



March 14, 2018

To Whom It May Concern,

IsoTis OrthoBiologics, a member of the SeaSpine Orthopedics Corporation family of companies, manufactures Allosync™ on behalf of Arthrex, Inc. Allosync™ is a private label of DynaGraft II and OrthoBlast II, previously cleared by the FDA as outlined below.

Arthrex Brand Name	Arthrex Catalog #	IsoTis Product Name	IsoTis Product 510(k)	IsoTis Device Listing #
Allosync™ Gel	ABS-2013-01 ABS-2013-05 ABS-2013-10	DynaGraft® II Gel	K040419	D244930
Allosync™ Putty	ABS-2012-01 ABS-2012-02 ABS-2012-05 ABS-2012-10	DynaGraft® II Putty		
Allosync™ CB Paste	ABS-2015-01 ABS-2015-03 ABS-2015-08	OrthoBlast® II Paste	K050642 K070751	D244937 D244945
Allosync™ CB Putty	ABS-2014-05 ABS-2014-10	OrthoBlast® II Putty		

Allosync™ Gel/Putty and Allosync™ CB Paste/Putty are identical to DynaGraft® II Gel/Putty and OrthoBlast® II Paste/Putty, respectively, in formulation, safety, effectiveness and indications. The only differences between the Arthrex and SeaSpine products is branding on the label, box artwork, and IFU.

Sincerely,

Caryn Sailor
Regulatory Affairs Specialist
SeaSpine Orthopedics Corporation/IsoTis OrthoBiologics, Inc.

K061880

AUG 15 2007

510(K) SUMMARY

ISOtis Accell DBM Family of Products

SUBMITTER'S NAME, ADDRESS, TELEPHONE NUMBER, CONTACT PERSON AND DATE PREPARED

IsoTis OrthoBiologics, Inc.
2 Goodyear
Irvine CA 92618 U.S.A.

PHONE: (949) 855-7168

CONTACT PERSON: Karon Morell

DATE PREPARED: August 10, 2007

NAME OF DEVICE:

Accell Family of Products (Accell DBM 100, Accell TBM,
A2i, and Accell Connexus)

COMMON OR USUAL NAME

Bone Void Filler

CLASSIFICATION NAME

21 C.F.R. § 888.3045 Resorbable calcium salt bone void
filler device

PREDICATE DEVICES

DynaGraft II Paste and Putty (K040419)
AlloMatrix® DBM Putty with inert carrier Sodium
Carboxymethylcellulose (K040980)
InterGro® DBM with inert carrier Lecithin (K031399)
Osteofil Paste DBM with inert carrier Porcine Collagen
(K043420)

INTENDED USE/INDICATIONS

The Accell Family of products are intended for filling voids and gaps in the skeletal system that are not intrinsic to the stability of the bony structure. The products are indicated for use as bone graft extenders in the spine, extremities and pelvis, or as bone void fillers in the extremities and pelvis. The voids or gaps may be surgically created defects or the result of traumatic injury to the bone.

DEVICE DESCRIPTION

Accell DBM family of products are used for orthopaedic bone grafting procedures. They are osteoconductive human allogenic demineralized bone filling materials for use as fillers for gaps or voids that are not intrinsic to the stability of the bony structure.

Accell DBM family of products are products that are manufactured using human donor demineralized bone and may contain up to 70% poloxamer reverse phase medium carrier (RPM). The demineralized bone is derived from human ground, cortical allograft bone. Poloxamer RPM is an inactive product ingredient that is utilized as a containing agent for the demineralized bone and provides appropriate product handling characteristics for the products.

The products of the Accell DBM family are comprised of the same DBM and RPM components as found in DynaGraft II Gel, FDA cleared under 510(k) number K040419 and Connexus cleared under 510(k)'s K050690 and K052098. In addition, the Accell DBM family of products may contain up to a maximum of 70% of RPM carrier. This is the concentration of RPM already cleared in DynaGraft II gel.

SUMMARY OF PERFORMANCE TESTING

The poloxamer RPM granules used to prepare the carrier in two of the Accell DBM family of products are characterized to confirm the chemical composition. The carrier is analyzed for pH, physical characteristics and appearance. A resorption study has been performed to examine the rate and extent of carrier elimination in male adult rats.

Resorption of the DBM was demonstrated during rabbit animal studies. After 12 weeks, very little of the DBM could be detected and most had been remodeled.

Viral inactivation studies have been performed for the demineralization process in combination with terminal sterilization processing.

Several animal studies were performed on both Connexus and DynaGraft II Gel and were submitted as part of their original 510(k) submissions (K050690 and K040419). Additional animal studies have been performed and previously submitted in the 510(k) supplements, for the Accell DBM family of products. These studies included rabbit tibial critical size defects and rabbit spinal fusion studies.

