ALCASIS™ GENTA ANTİBİOTİC BONE CEMENT Medium Viscosty USER MANUAL

1. PRODUCT DEFINITION:

ALCASIS™ Genta Bone Cement is a radiopaque, polymethyl methacrylate-based acrylic bone cement, which is used in orthopedic surgeries and freezes at specified standard times. It becomes ready for use as a result of the exothermic polymerization that occurs after the mixing of the powder and liquid two components. This mixture, which is polymerized before use, aims to increase the adhesion of joint implants to the bone in orthopedic surgeries.

2. COMPOSITION

Its package contains one Tyvek sack of cement powder(PMMA) and one amber glass ampoule (MMA).

• **LIQUID COMPONENT**	***10 ml ∓0.5 ml Ampoule***	***20 ml ∓1 ml Ampoule***	***30 ml ∓1 ml Ampoule***
Methyl Methacrylate (MMA) (%98)	98 % w/w	98 % w/w	98 % w/w
N, N dimethyl p-toluidene (%2)	2 % w/w	2 % w/w	2 % w/w
Hydroquinone	18-20 ppm	18-20 ppm	18-20 ppm

• **POWDER COMPONENT**	***20 gr ∓1 g***	***41 gr ∓2 g***	***60 gr ∓2 g***
Polymethyl Methacrylate (PMMA)	%86,78 w/w	%86,78 w/w	%86,78 w/w
Barium Sulfate	%9,76 w/w	%9,76 w/w	%9,76 w/w
Benzoyl Peroxide	%1,02 w/w	%1,02 w/w	%1,02 w/w
Gentamicin Sulfate	%2,44 w/w	%2,44 w/w	%2,44 w/w

3. INTENDED USE AND INDICATIONS OF THE EQUIPMENT

The indications of ALCASIS™ Genta Antibiotic Bone Cement are as follows;

- It is used in the revision operations caused by aseptic loosening of the prosthesis, after the infection of

the prosthesis by the gentamycin-susceptible organisms, and for the stable fixation of appropriate joint prostheses in primary operations, especially in the patients over 60 years old, and it provides additional protection against infection.

- Filling and stabilizing the bone defects within the scope of internal fixation treatment or endoprosthesis replacement surgery
- Fixation of total or partial joint endoprostheses robustly to the bone,
- Local antibiotics release is obtained by adding antibiotics in the bone cement and it becomes a rescuer especially in prosthesis surgeries with infection.
- Characteristics of Gentamycin in ALCASIS^{TM} Genta Antibiotic Bone Cement;
    - ✓ Wide antibacterial spectrum,
    - ✓ Good bactericidal effect at low concentrations,
    - ✓ Low resistance development,
    - ✓ Low binding rate to proteins,
    - ✓ Low allergy potential,
    - ✓ Ineffective or insignificant effect on bone cement-water mechanics,
    - ✓ Being resistant against chemical and thermal factors,
    - ✓ Very soluble in water,
    - ✓ Good release from the bone cement

4. COUNTERINDICATIONS OF THE EQUIPMENT:

ALCASIS^{TM} Genta Antibiotic Bone Cement cannot be used in below mentioned situations.

- Known or assumed hypersensitivity of the patient to Gentamycin or other components of the bone cement
- During pregnancy and breastfeeding
- In cases with severe renal impairment
- In the presence of an active or not fully treated infection in the bone area caused by strains that are insensitive to gentamycin.

5. MICROBIOLOGICAL PROPERTIES

5.1. Mechanism Of Action

- Bone cement is a cavity-filling material formed as a result of the methylmethacrylate polymerization triggered by the combination of prepolymerized solid particles and liquid monomers. Before each application, care should be shown to the paste and hardening times of the cement by reading the user's manual of the manufacturer. Since cement does not form a chemical bond with the bone and is not an adhesive with its physical characteristics, it is only used to fill the cavities between the bone and the implant. It is the weakest cement bone interface among the bone-cement-implant interfaces. The most important characteristic of cement is that it stabilizes the implant immediately. It provides an accurate primary stabilization for hte prosthesis, however, it does not increase secondary biological determination. Since it is a viscoelastic polymer, it provides the transfer of the loads reaching to the prosthesis via the elastic modulus close to the bone. It causes less stress shield at the proximal femur when compared to the cementless prostheses. In order for the cement to bind to the bone, the bone surface should be clean, its relation with the cortex should be present in a large area, its thickness should be as equal as possible in the metaphysis and medulla, and the cement should be applied with low viscosity and pressure.

