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Administrators quick reference to PMA approved **bone graft products**

1 Where is it used and pathway to market?

2 What is it?

3 Is there on label data to support FDA approval of the product?

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i-Factor™* Peptide Enhanced Bone Graft

Where is it used?

Indicated for use inside an allograft bone ring at one intervertebral disc level from C3-C4 to C6-C7.

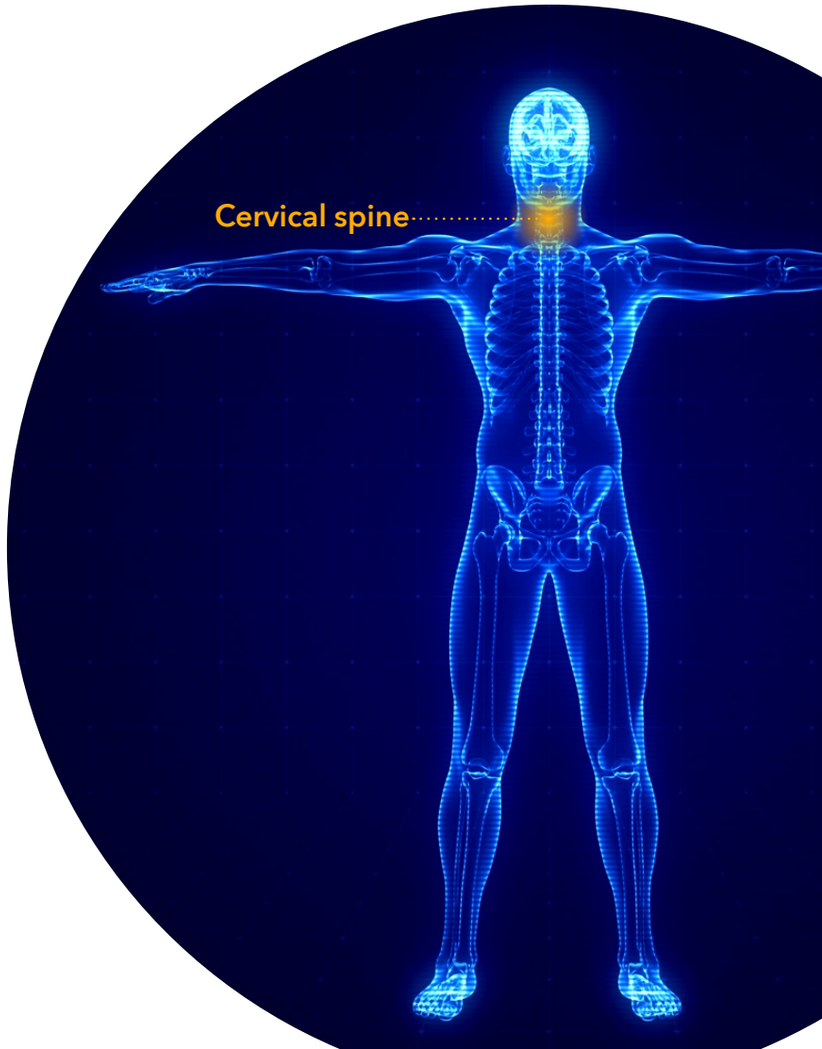
Pathway to market: i-Factor™* has 1 PMA approval (see IFU links).

What is it?

i-Factor™* peptide enhanced bone graft (also referred to as i-Factor™* bone graft or i-Factor™* putty) is a composite bone graft material consisting of multiple components - a synthetic peptide (P-15) adsorbed onto calcium phosphate particles, which are suspended in a hydrogel carrier. The i-Factor™* peptide enhanced bone graft **must** be used in combination with an allograft ring and a metallic anterior cervical plate.

Is there on label data to support FDA approval of the product?

1 Cervical Spine Study[1]



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Infuse™ Bone Graft

Where is it used?

