May 17, 2022

BONESUPPORT AB
℅ Hollace Saas Rhodes
Vice President, Orthopedic Regulatory Affairs
MCRA, LLC
803 7th Street NW, Floor 3
Washington, District of Columbia 20001

Re: DEN210044
Trade/Device Name: CERAMENT G
Regulation Number: 21 CFR 888.3046
Regulation Name: Resorbable calcium salt bone void filler containing a single approved aminoglycoside antibacterial
Regulatory Class: Class II
Product Code: QRR
Dated: September 27, 2021
Received: September 28, 2021

Dear Ms. Rhodes:

The Center for Devices and Radiological Health (CDRH) of the Food and Drug Administration (FDA) has completed its review of your De Novo request for classification of CERAMENT G, a prescription device under 21 CFR Part 801.109 with the following indications for use:

> CERAMENT G is a resorbable, gentamicin-eluting ceramic bone void filler intended for use as a bone void filler in skeletally mature patients as an adjunct to systemic antibiotic therapy and surgical debridement (standard treatment approach to a bone infection) as part of the surgical treatment of osteomyelitis in defects in the extremities. By eluting gentamicin, CERAMENT G can reduce the recurrence of chronic osteomyelitis from gentamicin-sensitive microorganisms in order to protect bone healing.
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> CERAMENT G can augment provisional hardware to help support bone fragments during the surgical procedure. The cured paste acts only as a temporary support media and is not intended to provide structural support during the healing process.
>
> CERAMENT G resorbs and is replaced by bone during the healing process.

Although this letter refers to your product as a device, please be aware that some granted products may instead be combination products. If you have questions on whether your product is a combination product, contact CDRHProductJurisdiction@fda.hhs.gov.

FDA concludes that this device should be classified into Class II. This order, therefore, classifies CERAMENT G, and substantially equivalent devices of this generic type, into Class II under the generic name resorbable calcium salt bone void filler containing a single approved aminoglycoside antibacterial.

FDA identifies this generic type of device as:

> **Resorbable calcium salt bone void filler containing a single approved aminoglycoside antibacterial.** A resorbable calcium salt bone void filler containing a single approved aminoglycoside antibacterial is a resorbable implant intended to fill bony defects of the extremities where there is an increased risk of infection. It is intended to resorb over time and be replaced by new bone. The product is intended for reduction of recurrence of chronic osteomyelitis of long bones. It is not intended to treat infection.

Section 513(f)(2) of the Food, Drug and Cosmetic Act (the FD&C Act) was amended by section 607 of the Food and Drug Administration Safety and Innovation Act (FDASIA) on July 9, 2012. This law provides two options for De Novo classification. First, any person who receives a "not substantially equivalent" (NSE) determination in response to a 510(k) for a device that has not been previously classified under the Act may request FDA to make a risk-based classification of the device under section 513(a)(1) of the Act. On December 13, 2016, the 21st Century Cures Act removed a requirement that a De Novo request be submitted within 30 days of receiving an NSE determination. Alternatively, any person who determines that there is no legally marketed device upon which to base a determination of substantial equivalence may request FDA to make a risk-based classification of the device under section 513(a)(1) of the Act without first submitting a 510(k). FDA shall, within 120 days of receiving such a request, classify the device. This classification shall be the initial classification of the device. Within 30 days after the issuance of an order classifying the device, FDA must publish a notice in the Federal Register announcing the classification.

On September 28, 2021, FDA received your De Novo requesting classification of CERAMENT G. The request was submitted under section 513(f)(2) of the FD&C Act. In order to classify CERAMENT G into class I or II, it is necessary that the proposed class have sufficient regulatory controls to provide reasonable assurance of the safety and effectiveness of the device for its intended use. After review of the information submitted in the De Novo request, FDA has determined that, for the previously stated indications for use, CERAMENT G can be classified in class II with the establishment of special controls for class II. FDA believes that class II (special) controls provide reasonable assurance of the safety and effectiveness of the device type. The identified risks to health and mitigation measures associated with the device type are summarized in the following table:

