enovis™

Bravo MV+G

EN(US)

Sterile radiopaque bone cement with antibiotic (Gentamicin)

Medium viscosity

Caution: Federal Law (USA) restrict this device to sale by or on the order of a physician

Device description

Bravo MV+G bone cement is a self-curing, radiopaque, polymethyl methacrylate based cement which is used for securing a metal or polymeric prosthesis to living bone in arthroplasty revision procedures such as hip replacement, knee replacement, ankle replacement, shoulder replacement and other joint replacements, specifically formulated for patients

- where the general or local conditions indicate an increased risk of infection
- with a compromised general state (malnutrition, diabetes, systemic infections,…)
- needing a revision of the hip or other joint prosthesis where a local infection has developed.

It contains and releases the aminoglycoside antibiotic gentamicin to protect the cured cement and contiguous tissue against contamination by microbes sensitive to gentamicin.

The bone cement has no intrinsic adhesive properties, its functioning relies on close mechanical interlock between the irregular bone surface and the prosthesis.

The bone cement is supplied as a two-component system, consisting of separate, sterile liquid and powder components, which are mixed together at the point of use to produce the cement.
The liquid component is sterilized by membrane filtration and aseptically filled into a sterile glass ampoule. The ampoule is contained within a sealed blister pack, which is sterilized using ethylene oxide. The powder component is contained in a polyethylene bag, within a peelable pouch and is sterilized by gamma radiation. The sterile powder component is supplied within an outer protective non-sterile laminated foil pouch. The manufacturing and packaging processes of **Bravo MV+G** are performed under strict quality procedures in a controlled environment, which conforms to applicable international standards.
Bravo MV+G bone cement is a medium viscosity cement, primarily intended for syringe application. If **Bravo MV+G** is applied digitally, the surgeon must use their clinical judgment to decide when the cement viscosity is suitable to allow the surgical procedure to continue.
The preparation, handling and application of **Bravo MV+G** bone cement must be performed only by qualified healthcare professionals, specifically trained in the procedure and under the direct supervision of the physician responsible for the procedure.
The manufacturer declines any liability in case of the use of **Bravo MV+G** bone cement not strictly corresponding to the specified intended use, or the use of **Bravo MV+G** bone cement by personnel not adequately qualified and trained.

Pack size	
Powder weight (g)	35.30
Liquid volume (ml)	20.00

Composition

The qualitative composition of **Bravo MV+G** bone cement is specified in the tables below:

Composition of the powder component
Polymethyl Methacrylate
Benzoyl Peroxide
Barium Sulfate
Gentamicin Sulfate

Composition of the liquid component
Methyl Methacrylate
N,N dimethyl-p-toluidine
Methyl Ether of Hydroquinone

Gentamicin content

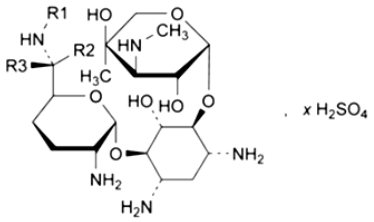
Pack size	
Gentamicin base (g)	0.5

Intended use

Bravo MV+G bone cement is indicated for use in the second stage of a two-stage revision for total joint arthroplasty after the initial infection has been cleared.
Bravo MV+G shall not be used for any use other than the specified intended use.

Microbiology overview

Gentamicin sulfate is a broad spectrum water-soluble antibiotic belonging to the group of aminoglycosides. It is manufactured by a fermentation process and consists of a mixture of related gentamicin components. The main constituents are gentamicins C1, C1a, C2 and C2a.



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

Molecular weight:
Gentamicin C1: 477.61
Gentamicin C1a: 449.55
Gentamicin C2: 463.58

Gentamicin C2a: 463.58
Gentamicin C2b: 463.58

Composition of gentamicins:
Gentamicin C1: 25.0 - 45.0%
Gentamicin C1a: 10.0 - 30.0%
Gentamicin C2+2A+2B: 35.0 - 55.0%

Impurities:
Usually also other minor aminoglycosides are found in a pharmaceutical gentamicin preparation.
Potential impurities arising from the manufacturing process include garamine, sisomicin and gentamicin B1. Gentamicin sulfate complies with the requirements of the monograph of the European Pharmacopoeia.