These studies confirmed that the Accell products raised no safety or performance issues and are substantially equivalent to the predicate device, DynaGraft II Gel Demineralized Bone Matrix.

OSTEOINDUCTIVE POTENTIAL

Each lot of DBM used to manufacture the Accell DBM family of products is tested for osteoinductive potential using an *in vitro* cell culture test. The *in vitro* cell culture assay has been validated to correlate to an athymic rat osteoinductive potential assay. It is unknown how osteoinductivity potential, measured via the *in vitro* cell culture or athymic rat assays, will correlate with human clinical performance.

VIRAL INACTIVATION VALIDATION

The methods for processing of the DBM contained in the Accell Family of products were evaluated for their viral inactivation potential. A selected panel of viruses representing various virus types, sizes, shapes and genomes were evaluated. The viral inactivation testing demonstrated suitable inactivation potential of the processing methods for a wide range of potential viruses.



Food and Drug Administration
9200 Corporate Boulevard
Rockville MD 20850

AUG 15 2007

IsoTis OrthoBiologics, Inc.
c/o Ms. Karen Morell
Director Quality Assurance and Regulatory Affairs
2 Goodyear
Irvine, CA 92618

Re: K061880
Trade Name: Accell Family of Products (Accell DBM 100, Accell TBM, A2i,
and Accell Connexus)
Regulation Number: 21 CFR 888.3045
Regulation Name: Resorbable calcium salt bone void filler devices
Regulatory Class: Class II
Product Code: MBP, MQV
Dated: May 28, 2007
Received: May 30, 2007

Dear Ms. Morell:

We have reviewed your Section 510(k) premarket notification of intent to market the device referenced above and have determined the device is substantially equivalent (for the indications for use stated in the enclosure) to legally marketed predicate devices marketed in interstate commerce prior to May 28, 1976, the enactment date of the Medical Device Amendments, or to devices that have been reclassified in accordance with the provisions of the Federal Food, Drug, and Cosmetic Act (Act) that do not require approval of a premarket approval application (PMA). You may, therefore, market the device, subject to the general controls provisions of the Act. The general controls provisions of the Act include requirements for annual registration, listing of devices, good manufacturing practice, labeling, and prohibitions against misbranding and adulteration.

If your device is classified (see above) into either class II (Special Controls) or class III (PMA), it may be subject to such additional controls. Existing major regulations affecting your device can be found in the Code of Federal Regulations, Title 21, Parts 800 to 898. In addition, FDA may publish further announcements concerning your device in the Federal Register.

Please be advised that FDA's issuance of a substantial equivalence determination does not mean that FDA has made a determination that your device complies with other requirements of the Act or any Federal statutes and regulations administered by other Federal agencies. You must comply with all the Act's requirements, including, but not limited to: registration and listing (21 CFR Part 807); labeling (21 CFR Part 801); good manufacturing practice requirements as set forth in the quality systems (QS) regulation (21 CFR Part 820); and if

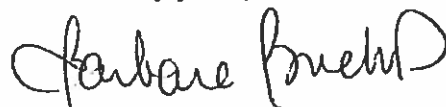
Page 2 - Ms. Karen Morell

applicable, the electronic product radiation control provisions (Sections 531-542 of the Act); 21 CFR 1000-1050.

This letter will allow you to begin marketing your device as described in your Section 510(k) premarket notification. The FDA finding of substantial equivalence of your device to a legally marketed predicate device results in a classification for your device and thus, permits your device to proceed to the market.

If you desire specific advice for your device on our labeling regulation (21 CFR Part 801), please contact the Office of Compliance at (240) 276-0120. Also, please note the regulation entitled, "Misbranding by reference to premarket notification" (21CFR Part 807.97). You may obtain other general information on your responsibilities under the Act from the Division of Small Manufacturers, International and Consumer Assistance at its toll-free number (800) 638-2041 or (240) 276-3150 or at its Internet address <http://www.fda.gov/cdrh/industry/support/index.html>.

Sincerely yours,



Mark N. Melkerson
Director
Division of General, Restorative
and Neurological Devices
Office of Device Evaluation
Center for Devices and
Radiological Health

Enclosure

Indications for Use Statement

510(k) Number (if known): K061880

Device Name: **Accell Family of Products (Accell DBM 100, Accell TBM, A2i, and Accell Connexus)**

Indications for Use:

The Accell Family of products are intended for filling voids and gaps in the skeletal system that are not intrinsic to the stability of the bony structure. The products are indicated for use as bone graft extenders in the spine, extremities and pelvis, or as bone void fillers in the extremities and pelvis. The voids or gaps may be surgically created defects or the result of traumatic injury to the bone.