Identified Risk	Mitigation Measures
Recurring or persistent or new infection	Clinical performance testing Animal performance testing Non-clinical performance testing Product characterization, including drug substance Antimicrobial susceptibility testing Container compatibility testing Sterilization validation Stability and shelf life testing Drug quality attribute performance testing Pharmaceutical manufacturing information Aminoglycoside antibacterial approval
Adverse tissue reaction	Clinical performance testing Animal performance testing Biocompatibility evaluation Pharmaceutical manufacturing information
Antimicrobial resistance	Antimicrobial susceptibility testing Antimicrobial resistance analysis Labeling
Transient electrolyte imbalance (e.g., hyperkalemia, hypercalcemia, or hypocalcemia)	Clinical performance testing Animal performance testing Labeling
Incomplete bone formation or lack of bone formation	Clinical performance testing Animal performance testing Postmarket surveillance Labeling
Pathologic fracture	Clinical performance testing Animal performance testing Labeling
Product migration or extrusion	Clinical performance testing Animal performance testing Labeling
Drug-induced toxicity (e.g., nephrotoxicity and ototoxicity)	Clinical performance testing Animal performance testing Product characterization, including drug substance Drug quality attribute performance testing Pharmaceutical manufacturing information Labeling

In combination with the general controls of the FD&C Act, the resorbable calcium salt bone void filler containing a single approved aminoglycoside antibacterial is subject to the following special controls:

(1) Clinical performance testing must demonstrate that the product performs as intended under anticipated conditions of use. Clinical testing must evaluate recurrence of chronic osteomyelitis of long bones.

Testing must describe safe aminoglycoside serum levels below toxic concentrations. Imaging data (e.g., radiographs) must evaluate product resorption and new bone formation at the location where the product has been placed.

(2) Animal performance testing must demonstrate that the product performs as intended under anticipated conditions of use. Testing must include the following:

(i) Testing must characterize the performance of the product in an appropriate animal model. The model must mimic the identified clinical use, e.g., in a large animal infection model of osteomyelitis. Testing must characterize aminoglycoside serum levels and characterize product resorption and replacement by new bone, including the characterization of the rates of product resorption and new bone formation over clinically relevant timeframes.

(ii) Testing must be conducted in a relevant animal model to evaluate the pharmacology and toxicology of the final, finished product.

(3) Non-clinical performance testing must demonstrate that the product performs as intended under anticipated conditions of use. Testing must characterize the product in appropriate *in vitro* models.

(i) Elution kinetics studies must be conducted to determine the *in vitro* drug release profile of the aminoglycoside from the product lot(s) used for the clinical performance testing studies.

(ii) Dissolution testing must characterize the resorption profile of the product.

(iii) The following physical and chemical properties must be characterized for *in situ* setting products:

(A) Setting pH and reaction temperature;

(B) Setting and working times;

(C) Force required to transfer the product from the mixing container to the site of action;

(D) Chemical composition of the *in vivo*-cured product; and

(E) Dimensional stability of the *in vivo*-cured product.

(4) Characterization of the product, including the drug substance and drug constituent part components (as applicable), must demonstrate that critical quality attributes and specifications, including compendial requirements, are met and must include:

(i) Identification of, and justification for, the specification for each individual component (including the drug substance) of the drug constituent part of the product.

(ii) Confirmation that the aminoglycoside and drug constituent part components (if present) specifications conform to any corresponding United States Pharmacopeia (USP) monographs. In

addition, the aminoglycoside specification must also include other tests that ensure the quality of the product. These tests may, for example, include appearance, solubility, identification, related substances, ratios of active components, assay measured using high performance liquid chromatography (HPLC), or potency measured using a bioassay.

(iii) Identification of, and justification for, the product specification(s) to be met on release of each batch and on stability, including description, identification, aminoglycoside assay, *in vitro* elution, degradation products, elemental impurities, content uniformity, residual solvents, sterility, and endotoxin. If the aminoglycoside is prepared as a solution before mixing with the other components, that specification must include appearance, pH, and particulates.

(iv) Identification of, and justification for, the specifications that apply to the freshly mixed product (pre-setting configuration) and the mixed product administered from the mixing device/device constituent part and allowed to set over a specified time (post-setting configuration). For *in vitro* elution/drug release specifications, the acceptance criteria must include data from the product lot(s) used in clinical performance (or equivalent) studies.

(A) The specification must include tests adequate to ensure the quality attributes of the pre-setting configuration considering the product design, including but not limited to, tests for appearance, setting time, and injectability or extrusion force.

(B) The specification must include tests adequate to ensure the quality attributes of the post-setting configuration considering the product design, including but not limited to, tests for appearance, aminoglycoside assay, aminoglycoside degradants, aminoglycoside elution/drug release, uniformity, sterility, endotoxins, setting reaction temperature, working time, and usable amount of the product.