Mechanism of action: The bactericidal action of gentamicin is attributed to its ability to inhibit protein synthesis. Gentamicin initially binds to the outer membrane of the cell creating aqueous channels allowing an influx of gentamicin across the inner membrane via electron transport. Once inside the membrane, the permeability of the bacterial cell membrane is altered and the genetic code is misread. Cellular death is directly attributed to the interference of protein synthesis for blockage of initiation and further translation, due to premature termination and the incorporation of incorrect amino acids. The strength of this action is dependent on the concentration level of gentamicin.

Pharmacokinetics (including absorption and metabolism): gentamicin is absorbed poorly from oral administration and is usually administered parenterally. This drug is water-soluble, concentrates in the kidneys and has low plasma protein binding (<20%). There is no evidence of gentamicin being metabolized. Elimination is almost exclusively via glomerular filtration in the kidneys before being excreted almost unchanged in urine. Compared to intramuscular administration, systemic concentration levels with bone cement are low, usually the maximum level is <1 µg/ml (<10%). There are no detectable systemic levels after seven days from administration. Gentamicin levels in urine after bone cement administration range from 10µg/ml initially to 1-2 µg/ml after seven days.

Pharmacodynamics and Gentamicin Activity Spectrum: its bactericidal action is explained by its mechanism of action. The reported range of minimum inhibitory concentration (MIC) is 0.06 to 8 µg/ml. Gentamicin has proven to be effective against many aerobic gram-negative bacteria strains, and has shown to not have much activity on anaerobes, fungi or yeasts. Gram-positive bacteria are less sensitive, with the exception of Staphylococcus aureus and Staphylococcus epidermidis, two important strains in device implant surgery. Gentamicin is active in vitro against more than 90% of strains of S. aureus and 75% of S. epidermidis. Some resistant Staphylococcus strains have been identified. Gentamicin is active against P. Aeruginosa, another frequent cause of bone and joint infections. Gentamicin has been shown to be effective against methicillin sensitive strains of Staphylococcus species but not as effective against methicillin resistant strains of Staphylococcus species. Staphylococcus species account for the majority of infected orthopaedic implant related infections. Gentamicin is not active against Streptococcus species and anaerobes.

Contraindications

The use of **Bravo MV+G** is contraindicated:

- in the presence of active or incompletely treated infection at the site where the bone cement is to be applied;
- in the presence of Myasthenia gravis;
- in patients with hypersensitivity to gentamicin or other aminoglycosides, to the contrast medium (barium sulfate) or to any of the other components of the bone cement. A history of hypersensitivity or serious toxic reactions to aminoglycosides may also contraindicate the use of any other aminoglycoside including gentamicin because of the known cross-sensitivity of patients to drugs in this class or to any other of the cement components;
- during pregnancy or breastfeeding;
- in case of serious renal insufficiency;
- in case of metabolic disorders;
- where the loss of musculature or the neuromuscular impairment in the affected limb would make the surgical procedure unjustifiable.

Precautions/Warnings

Bone cement preparation:

- Before using the **Bravo MV+G** bone cement, carefully check the packaging to ensure it has no damage compromising the sterility of the content.
- **Bravo MV+G** bone cement is supplied sterile for single use only. Do not re-use. Re-sterilization of any of the components of the cement must not be attempted.
- Ensure the inner packages and components are not damaged. The powder should be consistent (no agglomerations) and not yellow or brown in colour. The content of the vial should appear as a medium viscosity liquid. Do not use the liquid monomer if it shows any sign of thickening or premature polymerization. Always check the condition of the liquid monomer before performing the procedure. If the powder has a yellowish or brownish colour or if the liquid is syrupy, do not use the product. This indicates the product has not been stored properly.
- A dose is prepared by mixing the entire contents of the bag of cement powder with all the monomer liquid of an ampoule. The quantity of cement dough required depends on the specific surgical intervention and on the technique used. At least one additional dose of **Bravo MV+G** should be available before commencing the operation. The maximum recommended dose of the cement should be limited to:

Bone cement	No. of packaging
BRAVO MV+G	3

- The protective outer foil pouch and the outer peelable pouch are non-sterile and must not be transferred into the sterile field.
- After opening the package, it is mandatory, and the responsibility of the operator, to use an aseptic handling technique. Any error in handling and during transfer into the sterile field might affect bone cement sterility, the sterility of the surgical intervention and imply a risk of severe complications for the patient, such as infections and sepsis, even with a fatal outcome.
- The surgeon should, by specific training and experience, be thoroughly familiar with the properties, handling characteristics and application of antibiotic bone cements. The user is advised to practice the entire procedure of mixing, handling and introducing **Bravo MV+G** in similar environmental conditions to the operating room before using it for the first time. Detailed knowledge is also necessary of mixing systems and syringes used for application of the cement. Because the handling and curing characteristics of these cements vary with temperature and mixing technique, they are best evaluated by the surgeon's actual experience.
- The handling characteristics and setting time of bone cements are affected by:
  - temperature
  - humidity
  - vacuum mixing
- Refer to clinical timing and usage charts at the end of this leaflet for the effect of temperature on handling and setting times.
- Manual handling of the cement and body temperature will reduce the final setting time.
- Variations in humidity will affect the cement handling characteristics and setting time.
- Variations in setting time over the cement's shelf life can be minimized by storing the cement under the recommended conditions
- Before use, the surgeon shall become familiar with the effects of a particular mixing system on handling characteristics and the setting time of the cement, performing simulations of the procedure following the correct medical practice and instructions of the manufacturers of involved devices. Vacuum mixing can noticeably accelerate the setting time of the product.

Handling of the liquid monomer:

- As the liquid monomer is highly volatile and flammable, the operating room should be adequately ventilated to eliminate as much monomer vapor as possible. Ignition of monomer fumes caused by the use of electrocautery devices in surgical sites near freshly implanted bone cements has been reported.
- Caution should be exercised during the mixing of the two components to prevent excessive exposure to the concentrated vapors of the monomer, which may produce: nausea, dizziness, irritation of the respiratory tract, eyes, and possibly affect the liver; contact dermatitis. If the liquid component comes into contact with the eyes, wash with copious amounts of water.
- Concentrated vapors of the liquid component may have an adverse reaction with contact lenses. Since soft contact lenses are permeable to liquids and gases, they shall not be worn in the operating theatre if methyl methacrylate is being used.
- Methyl methacrylate has been demonstrated to cause hypersensitivity in susceptible persons, which may result in an anaphylactic response.
- 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 a second pair of gloves and strict observation of the mixing instructions may diminish the possibility of hypersensitivity reactions. Gloves made of PVP (polyethylene, ethylene vinylalcohol copolymer, polyethylene) and Viton®/butyl gloves have proved to provide good protection over a lengthy period. For safety's sake it is recommended that two pairs of gloves be worn over one another, e.g. one polyethylene surgical glove over an inner pair of standard latex surgical gloves. The use of latex or polystyrene-butadiene gloves on their own is inadequate. Please make enquiries with your supplier to establish which gloves are suitable for such an application.

Bone cement application:

- **Bravo MV+G** bone cement is not intended to be used routinely or as an alternative to systemic antibiotics in an infected arthroplasty.
- Clinical studies show the need to maintain strictly aseptic surgical procedures. Any deep infection of a surgical wound is a serious risk and will affect the successful outcome of the technique. 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 even for several years post-operatively.
- 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 the 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-pressurization of the bone cement should be avoided during the insertion of the bone cement and the implant in order to minimize 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 pressurization. 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 the introduction of the bone cement. Marrow cavities should be vented when the cement is introduced digitally.
- Consideration should be given to the use of acrylic bone cement:
  - in patients diagnosed with femoral neck fracture, as some published literature has indicated there is a potential for increased mortality compared with un-cemented techniques.
  - in the elderly or dehydrated.
- Inadequate fixation or unanticipated post-operative events may affect the cement-bone interface and lead to micromotion of the cement against bone surfaces with which the cement is in contact. 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 prosthesis to be implanted must be compatible with the use of bone cement.
- The completion of cement polymerization occurs in the patient and is an exothermic reaction with considerable release of heat. The long term effects of the heat produced in situ have not yet been established.