Prescription Use
(Part 21 C.F.R. 801 Subpart D)

AND/OR

Over-The-Counter Use
(21 C.F.R. 807 Subpart C)

(PLEASE DO NOT WRITE BELOW THIS LINE – CONTINUE ON ANOTHER PAGE IF NEEDED)

Concurrence of CDRH, Office of Device Evaluation (ODE)

Barbara Powell
(Division Sign-Off)
**Division of General, Restorative
and Neurological Devices**

510(k) Number K061880



DIRECTIONS FOR USE

AlloSync™

Demineralized Bone Matrix

CAUTION: Federal (U.S.) Law restricts the use of this device to sale by or on the order of a physician.

The inner package and its contents are sterile
For single patient use on a single occasion only

The demineralized bone matrix (DBM) in this product is derived from voluntarily donated human tissues.

INDICATIONS FOR USE

AlloSync™ is indicated for orthopedic applications as filler for gaps or voids that are not intrinsic to the stability of the bony structure. AlloSync is indicated to be packed gently into bony gaps in the skeletal system as a bone graft extender (extremities, spine, pelvis) and as bony void filler of the extremities and pelvis. These defects may be surgically created or from the result of traumatic injury to the bone.

DESCRIPTION

AlloSync is derived from selected donated human bone tissue that has been processed into particles. The bone particles are subsequently demineralized using a hydrochloric acid process. The demineralized bone matrix (DBM) is combined with a reverse phase carrier and formulated to a gel or putty-like consistency.

AlloSync is provided in a sterile, single patient use package. As biological materials, some variations in the product should be expected, such as in appearance and in handling.

CONTRAINDICATIONS

AlloSync is contraindicated where the device is intended as structural support in load-bearing bone and in articulating surfaces. Conditions representing relative contraindications include:

- Severe vascular or neurological disease
- Uncontrolled diabetes
- Severe degenerative bone disease
- Uncooperative patients who will not or cannot follow postoperative instructions, including individuals who abuse drugs and/or alcohol
- Renal impairment
- Active or latent infection in or around the surgical site
- Polymyxin B Sulfate, Bacitracin, Gentamycin and Iodine are used in the processing of the DBM used in AlloSync Gel and Putty and trace amounts may remain. Since it is impossible to quantify the levels at which any individual may have an allergic response, this product is contraindicated in patients with known sensitivity to these compounds.

PATIENT SELECTION FACTORS

Procedures involving bone grafting can experience highly variable results. Factors to be considered in selecting the bone grafting material and the surgical technique to be utilized are as follows:

- Age of the patient
- Quality of the patient's bone
- Location of the defect
- Anticipated loading conditions
- Proximity of the graft to a suitable blood supply
- Ability to achieve direct apposition of the graft to viable host bone
- Presence/addition of autogenous bone or bone marrow at the graft site
- Elimination of gaps in the graft site
- Ability to suitably stabilize the graft site
- Complete coverage of the graft material to prevent migration

INSTRUCTIONS FOR USE

These instructions are intended as guidelines for the use of AlloSync as a part of established surgical techniques. They are not intended to replace or change standard procedures for treatment of bone defects involving bone grafting and internal fixation. For best results, extreme care should be exercised to assure the correct graft material is selected for the intended application.

PREOPERATIVE PREPARATION

Aseptic techniques must be maintained to minimize the risk of post-operative complications. The amount needed is based on the type of procedure and size of the defect being treated. When AlloSync is being mixed with autograft, a ratio of 1:1 should be used. AlloSync does not require rehydration prior to use.

Radiographic evaluation of the defect site is essential to accurately assess the extent of the defect and to aid in the selection and placement of AlloSync and fixation devices. AlloSync does not possess sufficient mechanical strength to support the reduction of a graft site prior to tissue in-growth. Therefore, anatomical reduction and rigid fixation, in all planes, should be obtained independent of AlloSync.

For best results, AlloSync must fill the defect and contact as much viable bone as possible.

AlloSync must not be used to repair bone defects where complete soft tissue coverage cannot be achieved.

REMOVING THE PRODUCT FROM PACKAGING

For putty

1. Peel open outer package.
2. Using aseptic technique, transfer contents to a sterile field.
3. Peel open inner package and remove spatula and vial.
4. Twist off vial lid and remove putty using small spatula or other hand instrument.
5. Discard any unused portion.

For gel

1. Peel open outer package.
2. Using aseptic technique, transfer contents to a sterile field.
3. Peel open inner package and remove syringe.
4. Remove protective cap from syringe tip.
5. Depress the plunger to extrude the implant material.
6. Discard any unused portion.

POSTOPERATIVE CARE

Postoperative patient management should follow the same regimen as similar cases utilizing autogenous bone grafting. Standard postoperative practices should be followed, particularly as applicable to defect repairs involving the use of fixation devices. The patient should be cautioned against early weight bearing and premature ambulation that could lead to loosening and/or failure of the fixators or loss of reduction.