Indicated for use inside an approved Medtronic spinal fusion cage at one intervertebral level from L2-S1, open tibial fractures with IM nail fixation, sinus augmentation, and localized alveolar ridge augmentation for defects associated with extraction sockets.

Pathway to market: Infuse™ has 3 PMA approvals (see IFU links).

What is it?

Infuse™ bone graft consists of recombinant human bone morphogenetic protein-2 (rhBMP-2) placed on an absorbable collagen sponge (ACS). For spine indications, Infuse™ bone graft is inserted into a Medtronic Interbody Fusion Device to form the complete device. Infuse™ bone graft induces formation of new bone tissue at the site of implantation. These components must be used as a system for the prescribed indication. The bone morphogenetic protein solution component must not be used without the carrier/scaffold component or with a carrier/scaffold component different from the one described in the IFUs.

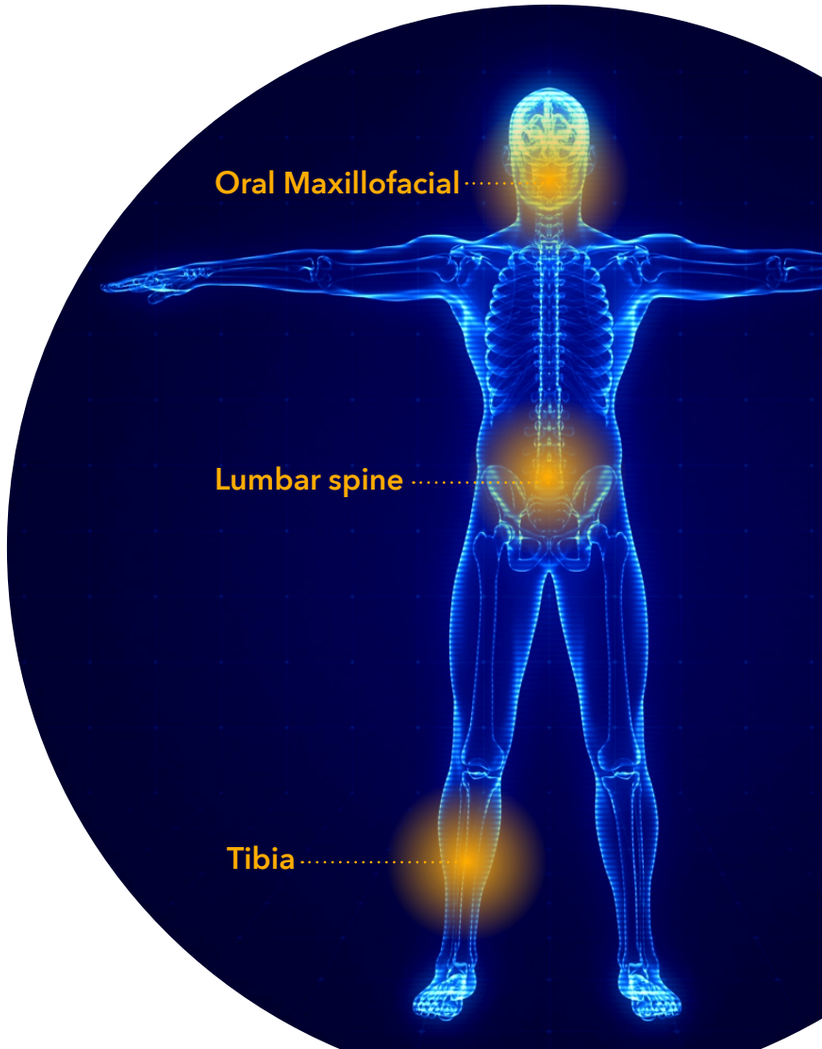
Infuse™ bone graft induces new bone tissue at the site of implantation.

Is there on label data to support FDA approval of the product?

