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01-50-1192
Date: 2010-05

COBALT™ HV BONE CEMENT WITH GENTAMICIN (G-HV)
Radiopaque Bone Cement containing Gentamicin
Methyl Methacrylate – Methyl Acrylate Copolymer

ATTENTION OPERATING SURGEON

DESCRIPTION
Cobalt™ HV Bone Cement with Gentamicin (G-HV) provides two separate, pre-measured and sterilized components which when mixed form a radiopaque, rapidly setting poly(methyl methacrylate)-based (PMMA) bone cement.

One component is supplied in a gas-permeable packet. It consists of 40 g powder (copolymer) with the following composition:

• Methylmethacrylate-methylacrylate copolymer with FD&C Blue No. 2 Aluminum Lake	33.42 - 33.86 grams
• Benzoyl peroxide, hydrous 75%	0.20 - 0.64 grams
• Zirconium dioxide	5.94 grams
• Gentamicin sulfate (equivalent to 0.50 g Gentamicin)	0.84 grams

The other component is supplied in a flexible pouch. It consists of 20 ml of liquid (monomer) with the following composition:

• Methylmethacrylate (stabilized with hydroquinone)	18.424 grams
• N,N-dimethyl-p-toluidine	0.376 grams

The liquid monomer is sterile filtered. The powder is sterilized with ethylene oxide. The gas-permeable packets containing the powder are sterilized with ethylene oxide. The exterior of the pouch containing the liquid is sterilized with vaporous hydrogen peroxide.

Blue pigment (FD&C Blue No. 2 Aluminum Lake) is added to the powder component to produce a bluish tint in the final cement. This renders it possible to distinguish between bone and cement within the surgical field.

When the powder (copolymer) and the liquid (monomer) are mixed, the dimethyl-p-toluidine in the liquid activates the benzoyl peroxide catalyst in the powder. This initiates the polymerization of the monomer, which then binds together granules of polymer. As polymerization proceeds, a sticky dough-like mass is formed, which, after about 30

seconds, can be manipulated for about 5 minutes (at 23°C [73°F]). (See curves and tables for temperature variations.)

Polymerization is an exothermic reaction with temperatures rising as high as 90°C, which occurs while the cement is hardening *in situ.* The released heat may damage bone or other tissues surrounding the implant. Although the spontaneous generation of heat accelerates the reaction, the polymerization of this self-curing resin occurs even if the temperature is reduced by irrigation with a cool physiologic saline solution.

MATERIALS

Methylmethacrylate-methylacrylate copolymer with FD&C Blue No. 2 Aluminum Lake
Benzoyl peroxide, hydrous 75%
Zirconium dioxide
Gentamicin sulfate (equivalent to 0.50 g Gentamicin)
Methylmethacrylate (stabilized with hydroquinone)
N,N-dimethyl-p-toluidine

ACTION

Cobalt™ HV Bone Cement with Gentamicin (G-HV) is an acrylic cement-like substance which allows seating and fixation of prosthesis to bone. After complete polymerization, the cement acts as a buffer for even weight distribution and other stresses between prosthesis and bone. Insoluble zirconium dioxide provides the radiopaque quality of the formulation.

INDICATIONS

Cobalt ™ HV Bone Cement with Gentamicin (G-HV) is indicated for use in arthroplasty procedures of the hip, knee, and other joints to fix plastic and metal prosthetic parts to living bone when reconstruction is necessary because of revision of previous arthroplasty procedures due to joint infection. The cement is intended to affix a new prosthesis in the second stage of a two-stage revision after the initial infection has been cleared.

CONTRAINDICATIONS

Cobalt™ HV Bone Cement with Gentamicin (G-HV) must not be used during pregnancy or the nursing period. Cobalt™ HV Bone Cement with Gentamicin (G-HV) is contraindicated in patients allergic to gentamicin or to other constituents of the bone cement. A hypersensitivity to any aminoglycoside is a contraindication to the use of gentamicin. A history of hypersensitivity or serious toxic reactions to aminoglycosides may also contraindicate the use of any other aminoglycoside because of known cross-sensitivity of patients to drugs in this class. The use of Cobalt™ HV Bone Cement with Gentamicin (G-HV) is contraindicated in patients with infectious arthritis, and in active infection of the joint or joints to be replaced.