Incompatibilities

- Aqueous solutions (e.g. ones containing antibiotics) must not be added to the bone cement because they have a considerable detrimental effect on the physical and mechanical properties of the cement.
-
- Pharmacological precautions/warnings specific to gentamicin:
- Prolonged exposure to gentamicin in situ may induce antibiotic resistant strains. This cement, therefore, may be inappropriate for revisions if a gentamicin-laden cement had been used in a previous surgery.
- Increased antibiotic resistance may be observed in patients with previous infections where bacteria were resistant to gentamicin.
- Resistance to gentamicin has occurred in some hospitals and is most commonly due to plasmid mediated alteration of the aminoglycoside. BRAVO MV+G bone cement may be effective against methicillin-sensitive strains of Staphylococcus aureus and Staphylococcus epidermidis but not as effective against methicillin-resistant strains of these organisms.
- The most common toxic effects of gentamicin are ototoxicity and nephrotoxicity. These toxic effects are concentration dependent. Gentamicin has been shown to inhibit protein synthesis causing nephrotoxicity and ototoxicity with frequencies of < 26% and 2-3% respectively. Nephrotoxicity may be clinically manifested by elevated serum creatinine, elevated BUN and a lowered creatinine clearance. At high concentrations, gentamicin has been linked to enzyme suppression during glycolysis resulting from poor glucose utilization and glycogen depletion. Selective accumulation in vestibular and cochlear tissue may result in ototoxicity, which can be irreversible. Neuromuscular blockage observed with gentamicin use is attributed to the potentiation of non-depolarizing blockers. This activity is exacerbated under anesthesia and is a particular concern with patients with myasthenia. This drug has been shown to cause neonatal renal impairment in animal studies.
- The use of BRAVO MV+G bone cement in patients with renal impairment, the elderly and those receiving concomitant nephrotoxic medications shall be seriously considered given the potential for nephrotoxicity and ototoxicicity.
- Possible allergic reactions are related to gentamicin bone cement use. Serious allergic reactions including anaphylaxis and dermatologic reactions including exfoliative dermatitis, toxic epidermal necrolysis, erythema multiforme and StevensJohnson Syndrome have been reported in patients on systemic gentamicin therapy. Although rare, fatalities have been reported.
- Other possible side effects which can occur from the use of gentamicin include hypomagnesaemia on prolonged therapy, antibiotic associated colitis, nausea, vomiting, rash and renal impairment.
- Potential allergenic impurities arising from the gentamicin manufacturing process include garamine, sisomicin and gentamicin B1.

Precautions during pregnancy, breastfeeding and in children.

- The safety and effectiveness of **Bravo MV+G** antibiotic bone cements in pregnant women or in children has not yet been established. **Bravo MV+G** antibiotic bone cements should not be used during the first third of pregnancy, and during the rest of the pregnancy period it should only be used in case of life-threatening illnesses. There are insufficient data on the use of gentamicin in pregnant women to evaluate any possible harmfulness. Aminoglycosides pass the placental barrier. Ototoxicity in the foetus cannot be excluded. Irreversible, bilateral congenital hearing loss has been reported in children after prenatal exposure to streptomycin. Hearing loss has also been documented for a few other aminoglycosides. In view of the concentration of gentamicin in the foetal kidney, nephrotoxicity is a potential hazard. Animal studies have shown ototoxicity and nephrotoxicity after prenatal exposure to gentamicin/aminoglycosides. For these reasons, the use of **Bravo MV+G** is advised against during pregnancy, unless the benefits for the mother outweigh the potential risk to the child.
- Lactation. Gentamicin is excreted in small amounts in human breast milk. Because of enhanced intestinal permeability in neonates, accumulation and ototoxicity cannot be excluded. For this reason, the benefits for the mother should outweigh the potential risk to the child before using **Bravo MV+G** during lactation.
- **Bravo MV+G** bone cements should only be used in children for limb preservation where no other procedure is likely to give a good chance of successful treatment.

Monitoring

Patients receiving **Bravo MV+G** bone cement should be periodically monitored with peak and trough levels of the antibiotic, serum electrolytes, serum renal function, urinalysis and audiograms (in the elderly and/or dehydrated patient in whom there is a higher risk of adverse events associated with gentamicin use).

Interactions with other medications

Consideration should be given to the administration of ototoxic or nephrotoxic drugs concurrently or immediately following the use of **Bravo MV+G** bone cement. This applies particularly to elderly patients.

Use of **Bravo MV+G** bone cement should be avoided with the following treatments:

- Concurrent/sequential use of other neurotoic / nephrotoxic antibiotics
- Other aminoglycosides
- Cephaloridine
- Viomycin
- Polymixin B
- Colistin
- Cisplatin
- Vancomycin

Owing to the administration of muscle relaxants or ether, the neuromuscular blocking properties of gentamicin may be intensified. However, this is unlikely on account of the very low serum levels reached.

Adverse events

Serious adverse events, some with a fatal outcome, associated with the use of acrylic bone cements include:
- Myocardial infarction.
- Cardiac arrest.