5 Lumbar Spine Studies[2-6]

5 OMF Studies[7-11]

1 Tibia Study[12]



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Brief Statement | Infuse™ Bone Graft

NOTE: The Perimeter™, Clydesdale™, Divergence-L™, Pivox™, and Anteralign™ TL devices must be used with any supplemental fixation cleared for use in the lumbar spine.

Warnings and Precautions – Infuse™ Bone Graft

- In an experimental rabbit study, rhBMP-2 has been shown to elicit antibodies that are capable of crossing the placenta. Reduced ossification of the frontal and parietal bones of the skull was noted infrequently (<3%) in fetuses of rabbit dams immunized to rhBMP-2; however, there was no effect noted in limb bud development. There are no adequate and well controlled studies in human pregnant women. Women of childbearing potential should be warned by their doctor of potential risk to a fetus and informed of other possible dental treatments.
- Women of childbearing potential should be advised that antibody formation to rhBMP-2 or its influence on fetal development has not been completely assessed. In the clinical trials supporting the safety and effectiveness of the Infuse™ Bone Graft for this indication, 4/184 (2.2%) patients treated with rhBMP-2/ACS and 0/91 (0.0%) patients treated with autograft bone developed antibodies to rhBMP-2. The effect of maternal antibodies to rhBMP-2, as might be present for several months following device implantation, on the unborn fetus is unknown. Additionally, it is unknown whether fetal expression of BMP-2 could re-expose mothers who were previously antibody positive. Theoretically, re-exposure may elicit a more powerful immune response to BMP-2 with possible adverse consequences for the fetus. However, pregnancy did not lead to an increase in antibodies in the rabbit study. Studies in genetically altered mice indicate that BMP-2 is critical to fetal development and that a lack of BMP-2 activity may cause neonatal death or birth defects. It is not known if anti-BMP-2 antibodies may affect fetal development or the extent to which these antibodies may reduce BMP-2 activity.
- Infuse™ Bone Graft should not be used immediately prior to or during pregnancy. Women of childbearing potential should be advised not to become pregnant for one year following treatment with Infuse™ Bone Graft.
- The safety and effectiveness of Infuse™ Bone Graft in nursing mothers has not been established. It is not known if BMP-2 is excreted in human milk.

Brief summary of indications, contraindications, and warnings for:
Infuse™ Bone Graft/LT-Cage™ Lumbar Tapered Fusion Device
Infuse™ Bone Graft/Inter Fix™ Threaded Fusion Device
Infuse™ Bone Graft/Inter Fix™ RP Threaded Fusion Device
Infuse™ Bone Graft/Perimeter™ Interbody Fusion Device
Infuse™ Bone Graft/Clydesdale™ Spinal System
Infuse™ Bone Graft/Divergence-L™ Anterior/Oblique Lumbar Fusion System
Infuse™ Bone Graft/Pivox™ Oblique Lateral Spinal System
Infuse™ Bone Graft/Anteralign™ Spinal System with Titan nanoLOCK™ Surface Technology

The Infuse™ bone graft/Medtronic Interbody Fusion Device is indicated for spinal fusion procedures in skeletally mature patients with degenerative disc disease (DDD) at one level from L2-S1, who may also have up to Grade I spondylolisthesis or Grade 1 retrolisthesis at the involved level.

The following interbody devices and surgical approaches may be used with Infuse™ bone graft:

- The LT-Cage™ lumbar tapered fusion device, implanted via an anterior open or an anterior laparoscopic approach at a single level.
- The Inter Fix™ or Inter Fix™ RP threaded fusion device, implanted via an anterior open approach at a single level.
- Certain sizes of the Perimeter™ interbody fusion device implanted via a retroperitoneal anterior lumbar interbody fusion (ALIF) at a single level from L2-S1or an oblique lateral interbody fusion (OLIF) approach at a single level from L5-S1.
- Certain sizes of the Clydesdale™ spinal system, implanted via an OLIF approach at a single level from L2-L5.
- Certain sizes of the Divergence-L™ anterior/ oblique lumbar fusion system implanted via an ALIF approach at a single level from L2-S1or an OLIF approach at a single level from L5-S1.
- Certain sizes of the PIVOX™ oblique lateral spinal system implanted via an OLIF approach at a single-level from L2-L5.
- The Anteralign™ Spinal System LS interbody device implanted via an ALIF approach at a single level from L2-S1 or an OLIF approach at a single-level from L5-S1.
- The Anteralign™ Spinal System TL interbody device implanted via an OLIF approach at a single-level from L2-L5.