(v) For the specifications noted in (i)-(iv) above, a description of the analytical procedures and a summary of the analytical procedures development and validation must be provided. For *in vitro* elution/drug release specifications, data must be provided to demonstrate method adequacy, e.g., in terms of discriminating power for changes/differences in critical quality attributes that could impact product performance, stability-indicating potential, and/or *in vitro-in vivo* correlation.

(5) An analysis must be provided that identifies and evaluates any contribution to the development and spread of antimicrobial resistance.

(6) Susceptibility testing to the aminoglycoside must be conducted for all bacterial isolates identified during the clinical performance testing specified in special control (1).

(7) If FDA determines that the clinical performance testing specified in special control (1) is insufficient to evaluate long-term safety of the product, post-market surveillance (PMS) must evaluate new bone formation at the location where the product has been placed in accordance with an FDA-agreed upon protocol.

(8) The product, including the delivery device constituent part(s) (e.g., delivery syringes) and patient-contacting surgical instruments, must be demonstrated to be biocompatible.

(9) The product and each of its components (i.e., aminoglycoside and the drug constituent part components (if present)) must be demonstrated to be compatible with their respective commercial container closure system/packaging.

(10) Performance data must support the sterility and pyrogenicity of the product. The performance data must confirm that the sterilization process has no significant adverse impact (e.g., the generation of new degradants) on the drug quality attributes (e.g., assay, elution) of the product.

(11) Performance data must support the claimed expiration dating period/shelf life by demonstrating continued sterility, stability (see special control (12)(ii)), package integrity, and product functionality over the identified expiration/shelf life. Data to demonstrate continued sterility, stability, and package integrity must be collected for each component and the final, finished product. In addition, product functionality must be demonstrated for the final finished product. Extension of the expiration/shelf life must be submitted in a premarket notification and supported by the data described in this special control (11).

(12) Performance data from testing batches at release and on stability must characterize the drug quality attributes of the final, finished product (see special control (4)), demonstrate product specifications are consistently met, and support the claimed expiration/shelf-life date. This information must include the following:

(i) Batch Release Testing: Batch release data on multiple lots of the final, finished product manufactured using the proposed commercial process must demonstrate that specifications for each component and the final, finished product are met. Data on multiple lots of the mixed product (pre- and post-setting) obtained when the final, finished product is used according to the directions in the instructions for use must demonstrate that the pre- and post-setting specifications are met.

(ii) Stability Testing: The final, finished product manufactured using the proposed commercial process and in the proposed commercial packaging must be stored under tightly controlled conditions and periodically tested to demonstrate the stability of the drug constituent part (all components) and the final, finished product. In addition, at each pre-determined stability time point the product must meet the pre- and post-setting specifications. Testing must include three batches placed under long-term storage and accelerated stability conditions and then one batch placed on long-term stability each year. Testing must verify that the acceptance criteria for each specification are met at each stability time point. Parameters that are not expected to change on stability, *e.g.*, elemental impurities, only need to be tested at batch release, and a justification must be provided.

(13) Pharmaceutical manufacturing information must be provided, and appropriate documentation be available on inspection or if requested by FDA, for the drug constituent part and the final, finished product to demonstrate that the production processes are properly developed, conducted, controlled, and monitored. This information must include the following:

(i) A description of the manufacturing process and controls, including in-process controls, to ensure consistent quality. Such information may be provided by reference to a drug master file (DMF).

(ii) A description of the commercial batch formula, including the quality standard (*e.g.*, USP/National Formulary) to be met for each excipient, and representative Certificates of Analysis (COAs) for excipients to confirm quality.

(iii) Information or reference to one or more DMFs regarding the drug substance to understand the impurity profile, and representative COAs for the drug substance to confirm quality.

(iv) Identification and qualification of in-process hold times for the drug constituent part, where applicable.

(v) A description of how compliance with the current good manufacturing practice (CGMP) requirements is achieved at the facilities manufacturing the drug constituent part and final, finished product. This includes identification of the activities that occur at each site, and for any facilities for which 21 CFR 211 is not the established CGMP operating system, a description of how the facilities perform the responsibilities related to the subset of 21 CFR 211 requirements established in 21 CFR 4 subpart A.

(14) The product must contain a single approved aminoglycoside antibacterial.

