
Name of Medicine

SMARTSET GMV ENDURANCE GENTAMICIN BONE CEMENT

Antibiotic Bone Cement containing Gentamicin Sulphate 2.9% w/w, equivalent to 1.7% w/w Gentamicin base in the prepared bone cement.

Presentation

SmartSet GMV Endurance Gentamicin Bone Cement is supplied as a two-component presentation consisting of bone cement powder, containing Gentamicin Sulphate, and bone cement liquid. These two components are mixed together before use to form the prepared bone cement. SmartSet GMV Endurance Gentamicin Bone Cement is available in 20 g or 40 g unit packs sizes. Each unit pack consists of 20 g or 40 g bone cement powder in a sterile bag and bone cement liquid in a sterile ampoule. (See PACKAGE QUANTITIES and FURTHER INFORMATION for full product descriptions.)

Uses

Actions

SmartSet GMV Endurance Gentamicin Bone Cement is a self-curing, radiopaque, polymethyl methacrylate based cements, containing antibiotic, used for securing a metal or polymeric prosthesis to living bone in arthroplasty procedures. The bone cement has no intrinsic adhesive properties, but relies instead on close mechanical interlock between the irregular bone surface and the prosthesis.

SmartSet GMV Endurance Gentamicin Bone Cement is a medium viscosity cement that is primarily intended for syringe application. If SmartSet GMV Endurance Gentamicin is applied digitally, the surgeon must use their clinical judgement to decide when the cement is of a suitable viscosity to allow the surgical procedure to continue.

The powder component is a white, finely divided powder, composed of a polymethyl methacrylate based polymer. The powder contains gentamicin sulphate for an ancillary, local antibiotic effect. Benzoyl peroxide is present in the powder component to initiate cement polymerisation when the powder and liquid components are mixed. The powder component also contains the radiopaque agent barium sulphate.

Gentamicin is a well-established potent aminoglycoside broad-spectrum antibiotic which is especially effective against infections caused by gram-negative bacteria. It is also stable to the heat generated during the cement setting process and to the gamma irradiation used to sterilise the bone

cement powder. Gentamicin incorporated into the bone cement is eluted rapidly from the cured cement into the body fluids at the operative site. Gentamicin is an aminoglycoside antibiotic derived from *Micromonospora purpurea*. It is commercially available as a pharmacopoeial material (BP, Ph.Eur), which is comprised of a complex mixture of the sulphates of Gentamicin C₁, Gentamicin C_{1A}, Gentamicin C₂ and, to a lesser extent, Gentamicin C_{2A}. The Gentamicins are characterised by 4,6-substitution on a central 2-deoxystreptamine ring with cyclic amino-sugars attached by glycosidic linkages; they are broad-spectrum, basic, heat stable, water soluble antibiotics which may be sterilised by gamma irradiation.

The Gentamicin complex is bactericidal and is thought to interfere with bacterial protein synthesis by binding irreversibly to the 30S subunit of the bacterial ribosome. It is effective against many strains of Gram-negative bacteria including species of *Escherichia*, *Enterobacter*, *Klebsiella*, *Salmonella*, *Serratia*, *Shigella*, *Proteus* and *Pseudomonas aeruginosa*. Although less active against Gram-positive bacteria, *Staphylococcus aureus* is highly sensitive; *Bacillus*, *Clostridium* and *Corynebacterium* species and *Listeria monocytogenes* may also be susceptible. Gentamicin is also active against some strains of Mycobacteria, and Mycoplasmas have been reported to be sensitive; fungi are resistant.

Pharmacokinetics

The antibiotic is eluted from the cured cements into the body fluids. The mechanism by which Gentamicin is released from bone cements is uncertain. The antibiotics may diffuse through the matrix or through pores in the cement, but essentially is only released from the surface layers. *In-vivo* and *in-vitro* studies show that the bulk of the Gentamicin release occurs within the first 72 hours.