The Infuse™ bone graft/Medtronic interbody fusion device consists of two components containing three parts– a spinal fusion cage, a recombinant human bone morphogenetic protein, and a carrier/scaffold for the bone morphogenetic protein and resulting bone.

These components must be used as a system for the prescribed indication described above. The bone morphogenetic protein solution component must not be used without the carrier/scaffold component or with a carrier/scaffold component different from the one described in this document. The INFUSE™ Bone Graft component must not be used without the Medtronic Interbody Fusion Device component.

NOTE: The Inter Fix™ threaded fusion device and the Inter Fix™ RP threaded fusion device may be used together to treat a spinal level. The LT-Cage™ lumbar tapered fusion device, the Perimeter™ interbody fusion device, and the Clydesdale™ spinal system implants are not to be used in conjunction with either the Inter Fix™ OR Inter Fix™ RP implants to treat a spinal level.

The Infuse™ bone graft/Medtronic interbody fusion device is contraindicated for patients with a known hypersensitivity to recombinant human Bone Morphogenetic Protein-2, bovine Type I collagen, or to other components of the formulation and should not be used in the vicinity of a resected or extant tumor, in patients with any active malignancy, or patients undergoing treatment for a malignancy; in patients who are skeletally immature; in pregnant women; or in patients with an active infection at the operative site or with an allergy to titanium, titanium alloy, or polyetheretherketone (PEEK).

There are no adequate and well-controlled studies in human pregnant women. In an experimental rabbit study, rhBMP-2 has been shown to elicit antibodies that are capable of crossing the placenta. Women of child bearing potential should be warned by their surgeon of potential risk to a fetus and informed of other possible orthopedic treatments. The safety and effectiveness of this device has not been established in nursing mothers. Women of child- bearing potential should be advised to not become pregnant for one year following treatment with this device.

Please see the Infuse™ bone graft package insert for the complete list of indications, warnings, precautions, adverse events, clinical results, definition of DDD, and other important medical information. The package insert also matches the sizes of those sized devices that are indicated for use with the appropriate Infuse™ gone graft kit. An electronic version of the package insert may be found at www.medtronic.com/manuals.

CAUTION: Federal (USA) law restricts this device to sale by or on the order of a physician with appropriate training or experience.

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PMA Products

i-Factor™* Peptide Enhanced Bone Graft

Infuse™ Bone Graft

- Brief Statement

Brief Statement | Infuse™ Bone Graft

BRIEF SUMMARY OF INDICATIONS, CONTRAINDICATIONS, WARNINGS, AND PRECAUTION FOR INFUSE™ BONE GRAFT FOR CERTAIN ORAL MAXILLOFACIAL AND DENTAL REGENERATIVE USES

Infuse™ bone graft is indicated as an alternative to autogenous bone graft for sinus augmentations, and for localized alveolar ridge augmentations for defects associated with extraction sockets.

The Infuse™ bone graft consists of two components – recombinant human Bone Morphogenetic Protein-2 (rhBMP-2) placed on an absorbable collagen sponge (ACS). These components must be used as a system for the prescribed indication. The bone morphogenetic protein solution component must not be used without the carrier/scaffold component or with a carrier/scaffold component different from the one described in the package insert.