The length of time a defect should remain in a reduced state of loading is determined by the complexity of the defect site and the overall physical condition of the patient. Hardware should not be removed until the defect is healed.

WARNINGS

- The product must be used prior to the expiration date.
- For single use only.
- Do not re-sterilize.
- Do not use if packaging has been damaged and/or the product has been compromised. In the event packaging has been compromised, discard the product. Damaged packaging should be returned to the manufacturer.
- Do not use to support reduction of a defect site. Rigid fixation techniques are recommended as needed to assure stabilization of the defect in all planes. Screws must gain purchase in the host bone as opposed to the AlloSync.
- Do not use to repair bone defects where soft tissue coverage cannot be achieved as complete post-operative wound closure is necessary.
- Do not overfill the graft site.

POTENTIAL ADVERSE EVENTS

Surgical procedures involving implantation of bone grafts are associated with the following risks:

- Superficial wound infection
- Deep wound infection with or without osteomyelitis
- Nonunion, delayed union and/or malunion
- Wound dehiscence
- Loss of reduction
- Refracture
- Cyst recurrence
- Hematoma
- Cellulitis

Adverse outcomes attributable to the product must be reported promptly to Arthrex, Inc and IsoTis OrthoBiologics, Inc. If any dissatisfaction with the product performance or packaging occurs, notify Arthrex, Inc. immediately and promptly return product and/or packaging to IsoTis OrthoBiologics, Inc.

PRECAUTIONS

- AlloSync is sterile for the duration of the product's shelf life, provided that the package is in its original sealed condition and that it is unopened and undamaged.
- As with all biological products, the tissue in AlloSync has the potential to transmit infectious agents despite processing treatments, extensive donor screening, tissue selection and laboratory testing. To date, there have been no reports of experimental or clinical viral seroconversion attributed to the use of demineralized bone.
- As with any surgical procedure, the possibility of infection exists.
- Although the production technique is designed to eliminate antigenic properties of the product, the possibility of such a reaction is present.
- Once the container seal has been compromised, the tissue product shall be either transplanted, if appropriate, or otherwise discarded.
- Use caution when filling a closed defect. Resistance during extrusion may be an indication of over pressurization. Excessive pressurization of the device could result in fat embolization and/or embolization of the material into the bloodstream.
- When introducing AlloSync, care must be taken to avoid excessive compaction.
- Appropriate placement and/or fixation are critical factors in the avoidance of potentially adverse effects.
- Overfilling the implantation site should be avoided to achieve a tension-free closure of the wound.

HUMAN TISSUE DONOR SELECTION

All tissue used in AlloSync is recovered from donors and by tissue banks in the United States in accordance with regulations and standards established by the U.S. Food and Drug Administration (FDA) and the American Association of Tissue Banks (AATB). The tissue bank (as identified on the product's outer packaging) has evaluated the tissue donor and determined that the donor met suitability criteria that were current at the time. The tissue bank's evaluation included review of the tissue donor's infectious disease test results, consent documents, medical and social interview, assessment of the donor's

body, available relevant medical records including previous medical history, laboratory test results, review of postmortem examination results (if applicable) and information from other sources or records which may pertain to donor eligibility including tissue procurement test results. The review did not reveal risk factors for, conditions indicating clinical and/or physical evidence of infectious disease, or communicable disease agents or diseases, including HIV (human immunodeficiency virus) or hepatitis, or risk factors for viral or prion-associated disease transmission as specified in 21 CFR 1271 Subpart C and Appendix II of the AATB standards.

SEROLOGICAL TESTING OF HUMAN TISSUE

Donor blood samples taken at the time of recovery were tested by laboratories registered with the FDA to perform donor testing and certified to perform such testing on human specimens in accordance with Clinical Laboratory Improvement Amendments of 1988 (CLIA) and 42 CFR Part 493, or that has met equivalent requirements as determined by the Centers for Medicare and Medicaid Services (CMS), and were found negative or nonreactive using FDA licensed, cleared or approved, tests for:

- HIV antibodies type 1 and type 2 (anti-HIV-1 and anti-HIV-2)
- HIV-1 Nucleic Acid testing (HIV NAT)
- Hepatitis B Surface antigen (HBsAg)
- Hepatitis B Core Antigen [anti-HBc (IgG and IgM)]
- Hepatitis B Virus Nucleic Acid Tests [HBV NAT]
- Hepatitis C Virus Nucleic Acid Test (HCV NAT)
- Hepatitis C Virus Antibody (anti-HCV)
- *Treponema pallidum* (Syphilis)

In addition, testing may have been conducted for Human T-Lymphotropic Virus type 1 and type 2 (anti-HTLV-1/II). The names and addresses of 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 or establishment determining the suitability of this human tissue are on file at the tissue bank and are available upon request. This tissue has been determined to be suitable for transplantation based on the results of screening and testing.