Relative contraindications include the following:

1. Uncooperative patient or patient with neurologic disorder who is incapable of following directions
2. Metabolic disorders which may impair bone formation
3. Osteomalacia
4. Distant foci of infections which may spread to the implant site

5. Rapid joint destruction, marked bone loss or bone resorption, vascular insufficiency, muscular atrophy, or neuromuscular disease
6. Hypotension
7. Congestive heart failure
8. Renal impairment

WARNINGS
NOTE: Adulteration of this bone cement may negatively affect performance characteristics.

Prior to using the Cobalt™ HV Bone Cement with Gentamicin (G-HV), surgeons should, by specific training and experience, be thoroughly familiar with the properties, handling characteristics, and application of the PMMA bone cement. (See Precautions and Mixing Technique) Because the handling and curing characteristics of this cement varies with temperature and mixing technique, they are best determined by the surgeon's actual experience. It is advisable for the surgeon to go through the entire mixing, handling and setting process *in vitro* before using the material in an actual surgical procedure.

Adverse cardiovascular reactions can include hypotension, hypoxemia, cardiac arrhythmia, bronchspasm, cardiac arrest, myocardial infarction, pulmonary embolism, cerebrovascular accident and possible death. Hypotensive reactions can occur between 10 and 165 seconds after application of PMMA bone cement and can last for 30 seconds to 5 or more minutes. Some hypotensive reactions have progressed to cardiac arrest. The blood pressure, pulse and respiration of patients should be monitored carefully during and immediately following the application of the PMMA bone cement. Any significant alteration in these vital signs should be corrected with appropriate measures. In addition, over-pressurization of the PMMA bone cement should be avoided during the insertion of the PMMA bone cement and implant in order to minimize the occurrence of pulmonary embolism.

The risk of pulmonary fat embolism and the severity of all Bone Cement Implantation Syndrome (BCIS) complications can be reduced by meticulous irrigation and drying of the intramedullary canal. Care should be taken to clean and aspirate the proximal portion of the femoral medullary canal just prior to insertion of bone cement. In high-risk patients, for example those sustaining hip fractures, care should be taken not to over-pressurize the cement and to insert the prosthesis slowly.

Application of bone cement with gentamicin may have the potential to trigger the typical adverse reactions of gentamicin, which are in particular, damage to hearing and to the kidneys. However, these adverse reactions are very unlikely to occur, as the serum levels required to cause damage are not reached. Serious allergic reactions have been reported rarely in patients on systemic gentamicin therapy. Therefore, the incidence of these serious allergic events may also occur in patients with gentamicin-loaded bone cement.

Device volatility and flammability and electrocautery devices: The operating room should be adequately ventilated to eliminate monomer vapors. Ignition of monomer vapors caused by use of electrocautery devices in surgical sites near freshly implanted bone cements has been reported.

Irritation of the respiratory tract, eyes, and the liver: Caution should be exercised during the mixing of the liquid and powder components of the PMMA bone cement to prevent excessive exposure to the concentrated vapors of the liquid component, which may produce irritation of the respiratory tract, eyes, and possibly the liver. **Personnel wearing contact lenses should not mix PMMA bone cement or be near the mixing of the PMMA bone cement.**

1. DO NOT USE if there is loss of sterility of the cement.
2. Discard and DO NOT USE opened or damaged packages of the bone cement. Use only product packaged in unopened and undamaged containers.
3. Loosening and fracture of either the cement or the prosthesis, or both, can occur due to disease, trauma, and inadequate cementing technique, mechanical failure of the materials or latent infection.
4. The liquid and powder components of this cement must be mixed thoroughly before using. Inadequate mixing will lead to inhomogeneity that will compromise the mechanical properties and clinical performance of the cement.
5. DO NOT USE bone cement after expiration date.

The surgeon should decide whether the benefits expected from an arthropolasty outweigh any possible long-term adverse effects.

PRECAUTIONS

Strict adherence to good surgical principles and technique are required during use of the cement. Deep wound infection is a serious postoperative complication and may require total removal of the prostheses and embedded cement. Deep wound infection may be latent and not manifest itself for several years postoperatively.

