Infuse™ Bone Graft

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Medtronic

ENGLISH

IMPORTANT MEDICAL INFORMATION

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

DESCRIPTION

Infuse™ Bone Graft consists of two components – a recombinant human bone morphogenetic protein solution and a collagen sponge which acts as a carrier for the bone morphogenetic protein and as a scaffold for new bone formation. **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 consists of recombinant human Bone Morphogenetic Protein-2 (rhBMP-2, known as dibotermin alfa) placed on an absorbable collagen sponge (ACS). Infuse™ Bone Graft induces new bone tissue at the site of implantation. Based on data from non-clinical studies, the bone formation process develops from the outside of the implant towards the center until the entire Infuse™ Bone Graft is replaced by trabecular bone.

rhBMP-2, an osteoinductive growth factor, is the active agent in Infuse™ Bone Graft. It consists of a disulfide-linked dimeric protein molecule with two major subunit species of 114 and 131 amino acids. Each subunit is glycosylated at one site with high-mannose-type glycans. rhBMP-2 is produced by a genetically engineered Chinese hamster ovary cell line.

rhBMP-2 and excipients are lyophilized. Upon reconstitution, each milliliter of rhBMP-2 solution contains: 1.5mg of rhBMP-2; 5.0mg sucrose, NF; 25mg glycine, USP; 3.7mg L-glutamic acid, FCC; 0.1mg sodium chloride, USP; 0.1mg polysorbate 80, NF; and 1.0mL of sterile water. The reconstituted rhBMP-2 solution has a pH of 4.5; is clear, colorless to slightly yellow; and is essentially free from plainly visible particulate matter. The concentration of rhBMP-2 is 1.5mg/ml.

The ACS is a soft, white, pliable, absorbent implantable matrix for rhBMP-2. ACS is made from bovine Type I collagen obtained from the deep flexor (Achilles) tendon. The ACS acts as a carrier for the rhBMP-2 and acts as a scaffold for new bone formation.

Each kit contains all the components necessary to prepare Infuse™ Bone Graft: the rhBMP-2, which must be reconstituted; sterile water; absorbable collagen sponge(s); syringes with needles; and instructions for preparation. The number of each item may vary depending on the size of the kit.

The rhBMP-2 is provided as a lyophilized powder in vials delivering 1.05 mg to 12 mg of protein. After appropriate reconstitution, the concentration of rhBMP-2 is 1.5mg/mL. The solution is then applied to the provided ACS. Infuse™ Bone Graft is prepared at the time of surgery and allowed a prescribed amount of time (no less than 15 minutes) before placement at the site of implantation. The Instructions for Preparation contain complete details on preparation of Infuse™ Bone Graft.

INDICATIONS

Infuse™ Bone Graft with an FDA-cleared intervertebral body fusion device and metallic screw-and-rod system is indicated for use in a transforaminal lumbar interbody fusion (TLIF) surgical approach at one or two adjacent levels from L2-S1 in the treatment of symptomatic degenerative disc disease (DDD) confirmed by patient history and radiographic studies and having at least six months of nonoperative treatment attempted prior to treatment with Infuse™ Bone Graft.

CONTRAINDICATIONS

Infuse™ Bone Graft 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 or with an allergy to titanium, titanium alloy, or polyetheretherketone.
- Known history of resected or extant tumor in the vicinity, or in patients with any active malignancy or undergoing treatment for a malignancy
- Patients who are skeletally immature or <22 years of age.
- Current or future pregnancy. The potential effects of rhBMP-2 on the human fetus have not been evaluated.
- Patients with an active infection at the operative site.

WARNINGS

- 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 surgeon of potential risk to a fetus and informed of other possible orthopedic 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 a previous clinical trial supporting the safety and effectiveness of Infuse™ Bone Graft used in other spine indications (ALIF/OLIF), 2/277 (0.7%) subjects treated with Infuse™ Bone Graft and 1/127 (0.8%) subjects 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 the Infuse™ Bone Graft.
- The safety and effectiveness of the Infuse™ Bone Graft in nursing mothers has not been established. It is not known if BMP-2 is excreted in human milk.

General

- Infuse™ Bone Graft should not be used in subjects suspected of having a malignancy at the site of application.
- The safety and effectiveness of the use of Infuse™ Bone Graft implanted at locations other than the lower lumbar spine OR used in surgical techniques where Infuse™ Bone Graft has not been indicated has not been established.
- The safety and effectiveness of the use of Infuse™ Bone Graft implanted in the cervical spine has not been established. This product is only approved for use in the lumbar spine as indicated above.
  - When anterior cervical spinal fusions were performed using Infuse™ Bone Graft, some cases of edema have been reported within the first postoperative week. In some of these cases, this swelling has been severe enough to produce airway compromise, sometimes requiring emergency surgery.
  - In a clinical trial comparing single-level anterior cervical fusion using Infuse™ Bone Graft to a control that did not use Infuse™ Bone Graft, 16.4% of subjects treated with Infuse™ Bone Graft reported dysphagia, compared to 7.3% of control subjects. Most of the dysphagia events occurred within the first four weeks after surgery, and most of these events were classified as non-serious (e.g. non-life-threatening events not requiring hospitalization). While dysphagia may occur following anterior cervical procedures, it may occur more frequently or to a greater extent in the presence of Infuse™ Bone Graft.
  - When anterior cervical fusions were performed using Infuse™ Bone Graft, the radiographic appearance of anterior heterotopic ossification (HO) was noted in some subjects, most commonly observed anterior and superior to the treated level. In some of the cases of severe HO, adjacent-level fusion and reduced motion were also noted. HO may occur more frequently or to a greater extent with the use of Infuse™ Bone Graft.