VIRAL INACTIVATION

The methods for processing of the DBM contained in AlloSync were evaluated for their viral inactivation potential. A selected panel of viruses representing various virus types, sizes, shapes and genomes were evaluated. The viral inactivation testing demonstrated suitable inactivation potential of the processing methods for a wide range of potential viruses.

OSTEOINDUCTIVE POTENTIAL

The osteoinductive potential of the Demineralized Bone Matrix (DBM) used in AlloSync Gel and Putty is determined via an *in vitro* assay. Results from the assay were correlated with results from implantation of DBM into an athymic mouse muscle pouch. Analysis of these results shows that the *in vitro* assay has been validated against the *in vivo* athymic mouse model and predicts with at least 95% confidence the *in vivo* osteoinductivity of the test material.

Each lot of DBM incorporated in AlloSync Gel and Putty is evaluated for osteoinductive potential using an *in vitro* assay. Testing each lot of DBM assures that only DBM with osteoinductive potential is used in AlloSync Gel and Putty. Although DBM used in the final product has been shown to be osteoinductive using an *in vitro* assay, the combination of DBM and a poloxamer has not been evaluated for osteoinductivity; therefore, it is unknown to what extent the formulation components may alter the osteoinductivity of the DBM. Additionally, it is unknown how osteoinductivity of the DBM component, measured via the *in vitro* assay, will correlate with human clinical performance of AlloSync Gel and Putty.

STERILIZATION

AlloSync has been sterilized by electron beam irradiation. The inner package and its contents are sterile. The package should be inspected prior to use to ensure the sterility barrier has not been compromised. This product is for single use only and **must not be re-sterilized**. The product must not be used beyond the stated expiration date.

If it appears that the product or its packaging has been compromised, both the product and the packaging should be returned to the manufacturer.

STORAGE

- Store at room temperature (15°C to 30°C) in a clean, dry place.
- Do not refrigerate or freeze.
- Do not expose to extreme heat.
- It is the responsibility of the tissue dispensing service and user (facility/clinician) to maintain the product under appropriate conditions prior to use.
- Discard any unused product.

RECIPIENT TRACING

The clinician or hospital is responsible for maintaining recipient records for the purpose of tracing tissue post-implantation. A Graft Tracing Record has been included for completion at the time of the surgical procedure. Upon completion, the Graft Tracing Record is to be sent back to the manufacturer. If the entire tissue product was discarded, return the Graft Tracing Record and explain the reason for discard. Chart labels are provided in each package for use on the patient's medical records. These labels provide traceability to the original tissue donor.

PRODUCT INFORMATION DISCLOSURE

IsoTis OrthoBiologics, Inc ("IsoTis") HAS EXERCISED REASONABLE CARE IN THE SELECTION OF MATERIALS AND THE MANUFACTURE OF THESE PRODUCTS. IsoTis EXCLUDES ALL WARRANTIES, WHETHER EXPRESSED OR IMPLIED, INCLUDING BUT NOT LIMITED TO, ANY IMPLIED WARRANTIES OF MERCHANTABILITY OR FITNESS FOR A PARTICULAR PURPOSE. IsoTis SHALL NOT BE LIABLE FOR ANY INCIDENTAL OR CONSEQUENTIAL LOSS, DAMAGE, OR EXPENSE, DIRECTLY OR INDIRECTLY ARISING FROM USE OF THIS PRODUCT. IsoTis NEITHER ASSUMES NOR AUTHORIZES ANY PERSON TO ASSUME FOR IT ANY OTHER OR ADDITIONAL LIABILITY OR RESPONSIBILITY IN CONNECTION

WITH THESE PRODUCTS. IsoTis INTENDS THAT THIS DEVICE SHOULD BE USED ONLY BY PHYSICIANS HAVING RECEIVED PROPER TRAINING IN THE USE OF THE DEVICE.

An explanation of the symbols used on product labeling is provided below.



Sterilized using irradiation



Consult Instructions for Use



Expiration date (YYYY-MM-DD)



Do not re-use



Temperature limitation

Rx ONLY

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



Catalog number



Lot number



Manufacturer



Do not use if package is damaged



Do not re-sterilize

Not made with natural rubber latex



Manufactured by:
IsoTis OrthoBiologics, Inc
2 Goodyear, Irvine, CA 92618 USA

U.S. Patents 6,309,659; 6,623,748; 7,205,337; 7,241,813

Manufactured for:
Arthrex, Inc.
1370 Creekside Blvd.
Naples, FL 34108
800-934-4404





DIRECTIONS FOR USE

AlloSync™ CB

Demineralized Bone Matrix with Cancellous Bone

CAUTION: Federal (U.S.) Law restricts the use of this device to sale by or on the order of a physician.