Infuse™ bone graft is contraindicated for patients with a known hypersensitivity to recombinant human Bone Morphogenetic Protein-2, bovine Type 1 collagen or to other components of the formulation and should not be used in the vicinity of a resected or extant tumor, in patients with any active malignancy or patients undergoing treatment for a malignancy, in pregnant women, or patients with an active infection at the operative site.

There are no adequate and well-controlled studies in human pregnant women. In an experimental rabbit study, rhBMP-2 has been shown to elicit antibodies that are capable of crossing the placenta. Women of child bearing potential should be warned by their surgeon of potential risk to a fetus and informed of other possible dental treatments. The safety and effectiveness of this device has not been established in nursing mothers. Women of child-bearing potential should be advised to not become pregnant for one year following treatment with this device.

Infuse™ bone graft has not been studied in patients who are skeletally immature (<18 years of age or no radiographic evidence of epiphyseal closure).

Please see the package insert for the complete list of indications, warnings, precautions, adverse events, clinical results, and other important medical information.

BRIEF SUMMARY OF INDICATIONS, CONTRAINDICATIONS, AND WARNINGS FOR: INFUSE™ BONE GRAFT

Infuse™ bone graft is indicated for treating acute, open tibial shaft fractures that have been stabilized with IM nail fixation after appropriate wound management. Infuse™ bone graft must be applied within 14 days after the initial fracture. Prospective patients should be skeletally mature.

Infuse™ bone graft consists of two components – recombinant human Bone Morphogenetic Protein-2 solution and a carrier/scaffold for the bone morphogenetic protein solution and resulting bone. **These components must be used as a system. The bone morphogenetic protein solution component must not be used without the carrier/scaffold component or with a carrier/scaffold component different from the one described in this document.**

Infuse™ bone graft is contraindicated for patients with a known hypersensitivity to recombinant human Bone Morphogenetic Protein-2, bovine Type 1 collagen or to other components of the formulation and should not be used in the vicinity of a resected or extant tumor, in patients with an active malignancy or patients undergoing treatment for a malignancy. Infuse™ bone graft should also not be used in patients who are skeletally immature, in patients with an inadequate neurovascular status, in patients with compartment syndrome of the affected limb, in pregnant women, or in patients with an active infection at the operative site.

There are no adequate and well controlled studies in human pregnant women. In an experimental rabbit study, rhBMP-2 has been shown to elicit antibodies that are capable of crossing the placenta. Women of child bearing potential should be warned by their surgeon of potential risk to a fetus and informed of other possible orthopedic treatments. The safety and effectiveness of this device has not been established in nursing mothers. Women of child-bearing potential should be advised to not become pregnant for one year following treatment with this device.

Please see the package insert for the complete list of indications, warnings, precautions, adverse events, clinical results, and other important medical information.

CAUTION: Federal (USA) law restricts this device to sale by or on the order of a physician with appropriate training or experience.

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PMA Products

i-Factor™* Peptide Enhanced Bone Graft

Infuse™ Bone Graft

- Brief Statement

Brief Statement | i-Factor™* Peptide Enhanced Bone Graft

Indications for Use:
The i-Factor™* peptide enhanced bone graft is indicated for use in skeletally mature patients for reconstruction of a degenerated cervical disc at one level from C3-C4 to C6-C7 following single-level discectomy for intractable radiculopathy (arm pain and/or neurological deficit), with or out without neck pain, or myelopathy due to single-level abnormality localized to the disc space, and corresponding to at least one of the following conditions confirmed by radiographic imaging (CT, MRI, X-rays); herniated nucleus pulposus, spondylosis (defined nu the presence of osteophytes), and/or visible loss of disc height as compared to adjacent levels, after failure of at least 6 weeks of conservative treatment. i-Factor™* peptide enhanced bone graft **must** be used inside an allograft bone ring and with supplemental anterior plate fixation.