Bone Formation

- Posterior bone formation outside of the disc space was observed in some subjects when DDD was treated by a posterior lumbar interbody fusion or transforaminal lumbar interbody fusion procedure. Although it was not clearly associated with key clinical outcome measures (e.g. leg pain) in most cases, bone formation outside of the disc space is not desirable and may potentially lead to nerve compression, requiring surgical intervention.
- Inappropriate use of the product, such as preparing it differently than prescribed, compressing the rhBMP-2/ACS implant more than necessary, or overfilling the volume intended for new bone formation, may change the concentration of the

rhBMP-2, which may inhibit the ability of the rhBMP-2/ACS to convert to bone and/or cause complications. Such use of the rhBMP-2/ACS implant may result in radiographic evidence of resorption. These findings may be asymptomatic or symptomatic. A sheep model developed to test the hypothesis that volume overfilling and/or hyper concentration of the rhBMP-2 solution results in radiographic evidence of bone resorption has preliminarily been evaluated and appears to be supportive of the hypothesized mechanism.

- Placement of rhBMP-2/ACS can cause initial resorption of trabecular bone that may be transient.
- Device migration has been reported with the use of rhBMP-2/ACS in spinal fusion surgery. Device migration has been reported in the presence and absence of bone resorption.
- Nerve compression associated with heterotopic bone formation has been reported in subjects undergoing spine surgery with rhBMP-2/ACS. Surgical intervention may be required to address the symptoms.

Fluid Collection/Edema

- The formation of fluid collections (sometimes encapsulated) in some cases resulted in nerve compression and pain, which may require clinical intervention (aspiration and/or surgical removal) if symptoms persist. Many of these reports have occurred when rhBMP-2/ACS was used in conjunction with unapproved approaches/devices or in a manner inconsistent with the instructions for use.
- While there is currently anecdotal and literature evidence to suggest that volume overfilling and/or hyperconcentration of the rhBMP-2 solution may lead to fluid formation and/or edema, animal models for scientifically evaluating these events do not presently exist.

PRECAUTIONS

Physician note: although the physician is the learned intermediary between the company and the patient, the important medical information given in this document should be conveyed to the patient.

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General

- The safety and effectiveness of repeat applications of Infuse™ Bone Graft have not been established.
- Infuse™ Bone Graft should only be used by surgeons who are experienced in spinal fusion procedures.
- Unless marked sterile and clearly labeled as such in an unopened sterile package provided by the company, any Interbody Fusion Devices and/or instruments used in surgery must be sterilized by the hospital prior to use according to the sterilization instructions provided in the product-specific package insert.
- Infuse™ Bone Graft is intended for single use only. Discard unused product and use a new device for subsequent applications.
- Prior to use, inspect the packaging, vials, and stoppers for visible damage. If damage is visible, do not use the product. Retain the packaging and vials and contact a Medtronic representative.
- Do not use after the printed expiration date on the label.

Hepatic and Renal Impairment

- The safety and effectiveness of Infuse™ Bone Graft in subjects with hepatic or renal impairment have not been established. Pharmacokinetic studies of rhBMP-2 indicate that the renal and hepatic systems are involved with its clearance.

Geriatrics

- Clinical studies of the Infuse™ Bone Graft did not include sufficient numbers of subjects 65 years and older to determine whether they respond differently from younger subjects.

Bone Formation

- The safety and effectiveness of the Infuse™ Bone Graft have not been demonstrated in subjects with metabolic bone diseases.
- The potential for heterotopic or undesirable exuberant bone formation exists.

Antibody Formation/Allergic Reactions

- The safety and effectiveness of Infuse™ Bone Graft have not been demonstrated in subjects with autoimmune disease.
- The safety and effectiveness of Infuse™ Bone Graft have not been demonstrated in subjects with immunosuppressive disease or suppressed immune systems resulting from radiation therapy, chemotherapy, steroid therapy, or other treatments.

Immunogenicity

- As with all therapeutic proteins, there is a potential for immune responses to be generated to Infuse™ Bone Graft. In previous studies, the immune response to Infuse™ Bone Graft was evaluated in 349 investigational subjects and 183 control subjects receiving anterior lumbar interbody fusions.
- Anti-rhBMP-2 antibodies: 2/349 (0.6%) subjects receiving Infuse™ Bone Graft developed antibodies vs.1/183 (0.5%) in the control group.
- Anti-bovine Type I collagen antibodies: 18.1% of subjects receiving Infuse™ Bone Graft developed antibodies to bovine Type I collagen vs. 14.2% of control subjects. No subjects in either group developed anti-human Type I collagen antibodies.
- The presence of antibodies to rhBMP-2 was not associated with immune mediated Adverse Events (AEs) such as allergic reactions. The neutralizing capacity of antibodies to rhBMP-2 is not known.
- The incidence of antibody detection is highly dependent on the sensitivity and specificity of the assay. Additionally, the incidence of antibody detection may be influenced by several factors, including sample handling, concomitant medications, and underlying disease. For these reasons, comparison of the incidence of antibodies to Infuse™ Bone Graft with the incidence of antibodies to other products may be misleading.