The inner package and its contents are sterile
For single patient use on a single occasion only

The demineralized bone matrix (DBM) in this product is derived from voluntarily donated human tissues.

INDICATIONS FOR USE

For orthopedic use, the AlloSync™ CB Paste and Putty are intended for use as an autograft extender (extremities, spine and pelvis) and as a bone void filler (extremities and pelvis) for bony voids or gaps that are not intrinsic to the stability of the bony structure. The AlloSync CB products are indicated to be packed gently into bony defects of the skeletal system. These defects may be surgically created or from the result of traumatic injury to the bone.

DESCRIPTION

AlloSync CB is derived from selected donated human bone tissue that has been processed into particles. The particles are subsequently demineralized using a hydrochloric acid process. The demineralized bone matrix (DBM) is combined with a reverse phase carrier, cancellous chips from the same donor, and then formulated to a paste or putty-like consistency.

AlloSync CB is provided in a sterile, single patient use package. As biological materials, some variations in the product should be expected, such as in appearance and in handling.

CONTRAINDICATIONS

AlloSync CB is contraindicated where the device is intended as structural support in load-bearing bone and in articulating surfaces. Conditions representing relative contraindications include:

- Severe vascular or neurological disease
- Uncontrolled diabetes
- Severe degenerative bone disease
- Uncooperative patients who will not or cannot follow postoperative instructions, including individuals who abuse drugs and/or alcohol
- Renal impairment
- Active or latent infection in or around the surgical site
- AlloSync CB Putty contains cancellous particles up to 4 mm in size. Do not use for Dental Applications
- Polymyxin B Sulfate, Bacitracin, Gentamycin and Iodine are used in the processing of the DBM used in AlloSync CB Putty and Paste and trace amounts may remain. Since it is impossible to quantify the levels at which any individual may have an allergic response, this product is contraindicated in patients with known sensitivity to these compounds.

PATIENT SELECTION FACTORS

Procedures involving bone grafting can experience highly variable results. Factors to be considered in selecting the bone grafting material and the surgical technique to be utilized are as follows:

- Age of the patient
- Quality of the patient's bone
- Location of the defect
- Anticipated loading conditions
- Proximity of the graft to a suitable blood supply
- Ability to achieve direct apposition of the graft to viable host bone
- Presence/addition of autogenous bone or bone marrow at the graft site
- Elimination of gaps in the graft site
- Ability to suitably stabilize the graft site
- Complete coverage of the graft material to prevent migration

INSTRUCTIONS FOR USE

These instructions are intended as guidelines for the use of AlloSync CB as a part of established surgical techniques. They are not intended to replace or change standard procedures for treatment of bone defects involving bone grafting and internal fixation. For best results, extreme care should be exercised to assure the correct graft material is selected for the intended application.

PREOPERATIVE PREPARATION

Aseptic techniques must be maintained to minimize the risk of post-operative complications. The amount needed is based on the type of procedure and size of the defect being treated. When AlloSync CB is being mixed with autograft, a ratio of 1:1 should be used. AlloSync CB does not require rehydration prior to use.

Radiographic evaluation of the defect site is essential to accurately assess the extent of the defect and to aid in the selection and placement of AlloSync CB and fixation devices. AlloSync CB does not possess sufficient mechanical strength to support the reduction of a graft site prior to tissue in-growth. Therefore, anatomical reduction and rigid fixation, in all planes, should be obtained independent of AlloSync CB.

For best results, AlloSync CB must fill the defect and contact as much viable bone as possible.

AlloSync CB must not be used to repair bone defects where complete soft tissue coverage cannot be achieved.

REMOVING THE PRODUCT FROM PACKAGING

For putty

1. Peel open outer package.
2. Using aseptic technique, transfer contents to a sterile field.
3. Peel open inner package and remove spatula and vial.
4. Twist off vial lid and remove putty using small spatula or other hand instrument.
5. Discard any unused portion.

For paste

1. Peel open outer package.
2. Using aseptic technique, transfer contents to a sterile field.
3. Peel open inner package and remove syringe.
4. Remove protective cap from syringe tip.
5. Depress the plunger to extrude the implant material.
6. Discard any unused portion.

POSTOPERATIVE CARE

Postoperative patient management should follow the same regimen as similar cases utilizing autogenous bone grafting. Standard postoperative practices should be followed, particularly as applicable to defect repairs involving the use of fixation devices. The patient should be cautioned against early weight bearing and premature ambulation that could lead to loosening and/or failure of the fixators or loss of reduction.

The length of time a defect should remain in a reduced state of loading is determined by the complexity of the defect site and the overall physical condition of the patient. Hardware should not be removed until the defect is healed.