Contraindications:
The i-Factor™* peptide enhanced bone graft should not be used in situations where there is:
- An absence of load bearing structural support at the graft site
- Sensitivity to any components of i-Factor™* peptide enhanced bone graft
- Acute or chronic infections, systemic or at the operative site
- Metabolic or systemic disorders that affect bone or wound healing
- Compromised renal or hepatic function

Warnings:
- i-Factor™* peptide enhanced bone graft is designed for single patient use only. Attempting to reuse the putty will adversely affect product sterility and physical handling characteristics. DO NOT attempt to re-sterilize or re-use. Discard unused contents.
- Women of child-bearing potential should avoid becoming pregnant for one year after being treated with i-Factor™* peptide enhanced bone graft. The influence of i-Factor™* peptide enhanced bone graft on pregnant women and on fetal development is unknown.
- The effect of i-Factor™* peptide enhanced bone graft on nursing women has not been evaluated. It is not known if i-Factor™* peptide enhanced bone graft is excreted in human milk.
- The safety and effectiveness of i-Factor™* peptide enhanced bone graft when mixed with any additional components, e.g., autograft, allograft, other bone grafting materials, blood, saline or bone marrow aspirate, has not been established.
- The safety and effectiveness of i-Factor™* peptide enhanced bone graft used with implants other than allograft bone rings and anterior cervical plates, or applied in anatomic sites other than the cervical spine have not been established.
- The safety and effectiveness of i-Factor™* peptide enhanced bone graft has not been established in patients with pathology at more than one level and/or pathology not localized to the disc space.
- The safety and effectiveness of i-Factor™* peptide enhanced bone graft in patients who are not skeletally mature has not been established.
- The safety and effectiveness of i-Factor™* peptide enhanced bone graft in patients with hepatic or renal impairment has not been established.
- The safety and effectiveness of i-Factor™* peptide enhanced bone graft in patients with metabolic bone disease has not been established.

As with any surgical procedure, care should be exercised in treating individuals with pre-existing conditions that may affect the success of the surgical procedure.
- Bleeding disorders of any etiology: The safety and effectiveness of i-Factor™* peptide enhanced bone graft has not been established in patients with bleeding disorders of any etiology.
- Long-term steroidal therapy: The safety and effectiveness of i-Factor™* peptide enhanced bone graft has not been established in patients who have had long term steroidal therapy.
- Immunosuppressive therapy or high dosage radiation therapy: The safety and effectiveness of i-Factor™* peptide enhanced bone graft has not been established in patients who have had immunosuppressive therapy or high dosage radiation therapy.

Potential Adverse Events:
As with any surgery, surgical treatment of cervical degenerative disc disease is not without risk. A variety of complications related to the surgery or the use of i-Factor™* peptide enhanced bone graft may occur. The following is a list of potential adverse events that could be associated with the use of i-Factor™* peptide enhanced bone graft, some of which were identified in the i-Factor™* peptide enhanced bone graft clinical trial results. These adverse events include: (1) those associated with any surgical procedure; (2) those associated with anterior cervical discectomy and fusion (ACDF) surgery; and (3) those that may occur specifically with the use of i-Factor™* peptide enhanced bone graft. These risks may occur singly or in combination and may be severe and/or negatively impact patient outcomes. In addition to the risks listed below, there is also the risk that the procedure may not be effective and may not relieve or may cause worsening of symptoms. Additional surgery may be required to correct some of the potential adverse effects.

1. Risks associated with any surgical procedure:
   - Anesthesia complications including an allergic reaction or anaphylaxis
   - Infection (wound, local, and/or systemic) or abscess
   - Wound complications including hematoma, site drainage, infection dehiscence and/or necrosis
   - Mild to severe swelling, edema
   - Soft tissue damage or fluid collections, including hematoma or seroma
   - Pain/discomfort at the surgical incision and/or skin or muscle sensitivity over the incision, which may result in skin breakdown, pain, and/or irritation
   - Heart or vascular complications including bleeding, hemorrhage or vascular damage resulting in catastrophic or potentially fatal bleeding, ischemia, myocardial infarction, abnormal blood pressure, venous thromboembolism including deep vein thrombosis and pulmonary embolism, thrombophlebitis, or stroke
   - Pulmonary complications including atelectasis or pneumonia
   - Impairment of the gastrointestinal system including ileus or bowel obstruction
   - Impairment of the genitourinary system including incontinence, bladder dysfunction, or reproductive system complications
   - Neurological complications including nerve damage, paralysis, seizures, changes to mental status, or reflex sympathetic dystrophy
   - Complications of pregnancy including miscarriage or congenital defects
   - Inability to resume activities of daily living
   - Death