In the powder part of the cement, PMMA or MMA copolymers containing dibenzoyl peroxide (BPO) take place, which has the characteristic of initializing the reaction. The powder also contains radioopacifier, zirconium dioxide or barium sulfate. In addition, antibiotics or dye can be added in the powder. Either the dying material or antibiotic or the radioopafication material has a role in the chemical reactions. The initial reaction and free radicals are formed after the interaction of BPO, which is in the powder and is the initiator of the reaction, and the activator DMpT in the liquid. Upon mixing the powder with the liquid, the powder becomes a sticky and viscous liquid by absorbing the liquid. This pasty structure is formed as a result of a chemical reaction called radical polymerization and the liquid monomers turn into polymers. When two of the increasing polymer chains encounter, they combine with each other and form a non-reactive polymer molecule. Thus, there are no free radicals in the environment. During this exothermic reaction, heat is given off to outside. 52 kJ (kilo joule) heat is formed for one hundred grams of MMA. Maximum heat generation is affected by the chemical content of the cement, powder-liquid ratio, and the radio-opacifying material and the temperature is between about 60 and 120°C. Although high temperature causes necrosis, impairment of local circulation, and fibrous tissue formation, incomplete polymerization can lead to chemical necrosis. As shown in the in vitro studies, if the mass of cement is thick, the ambient temperature is high, and monomer/polymer ratio is increased, more heat is generated during the hardening (freezing) of cement. It is known that collagen is denatured over 56°C. However, in the in vivo studies, it is highlighted that temperature generally does not exceed 50°C. Among the reasons, the cooling effect of the local blood stream, dissipation of heat due to the metal handle of the prosthesis, the relatively wide bone-cement interface, and poor heat conduction of the cement can be specified.

- Gentamycin, taking place in the aminoglycosides class, is a fast bactericidal drug crossing the bacterial cell membrane via active transport. They are ineffective on anaerobe bacteria because they use active transport. Because active transport requires oxygen. The aminoglycoside entering the bacterial cell causes the genetic code to be misread and thus, disrupts protein synthesis. Combination with antibiotics (such as beta-lactams, vancomycin), that are the cell wall synthesis inhibitors, increases their effects.

5.2. Mechanism of Resistance

- Natural and adventitious resistance to gentamycin is shown in both gram negative and gram positive bacteria. Gentamycin resistance may be formed due to the reduced permeability in the bacterial cell wall, the change in the ribosomal binding site, or the presence of plasmid-mediated resistance factor obtained by conjugation. Plasmid-mediated resistance enables the resistant bacteria to enzymatically modify the drug via acetylation, phosphorylation, or adenylation, and can be transferred between the organisms of the same type or different types. Resistance to other aminoglycosides and several other anti-infective agents (e.g. chloramphenicol, sulfonamides, tetracycline) can be transferred via the same plasmid. The prevalence of resistance may vary geographically for particular species, and local knowledge about resistance is desirable, particularly when treating severe infections.

5.3. Sensitivity

The table below summarizes the sensitivity spectrum of Gentamicin.

Commonly susceptible species
Aerobic Gram-positive
Staphylococcus aureus (methicillin-sensitive)
Aerobic Gram-negative
Enterobacter
Escherichia coli [2]
Klepsiella

Proteus spp, indole positive (P. vulgaris) Salmonella enteritica Serratia [3] **Species for which acquired resistance may be a problem** Aerobic Gram-positive Staphylococcus aureus (methicillin resistent) Staphytococcus epidennis [4] Aerobic Gram-negative Citrobacter Pseudomonas aeruginosa Proteus spp, indol negative (P. mirabilis) **Inherently resistant species** Anaerobic Gram-positive Enterococcus spp, Streptococcus spp. [5] Anaerobic Bacteroides spp. Clostridium spp.