Gentamicin is excreted by glomerular filtration, almost entirely as unchanged drug. The only metabolic reaction in humans is conjugation and gentamicin has no pharmacologically active metabolites. A small amount is excreted in the bile and there is no evidence of enterohepatic circulation. Gentamicin persists in tissues for long periods and undergoes reabsorption from the lumen of the proximal tubules. Concentrations in the renal cortical tissue sometimes reach levels 100 times higher than in the serum. Serum protein binding is estimated at 25% or less.

Indications

SmartSet GMV Endurance Gentamicin Bone Cement is indicated for the fixation of prostheses to living bone in arthroplasty procedures of joints in which infection by Gentamicin sensitive organisms is a potential risk. The cement is indicated for use in children only in the case of limb preservation where no other procedure is likely to give a good chance of successful treatment.

The cement should be used with an appropriate prosthesis.

Dosage and Administration

SmartSet GMV Endurance Gentamicin Bone Cement is packed in two sizes (see PRESENTATION). A standard dose of bone cement is prepared by mixing the entire liquid contents of the ampoule with the entire contents of the powder bag. The amount of mixed cement required for clinical use is determined by the surgeon in each individual case. The surgeon applies the cement digitally or via syringe and inserts the prosthesis when the cement is in the doughy state. The cement dough polymerises in situ and secures the prosthesis in place. The cement is for single use and once implanted remains in-situ permanently, unless revision surgery is deemed necessary. The major phase of Gentamicin release occurs during the first 72 hours after implantation.

Information for Use

(see also WARNINGS AND PRECAUTIONS)

Preparation

The following section applies only to the use of bone cements in total joint replacement techniques.

The following statements should be read carefully prior to the use of SmartSet GMV Endurance Gentamicin Bone Cement.

1. Bone cements are heat sensitive. Any increase or decrease in temperature (either ambient, and/or of the cement components and mixing equipment) from the recommended temperature of 73°F (23°C) will affect the handling characteristics and setting time of the cement. **Note: Manual handling and body temperature will reduce the final setting time.**
2. Variations in humidity will affect the cement handling characteristics and setting time.
3. The handling characteristics and setting time may vary if the cement components or mixing equipment have not been fully equilibrated to 73°F (23°C) before use. It is recommended that the unopened product is stored at 73°F (23°C) for a minimum of 24 hours before use.
4. As with all bone cements, variations in the expected setting time over the cement's shelf life can occur. This variation in setting time can be reduced to a minimum providing the cement is stored under the recommended conditions throughout its shelf life.
5. Vacuum mixing of cement can noticeably accelerate the setting time of the product. The surgeon should read the manufacturer's instructions and be familiar with the mixing system together with the cement prior to use.

Cement Preparation

The protective outer foil pouch, the outer peelable pouch of the powder component and the blister pack enclosing the ampoule of liquid component, should be opened by a circulating nurse. The inner bag (or pouch) containing

the powder component and the sterile ampoule containing the liquid component are aseptically transferred into the sterile operative area. The sterile bag (or pouch) containing the powder component is opened with sterile scissors and the entire contents are emptied into a suitable clean, dry, sterile mixing vessel made from an inert material (such as glass, ceramic, stainless steel, or non-reactive plastics). The sterile ampoule containing the liquid component is opened and the entire contents are emptied evenly onto the powder in the mixing vessel.

A standard dose of bone cement is prepared by mixing the entire liquid contents of the ampoule with the entire contents of the powder bag. The amount of mixed cement required for clinical use is determined by the surgeon in each individual case.

Mixing and Digital Application

SmartSet GMV Endurance Gentamicin Bone Cement can be applied digitally, in which case the surgeon must use their clinical judgement to decide when the cement is of a suitable viscosity to allow the surgical procedure to continue.

Prior to cement application, it is recommended that a cement restrictor is always used during cementation of the femur and that this is introduced at the required depth.

The cement is mixed thoroughly but carefully to minimise the entrapment of air. Once a dough is formed the surgeon should wait until the cement no longer adheres to the glove. The cement can then be taken into gloved hands and kneaded thoroughly. It is vital that premature insertion of cement is avoided as this may lead to a drop in the patient's blood pressure. To avoid this, the appearance of the cement should be observed to ensure the surface has become dull as opposed to shiny. Also cement should not adhere excessively to the surgeon's gloves. Note, this stage will occur at different times for different cement types. The time of cement application and prosthesis insertion is at the discretion of the surgeon and will depend upon the surgical procedure used.