WARNINGS

- The product must be used prior to the expiration date.
- For single use only.
- Do not re-sterilize.
- Do not use if packaging has been damaged and/or the product has been compromised. In the event packaging has been compromised, discard the product. Damaged packaging should be returned to the manufacturer.
- Do not use to support reduction of a defect site. Rigid fixation techniques are recommended as needed to assure stabilization of the defect in all planes. Screws must gain purchase in the host bone as opposed to the AlloSync CB.
- Do not use to repair bone defects where soft tissue coverage cannot be achieved as complete post-operative wound closure is necessary.
- Do not overfill the graft site.

POTENTIAL ADVERSE EVENTS

Surgical procedures involving implantation of bone grafts are associated with the following risks:

- Superficial wound infection
- Deep wound infection with or without osteomyelitis
- Nonunion, delayed union and/or malunion
- Wound dehiscence
- Loss of reduction
- Refracture
- Cyst recurrence
- Hematoma
- Cellulitis

Adverse outcomes attributable to the product must be reported promptly to Arthrex, Inc. and IsoTis OrthoBiologics, Inc. If any dissatisfaction with the product performance or packaging occurs, notify Arthrex, Inc. immediately and promptly return product and/or packaging to IsoTis Orthobiologics, Inc.

PRECAUTIONS

- AlloSync CB is sterile for the duration of the product's shelf life, provided that the package is in its original sealed condition and that it is unopened and undamaged.
- As with all biological products, the tissue in AlloSync CB has the potential to transmit infectious agents despite processing treatments, extensive donor screening, tissue selection and laboratory testing. To date, there have been no reports of experimental or clinical viral seroconversion attributed to the use of demineralized bone.
- As with any surgical procedure, the possibility of infection exists.
- Although the production technique is designed to eliminate antigenic properties of the product, the possibility of such a reaction is present.
- Once the container seal has been compromised, the tissue product shall be either transplanted, if appropriate, or otherwise discarded.
- Use caution when filling a closed defect. Resistance during extrusion may be an indication of over pressurization. Excessive pressurization of the device could result in fat embolization and/or embolization of the material into the bloodstream.
- When introducing AlloSync CB, care must be taken to avoid excessive compaction.
- Appropriate placement and/or fixation are critical factors in the avoidance of potentially adverse effects.
- Overfilling the implantation site should be avoided to achieve a tension-free closure of the wound.

HUMAN TISSUE DONOR SELECTION

All tissue used in AlloSync CB is recovered from donors and by tissue banks in the United States in accordance with regulations and standards established by the U.S. Food and Drug Administration (FDA) and the American Association of Tissue Banks (AATB). The tissue bank (as identified on the product's outer packaging) has evaluated the tissue

The tissue bank's evaluation included review of the tissue donor's infectious disease test results, consent documents, medical and social interview, assessment of the donor's body, available relevant medical records including previous medical history, laboratory test results, review of postmortem examination results (if applicable) and information from other sources or records which may pertain to donor eligibility including tissue procurement test results. The review did not reveal risk factors for, conditions indicating clinical and/or physical evidence of infectious disease, or communicable disease agents or diseases, including HIV (human immunodeficiency virus) or hepatitis, or risk factors for viral or prion-associated disease transmission as specified in 21 CFR 1271 Subpart C and Appendix II of the AATB standards.

SEROLOGICAL TESTING OF HUMAN TISSUE

Donor blood samples taken at the time of recovery were tested by laboratories registered with the FDA to perform donor testing and certified to perform such testing on human specimens in accordance with Clinical Laboratory Improvement Amendments of 1988 (CLIA) and 42 CFR Part 493, or that has met equivalent requirements as determined by the Centers for Medicare and Medicaid Services (CMS), and were found negative or nonreactive using FDA licensed, cleared or approved, tests for:

- HIV antibodies type 1 and type 2 (anti-HIV-1 and anti-HIV-2)
- HIV-1 Nucleic Acid testing (HIV NAT)
- Hepatitis B Surface antigen (HBsAg)
- Hepatitis B Core Antigen [anti-HBc (IgG and IgM)]
- Hepatitis B Virus Nucleic Acid Tests [HBV NAT]
- Hepatitis C Virus Nucleic Acid Test (HCV NAT)
- Hepatitis C Virus Antibody (anti-HCV)
- *Treponema pallidum* (Syphilis)

In addition, testing may have been conducted for Human T-Lymphotropic Virus type 1 and type 2 (anti-HTLV-I/II). The names and addresses of 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 or establishment determining the suitability of this human tissue are on file at the tissue bank and are available upon request. This tissue has been determined to be suitable for transplantation based on the results of screening and testing.

