INTERSPACE® KNEE ATS

TEMPORARY AUGMENTED TIBIAL STEM SPACER WITH GENTAMICIN

INDICATIONS FOR USE:

InterSpace Knee ATS is indicated for temporary use (maximum 180 days) as an adjunct to total knee replacement (TKR) in skeletally mature patients undergoing a two-stage procedure due to a septic process, and where a large tibial defect is present. InterSpace Knee ATS is applied on the tibial plate following removal of the existing implant and radical debridement. The device must be combined with the tibial component of InterSpace Knee. The device is intended for use in conjunction with systemic antimicrobial antibiotic therapy (standard treatment approach to an infection).

InterSpace Knee ATS 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 material (gentamicin/ polymethylmethacrylate), the Interspace Knee ATS is only indicated for patients who will consistently use traditional mobility assist devices (e.g. crutches, walkers, canes) throughout the implantation period.

PRODUCT DESCRIPTION:

Interspace Knee ATS is a one-piece tibial augment made of fully formed polymethyl-methacrylate (PMMA) radiopaque bone cement containing 1.87% gentamicin base. This component is available in different sizes and must be coupled, using antibiotic loaded bone cement, such as Cemex Genta, with the tibial component of the following Interspace Knee:

InterSpace Knee ATS	Combination with InterSpace® Knee
InterSpace Knee ATS 60/07 (ref. SPK0422)	InterSpace Knee S (ref. SPK0022) or InterSpace Knee M (ref. SPK0122)
InterSpace Knee ATS 60/12 (ref. SPK0522)	
InterSpace Knee ATS 80/07 (ref. SPK0622)	InterSpace Knee L (ref. SPK0222) or InterSpace Knee XL (ref. SPK0322)
InterSpace Knee ATS 80/12 (ref. SPK0722)	

Interspace Knee ATS combined with InterSpace Knee mimics an ultra-congruent condylar knee prosthesis. The design allows for motion of the leg for basic mobility (sitting, standing, walking) under limited weight bearing conditions (e.g. crutches, walkers, canes).

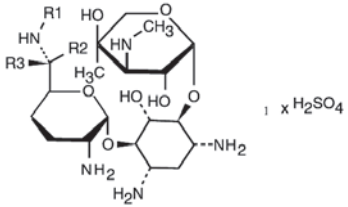
CONTRAINDICATIONS:

Use of Interspace Knee ATS 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.
- Bone loss precluding adequate support of the prosthesis.
- Lack of adequate competence (anatomical and functional) of peripheral ligamentous apparatus and extensor mechanism.
- 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 TKR cannot be confirmed.
- The infected TKR 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 TKR 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 knee 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 throughout the implantation period (e.g. crutches, canes, walkers etc).
- Myasthenia gravis

MICROBIOLOGY:

Gentamicin sulphate is an aminoglycoside antibiotic derived from the actinomycete Micromonospora purpurea. Gentamicin is a complex of the gentamicins C1, C1a, C2 C2a and C2b as shown. The molecular weight is 449.55. The compound is supplied as sulphate.



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
C2a	$C_{20}H_{41}N_5O_7$	H	H	CH_3
C2b	$C_{20}H_{41}N_5O_7$	CH_3	H	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 e 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. In vitro it is bactericidal against Gram-positive and Gram-negative bacteria.

Gentamicin is active against sensitive strains of enterococci and streptococci at concentrations which can be achieved clinically only when combined with a penicillin or vancomycin. 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	Gram Negative Bacteria
Staphylococcus aureus *Streptococcus pyogenes* *Streptococcus pneumoniae* *Streptococcus faecalis* *Listeria monocytogenes*	*Citrobacter* *Enterobacter* *Escherichia coli* *Klebsiella spp.* *Proteus mirabilis* *Proteus vulgaris* *Morganella morganii* *Providencia spp.* *Salmonella spp.* *Serratia* *Shigella spp.* *Pseudomonas aeruginosa*
**Kucers A, Bennett N. The use of antibiotics 4th Ed. 1987, Butterworth-Heinemann Ltd*	

Bibliography

- Goodman & Gilman's The Pharmacological Basis of Therapeutics - 2011, XII Ed., Chapter 54 (Henry F. Chambers); McGraw Hill, New York.
- Kucers A, Bennett N. The use of antibiotics - 4th Ed. 1987, Butterworth-Heinemann Ltd (*)

PHARMACOLOGICAL WARNINGS:

In vitro elution studies (microbiological method) has shown that the amount of gentamicin released never exceeds the recommended systemic adult dose for gentamicin (5-7 mg/kg/day) according to the Goodman and Gilman's recommendations (adults with normal renal function). It is therefore unlikely that the amount of gentamicin released from the device and absorbed locally will result in serum levels in the toxic range.