ADVERSE EVENTS

Infuse™ Bone Graft was implanted in a one-level TLIF surgical approach in 261 investigational subjects (129 using a 2.1 mg/level dose, and 132 using a 4.2 mg/level dose) and compared to 123 control subjects who received local bone autograft, supplemented with cancellous allograft as needed.

Similarly, Infuse™ Bone Graft was implanted in a two-level TLIF surgical approach in 62 investigational subjects (34 using a 2.1 mg/level dose, and 28 using a 4.2 mg/level dose) and compared to 34 control subjects who received local bone autograft, supplemented with cancellous allograft as needed.

Adverse event (AE) rates presented are based on the number of subjects having at least one occurrence for a particular AE divided by the total number of subjects in that treatment group.

AEs up to 24 months in AT Population for one-level subjects by System Organ Class (SOC)

	One-Level Subjects (N = 384)					
	Up to 24 Months					
	Infuse 2.1 (N = 129)		Infuse 4.2 (N = 132)		Control (N = 123)	
System Organ Classes (SOC)	#Patients	Cumulative Rate(%)*	#Patients	Cumulative Rate(%)*	#Patients	Cumulative Rate(%)*
Patients Who Had Any Adverse Events	98	88.6	109	89.8	96	87.5
Injury, Poisoning And Procedural Complications	43	38.6	52	45.3	43	40.0
Musculoskeletal And Connective Tissue Disorders	42	38.4	60	52.2	46	44.5
Infections And Infestations	36	37.8	38	36.7	38	39.3
Nervous System Disorders	35	33.6	41	34.7	35	32.0
Gastrointestinal Disorders	17	17.7	19	19.9	15	14.0
Renal And Urinary Disorders	11	12.0	10	8.7	11	10.8
Vascular Disorders	10	11.9	14	14.1	2	1.8
General Disorders And Administration Site Conditions	8	6.4	15	14.6	8	6.7
Investigations	7	6.3	6	6.7	7	6.3
Blood And Lymphatic System Disorders	5	5.2	1	0.8	5	4.2
Respiratory, Thoracic And Mediastinal Disorders	4	4.5	10	9.9	7	6.6
Skin And Subcutaneous Tissue Disorders	4	4.4	6	6.2	4	4.0
Psychiatric Disorders	5	4.1	6	6.3	8	7.2
Eye Disorders	4	3.6	3	4.2	2	1.9
Ear And Labyrinth Disorders	2	2.6	3	3.2	0	0.0
Metabolism And Nutrition Disorders	3	2.5	7	6.1	9	9.3
Surgical And Medical Procedures	2	2.5	1	0.8	2	2.0
Congenital, Familial And Genetic Disorders	2	2.1	0	0.0	1	1.0
Cardiac Disorders	2	2.0	4	3.6	5	6.1
Neoplasms Benign, Malignant And Unspecified (Incl Cysts And Polyps)	2	1.8	6	7.5	6	7.0
Reproductive System And Breast Disorders	2	1.7	6	6.0	5	5.4
Hepatobiliary Disorders	1	1.1	2	3.8	3	3.0
Product Issues	1	0.9	1	0.8	2	2.2
Immune System Disorders	1	0.8	1	0.8	0	0.0
Endocrine Disorders	0	0.0	0	0.0	0	0.0

*Cumulative adverse rates were reported due to the difference in length of follow-up. This is the estimated percentage of participants who had the event by 24 months, accounting for the total time each participant remained in the study, even if they left early.

AEs up to 24 months in AT Population for two-level subjects by System Organ Class (SOC)

	Two-Level Subjects (N = 96)					
	up to 24 Months					
	Infuse 2.1 (N = 34)		Infuse 4.2 (N = 28)		Control (N = 34)	
System Organ Classes (SOC)	#Patients	Cumulative Rate(%)*	#Patients	Cumulative Rate(%)*	#Patients	Cumulative Rate(%)*
Patients Who Had Any Adverse Events	27	83.6	23	94.1	25	85.2