Implant insertion should be carried out at a time appropriate for the bone/joint and prosthesis design concerned. In general, implant insertion should be delayed until the cement has developed a sufficient degree of viscosity to resist excessive displacement by the implant. However, implant insertion should not be delayed such that there is a risk that the procedure cannot be completed due to cement hardening.

Following introduction the implant must be firmly held in position to avoid movement and pressurisation must be maintained until the cement finally hardens. Excess bone cement must be removed before the cement has completely hardened.

Syringe Application

SmartSet GMV Endurance Gentamicin may be applied using a suitable cement gun and syringe.

The bone cement is prepared and mixed as described previously by adding all of the liquid component to all the powder component. The cement is then transferred into a suitable cement gun cartridge. The surgeon should use their experience to judge when the cement has reached an appropriate viscosity to be extruded. This will not occur until after the cement has formed a dough. A small amount of cement should be extruded from the syringe and visually assessed to ensure that the surface of the cement appears dull and excessive flow under gravity has ceased. Note, this stage will occur at different times for different cement types.

Prior to extrusion, it is recommended that a cement restrictor be inserted, at the required depth, into the prepared bone cavity. Introduction of bone cement into the prepared cavity should be carried out in a retrograde fashion. Once the cavity is filled it is strongly advised that adequate pressurisation is applied and maintained up to the point of hardening. Implant insertion should be carried out at a time appropriate for the bone/joint and prosthesis design concerned. In general, implant insertion should be delayed until the cement has developed a sufficient degree of viscosity to resist excessive displacement by the implant. However, implant insertion should not be delayed such that there is a risk that the procedure cannot be completed due to cement hardening.

Following introduction the implant must be firmly held in position to avoid movement and pressurisation must be maintained until the cement finally hardens. Excess bone cement must be removed before the cement has completely hardened.

For both digital and syringe application the handling characteristics and setting times are affected by ambient temperature. Please refer to the end of the instruction leaflet for guidance charts (Note: the usage charts were generated under controlled laboratory conditions). The charts provide information that is important to the successful outcome of the surgical procedure if the bone cement is to be used at a temperature other than that recommended 73°F (23°C)).

Limits of Usefulness

- Store below 77°F (25°C) and protect from light.
- Store at the recommended mixing temperature of 73°F (23°C) for a minimum of 24 hours before use.
- The setting time of the cement can be reduced if a vacuum mixing system is used.
- Sterility is only guaranteed if the packaging is unopened or undamaged.

- SmartSet GMV Endurance Gentamicin Bone Cement is for single use only, do not reuse. Resterilisation of any of the components must not be attempted.

Contraindications

The use of SmartSet GMV Endurance Gentamicin Bone Cement is contraindicated in the presence of the condition Myasthenia Gravis.

The use of SmartSet GMV Endurance Gentamicin Bone Cement is contraindicated in patients with hypersensitivity to gentamicin or to any other of the cement components.

Warnings and Precautions

Warnings

Follow carefully the supplied instructions for handling and mixing SmartSet GMV Endurance Gentamicin Bone Cement.