1. **Contact dermatitis:** The liquid component (monomer) has caused contact dermatitis in those handling and mixing PMMA bone cement. Strict adherence to the instructions for mixing the powder and liquid components may reduce the incidence of contact dermatitis.
2. **Hypersensitivity reaction for operating room personnel:** The liquid component of the PMMA bone cement is a powerful lipid solvent. It should not contact rubber or latex gloves. Should contact occur, the gloves may dissolve and tissue damage may occur. Wearing a second pair of gloves and strict adherence to the mixing instructions may diminish the possibility of hypersensitivity reactions. The mixed bone cement should not make contact with gloved hand until the cement has acquired the consistency of dough. This usually occurs between one and two minutes after the liquid and powder components are mixed.
3. **Hypersensitivity reactions for patients:** The gentamicin content of Cobalt™ HV Bone Cement with Gentamicin (G-HV) may cause hypersensitivity reactions in isolated cases.
4. **Inadequate post-operative fixation:** Inadequate fixation or unanticipated postoperative events may affect the PMMA bone cement/bone interface and lead to micro-motion of cement against the bone surface. A fibrous tissue layer may develop between the PMMA bone cement and the bone that may cause loosening of the prosthesis. Thus, continued, periodic follow-up is advised for all patients.

5. **Exothermic reaction:** Polymerization of the PMMA bone cement is an exothermic reaction that occurs while the PMMA bone cement is hardening *in situ*. The released heat may damage bone or other tissue adjacent the implant.
6. **Extrusion:** Extrusion of the PMMA 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 the bone cement beyond the region of its intended use; local neuropathy; local vascular erosion and occlusion; and intestinal obstruction because of adhesions and stricture of the ileum from the heat released during the exothermic polymerization.
7. **USE IN PREGNANCY: The safety and effectiveness of the PMMA bone cement in pregnant women has not been established. PMMA bone cement may adversely affect fetal health.**
8. **PEDIATRIC USE: The safety and effectiveness of the PMMA bone cement in children has not been established. PMMA bone cement may adversely affect bone growth.**
9. **Expiration dating:** PMMA bone cement should not be used after the expiration date because the effectiveness of the device may be compromised.
10. **Disposal:** Expired cement should be mixed according to Instructions for Use prior to disposal. Because of the volatility and flammability of the liquid monomer of the PMMA bone cement, liquid monomer that has leaked or is leaking from the package should be collected and evaporated in a well-ventilated hood or absorbed by an inert material and transferred in a suitable container (one that does not react with the PMMA bone cement) for disposal.
11. **Incompatibility:** Aqueous (e.g. antibiotic containing) solutions must not be mixed with the bone cement, as this reduces the strength considerably.
12. **Monitoring:** Patients receiving Cobalt HV Bone Cement with Gentamicin should be periodically monitored with peak and trough levels of gentamicin, serum electrolytes, serum renal function, urinalysis, and audiograms (in elderly and/or dehydrated patient in whom there is a higher risk of adverse events associated with gentamicin use).
13. **Use of gentamicin should be avoided in the following situation.**
    Concurrent/sequential use of:
    - Other neurotoxic/nephrotoxis antibiotics
    - Other aminoglycosides
    - Cephalorodine
    - Viomycin
    - Polymixin B
    - Colistin
    - Cisplatin
    - Vancomycin
14. **Dose in patients with renal impairment:** Since no adjustment can be made to the dose in the gentamicin-loaded cement, a risk versus benefit assessment should be made before use in patients with renal impairment.
15. **Drug resistant bacteria:** Using Cobalt™ HV Bone Cement with Gentamicin (G-HV) 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.

Avoid over pressurization of the bone cement because this may lead to extrusion of the bone cement beyond the site of its intended application and damage to the surrounding tissues.

ADVERSE EVENTS

The most serious adverse events, including death, reported with the use of acrylic bone cements are:

- Cardiac arrest
- Myocardial infarction
- Pulmonary embolism
- Cerebrovascular accident
- Sudden death

The most frequent adverse events reported are:

- Transitory fall in blood pressure
- Thrombophlebitis
- Hemorrhage and hematoma
- Loosening or displacement of the prosthesis
- Superficial or deep wound infection
- Trochanteric bursitis
- Short-term cardiac conduction irregularities

Nephrotoxicity

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

Neurotoxicity

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

Other adverse events reported are:

- Heterotopic new bone formation
- Trochanteric separation

OTHER POTENTIAL ADVERSE EVENTS REPORTED INCLUDE:

- Application of Cobalt™ HV Bone Cement with Gentamicin may have the potential to trigger the typical adverse reactions of gentamicin, which are in particular, damage to hearing and to the kidneys. However, these adverse reactions are very unlikely to occur as the serum levels remain well below levels required to cause damage. Concurrent administration of muscle relaxants and ether may potentiate the neuromuscular blocking properties of gentamicin. However, the low serum concentrations significantly reduce the risk of occurrence of this adverse event. The use of antibiotic-loaded bone cement may lead to development of resistant microorganisms and the

physician should weigh the risks vs. benefits to the patient before using Cobalt™ HV Bone Cement with Gentamicin (G-HV) in each case.