System Organ Classes (SOC)	Two-Level Subjects (N = 96) up to 24 Months					
	Infuse 2.1 (N = 34)		Infuse 4.2 (N = 28)		Control (N = 34)	
	#Patients	Cumulative Rate(%)*	#Patients	Cumulative Rate(%)*	#Patients	Cumulative Rate(%)*
Injury, Poisoning And Procedural Complications	21	73.2	9	33.6	10	34.4
Musculoskeletal And Connective Tissue Disorders	18	59.5	12	53.6	14	47.2
Infections And Infestations	14	51.1	7	35.3	11	41.5
Nervous System Disorders	11	35.8	16	66.0	10	40.0
Gastrointestinal Disorders	8	28.2	5	20.8	4	20.5
Vascular Disorders	6	24.1	4	21.0	2	6.3
General Disorders And Administration Site Conditions	7	21.0	5	23.0	5	21.9
Renal And Urinary Disorders	4	21.0	3	13.5	2	8.0
Metabolism And Nutrition Disorders	6	18.1	0	0.0	4	24.0
Reproductive System And Breast Disorders	2	12.9	1	7.4	1	7.7
Cardiac Disorders	3	10.5	0	0.0	3	11.1
Blood And Lymphatic System Disorders	3	8.8	3	11.9	0	0.0
Skin And Subcutaneous Tissue Disorders	3	8.8	2	8.3	2	9.8
Product Issues	1	6.7	0	0.0	3	17.4
Investigations	2	6.2	3	12.1	3	10.8
Psychiatric Disorders	2	6.1	0	0.0	4	20.4
Ear And Labyrinth Disorders	1	4.3	1	4.3	1	3.3
Neoplasms Benign, Malignant And Unspecified (Incl Cysts And Polyps)	1	4.3	1	7.4	1	3.3
Endocrine Disorders	1	3.2	0	0.0	0	0.0
Eye Disorders	1	3.0	1	4.9	1	7.7
Respiratory, Thoracic And Mediastinal Disorders	1	2.9	1	7.4	3	9.7
Congenital, Familial And Genetic Disorders	0	0.0	1	7.4	1	8.0
Hepatobiliary Disorders	0	0.0	0	0.0	0	0.0
Immune System Disorders	0	0.0	1	4.3	0	0.0

*Cumulative adverse rates were reported due to the difference in length of follow-up. This is the estimated percentage of participants who had the event by 24 months, accounting for the total time each participant remained in the study, even if they left early.

The analysis of AEs reported in the study revealed varying rates of complications among treatment groups. For one-level subjects up to 24 months, the cumulative rate of AEs was 88.6% for the Infuse 2.1 mg group, 89.8% for the Infuse 4.2 mg group, and 87.5% for the Control group, with no statistically significant differences observed. Specific AEs such as blood and lymphatic system disorders, cardiac disorders, and infections showed similar trends across groups, with the Infuse 2.1 mg and Infuse 4.2 mg groups generally reporting comparable or lower rates than the control treatment.

For two-level subjects up to 24 months, the cumulative rate of AEs was 83.6% for the Infuse 2.1 mg group and 94.1% for the Infuse 4.2 mg group, compared to 85.2% for the control treatment. Notably, the incidence of injury, poisoning, and procedural complications was significantly higher in the Infuse 2.1 mg group compared to the control treatment for two-level subjects. Additionally, for two-level subjects, the incidence of psychiatric disorders was significantly higher in the Infuse 4.2 mg group compared to the control treatment. The incidence of AEs related to the TLIF graft material/interbody device, including implant displacement/loosening and mispositioning, was about the same across the investigational groups and the control group up to 24 months for both one-level (38.0% and 40.1% for Infuse 2.1 mg and Infuse 4.2 mg, respectively, compared to 35.5% for the control treatment) and two-level subjects (45.7% and 65.5% for Infuse 2.1 mg and Infuse 4.2 mg, respectively, compared to 57.5% for the control treatment). Overall, Infuse™ Bone Graft demonstrated a safety profile similar to that of local bone autograft.

Potential Adverse Events

The following is a list of potential AEs that may occur with spinal fusion surgery with Infuse™ Bone Graft with an FDA approved intervertebral body fusion device. Some of these AEs may have been previously reported in the AE table or have been reported to the manufacturer. Additional surgery may be necessary to correct some of these potential AEs.

Potential adverse effects associated with any surgical procedure include:

- Anesthesia complications, including allergic reaction, anaphylaxis, or other reactions to anesthesia
- Reaction to transfused blood

- Anemia
- Blood loss/hemorrhage
- Heart or vascular complications, including:
- Excessive bleeding or injury to blood vessels
- Edema
- Hematoma or seroma
- Hypotension or hypertension
- Ischemia
- Cardiac event
- Myocardial infarction
- Embolism, including pulmonary embolism
- Thrombosis
- Thromboembolism
- Thrombophlebitis
- Phlebitis
- Stroke
- Hemorrhage or vascular damage resulting in catastrophic or potentially fatal bleeding
- Septicemia
- Cerebral vascular accident (stroke)
- Pulmonary complications, including atelectasis, pneumothorax, pneumonia, pulmonary edema, and respiratory distress
- Blindness secondary to pressure on the eye during surgery
- False aneurysm
- Headache
- Infection (wound, local, and/or systemic) abscess, or cellulitis
- Soft tissue damage or fluid collections, including edema, hematoma, or seroma, which may require drainage, aspiration, debridement, or other intervention
- Surgical wound dehiscence, necrosis, or scarring of tissue around the wound
- Post-surgical pain, bruising, tenderness or discomfort at the surgical site or incision and/or skin or muscle sensitivity over the incision which may result in skin breakdown, pain, and/or irritation
- Impairment of the gastrointestinal system including ileus or bowel obstruction, nausea, or vomiting
- Impairment of the genitourinary system including incontinence, bladder dysfunction, urinary tract infection, or reproductive system complications
- Neurological complications including nerve damage, paralysis, seizures or convulsions, changes to mental status, or reflex sympathetic dystrophy
- Psychological illness
- Injury to muscles, or organs
- Insomnia
- Narcotic addiction
- Numbness
- Complications of pregnancy including miscarriage or congenital defects
- Inability to resume activities of daily living
- Death