VIRAL INACTIVATION

The methods for processing of the DBM contained in AlloSync CB were evaluated for their viral inactivation potential. A selected panel of viruses representing various virus types, sizes, shapes and genomes were evaluated. The viral inactivation testing demonstrated suitable inactivation potential of the processing methods for a wide range of potential viruses. The AlloSync CB product contains cancellous bone which has been added to the demineralized bone matrix. Since the cancellous bone chips are not demineralized, the degree of viral inactivation of this component is not fully known. The cancellous bone has been processed in antimicrobial, antiviral, and antiseptic solutions for reduction of the risk of transmissible viral diseases from human tissue products. The risk of disease transmission with the cancellous bone component remains low due to multiple safeguards including donor screening, serologic testing, tissue cleaning process, and terminal sterilization of the finished device.

OSTEOINDUCTIVE POTENTIAL

The osteoinductive potential of the Demineralized Bone Matrix (DBM) used in AlloSync CB Putty and Paste is determined via an *in vitro* assay. Results from the assay were correlated with results from implantation of DBM into an athymic mouse muscle pouch. Analysis of these results shows that the *in vitro* assay has been validated against the *in vivo* athymic mouse model and predicts with at least 95% confidence the *in vivo* osteoinductivity of the test material.

Each lot of DBM incorporated in AlloSync CB Putty and Paste is evaluated for osteoinductive potential using an *in vitro* assay. Testing each lot of DBM assures that only DBM with osteoinductive potential is used in AlloSync CB Putty and Paste. Although DBM used in the final product has been shown to be osteoinductive using an *in vitro* assay, the combination of DBM, poloxamer and cancellous bone chips has not been evaluated for osteoinductivity; therefore, it is unknown to what extent the formulation components may alter the osteoinductivity of the DBM. Additionally, it is unknown how osteoinductivity of the DBM component, measured via the *in vitro* assay, will correlate with human clinical performance of AlloSync CB Putty and Paste.

STERILIZATION

AlloSync CB has been sterilized by electron beam irradiation. The inner package and its contents are sterile. The package should be inspected prior to use to ensure the sterility barrier has not been compromised. This product is for single use only and **must not be re-sterilized**. The product must not be used beyond the stated expiration date.

If it appears that the product or its packaging has been compromised, both the product and the packaging should be returned to the manufacturer.

STORAGE

- Store at room temperature (15°C to 30°C) in a clean, dry place.
- Do not refrigerate or freeze.
- Do not expose to extreme heat.
- It is the responsibility of the tissue dispensing service and user (facility/clinician) to maintain the product under appropriate conditions prior to use.
- Discard any unused product.

RECIPIENT TRACING













The clinician or hospital is responsible for maintaining recipient records for the purpose of tracing tissue post-implantation. A Graft Tracing Record has been included for completion at the time of the surgical procedure. Upon completion, the Graft Tracing Record is to be sent back to the manufacturer. If the entire tissue product was discarded, return the Graft Tracing Record and explain the reason for discard. Chart labels are provided in each package for use on the patient's medical records. These labels provide traceability to the original tissue donor.

PRODUCT INFORMATION DISCLOSURE

IsoTis OrthoBiologics, Inc ("IsoTis") HAS EXERCISED REASONABLE CARE IN THE SELECTION OF MATERIALS AND THE MANUFACTURE OF THESE PRODUCTS.

IsoTis EXCLUDES ALL WARRANTIES, WHETHER EXPRESSED OR IMPLIED, INCLUDING BUT NOT LIMITED TO, ANY IMPLIED WARRANTIES OF MERCHANTABILITY OR FITNESS FOR A PARTICULAR PURPOSE. IsoTis SHALL NOT BE LIABLE FOR ANY INCIDENTAL OR CONSEQUENTIAL LOSS, DAMAGE, OR EXPENSE, DIRECTLY OR INDIRECTLY ARISING FROM USE OF THIS PRODUCT. IsoTis NEITHER ASSUMES NOR AUTHORIZES ANY PERSON TO ASSUME FOR IT ANY OTHER OR ADDITIONAL LIABILITY OR RESPONSIBILITY IN CONNECTION WITH THESE PRODUCTS. IsoTis INTENDS THAT THIS DEVICE SHOULD BE USED ONLY BY PHYSICIANS HAVING RECEIVED PROPER TRAINING IN THE USE OF THE DEVICE.

An explanation of the symbols used on product labeling is provided below.

	Sterilized using irradiation
	Consult Instructions for Use
	Expiration date (YYYY-MM)
	Do not re-use
	Temperature limitation
Rx ONLY	Caution: Federal (USA) law restricts this device to sale by or on the order of a physician or practitioner
	Catalog number
	Lot number
	Manufacturer
	Do not use if package is damaged
	Do not re-sterilize
	Not made with natural rubber latex
	Manufactured by: IsoTis OrthoBiologics, Inc 2 Goodyear, Irvine, CA 92618 USA

U.S. Patents 6,309,659; 6,623,748; 7,205,337; 7,241,813

Manufactured for:
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