- Cardiac embolism
- Cerebrovascular accident.
- Pulmonary embolism.
- Anaphylaxis.

The most frequent adverse reactions reported with acrylic 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 tissue formation.
- Trochanteric separation.

Other potential adverse events reported for bone cements include:

- Hypotension.
- 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 polymerization.
- 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 polymerization.
- Possible death

Adverse reactions to gentamicin sulfate are not anticipated at the low levels used within **Bravo MV+G** bone cement. However the following adverse reactions have been associated with larger doses, typical of prescribed dosages of gentamicin sulfate:

Neurotoxicity -
• manifested as both auditory and vestibular ototoxicity, including irreversible hearing loss
• numbness
• skin tingling
• muscle twitching
• convulsions

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

Some clinical studies have referenced methicillin and gentamicin resistant strains of staphylococcus aureus and staphylococcus epidermidis as being responsible for clinical failures of hip and/or knee arthroplasties due to deep tissue infections.

The patient shall be made aware and accept potential risks and complications connected with the use of bone cement with gentamicin. The patient needs to be informed about the measures that could be taken to reduce possible negative effects.

Directions for use

The preparation and application of **Bravo MV+G** bone cement takes place in four subsequent phases:

I. mixing;
II. waiting (in this phase the bone cement, when touched, sticks to the gloves);
III. application (in this phase the bone cement has the aspect of a fluid dough, it does not stick and can be handled, injected by a syringe and a cannula);
IV. setting (in this phase the bone cement should have already been implanted and hardening completed. Non-implanted bone cement in this phase becomes too viscous, it cannot be used anymore and must be discarded).

The duration of phases II to IV depends on the ambient temperature and humidity. A higher temperature accelerates hardening, while a lower temperature slows it down (see fig. 1).
Prepare the mix in the appropriate type of container for the selected type of application (manual or syringe).

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 to the sterile operative area.
- Keeping the bottle neck free from the finger protector and holding the vial head at the larger point, open and pour the entire content into a suitable clean, dry, sterile mixing vessel made from an inert material (such as glass, ceramic, stainless steel or non-reactive plastics). To prevent possible glass debris falling into the container, do not break the vial on the mixing bowl.
- The sterile bag (or pouch) containing the powder component is opened with sterile scissors and the entire content is emptied into the container.
- A standard dose of bone cement is prepared by mixing the entire liquid content of the ampoule(s) with the entire content of the powder bag. It is not possible to partially use the content of a powder bag or vial. Procedures that are not allowed, including any kind of re-use, severely compromise the physical and chemical characteristics of bone cement, both during the preparation phase and after the implant and may compromise the sterility of the material, the sterility of the surgical intervention and imply a risk of severe complications for the patient, such as infections and sepsis. The amount of mixed cement required for clinical use is determined by the surgeon in each individual case.

Mixing and Digital Application

- **Bravo MV+G** can be applied digitally. The surgeon must use their clinical judgement to decide when the cement viscosity is suitable to allow the surgical procedure to continue.
- The cement is mixed thoroughly but carefully to minimize the entrapment of air. If using a mixing or application device for surgical cements, follow the manufacturer's instructions. Use a regular stirring action, not too fast, and continue for one minute. Do not exceed the mixing time.
- Viscosity increases progressively as a consequence of the polymerization reaction, during phases II to IV. Wait until completion of phase II (waiting phase) and then proceed with the application (phase III, the cement has become dough). Follow the manufacturer's instructions for the syringe and access tools used.
- 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 the gloved hands and kneaded thoroughly. It is vital that premature insertion of the 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. In addition, the cement should not adhere excessively to the surgeon's gloves. 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 im-

plant. However, implant insertion should not be delayed to the extent 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 pressurization must be maintained until the cement finally hardens. Excess bone cement must be removed before the cement has completely hardened.

Syringe application
- The use of **Bravo MV+G** bone cement is recommended with G21 accessories PicoMix Syringe and PicoMix Gun.
- The bone cement is prepared and mixed as described previously by adding all of the powder component to all the liquid 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.
- Prior to extrusion, it is recommended that a cement restrictor be inserted, at the required depth, into the prepared bone cavity. The 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 pressurization 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 to the extent that there is a risk that the procedure cannot be completed due to excessive cement hardening.
- After the introduction, the implant must be firmly held in position to avoid movement, and pressurization 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).