Potential adverse effects associated with an instrumented TLIF surgery (one- and two-levels) with any type of bone graft include:

- Risks to neurological structures
- Dural tear dural leak and/or dural injury with or without CSF leakage
- Arachnoiditis
- Compressive neuropathy
- Neurologic deterioration - injury to nerves or nerve roots associated with the spinal cord (resulting in pain, weakness, paralysis (partial or complete), paresthesia, altered reflexes, numbness, tingling, or other changes in sensation)
- Coordination abnormalities
- Gait disturbance
- Headache
- Otitis media
- Tremors
- Cerebrospinal fluid leakage
- Cerebrospinal fistula
- Reflex Sympathetic Dystrophy (RSD) / Chronic Regional Pain Syndrome (CRPS)
- Cauda equina syndrome
- Damage to nerves, blood vessels, and nearby tissues
- Impaired muscle or nerve function
- Epidural bleeding, hematoma, or fibrosis
- Bone necrosis
- Degenerative changes in adjacent segment
- Surgery at incorrect level
- Osteolysis
- Loss of bowel or bladder function
- Incontinence (loss of bowel or bladder control)

- Fracture of the vertebrae, spinous process, or other damage to bony structures during or after surgery
- Postoperative muscle and tissue pain
- Development of disc degeneration at adjacent levels
- Inflammatory conditions
- Loss of disc height
- Disc herniation
- Undesirable change in lordosis
- Scarring or soft tissue damage
- Spinal instability
- Spondylolisthesis, acquired (vertebral slippage)
- Retrolisthesis
- Spinal stenosis (narrowing of the spinal canal)
- Spondylosis
- Facet joint deterioration
- Infection of the bone, or surrounding soft tissue
- Musculoskeletal spasms (back or leg)
- Perineural fibrosis
- Surgery may not reduce the preoperative pain
- Pain and discomfort associated with the presence of implants
- Pain and discomfort associated with the surgical procedure (e.g., cutting of muscles, ligaments, and tissue) and healing
- The spine may undergo adverse changes or deterioration including loss of proper spinal curvature, correction, height, and/or reduction, or malalignment, and another surgery may be required
- Adverse bone/implant interface reaction
- Extrusion or migration of the bone graft, resulting in pain, neural impingement, physical impairment, or loss of function, any of which may require revision surgery
- Abnormal bone formation in an unintended location
- Excessive or incomplete bone formation

Potential adverse effects associated with the use of Infuse™ Bone Graft include:
- Allergic/immune reaction to the components of Infuse Bone Graft

CLINICAL RESULTS

Clinical data to support the safety and effectiveness of Infuse™ Bone Graft were collected as part of a prospective, randomized, blinded, controlled pivotal study in subjects undergoing a TLIF at one or two levels, as compared to the control (autogenous local bone autograft supplemented with cancellous allograft as needed). Subjects were enrolled and randomized in the trial according to a 1:1:1 Infuse™ Bone Graft l 2.1 mg/level group: Infuse™ Bone Graft 4.2 mg/level group: control group) treatment ratio. The subjects, the Committee responsible for adjudicating AE relatedness and the independent radiological reviewers were blinded to the randomization treatment groups.

Clinical and Radiographic Effectiveness Parameters

Subjects were evaluated at multiple time points throughout the study: preoperatively (within 12 months of enrollment), intraoperatively, and postoperatively up to 24 months, with annual follow-ups thereafter. Throughout the clinical trial, complications and AEs—whether device-related or not—were monitored. Success was determined based on data collected during the initial 24 months of follow-up.

The study's primary endpoints included overall success and radiographic fusion success. Overall success was defined as a composite endpoint, incorporating both safety and effectiveness criteria at 24 months. To achieve overall success, the following criteria had to be met: 1) radiographic fusion success, 2) Oswestry Disability Index (ODI) success, 3) neurological success, 4) no Serious Adverse Events (SAEs) that are "related" to TLIF grafting material or interbody device, and 5) No secondary surgeries that are classified as failure, which is defined as any secondary surgeries at the index level(s) "related" to TLIF grafting material or interbody device.

Patient Demographics and Accountability

A total of 379 one-level subjects and 101 two-level subjects were enrolled and randomized. A total of 129 one-level and 34 two-level subjects were treated with an Infuse™ Bone Graft dose of 2.1 mg, 128 one-level and 32 two-level subjects received an Infuse™ dose of 4.2 mg, and 122 one-level and 35 two-level subjects were enrolled as control and did not receive Infuse™. For the majority of the demographic parameters, there were no differences across the three populations.