Nonetheless trough concentrations which exceed 2µg/ml for longer than 10 days have been associated with toxicity (systemic administration). The device 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 device may increase the potential of toxic drug reactions.

The device should be used with caution in patients who are predisposed to or who have pre-existing 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 the use of InterSpace Knee ATS combined with InterSpace Knee. 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

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

InterSpace Knee ATS Risks
- gentamicin toxicity: ototoxicity; nephrotoxicity
- PMMA sensitivity
- recurrent infection
- device breakage
- device dislocation
- device loosening
- debris release
- foreign body reaction
- difficulty in removing 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 are 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 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 Knee ATS device should be avoided (e.g. obesity, participation in active sports, unprotected weight bearing, likelihood of falls etc.).
- Report any pain, discomfort or trauma with the affected limb.
- The InterSpace Knee ATS must be explanted after the temporary use.

Because the InterSpace Knee ATS 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 Knee ATS during pregnancy, breast-feeding. Knee 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 Knee ATS is safe to use in children. The device should only be used in skeletally mature individuals.

PRECAUTIONS FOR USE:

Familiarity with and attention to InterSpace Knee surgical technique and familiarity with proper use of the InterSpace Knee ATS and InterSpace Knee is essential for successful use of the device. Only surgeons who have read the surgical technique regarding InterSpace Knee 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 Knee ATS 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 knee. It is recommended to always implant the largest component size possible. It is essential that the patient use mobility assist devices (e.g. crutches, walker) 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. 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 Knee ATS. 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 Knee ATS in cases where the existing implant components cannot be completely explanted. Do not use the InterSpace Knee ATS 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 Knee ATS 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 Knee ATS 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, IMPLANTATION AND EXPLANTATION:

It is important to maintain strictly aseptic surgical techniques. Avoid washing with aqueous solutions the spacer before or after implantation to maintain optimal levels of antibiotic release.

Selection of the proper size InterSpace Knee ATS 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) reading appropriate literature, (2) training in the operative skills and techniques required for InterSpace Knee arthroplasty revision surgery, and (3) reviewing information regarding use of instrumentation for sizing, implantation and explantation of the component.

For the implant size selection, transparent radiograph overlays and InterSpace Knee ATS Trial devices are available.

Caution: the thickness generated by the cement used for the fixation is not reflected in these templates.

To prevent dislocation, the same measures taken for a permanent total knee replacement (TKR) are advised, plus other specifics such as:

1) Choosing the correct size (see below InterSpace Knee ATS Size Choice);

2) Proper cement fixation (Cemex Genta) of the components;

3) Insertion with appropriate joint tension of the soft tissues around the knee joint;

4) Application of an orthopaedic abduction brace, possibly articulated, to assist with flexion for cases with greater risk of dislocation.

INTERSPACE KNEE ATS SIZE CHOICE:

The most suitable size is selected based on:

a) Dimensions of the removed implant;

b) The type of bone defect.

c) Ligamentous apparatus state;

d) Flexion and extension gaps.

The size to be implanted is that which:

- Is nearest to the size of the removed implant; and
- Achieves the best compromise between stability and joint mobility during the operation. It is important to achieve stable full extension and 90° flexion.

InterSpace Knee ATS Templates (pre-operative planning) and Trials (intra-operative planning) are available to choose the size of the implant.

INTERSPACE KNEE ATS TRIAL PLACEMENT:

Position the InterSpace Knee ATS Trial combined with InterSpace Knee Trial into the joint space and reduce the knee. The knee should not be too tight during trialing as it will tighten further upon cement fixation of the femoral component. Tightness may be relieved through downsizing and/or recontouring the femoral bone to achieve a satisfactory fit.