Storage

- Store the sealed outer pack between 5°C (41°F) and 25°C (77°F) and protect it from light to prevent premature polymerization of the liquid monomer component.
- Do not use the product after the expiry date.
- Do not use the content of damaged or open packages.

Disposal

Dispose of expired, un- usable or damaged packages of **Bravo MV+G** bone cement, following rules and procedures applicable to this kind of hospital waste.

Digital Introduction

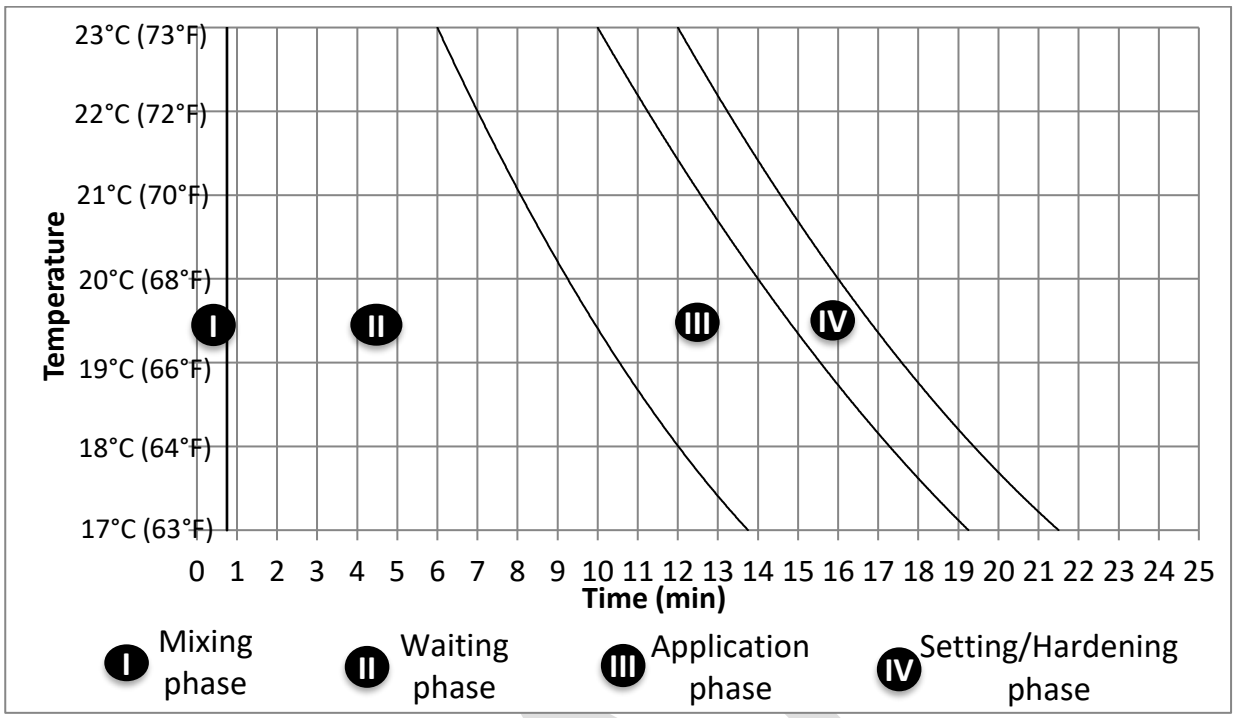


Fig.1 Chart of mixing, waiting, application and setting/hardening phases timing for digital application, as function of the ambient temperature.
Times shown in the chart were obtained by performing tests under 50 ± 10 % relative humidity.
Times are approximations, and may be shorter or longer depending on surgical technique and the mixing/delivery system used.