Summary of surgical indication and surgical information by treatment group based on all subjects

Variable	One-Level Subjects (N = 379)			Two-Level Subjects (N = 101)		
	Infuse 2.1 (N = 129)	Infuse 4.2 (N = 128)	Control (N = 122)	Infuse 2.1 (N = 34)	Infuse 4.2 (N = 32)	Control (N = 35)
Primary Diagnosis (m/n, %)						
Instability	46/129 (35.7%)	53/128 (41.4%)	46/122 (37.7%)	8/34 (23.5%)	7/32 (21.9%)	8/35 (22.9%)

Variable	One-Level Subjects (N = 379)			Two-Level Subjects (N = 101)		
	Infuse 2.1 (N = 129)	**Infuse 4.2 (N = 128)**	**Control (N = 122)**	**Infuse 2.1 (N = 34)**	**Infuse 4.2 (N = 32)**	**Control (N = 35)**
Recurrent Disc Herniation	12/129 (9.3%)	11/128 (8.6%)	8/122 (6.6%)	2/34 (5.9%)	2/32 (6.3%)	2/35 (5.7%)
Stenosis	71/129 (55.0%)	64/128 (50.0%)	68/122 (55.7%)	24/34 (70.6%)	23/32 (71.9%)	25/35 (71.4%)
Has the subject had previous lumbar spinal surgery (m/n, %)	16/129 (12.4%)	20/128 (15.6%)	24/122 (19.7%)	1/34 (2.9%)	6/32 (18.8%)	4/35 (11.4%)
Mean (SD) Operation Time, minutes	174.1 (66.8)	175.1 (69.8)	166.5 (56.4)	221.4 (43.7)	221.1 (61.7)	203.9 (51.2)
Mean (SD) Total Estimated Blood Loss (mL)	161.3 (148.1)	157.0 (125.0)	152.2 (112.0)	281.8 (159.4)	265.6 (282.0)	269.4 (237.9)
Mean (SD) Length of Hospital Stay (days)	3.4 (2.1)	3.5 (2.2)	3.6 (2.6)	4.7 (2.8)	3.3 (1.9)	3.7 (2.4)
Treatment Level (m/n, %) *						
L2-L3	0/129 (0.0%)	1/128 (0.8%)	0/122 (0.0%)	---	---	---
L3-L4	4/129 (3.1%)	6/128 (4.7%)	7/122 (5.7%)	0/34 (0.0%)	1/32 (3.1%)	0/35 (0.0%)
L4-L5	102/129 (79.1%)	91/128 (71.1%)	91/122 (74.6%)	0/34 (0.0%)	3/32 (9.4%)	3/35 (8.6%)
L5-S1	23/129 (17.8%)	30/128 (23.4%)	21/122 (17.2%)	---	---	---
L5-L6	0/129 (0.0%)	0/128 (0.0%)	1/122 (0.8%)	---	---	---
L2-L3; L3-L4	---	---	---	1/34 (2.9%)	0/32 (0.0%)	0/35 (0.0%)
L3-L4; L4-L5	0/129 (0.0%)	0/128 (0.0%)	2/122 (1.6%)	19/34 (55.9%)	17/32 (53.1%)	8/35 (22.9%)
L4-L5; L5-S1	---	---	---	14/34 (41.2%)	11/32 (34.4%)	24/35 (68.6%)
Surgical Access (m/n, %)						
Minimally Invasive (i.e. Metrx or Quadrant)	53/129 (41.1%)	53/128 (41.4%)	49/122 (40.2%)	5/34 (14.7%)	6/32 (18.8%)	4/35 (11.4%)
Open	76/129 (58.9%)	75/128 (58.6%)	73/122 (59.8%)	29/34 (85.3%)	26/32 (81.3%)	31/35 (88.6%)
Mean (SD) Volume of Local Bone Autograft Implanted (cc)	6.7 (5.3)	6.1 (4.0)	7.0 (5.5)	Sup: 8.6 (6.6) Inf: 8.3 (6.1)	Sup: 8.1 (4.9) Inf: 7.5 (4.7)	Sup: 9.0 (5.6) Inf: 10.5 (5.7)
Mean (SD) Volume of Allograft Bone Implanted (cc)	9.3 (7.6)	9.8 (7.5)	11.0 (9.3)	Sup: 8.2 (10.4) Inf: 11.5 (14.1)	Sup: 8.7 (5.7) Inf: 9.2 (5.5)	Sup: 6.9 (3.4) Inf: 8.8 (1.5)

* Two subjects were randomized as one-level subject, but two levels were treated, seven subjects were randomized as two-level subjects, but only one level was treated.

Clinical and Radiographic Effectiveness Evaluation

Individual subject success was defined as Overall Success in each of the composite endpoints involving safety and effectiveness measures which satisfied the following criteria at 24 months:

- Radiographic fusion success must be met. Radiographic fusion success must show evidence of bridging bone and no evidence of motion (less than 2 mm translational motion and less than 3^{o} in angular motion at each treated level).
- ODI success must be met. ODI success was defined as postoperative pain/disability improvement of at least 15 points from the preoperative score (Preoperative Score - Postoperative Score ≥ 15 points).
- Neurological success must be met. Neurological success was defined as maintenance or improvement in four key neurological assessments: motor function, sensory function, reflexes, and straight leg raise at a postoperative time period as compared to the corresponding elements before surgery (preoperative).
- No SAEs that are “related” to TLIF grafting material or interbody device.
- No secondary surgeries that are classified as failure, which is defined as any secondary surgeries at the index level(s) “related” to TLIF grafting material or interbody device.