[2]ICU level of resistance ≥ % 10

[3] Up-to-date data are not available in publications.

Sensitivity is expected in view earlier sources, references and recommendations for treatment.

- Degree of resistance of more than 50% in at least one region
- Clinical effectiveness is described in treatment of enterococci and streptocci endocarditis combination with penicillin in absence of high levels of resistance (enterococci).

5.4. Pharmacokinetics

- Gentamycin is soluble in water, concentrated in the kidneys, and it has limited protein binding in the plasma. There is no evidence that gentamycin is metabolized. Ellmination is conducted almost completely via renal filtration and is excreted in the urine. It has been shown in vitro that Gentamycin can be found in the bone cement complex for over a year. As in vivo, antibiotics are found in synovial fluid, blood, and urine after implantation. Levels are well-below the levels achieved by the typical parenteal administration of Gentamycin and well-below the toxic levels. Systemic concentrations of Gentamycin from the application of bone cement become undetectable within a few days after the intervention. Overdose of Gentamycin is much unlikely as it has been reported in several studies regarding the use of Gentamycin in bone cements at the concentration level used in ALCASIS Genta Antibiotic Bone Cement. The reason is that only low serum concentrations are obtained a few hours after the intervention at the recommended dose. (Wahlig et al: Pharmacokinetic study of Gentamicin-loaded cement in total hip replacements. Comparative effects of varying dosage. J. Bone Joint Surg. 66-B: 175–179).

6. SIDE EFFECTS

- Temporary decrease in blood pressure may be rarely seen after preparation of prosthesis bed or immediately after implantation of endoprosthesis with PMMA bone cements. In individual basis, serious complications such as cardiac arrest, anaphylactic shock and heavy allergic reactions resulting even in death may take place.
- In order to avoid pulmonary and cardiovascular complications in the form of pulmonary emboli and cardiac arrest, it is advised to rinse the implantation zone with isotonic solution (pulse lavage practice) before the bone cement is placed. In case of occurrence of pulmonary and

cardiovascular complications, it is necessary to keep the blood volume under control and to increase it, if necessary. In case of acute respiratory insufficiency, anesthesiological measures should be taken.

- Following adverse effects have been observed in the polymethylene methacrylate bone cements: Trombophlebitis, hemorrhage, trochanteric bursitis.
- Other side effects observed: Myocardia infraction, short term cardiac arrhythmia, cerebrovascular incident. In addition, complications are likely to happen during surgical procedure.
- Typical side effects for this antibiotic may occur due to the contribution of gentamycin. These side effects are unlikely to occur due to the formation of extremely low serum levels.
- It is important to consider that gentamycin has neuromuscular blocking properties. Therefore, extreme caution is required while using in the patients having a history of neuromuscular diseases (e.g. myasthenia gravis).
- The neuromuscular blocking effect of gentamycin may be strengthened due to the administration of myorelaxants and ether. However, this probability is low due to the formation of extremely low serum levels.
- Monomer is a volatile substance. You should protect yourself from its vapour. Enclosed spaces should be ventilated well.
- It is a liquid, volatile and flammable substance. Do not operate electric coagulation instruments and similar equipment.
- Definitely follow the user manual when mixing the bone cement.
- Do not touch the cement with bare hands.
- Protect your eyes.