Patients should be carefully monitored for any change in blood pressure during and immediately following the application of bone cement. Adverse patient reactions affecting the cardiovascular system have been associated with the use of bone cements, these include: hypotension, hypoxemia, cardiac arrhythmia, bronchospasm, cardiac arrest, myocardial infarction, pulmonary embolism, cerebrovascular accident and possible death. Hypotensive reactions have occurred between 10 and 165 seconds following application of bone cement; they have lasted from 30 seconds to 5 or more minutes. Some have progressed to cardiac arrest. In addition, the over-pressurisation of the bone cement should be avoided during the insertion of the bone cement and the implant in order to minimise the occurrence of pulmonary embolism. The preparation of the bone marrow cavity results in marrow contents entering the blood stream. Prior to the application of bone cement to the bone, the cavity should be thoroughly cleaned by brushing and washing (lavage) to remove fat, marrow and other debris. The cavity should be kept as dry as possible to prevent blood and debris becoming mixed with the cement. Thorough cleaning of the bone reduces the risk of marrow content being forced into the vascular system during the insertion of bone cement and subsequent pressurisation. The expulsion of bone marrow has been associated with the occurrence of pulmonary embolisms, and this risk has been found to be increased in patients with highly osteoporotic bone and patients diagnosed with femoral neck fracture. Reaming of the marrow cavity can have similar effects on mean arterial pressure as introduction of the bone cement. Marrow cavities should be vented when the cement is introduced digitally.

The premature insertion of bone cement may lead to a drop in blood pressure, which has been linked to the availability of methyl methacrylate at the surface of the product, although this has not been proven. This drop in blood

pressure, on top of hypotension induced either accidentally or intentionally, can lead to cardiac arrhythmias or to an ischemic myocardium. To reduce this risk the surgeon should avoid early insertion of the cement and it is recommended that the mixing and preparation instructions are followed closely. As a general guide, prior to insertion the cement surface should appear dull and should not stick to the surgeon's gloves. The hypotensive effects of methyl methacrylate are potentiated if the patient is suffering from hypovolemia.

The surgeon should, by specific training and experience, be thoroughly familiar with the properties, handling characteristics and application of the antibiotic bone cements. Because the handling and curing characteristics of bone cements vary with temperature and mixing technique, they are best determined by the surgeon's actual experience.

Strict adherence to good surgical principles and techniques is essential. Deep wound infection is a serious post-operative complication and may require total removal of the embedded cement. Deep wound infection may be latent and not manifest itself for several years post-operatively.

Consideration should be given to the use of antibiotic bone cement in patients diagnosed with femoral neck fracture, as some published literature has indicated there is a potential for increased mortality compared with uncemented techniques.

As the liquid monomer is highly volatile and flammable, the operating room should be adequately ventilated to eliminate as much monomer vapour as possible. Ignition of monomer fumes caused by use of electrocautery devices at surgical sites near freshly implanted bone cements has been reported. Store the sealed outer pack below 77°F (25°C) and protect it from light to prevent premature polymerisation of the liquid monomer component. Always check the condition of the liquid monomer before performing the procedure. Do not use the liquid monomer if it shows any sign of thickening or premature polymerisation. Do not use the product after the expiration date.

Caution should be exercised during the mixing of the two components to prevent excessive exposure to the concentrated vapours of the monomer, which may produce irritation of the respiratory tract, eyes, and possibly the liver. If the liquid component comes into contact with the eyes, wash with copious amounts of water. Concentrated vapours of the liquid component may have an adverse reaction with contact lenses. Personnel wearing contact lenses should be informed and limit their exposure. Guidance from contact lens manufacturers regarding exposure to irritating and noxious vapours should always be followed.

Methyl methacrylate has been demonstrated to cause hypersensitivity in susceptible persons, which may result in an anaphylactic response. Inadequate fixation or unanticipated post-operative events may affect the cement-bone interface and lead to micromotion of the cement against bone surfaces, which the cement is in contact with. A fibrous tissue layer may

develop between the cement and the bone. Long term follow-up is advised for all patients on a regular scheduled basis.

The completion of cement polymerisation occurs in the patient and is an exothermic reaction with considerable liberation of heat. The long term effects of the heat produced *in situ* have not yet been established.

The safety and effectiveness of SmartSet GMV Endurance Gentamicin Bone Cement in pregnant women or in children has not yet been established. SmartSet GMV Endurance Gentamicin Bone Cement should not be used during the first third of pregnancy, and during the rest of the pregnancy period should only be used in life-threatening illnesses. SmartSet GMV Endurance Gentamicin Bone Cement should only be used in children for limb preservation where no other procedure is likely to give a good chance of successful treatment.