The primary endpoints of this study are overall success at 24 months and radiographic fusion success at 24 months. The primary objectives of the study are to demonstrate noninferiority in overall success at 24 months and superiority of radiographic fusion success at 24 months for at least one investigational group as compared to the control group.

The study met its primary objectives by demonstrating noninferiority in overall success at 24 months, and superiority of radiographic fusion success at 24 months for both Infuse 2.1 mg and 4.2 mg compared to the Control group for 1-level and 2-level subjects.

Overall Success in the As Randomized and Treated (ART) population by treatment group

Variable	One-Level Subjects (N = 129, 128, 122 for 2.1 mg, 4.2 mg and Ctrl)						Two-Level Subjects (N = 34, 32, 35 for 2.1 mg, 4.2 mg and Ctrl)					
	12 Months			24 Months			12 Months			24 Months		
	2.1 mg	4.2 mg	Ctrl	2.1 mg	4.2 mg	Ctrl	2.1 mg	4.2 mg	Ctrl	2.1 mg	4.2 mg	Ctrl
ODI Success	89/97 (91.8%)	87/97 (89.7%)	87/93 (93.5%)	67/71 (94.4%)	62/64 (96.9%)	65/70 (92.9%)	22/26 (84.6%)	21/24 (87.5%)	21/25 (84.0%)	17/19 (89.5%)	14/18 (77.8%)	14/16 (87.5%)
Radiographic Fusion Success	**66/96 (68.8%)**	**72/94 (76.6%)**	**48/90 (53.3%)**	**63/72 (87.5%)**	**54/60 (90.0%)**	**42/68 (61.8%)**	**19/24 (79.2%)**	**18/24 (75.0%)**	**11/25 (44.0%)**	**15/19 (78.9%)**	**13/15 (86.7%)**	**7/16 (43.8%)**
Neurological Success	81/96 (84.4%)	91/95 (95.8%)	85/95 (89.5%)	60/71 (84.5%)	57/63 (90.5%)	63/70 (90.0%)	21/26 (80.8%)	19/23 (82.6%)	21/25 (84.0%)	16/19 (84.2%)	16/19 (84.2%)	12/15 (80.0%)
SAEs that are related to TLIF grafting material or interbody device	1	5	3	3	7	3	1	0	1	1	1	1
Secondary surgeries that are classified as failure	1	3	2	2	4	2	0	0	1	0	0	1
Overall success	**56/97 (57.7%)**	**60/96 (62.5%)**	**42/91 (46.2%)**	**48/70 (68.6%)**	**47/67 (70.1%)**	**37/69 (53.6%)**	**14/26 (53.8%)**	**13/23 (56.5%)**	**8/25 (32.0%)**	**11/19 (57.9%)**	**9/15 (60.0%)**	**3/15 (20.0%)**

The table above presents the success rate of overall success, and it is components, including radiographic fusion success at 12 months and 24 months.

Among one-level subjects at 24 months, overall success rates were 68.6% and 70.1% for Infuse 2.1 mg and 4.2 mg, respectively, versus 53.6% for Control. For two-level subjects, overall success rates were 57.9% and 60.0% for both Infuse 2.1 mg and 4.2 mg groups, compared to 20.0% for Control.

At 24 months, one-level subjects achieved radiographic fusion success rates of 87.5% and 90.0% (Infuse 2.1 mg and 4.2 mg, respectively) versus 61.8% for Control, while two-level subjects showed rates of 78.9% and 86.7% (Infuse 2.1 mg and 4.2 mg, respectively) versus 43.8% for Control.

Safety and Immune Response Evaluation

The assessment of safety in the study included an evaluation of reported AEs and safety endpoints for subjects undergoing TLIF procedures with Infuse™ Bone Graft at one or two lumbar levels. AEs were monitored over the 24-month reporting period, with cumulative rates found to be similar across all treatment groups (Infuse 2.1 mg, Infuse 4.2 mg, and Control). SAEs were significantly higher in the Infuse 4.2 mg group (41.3%) compared to the Control group (24.6%). However, none of the individual rates of SAEs in the Infuse groups showed any significant differences compared to the individual rates in the Control group.

Specific AEs, such as vascular disorders (11.9%, 14.1% and 1.8% in 2.1mg, 4.2mg and Control), and urinary tract infections (4.3%, 4.3% and 0.0% in 2.1mg, 4.2mg and Control), showed statistical differences (based on nominal p-values) between 2.1mg group and the Control group, 4.2 mg group and the Control group.

Rates of secondary surgeries were similar across all groups.

Notably, heterotopic ossification was more frequently observed in the Infuse groups, but no correlation was identified between radiographic observation of HO and reported adverse events (AEs) that could potentially result from HO.