- Pyrexia due to an allergy or histological reaction to bone cement
- Hematuria
- Dysuria
- Bladder fistula
- Local neuropathy
- Local vascular erosion and occlusion
- Adhesions and stricture of the ileum due to the heat released during polymerization.
- Delayed sciatic nerve entrapment due to extrusion of the bone cement beyond the region of its intended application.

Adverse reactions affecting the cardiovascular system have been attributed to leakage of unpolymerized liquid monomer into the circulatory system. Data indicate that the monomer undergoes rapid hydrolysis to methacrylic acid and that a significant fraction of the circulating methacrylate is in the form of the free acid, rather than of the methyl ester. Correlation between changes in circulating concentrations of the methyl methacrylate/methacrylic acid and changes in blood pressure has not been established.

Hypotensive episodes reported are more marked in patients with elevated or high normal blood pressure in hypovolemia and in patients with pre-existing cardiovascular abnormalities. Elevations in plasma histamine levels subsequent to introduction of cement have also been reported.

Reports of sometime fatal cardiac arrest suggest that elderly osteoporotic patients undergoing hip replacement surgery for fractures of the femoral neck are at greater risk than those receiving elective joint replacement for arthritic disease. Risk is also higher in patients with pre-existing cardiovascular disease. Although the etiology of cardiac arrest is unclear, it may well be either direct embolic effects or secondary to hypoxia produced by pulmonary embolic phenomena. Introduction of liquid cement under pressure into a clean medullary canal has been shown to appreciably enhance the filling of the bone cavities with marked improvement in the security of the bone cement interface. Care must be exercised in introducing the cement continuously from distal to proximal to avoid laminations in the cement**.**

DOSAGE AND ADMINISTRATION

Cobalt™ HV Bone Cement with Gentamicin (G-HV) copolymer powder is double packaged. The inner gas permeable packet is sterilized with ethylene oxide and is enclosed in a foil-lined, protective overwrap. (At least one extra unit of Cobalt™ HV Bone Cement with Gentamicin (G-HV) should be available before starting a surgical procedure.) The packet containing the sterile filtered liquid monomer is packaged in a protective gas-permeable overwrap pouch. The outside of the liquid packet and inside of overwrap pouch are sterilized by exposure to vaporous hydrogen peroxide

A unit is prepared by mixing the entire contents of one (1) packet of powder (40 g copolymer) with one (1) packet of liquid (20 ml monomer). One or two units will usually

suffice, although this will depend upon the specific surgical procedure and the techniques employed. Each unit is prepared separately.

The following are required for preparation of the bone cement:

- Sterile working area
- Sterile porcelain or stainless steel bowls or a plastic bowl approved for use with monomers
- Sterile mixing spoons or spatulas.

Note: For vacuum mixing, refer to manufacturer instructions.

A circulating nurse or assistant opens the peelable outer pouch of both powder and liquid components, and the sterile powder packet and liquid packet are aseptically placed on a sterile table. The powder packet and the liquid packet are opened under sterile conditions. Since each packet of powder contains a pre-measured quantity of copolymer to react with a pre-measured quantity of monomer, care should be taken to mix the entire contents of one powder packet with the entire contents of one liquid packet. Partial amounts should not be used.

MIXING INSTRUCTIONS FOR BOWL MIXING
Note: Cement can also be mixed in a vacuum mixing system. Refer to manufacturer instructions.

Pour the liquid into a bowl. Add the powder. Stir with a spatula vigorously, but carefully, for about 30 seconds.

IN ORDER TO ASCERTAIN THAT THE DOUGH-LIKE MASS DOES NOT STICK TO THE RUBBER GLOVES, DEPENDING ON ROOM TEMPERATURE WAIT ANOTHER 30 SECONDS to 120 SECONDS (SEE CURVES).