Syringe Application

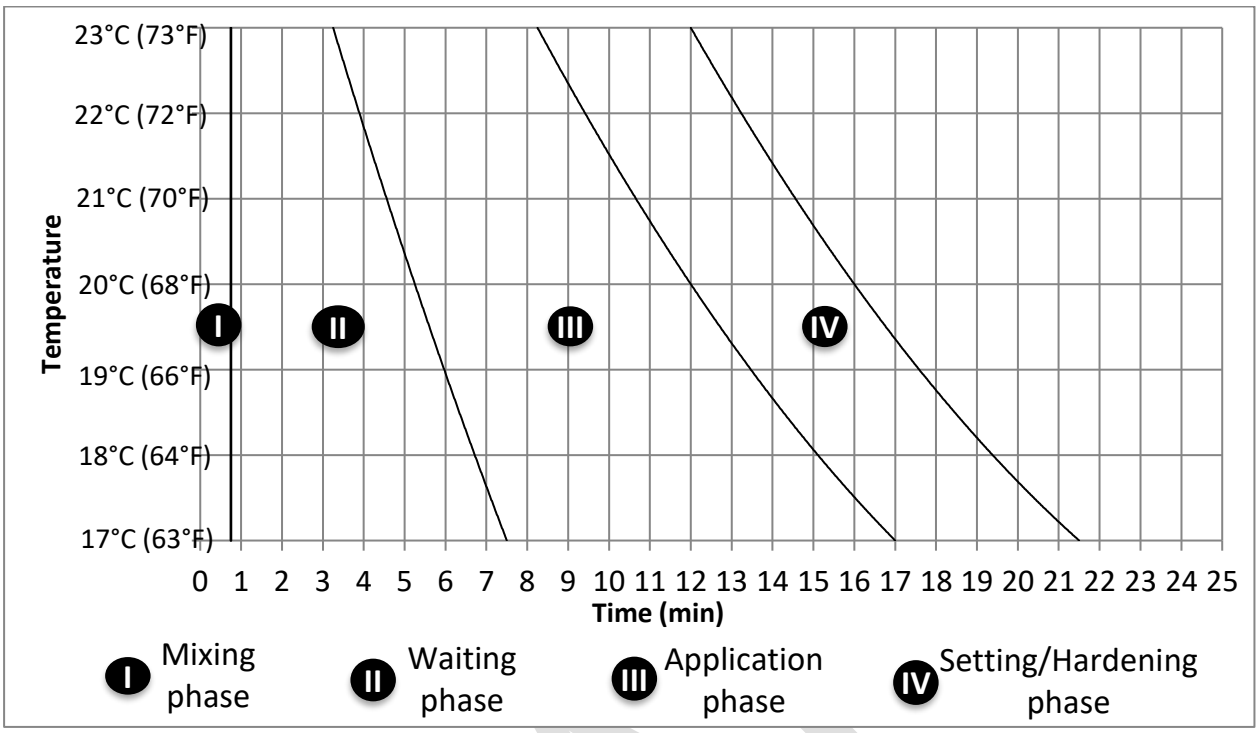
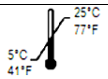
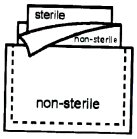


Fig.2 Chart of mixing, waiting, application and setting/hardening phases timing for syringe application, as function of the ambient temperature.
Times shown in the chart were obtained by performing tests under 50 ± 10 % relative humidity.
Times are approximations, and may be shorter or longer depending on surgical technique and the mixing/delivery system used

Symbols

Symbols	Description
 ISO 15223-1 5.4.2	Do not re-use
 ISO 15223-1 5.2.6	Do not resterilize
ISO 15223-1 5.1.4	Use-by date
 ISO 15223-1 5.1.6	Catalogue number
 ISO 15223-1 5.1.5	Batch code
 ISO 15223-1 5.3.2	Keep away from sunlight
 ISO 15223-1 5.4.4	Caution
 ISO 15223-1 5.4.3	Consult instructions for use or consult electronic instruction for use
 ISO 15223-1 5.2.4	Sterilized using irradiation
 ISO 15223-1 5.2.3	Sterilized using ethylene oxide
 ISO 15223-1 5.2.2	Sterilized using aseptic processing techniques
 ISO 15223-1 5.2.13	Single sterile barrier system with protective packaging inside
 ISO 15223-1 5.3.7	Temperature limit : Store between 5°C (41°F) and 25°C (77°F)

 ISO 15223-1 5.2.8	Do not use if the package is damaged and consult instruction for use
 ISO 15223-1 5.1.1	Manufacturer
 ISO 15223-1 5.1.9	Distributor
 *	The inner pouch (first pouch) is sterile. The pouch in the middle (second pouch) and the external pouch (third pouch) are not sterile
 *	The liquid in the vial is sterilized using aseptic processing techniques, the vial is sterilized using ethylene oxide
 *	CAUTION: Federal (USA) law restricts this device to sale by or on the order of a physician.

Symbols indicated in this table are derived from ISO 15223-1, with the exception of those indicated with *

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