(15) Labeling must include the following:

(i) Identification of the maximum volume of the product that may be safely implanted;

(ii) A detailed summary of the product's technical parameters;

(iii) An expiration date/shelf life;

(iv) A list of probable adverse events associated with the use of the product, including those observed during clinical performance studies;

(v) Warning about the risk of antimicrobial resistance and the risk of systemic adverse effects from the aminoglycoside;

(vi) Precaution against implanting into patients with calcium-metabolism issues; overfilling; adding other substances other than those provided (in absence of data on the use of the product mixed with other substances); overpressuring the product because this may lead to extrusion of the product beyond the site of its intended application and damage to surrounding tissues, and since this may lead to fat embolization or embolization of the product material into the bloodstream; and disturbing the product (over a specific time frame) once it begins to harden;

(vii) Instructions about proper placement and containment in the desired treatment area; adequate fixation (as necessary); product working time and setting time with any special instructions with respect to drying the surgical field and/or not irrigating the defect site prior to final setting of the

product (for a product intended to set in vivo); how and when excess material should be removed from the defect site;

(viii) When available, and according to the timeframe included in the post-market surveillance (PMS) protocol agreed upon with FDA as specified in special control (7), a detailed summary of the PMS data must be provided, including:

(A) Updates to the labeling to accurately reflect outcomes or necessary modifications based upon data collected during the PMS experience; and

(B) Inclusion of results and adverse events associated with utilization of the product during the PMS.

In addition, this is a prescription device and must comply with 21 CFR 801.109.

Section 510(m) of the FD&C Act provides that FDA may exempt a class II device from the premarket notification requirements under section 510(k) of the FD&C Act, if FDA determines that premarket notification is not necessary to provide reasonable assurance of the safety and effectiveness of the device type. FDA has determined premarket notification is necessary to provide reasonable assurance of the safety and effectiveness of the device type and, therefore, the device is not exempt from the premarket notification requirements of the FD&C Act. Thus, persons who intend to market this device type must submit a premarket notification containing information on the resorbable calcium salt bone void filler containing a single approved aminoglycoside antibacterial they intend to market prior to marketing the device.

Please be advised that FDA's decision to grant this De Novo request does not mean that FDA has made a determination that your device complies with other requirements of the FD&C Act or any Federal statutes and regulations administered by other Federal agencies. You must comply with all the FD&C Act's requirements, including, but not limited to: registration and listing (21 CFR Part 807); labeling (21 CFR Part 801); medical device reporting (reporting of medical device-related adverse events) (21 CFR 803) for devices or postmarketing safety reporting (21 CFR 4, Subpart B) for combination products (see https://www.fda.gov/combination-products/guidance-regulatory-information/postmarketing-safety-reporting-combination-products); good manufacturing practice requirements as set forth in the quality systems (QS) regulation (21 CFR Part 820) for devices or current good manufacturing practices (21 CFR 4, Subpart A) for combination products; and if applicable, the electronic product radiation control provisions (Sections 531-542 of the FD&C Act; 21 CFR 1000-1050).

A notice announcing this classification order will be published in the Federal Register. A copy of this order and supporting documentation are on file in the Dockets Management Branch (HFA-305), Food and Drug Administration, 5630 Fishers Lane, Room 1061, Rockville, MD 20852 and are available for inspection between 9 a.m. and 4 p.m., Monday through Friday.

As a result of this order, you may immediately market your device as described in the De Novo request, subject to the general control provisions of the FD&C Act and the special controls identified in this order.

For comprehensive regulatory information about medical devices and radiation-emitting products, please see Device Advice (https://www.fda.gov/medical-devices/device-advice-comprehensive-regulatory-assistance)

and CDRH Learn (https://www.fda.gov/training-and-continuing-education/cdrh-learn). Additionally, you may contact the Division of Industry and Consumer Education (DICE) to ask a question about a specific regulatory topic. See the DICE website (https://www.fda.gov/medical-devices/device-advice-comprehensive-regulatory-assistance/contact-us-division-industry-and-consumer-education-dice) for more information or contact DICE by email (DICE@fda.hhs.gov) or phone (1-800-638-2041 or 301-796-7100).

If you have any questions concerning the contents of the letter, please contact Aric Kaiser, M.S. at 301-796-6425.

Sincerely,

Raquel A. Peat -S

CAPT Raquel Peat, Ph.D., M.P.H., USPHS
Director
OHT6: Office of Orthopedic Devices
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