2. Risks specifically associated with anterior cervical discectomy and fusion (ACDF) surgery, some of which were observed with use of i-Factor™* peptide enhanced bone graft:
   - Failure of fusion, with requirement for secondary surgical intervention
   - Early or late loosening, breakage or migration of internal fixation and/or graft material
   - Vertebral body fracture
   - Failure of symptom relief
   - Nonunion, malunion or delayed union
   - Worsening of neurologic status, arachnoiditis
   - Adjacent level degeneration
   - External chylorrhea or chylothorax
   - Recurrent laryngeal nerve injury with hoarseness
   - Superior laryngeal nerve injury and dysphagia
   - Tracheal, esophageal, or pharyngeal perforation
   - Dural injury with cerebrospinal fluid leakage, fistula, headache

Brief Statement | i-Factor™* Peptide Enhanced Bone Graft

- Scar formation or other problems with the surgical incision
- Vascular injury resulting in stroke, hemorrhage and possible death

3. Potential adverse events that may occur specifically with the use of i-Factor™* peptide enhanced bone graft include:
   - Extrusion or migration of the i-Factor™* peptide enhanced bone graft, as is possible with any bone graft, resulting in pain, neural impingement, physical impairment, or loss of function; any of which may require revision surgery
   - Allergic reaction to components of i-Factor™* peptide enhanced bone graft
   - Abnormal bone formation in an unintended location
   - Excessive or incomplete bone formation

For more detailed information on the specific adverse effects that occurred during the clinical trial, please refer to the Safety Results Section (Summary of IDE Clinical Study).

How Supplied:
The i-Factor™* peptide enhanced bone graft is provided in a pre-filled syringe. The syringe is comprised of the syringe barrel, plunger rod, plunger tip, and syringe cap. The pre-filled syringe of i-Factor™* peptide enhanced bone graft is packaged in an outer sterile barrier chevron-style peel pouch and inner vapor barrier foil pouch. The syringe barrel and plunger tip are lubricated with a thin layer of Dow Corning 360 Medical Fluid - 1000 CST (polydimethylsiloxane).

Storage:
The product should be stored in its original packaging at ambient room temperature.

Dosage and Administration:
i-Factor™* peptide enhanced bone graft is supplied to the clinician as a sterile device in a single-use, pre- filled syringe containing the graft material. No mixing or other preparation is required. The clinician simply removes the syringe from the sterile barrier package, removes the syringe cap, and dispenses the material.

Directions for Use:
The clinician should remove the syringe cap and dispense i-Factor™* peptide enhanced bone graft by depressing the syringe plunger. i-Factor™* peptide enhanced bone graft may be dispensed directly into the allograft ring or into a separate sterile receptacle where it can be transferred using traditional surgical instrumentation or by hand. The central cavity of the allograft ring should be filled with i-Factor™* peptide enhanced bone graft. With the exception of filling the allograft cavity with i-Factor™* peptide enhanced bone graft, a standard instrumented ACDF technique should be followed.

i-Factor™* peptide enhanced bone graft should only be placed in an allograft ring where it can be contained adequately.

NOTE: When opening the foil pouch containing the i-Factor™* peptide enhanced bone graft syringe, a very small amount of water may be retained within the pouch. This is a normal part of the steam sterilization process and does not affect the integrity or sterility of the product.

Manufactured by:
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40002-07-3

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