7. TO BE TAKEN

During use by the operation team;

- The user should be familiar with features, operation and implementation of ALCASIS^{TM} Genta before use. The user is advised to exercise the mixture, process and placement of ALCASIS^{TM} Genta completely before the first use. Although mixing systems and syringes are used during cement implementation, detail information is required.
- Monomer liquid is highly volatile and flammable, therefore special precautions should be taken especially during use in the operation environment. Since, the monomer, at the same time, is a strong liquid solvent; it should not be contacted with body, directly. While processing with the monomer or prepared ALCASIS^{TM} Genta Antibiotic bone cement, gloves providing protection against penetration of monomer methylene methacrylate into the body should be used. The gloves made up of PVP (three-layer polyethylene, ethylene vinyl alcohol copolymer, polyethylene) are proven to provide long term, well protection. It is advised to wear two gloves on each other. For instance, one pair of polyethylene glove can be worn over one pair of standard latex surgical glove. It is not enough to wear latex or polystyrene-butadiene gloves alone. Please consult your vendor to determine which gloves will be suitable for such implementation.

- Monomer steam may irritate respiratory channels and eyes, and is likely to harm the liver. Irritations arising from contact with monomer have been informed. Soft contact lens manufacturers advise to remove the lenses in the environments where there are harmful or irrigative steams. Since soft contact lenses are permeable of liquids and gases, they should not be used with methylene methacrylate at operation environment.

Usage on patient;

- During and immediately after the placement of the bone cement, the blood pressure, pace and respiration should be monitored carefully. Any significant change in them should be immediately removed by taking appropriate measures.
- İmmediately before the placement of bone cement by using ALCASIS™ Genta, the bone should be cleaned, aspired and dried.
- Liquid solutions (i.e., antibiotic solutions) should not be mixed with the bone cement, because they have serious adverse effects on physical and mechanical features of the cement.

8. WARNINGS

- The product is a single-use product. Do not use opened packages (powder or liquid component) through re-sterilization.
- Temperature of the operating room should be 23 °C. Temperature above this value may shorten the operating duration. And working at a temperature below this value will cause to spend longer time with respect to cement curing, prosthesis positioning and cement freezing times. (see Graphic)
- Mix entire bone cement ingredients within the package.
- Any bone cement packages should be used or discarded immediately after opened, and should not be stored for use in another operation.
- Pay attention to minimize the air compression during mixing stage.
- Watch expiry date on the package before opening the product.

9. AMOUNT REQUIRED

- When cement powder and monomer liquid mix, a fast polymerizing and shapeable pastry forms, which is placed into bone cavities for fixation and/or filling purposes.
- Mixing the entire cement power content of a sack with the entire manomer liquid in an ampoule constitutes one dosage.
- The cement pastry amount required is based on specific surgical intervention to be performed and technics to be used. Before starting to the operation, at least one more ALCASIS™ Genta dose should be made ready as backup.

10. OPENING UNDER STERILE CONDITIONS

- Open the outer blister package at the specified opening point under sterile conditions and in such a way that when Tyvek paper sack and glass ampoule it contains shall remain sterile when they are removed.
- Prior to opening the inner Tyvek paper sack at the marked place, collect the contents in the bottom by shaking or lightly tapping it, so that the powder loss is avoided when the bag is opened at top.
- In order to facilitate the opening of glass ampule, a break point previously designated at the neck region between the ampule body and head has been created.
- In order to avoid mixing of glass breaks into the cement, do not open the ampule over the mixing device.

11. MIXING OF COMPONENTS

- It is recommended first to measure and set aside the liquid and then add the powder to it. If you act in the reverse order, immediate polymerization on the surface may cause formation of powder clusters.
- Relativity ratios of both two components, that are powder and monomer, are equalized fully. Therefore, bag and ampule should be completely emptied in order to get an optimum mixture.
- Components can be mixed with a vacuum mixing system or manually.
- Mixing, holding, operating and freezing times of ALCASIS™ are given in the diagrams at the end of the user instructions. Please note that they are only indicative information, because working and freezing times depend on temperature, mixing process and humidity rate and especially the direct ambient temperature, e.g. temperatures of cement powder, mixing system, table and hands are important.
- High temperature shortens the holding, operating and freezing times.