At this state knead further for about 15 seconds to 30 seconds. Thus, it becomes more homogeneous, and mixed air bubbles disappear for the most part. On the other hand, if the kneading process is extended too long, the polymerization may proceed to a point where the mass is no longer soft and pliable, making manipulation and application to bone difficult.

Working time may be affected by temperature (see curve and table for working and hardening times). Additionally, the moisture level in any bone cement powder has an effect on polymerization; cement powder with a higher water content will set faster, while drier cement powder will result in slower set times. The outer paper-foil pouch acts as a moisture barrier for Cobalt™ HV Bone Cement with Gentamicin (G-HV). To minimize fluctuation of set-times, do not remove the powder component's moisture barrier until it is time to mix the cement. Maintaining a constant and moderate (40% RH – to 55% RH) humidity in the operating room will also lead to more consistent cement handling performance. The ideal working consistency of the Cobalt™ HV Bone Cement with Gentamicin (G-HV) or manual application to bone is best determined by the surgeon based upon experience in using the preparation. To assure adequate fixation, the prosthesis should be held securely in place without movement until the bone cement has fully hardened. Excessive cement must be removed while it is still soft. If additional cement is required during the surgical procedure,

another packet of liquid and packet of powder may be mixed as described above. The resulting kneadable mass may be applied to previously hardened bone cement.

The completion of polymerization occurs in the patient and is associated with the liberation of heat. To more rapidly dissipate the heat, the polymerizing cement may be irrigated with a cool physiologic saline solution.

STORAGE

Store package in a dry, ventilated place between 6°C and 23°C (43°F and 74°F). Improper exposure to high temperatures may result in full or partial polymerization of monomer liquid, or reduction in initiator (benzoyl peroxide) content in powder component. These changes could significantly affect cement handling properties, mechanical properties, and clinical result.

Ascertain that sufficient material be removed from stocks and stored at about 23 °C (73 °F), or at the temperature appropriate to give desired cement handling and setting properties, for 24 hours before use.

The outer paper-foil pouch of the Cobalt™ HV Bone Cement with Gentamicin (G-HV) packaging serves as a moisture barrier. Since moisture levels in any bone cement powder has an effect on polymerization, the package should remain sealed until time to mix the cement. An opened package must not be used.

The copolymer powder does not withstand heat sterilization treatment. DO NOT RESTERILIZE. Device is single use only. If a packet is accidentally opened, it must not be used.

CAUTION

Federal Law (USA) restricts this device to sale by or on the order of a physician.

HOW SUPPLIED

Carton consisting of:
1 packet of copolymer powder containing 40 g
1 packet of liquid monomer containing 20 ml

The following tables and graphs were generated using standard methods including a temperature controlled environment. Warming of bone cement by any manual manipulation and the eventual application to the surgical site will accelerate the onset and completion of the final hardening phase. The extent of acceleration depends on the timing of manipulation and application. Early and extended warming will have the largest effect on cement hardening.

Typical working data for mixing Cobalt™ HV Bone Cement with Gentamicin (G-HV)
Open Bowl Mixing at Ambient Temperatures

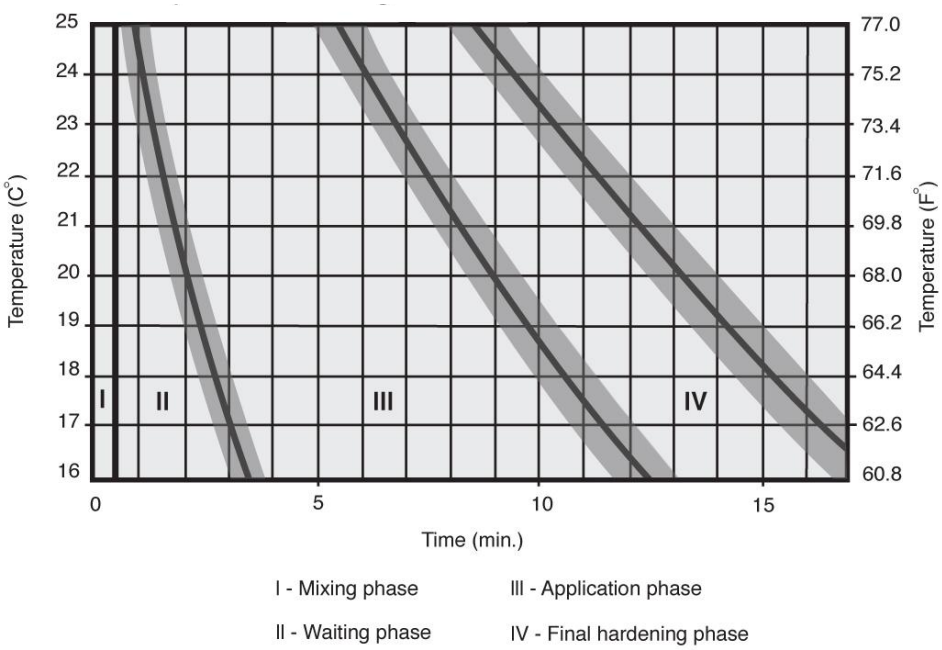
Ambient and component temperature	**18º C**	**20º C**	**23º C**
Mixing	0’30”	0’30”	0’30”
Start of application phase	2’55”	2’20”	1’35”
End of application phase	10’40”	9’10”	7’00”
Hardening	14’50”	12’50”	10’10”