Caution: InterSpace Knee ATS Trials must not be implanted.

INTERSPACE KNEE ATS IMPLANTATION:

Thoroughly irrigate the joint with pulsatile lavage prior to implanting the components. Take time to ensure the bone is dried and use clean, dry gloves for handling and implementing the InterSpace Knee ATS.

Place the femoral component of the InterSpace Knee following the related Surgical Technique.

Connect InterSpace Knee ATS to the tibial component of InterSpace Knee applying a layer of highly viscous, very thick (doughy) Cemex Genta bone cement between the two components.

Apply a layer of bone cement to the non-articulating surface of combined tibial and ATS components as well as the proximal surface of the tibia. Then, manually position the combined components on the proximal tibia, taking care to remove all excess of bone cement.

Caution: Make sure that the entire contact surfaces of the components are cemented to create continuity between them. Missing or insufficient cement may weaken the structure of the device.

Reduce the knee, move into extension and flex-extend the knee several times, all prior to the final setting of the cement. This allows the femoral component to "self-center" the tibial component, ensuring proper tracking of the InterSpace Knee. Final curing of the bone cement should be accomplished with the knee in extension.

Final reduction of the knee

Care must be taken to ensure that no unpolymerized bone cement remains on the articulating surfaces that could fuse the joint and/or accelerate the wear process.

Reduce the knee and close in standard fashion. The knee must be stable, not too tight, and have a joint extension ranging from 0 to 90 degrees.

Note: Care should be taken to keep the wound dry once the final spacer implant has been placed. Any attempt to wipe or lavage the joint can result in a loss of antibiotic at the surface of the implant.

Post-operative treatment

As a general rule, post-operative treatment is superimposable with a primary knee 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 tibia, bone trophism and the clinical conditions of the patient during rehabilitation stages.

In particular, excessive weight-bearing and forced mobilization should be avoided to minimize the risk of InterSpace damaging the biological structure.

Temporary use of an articulated post-operative orthosis may be prescribed if the surgeon deems it necessary on the basis of the stability achieved and the condition of the extensor apparatus.

Explantation

The InterSpace Knee ATS device 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 aide 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.

DISPOSAL

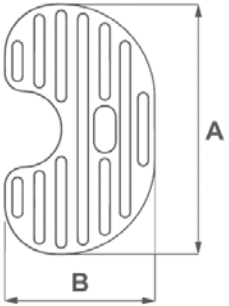
Disposal of the device should be in accordance with local waste regulations.

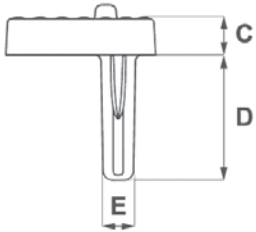
HOW SUPPLIED:

InterSpace Knee ATS is 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 (mm)	B (mm)	C (mm)	D (mm)	E (mm)	Gentamicin Base (g)
SPK0422	60	36	7	32	11	0.3
SPK0522	60	36	12	32	11	0.5
SPK0622	80	48	7	40	11	0.5
SPK0722	80	48	12	40	11	0.8

InterSpace Knee ATS	Gentamicin Base (g)	Combination with Interspace Knee	Gentamicin Base (g)	Total Gentamicin Base (g)
InterSpace Knee ATS 60/07 (ref. SPK0422)	0.3	InterSpace Knee S (ref. SPK0022)	0.9	1.2
		InterSpace Knee M (ref. SPK0122)	1.3	1.6
InterSpace Knee ATS 60/12 (ref. SPK0522)	0.5	InterSpace Knee S (ref. SPK0022)	0.9	1.4
		InterSpace Knee M (ref. SPK0122)	1.3	1.8
InterSpace Knee ATS 80/07 (ref. SPK0622)	0.5	InterSpace Knee L (ref. SPK0222)	1.8	2.3
		InterSpace Knee XL (ref. SPK0322)	2.7	3.2
InterSpace Knee ATS 80/12 (ref. SPK0722)	0.8	InterSpace Knee L (ref. SPK0222)	1.8	2.6
		InterSpace Knee XL (ref. SPK0322)	2.7	3.5

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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