

INSTRUCTIONS FOR USE



For Single Patient Use on a Single Occasion Only

Product exposed to e-beam irradiation at approximately 25KGy. This allograft product is derived from voluntarily donated human tissues from a single human donor.

Indications for Use:

Origen™ DBM with BioActive Glass is indicated to be gently placed into bony voids or gaps of the skeletal system that are not intrinsic to the stability of the bony structure. (e.g., the extremities and pelvis). These defects may be surgically created osseous defects or osseous defects created from traumatic injury to the bone. The product provides a bone graft substitute that remodels into the recipient's skeletal system.

Contraindications:

Origen™ DBM is contraindicated where the device is intended as structural support in load-bearing bone and in articulating surfaces. Infection at the surgical site and/or distant foci of infections that may spread to the surgical site is a contraindication.

Do not use Origen™ DBM if package integrity has been compromised

POSSIBLE ADVERSE EFFECTS

Possible adverse effects include but are not limited to:

- Wound complications including hematoma, site drainage, bone fracture, infection, and other complications that are possible with any surgery.
- The transmission of known pathogens including Human Immunodeficiency Virus 1/2, Hepatitis B and C, Human T-Lymphotropic Virus I and II, Syphilis, bacteria, and fungi.
- Incomplete or lack of osseous ingrowth into bone void, as is possible with any bone void filler.

In the event of a severe adverse reaction to the product, a second surgery may be required to remove any remaining product.

Description:

Origen™ DBM is a bone void filler comprised of a gelatin carrier, bioactive glass (45s5) and human demineralized bone matrix (DBM) intended for transplantation. Origen™ DBM has been formulated to reconstitute into a paste upon addition of a sterile fluid (sterile saline, water for injection). Origen™ DBM is provided in a sterile, single-use syringe. Since Origen™ DBM contains biological materials, some variations in product appearance and handling should be expected. Origen™ DBM is pyrogen free.

Tissue Donor Selection:

All human tissue used in the manufacture of Origen™ DBM is recovered by tissue banks in the United States of America in accordance with standards established by the American Association of Tissue Banks (AATB). The tissue bank has evaluated the tissue donor and determined that the donor met suitability criteria that were current at the time of tissue recovery. The tissue bank's evaluation included review of the tissue donor's infectious disease test results; consent documents;

donor's medical history and behavior risk assessment; available relevant medical records including previous medical history; laboratory test results; existing autopsy or coroner reports, if applicable; and information from other sources or records which may pertain to donor suitability including tissue procurement test results. Origen™ DBM is manufactured only from donors that do not reveal risk factors for, or clinical or physical evidence of, significant active infection, including human immunodeficiency virus (HIV) or hepatitis infection, as well as risk factors for viral or prion-associated disease transmission as specified in Appendix II of the AATB standards.

Serological Testing:

The tissue bank performs serological testing of each tissue donor at a CLIA approved laboratory using FDA-approved test kits. Samples of this donor's blood were taken at the time of tissue recovery were tested and found to be negative for (at minimum): hepatitis B surface antigen (HBsAg), hepatitis B core antibody (HBcAb), HIV antibodies type 1 and type 2 (anti-HIV-1 and anti-HIV-2), antibody to human T-lymphotropic virus type 1 and type 2 (anti-HTLV-I/II), hepatitis C virus antibody (anti-HCV) and syphilis. In addition, this donor was tested and found to be negative for HIV type 1 p24 antigen (HIV-1-p24 Ag). The contact information for the testing laboratories, the listing and interpretation of all required infectious disease tests, a listing of the documents reviewed as part of the relevant medical records and the name of the person/establishment determining the suitability of the human tissue component of this device are on file at Nanotherapeutics and are available upon written request. The allograft component of this device has been determined to be suitable for transplantation.

Instructions for Use:

- Peel open outer package using sterile technique and transfer inner pouch to a sterile field.
- Peel open inner pouch and remove syringes (product syringe and fluid transfer syringe).
- Fill fluid transfer syringe with sterile reconstitution fluid (sterile saline, water for injection) per the Table below.