12. PREPARATION WITH VACUUM MIXING SYSTEMS

- In order to obtain bone cement with less air inclusion, liquid and powder are mixed under vacuum.
- For this reason, an air-proof mixing system is used so that adequate vacuum is acquired in the mixing vessel for a short period of time (absolute pressure of about 200 mbar).
- It is advised to cool the cement components in advance for at least 24 hours at 4–7°C. .
- Right before the mixing procedure of cement components, the cooler should be removed from the device and placed into the mixing device.
- Please perform the filling and mixing procedures under sterile conditions. Unless and otherwise advised, the mixing period is 30 seconds.
- Previous cooling extends operating and freezing times.
- The initial viscosity of ALCASIS™ Genta is low compared to the cement not cooled

previously.

- Finally, a mixture in form of homogenous and white paste occurs. This composition is ready for process at the moment when it takes a form not sticking to the plastic glove.
- Mixing (of liquid and powder components) is performed in a sterile ceramic, stainless steel and polypropylene container.

13. MANUAL PREPARATION

- Cement components should be filled into the mixing vessel just right before the mixing procedure.
- Filling and mixing procedures should be carried out under sterile conditions.

- Mixing period is 30 seconds. Within this period, two components mix by means of thoroughly mixing.
- Finally, a mixture in form of homogenous and white paste occurs. This composition is ready for process at the moment when it takes a form not sticking to the plastic glove.
- All the time, mix entire content of one bag with entire content of one monomer liquid ampule Mixing (of liquid and powder components) is performed in a sterile ceramic, stainless steel and polypropylene container.

14. BONE CEMENT USE

- For proper fixation, prosthesis should be placed and kept in place for a specified working time until the bone cement hardens completely.
- Mixing (of liquid and powder components) is performed in a sterile ceramic, stainless steel and polypropylene container.
- Excess of cement should be removed when they are soft.
- Prior to using the bone cement, the surgeon and other personnel to apply it should be acquainted with characteristics of the cement.
- Surgeant should have sufficient information about ALCASIS^{TM} Genta Bone Cement as well as tools to be used. To this end, it is recommended that the surgeant should try the bone cement in vitro under the specified environmental conditions prior to starting to use it continuously, and that to be acquainted with the critical characteristics of the cement such as liquidity, Fluidity and freezing time.
- You are recommended to comply with normal application rules of ALCASIS^{TM} Genta bone cement.

15. STORING

Do not store above 25 °C (77 °F). Store within the sealed original package in a clean and dry warehouse.

16. SHELF LIFE / STERILITY

- Shelf life is printed on the box, outer blister, ampoule blister and Tyvek sack.

- If the specified date has expired, do not use ALCASIS^{TM} Genta.
- Contents of the blister packages or ampoule blisters, opened or damaged, cannot be sterilized again and, therefore, should be disposed.
- If the cement powder turns to yellow in colour, do not use ALCASIS^{TM}.Liquid component of ALCASIS^{TM} Genta is sterilized in a bottle by method of liquid filtration method (aseptic) and the powder part of it is sterilized with ethylene oxide in a sterile barrier after it is put into a common blister package.

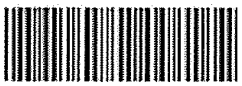
17. PATIENT POPULATION

- Bone cement is suitable for all patient population except for the patients who have no known or assumed excessive sensitivity to the bone cement ingredients, and who are not at the pregnancy and lactation period.
- It is not used in patients who carry an active or not fully treated infection in the bone region caused by strains insensitive to gentamicin.

18. TARGET USERS

- Designed for use by health professionals.

Symbols and Definitions as per EN 15223-1:2016 Standard

	Lot Number
	Production Date
	Expiry Date
	Do not expose to direct sunlight
	Avoid contact with water
	Barcode Number
	Do not sterilize for second time
	Do not use for second time
	See the user manual
	Do not use if package is damaged
	Manufacturer information
	Reference Number
	Maximum Temperature
	Sterilized Ethylene Oxide
	It is sterilized by liquid aseptic method