D (mm)	E (mm)	F (mm)	Gentamicin Base
SPC0023	46	54.6	96	10	11	9	1.1 g
SPC0123	54	60	94.3	10.5	16	9	1.6 g
SPC0223	60	73	95.8	11	16	9	2.6 g
SPC0323	46	54.6	211	10	11	9	1.2 g
SPC0423	54	60	209.2	10.5	16	9	1.8 g
SPC0523	60	73	211	11	16	9	2.8 g

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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