Product Size	Reconstitution Fluid Volume
10 cc	7.0 cc
5 cc	3.5 cc
2 cc	1.5 cc
- Attach fluid transfer syringe to female luer port on the product syringe and hold the assembly vertically with the product syringe over the fluid transfer syringe.
- While holding the assembly upright, inject reconstitution fluid into product syringe. Then compress the plunger in the product syringe until all the air is removed and the powder is wetted. Stop compressing if reconstitution fluid starts to appear on the top side of the plunger tip.
- Wait 30 seconds for the fluid to absorb into the powder.
- Grasp the valve assembly at the end of the product syringe and twist to remove the valve and fluid transfer syringe.
- Apply constant, steady pressure to the product plunger to express the paste gently into the cavity. Take care not to over-pressurize the defect site since this may lead to fat embolization or embolization of the device material into the bloodstream. Product may become more difficult to express after ten (10) minutes.
- Discard appropriately any unused product as well as the fluid transfer syringe.

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WARNINGS AND PRECAUTIONS

- ◆ Origen™ DBM is intended to be bacteriologically sterile during the stated shelf life in an unopened and undamaged package. The product may be used up to the expiration date.
- ◆ Do not use if the package has been damaged and/or the product has been contaminated. In the event of contamination, discard the entire product. Damaged product and/or packaging may be returned to Nanotherapeutics, Inc.
- ◆ Since Origen™ DBM is not a load bearing graft material, appropriate placement and/or fixation are critical factors in the avoidance of potentially adverse effects.
- ◆ It is important to protect against over-pressurizing the defect site since this may lead to fat embolization or embolization of the device material into the bloodstream.
- ◆ As with all biological products, the tissue component of Origen™ DBM has the potential to transmit infectious agents despite processing treatments, extensive donor screening, tissue selection and laboratory testing.
- ◆ The use of this product does not alter the inherent risks of infection attendant with any surgical procedure.
- ◆ Caution should be used in the use of this device in uncooperative patients, or patients with neurological disorders who are incapable of following directions (including weight control and activity levels) and in patients with disorders or diseases which may impair bone formation have not been established.
- ◆ Origen™ DBM should only be used on pregnant women in consultation with their primary care physician.
- ◆ Although the production techniques used on this product minimize the antigenic properties of the product, the possibility of an antigenic response exists.
- ◆ Adverse outcomes that are potentially attributable to this product must be reported promptly to Blackstone Medical, Inc./Orthofix Inc. Any dissatisfaction with the product performance or packaging should be reported promptly to Blackstone Medical, Inc. or Orthofix Inc.
- ◆ The production of Origen™ DBM is completed under environmentally controlled conditions. All steps are rigorously quality controlled. The tissue component of this device may have been processed with isopropyl alcohol, phosphate buffer and/or hydrochloric acid and, as such, may contain trace amounts of these processing agents. Caution should be exercised if the patient is allergic to these processing agents.

Osteoinductive Potential:

Each lot of DBM incorporated into Origen™ DBM with Bioactive Glass is evaluated for osteoinductive potential using an *in vitro* bioassay. Results from this bioassay were correlated to the athymic rat model. Testing each lot of DBM with this cell bioassay assures that only DBM with osteoinductive potential is used in Origen DBM. The combination of DBM, Bioactive Glass and porcine gelatin has not been evaluated for osteoinductivity; therefore, it is unknown to what extent the formulation components may alter the osteoinductive character of the DBM. Therefore it is unknown how the OI of the DBM component, measured via the *in vitro* bioassay, will correlate with human clinical performance of Origen DBM with Bioactive Glass.

Sterilization:

Product exposed to e-beam irradiation at approximately 25KGy. A sterilization indicator label is located on the product packaging and indicates that irradiation exposure has occurred.

DO NOT RE-STERILIZE THIS PRODUCT!

Storage Conditions:

Do not expose product to extreme heat or cold. Store the product away from direct sunlight at room temperature in a clean, dry place. It is the responsibility of the user facility/physician to maintain the product under appropriate conditions prior to use.

Recipient Tracking:

Important Notice to End User: The clinician or hospital is responsible for maintaining recipient records for the purpose of tracking tissue post-implantation. A graft tracking record has been included for completion at the time of the surgical procedure. A completed copy is to be retained in the patient record and the original should be sent to Nanotherapeutics, Inc. as indicated on the form. If the entire product is discarded for any reason, please return the graft tracking record form and note the reason for discard.

Patents Pending.

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

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