Precautions

The use of antibiotic bone cement requires collaboration and consultation between the surgeon and the anaesthetist. The anaesthetist should be told during the operation when the bone cement is implanted.

Contact of monomer with the skin or mucous membranes should be avoided. The liquid component of bone cements has caused contact dermatitis in those handling and mixing them. Strict adherence to the instructions for mixing the powder and liquid components may reduce the incidence of this complication. The liquid component of bone cement is a powerful lipid solvent. This liquid component should not be allowed to come into contact with surgical gloves. Wearing of a second pair of surgical gloves and strict adherence to the mixing instructions may diminish the possibility of hypersensitivity reactions. The setting time of the cement can be reduced if a vacuum mixing system is used. The surgeon should read the manufacturer's instructions and be familiar with the mixing system together with the cement prior to use. Upon application of the bone cement it is important to maintain the positioning of the prosthetic component until the completion of the polymerisation process. This must be done in order to maintain proper fixation. It is recognised that for some applications, for example femoral head resurfacing, the early use of cement is preferred in some cases. There is currently little or no consensus, or long term clinical data, as to the potential risks to the patient associated with this method. This should be borne in mind when choosing to adopt such practices.

Implantation of a foreign body in the tissues increases the normal risk of infection associated with surgery following operation. Evidence from clinical investigations clearly indicates the necessity for strict compliance to good aseptic surgical technique. Following the operation the patient should be advised that in the event of an intercurrent infection they must immediately seek medical advice in order to reduce the risk of infection to the implant. Extrusion of the bone cement beyond the region of its intended application may occur resulting in the following complications: hematuria; dysuria; bladder fistula; delayed sciatic nerve entrapment from extrusion of bone cement

beyond the region of its intended application; local neuropathy; local vascular erosion and occlusion; and intestinal obstruction due to adhesions and stricture of the ileum from the heat released during the exothermic polymerisation.

Ensure that the powder and liquid components to be mixed together have the same lot number, since the monomer and polymer components are individually formulated for each batch. It is essential to add all of the liquid and powder components together when mixing the cement, since the components are premeasured to give optimum results.

To prevent any possible contamination of the cement with glass fragments, do not break the ampoule containing the liquid component over the mixing device.

SmartSet GMV Endurance Gentamicin Bone Cement is supplied sterile for single use only. Do not re-use. Sterility is only guaranteed if the packaging is unopened or undamaged. Resterilisation of any components of the cements must not be attempted.

As the monomer is volatile and flammable, any waste liquid component should be evaporated under a well-ventilated hood or absorbed by an inert material and transferred to a suitable container (which does not react with the monomer) for disposal. Prior to disposal the surplus bone cement should be allowed to set. The polymer component and waste powder should be disposed of as clinical waste.

Adverse Effects

Serious adverse events, some with fatal outcome, associated with the use of bone cements include:

- Myocardial infarction.
- Cardiac arrest.
- Cerebrovascular accident.
- Pulmonary embolism.
- Anaphylaxis.

The most frequent adverse reactions reported with bone cements are:

- Transitory fall in blood pressure.
- Elevated serum gamma-glutamyl-transpeptidase (GGTP) up to 10 days post-operation.
- Thrombophlebitis.
- Hemorrhage and hematoma.
- Pain and/or loss of function.
- Loosening or displacement of the prosthesis.
- Superficial or deep wound infection.
- Trochanteric bursitis.
- Short-term cardiac conduction irregularities.

- Heterotopic new bone formation.
- Trochanteric separation.

Other potential adverse events reported for bone cements include:

- Hypoxemia.
- Cardiac arrhythmia.
- Bronchospasm.
- Adverse tissue reaction.
- Pyrexia due to allergy to the bone cement.
- Hematuria.
- Dysuria.
- Bladder fistula.
- Local neuropathy.
- Local vascular erosion and occlusion.
- Transitory worsening of pain due to heat released during polymerisation.
- Delayed sciatic nerve entrapment due to extrusion of the bone cement beyond the region of its intended application.
- Intestinal obstruction because of adhesions and stricture of the ileum due to the heat released during cement polymerisation.