Vacuum Mixing at Ambient Temperatures

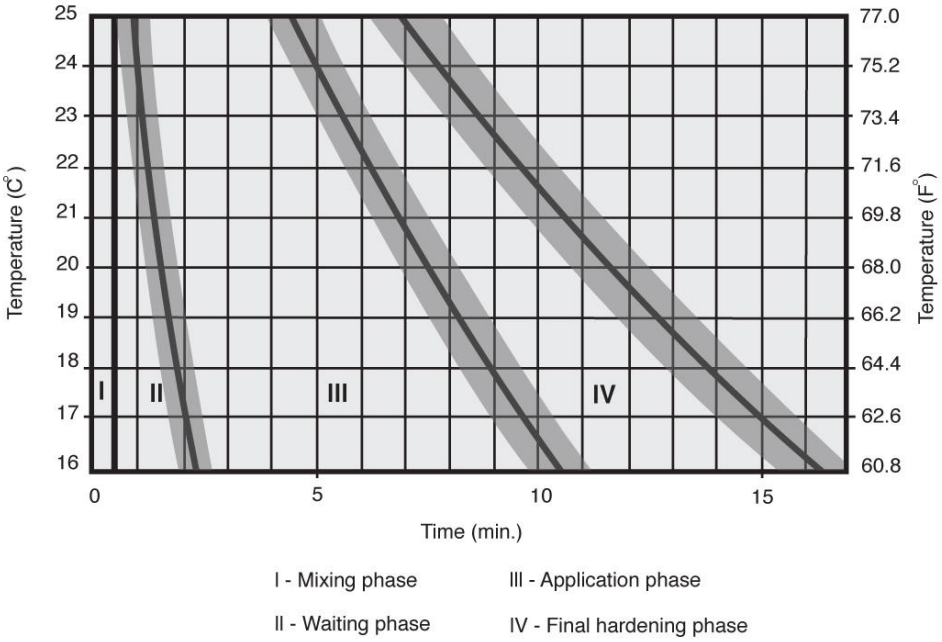
Ambient and component temperature	**18º C**	**20º C**	**23º C**
Mixing	0’30”	0’30”	0’30”
Start of application phase	1’55”	1’35”	1’05”
End of application phase	9’10”	7’45”	5’50”
Hardening	12’55”	11’00”	8’30”

Note: Cobalt™ HV BONE CEMENT WITH GENTAMICIN (G-HV) *is not a low viscosity cement.*

Handling and Setting Times vs. Temperature
for open bowl mixing of Cobalt ™ HV Bone Cement with Gentamicin (G-HV)



Handling and Setting Times vs. Temperature
for vacuum mixing of Cobalt ™ HV Bone Cement with Gentamicin (G-HV)



Comments regarding this device can be directed to Attn: Regulatory Dept., Biomet, P.O. Box 587, Warsaw, IN 46581, FAX: 574-372-3968.

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Symbol Legend
Manufacturer
Date of Manufacture
Do Not Reuse
Caution
STERILE EO — Sterilized using Ethylene Oxide
STERILE R — Sterilized using Irradiation
STERILE — Sterile
STERILE A — Sterilized using Aseptic Processing Techniques
STERILE — Sterilized using Steam or Dry Heat
Use By
WEEE Device
REF — Catalogue Number
LOT — Batch Code
FLAMMABLE — Flammable
EC REP — Authorized Representative in the European Community