Interactions

SmartSet GMV Endurance Gentamicin Bone Cement should not be administered concurrently with other potentially ototoxic or nephrotoxic drugs.

Overdosage

Nil.

Pharmaceutical Precautions

Shelf life: 36 months.

Special precautions for storage: Store below 25°C and protect from light.

Store at the recommended mixing temperature of 23°C for a minimum of 24 hours before use.

Sterility is only guaranteed if the containers are undamaged. Resterilisation of any of the components should not be attempted.

Package Quantities

UNIT SIZE	Powder (g)	Liquid (g)
80g	80	2 x 18.88
40g	40	18.88
20g	20	9.44

See FURTHER INFORMATION for full product descriptions.

Further Information

Product descriptions:

SmartSet GMV Endurance Gentamicin Bone Cement consists of a two-component system, a polymeric powder component and a monomeric liquid component. The bone cement powder is contained in a sterile polyethylene bag, within a peelable pouch within a protective non-sterile laminated foil pouch. The bone cement liquid is contained in a sterile ampoule comprising an ampoule safety cap on its tip that is contained within a blister pack. The interiors of the blister pack and peelable pouch are sterile.

Sterilisation of the bone cement liquid is achieved by filtration, whilst the blister pack is sterilised by ethylene oxide. The bone cement powder in the powder bag and peelable pouch is sterilised by gamma irradiation.

80g unit pack size: - One pack sterile bone cement powder (80g) containing Gentamicin Sulphate 4.22% w/w¹ and two ampoules containing sterile bone cement liquid (2 x 18.88g).

40g unit pack size: - One pack sterile bone cement powder (40g) containing Gentamicin Sulphate 4.22% w/w¹ and one ampoule containing sterile bone cement liquid (18.88g).

20g unit pack size: - One pack sterile bone cement powder (20g) containing Gentamicin Sulphate 4.22% w/w¹ and one ampoule containing sterile bone cement liquid (9.44g).

¹ Variable dependent upon potency and equivalent to 1.0g (1.0 M.I.U.) Gentamicin base in 40g unit; 0.5g (0.5 M.I.U.) in 20g unit

Excipients:

Bone cement powder: polymethylmethacrylate, methylmethacrylate / styrene copolymer, benzoyl peroxide, barium sulphate.

Bone cement liquid: methylmethacrylate, N,N-dimethyl-p-toluidine, hydroquinone.

Preclinical safety information:

The two most important organs that are susceptible to gentamicin toxicity are the ear and kidney. In large-scale retrospective surveys of systemic clinical treatment, the frequency of ototoxicity in humans has been about 2-3%. The frequency of nephrotoxicity has varied widely and values of as much as 26% have been reported. The sensitivity of these organs is due to selective accumulation in the perilymph and vestibular and cochlear tissues and in the renal cortical cells of the proximal tubule.

The reasons for this toxicity have been extensively researched in animals and man . It is a function of the chemical properties of gentamicin and is concentration dependent. Therefore, the pharmacokinetics of gentamicin and its release from the cement formulation are relevant to this aspect of safety. Neuromuscular blockade is also a reported side-effect of human systemic treatment and, as a result, gentamicin may unmask or aggravate myasthenia gravis and cause post-operative respiratory distress.

Gentamicin, at relatively high dosages, has been reported to accumulate in the foetal tissues of rats and guinea pigs, and may consequently affect renal development in neonates.

The toxicity of gentamicin is an extension of its pharmacology relating to its cationic binding to phospholipids and its concentration in susceptible tissues, ie. ear and kidney, arising from blood concentrations above 10-20 micrograms/mL .

Gentamicin is readily soluble and the bone cement preparation releases significant concentrations initially allowing some measurable systemic levels (but below 2 micrograms/mL). Local concentrations are higher and at therapeutic levels thus assuring control of any immediate infections following surgery.

Medicine Classification

Prescription Medicine.

Name and Address

Johnson & Johnson Medical New Zealand
13 a Gabador Place
Mt Wellington Auckland
Phone 64 9 5741783
Toll Free 0800433789

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