Overall, Infuse treatments demonstrated superior efficacy compared to the Control group, with comparable safety profiles. These results support the use of Infuse Bone Graft in TLIF procedures at one or two lumbar levels.

In a separate study, antibodies to rhBMP-2 and bovine Type I collagen were assessed preoperatively and at 6 weeks, 3 months, and 6 months postoperatively. Antibodies to human Type I collagen were evaluated only if the antibody response to bovine Type I collagen was positive.

HOW SUPPLIED

Infuse™ Bone Graft is supplied in various kit sizes containing all the components necessary to prepare the device [i.e. the collagen sponge(s), a vial with the lyophilized growth factor, a vial with sterile water for reconstituting the growth factor, syringes, and needles].

STORAGE CONDITIONS

Store Infuse™ Bone Graft at room temperature [59 to 86°F (15-30°C)].

DOSAGE AND ADMINISTRATION

Infuse™ Bone Graft is prepared immediately prior to use from a kit containing all necessary components. Once prepared, Infuse™ Bone Graft contains rhBMP-2 at a concentration of 1.5mg/mL.

The size of the Infuse™ Bone Graft is 1.4cc (2.1 mg rhBMP-2) or 2.8cc (4.2 mg rhBMP-2) per treated spinal level. Refer to the Infuse™ Bone Graft Instructions for Preparation and Infuse™ Bone Graft TLIF Surgical Technique for further information.

Only store the components in this Infuse™ Bone Graft kit in the manner described on the package, only mix the components in the manner described in the directions, only add the reconstituted rhBMP-2 to the ACS carrier provided in the manner described and only use in the quantity and indication specified in the package insert. Any other storage, mixture, or administration may cause unanticipated AEs.

DIRECTIONS FOR USE

Infuse™ Bone Graft is prepared at the time of surgery in the surgical suite by reconstituting the lyophilized rhBMP-2 with sterile water (see Instructions for Preparation) and then uniformly applying the reconstituted rhBMP-2 solution to the ACS. Infuse™ Bone Graft is then implanted through a transforaminal surgical approach (see the Surgical Technique manual). If Infuse™ Bone Graft is not used within two hours after reconstitution, it must be discarded.

Infuse™ Bone Graft must not be sterilized by the hospital.

PRODUCT COMPLAINTS

To report product problems, contact Medtronic.

DEVICE RETRIEVAL EFFORTS

Should it be necessary to remove Infuse™ Bone Graft, please call Medtronic prior to the scheduled surgery to receive instructions regarding data collection, including histopathological, mechanical, and AE information.

FURTHER INFORMATION

No warranties, express or implied, are made. Implied warranties of merchantability and fitness for a particular purpose or use are specifically excluded.

FRONT COVER
[*Title and cover image*]

PAGE 1
Patient Information Brochure
This Patient Guide is designed to help you make an informed decision about treatment for your back pain and related problems. Your doctor has proposed surgery to relieve your back pain and related problems using Infuse™ Bone Graft with an Interbody Fusion Device.

Your doctor has determined that you would benefit from spinal surgery after carefully examining you, reviewing your history and x-rays, and taking into account the results of other diagnostic studies and previous non-surgical treatments. Specifically, your doctor has determined that you would benefit from having spinal surgery that fuses (connects) certain bones of your back together to prevent them from moving relative to each other.

Your Lower Back
The bony vertebrae, which encircle and protect your spinal cord, are separated by shock-absorbing discs. The discs give your spine the flexibility to move. Nerves branching from the spinal cord pass through openings in the vertebra to other parts of your body. Several of these nerves form the sciatic nerve, which runs down your leg. Each disc has a spongy center (nucleus) surrounded by tough outer rings.

As discs lose their water content because of disease or age, they lose their height, bringing the vertebrae closer together. As a result, the nerve openings in your spine become more narrow, and the discs don't absorb the shocks as well, particularly when you are walking, running, or jumping. Wear and tear, poor posture, and incorrect body movements can also weaken the disc, causing disc degeneration. Disc degeneration may cause back and/or leg pain, as well as functional problems, such as tingling or numbness in your legs or buttocks or difficulty walking. Doctors call this degenerative disease of the lumbosacral spine or degenerative disc disease (DDD).

PAGE 2
[*Illustrations of healthy lumbar spine, disc herniation, and disc degeneration*]

PAGE 3
Implant Descriptions

Interbody Fusion Device
In an interbody spine fusion, part of the degenerated disc is removed, and an intervertebral body fusion device or interbody device is inserted between the vertebrae to restore disc height, thereby relieving pressure on your nerves. Bone grafts are used with the implant to encourage bone growth and fusion.

Infuse™ Bone Graft
Infuse Bone Graft consists of a protein (rhBMP-2) on an absorbable collagen sponge (ACS) and stimulates bone growth at the site of implantation. Depending on the surgical approach, Infuse Bone Graft is placed either next to or inside of the interbody device. The protein is a manufactured version of a natural protein normally found in small quantities in the body. During surgery, the protein solution is soaked into the ACS. The ACS acts as a scaffold for the formation of new bone that the protein stimulates. The ACS is a sponge manufactured from bovine (cow) collagen. It is designed to resorb or disappear over time.

Posterior supplemental fixation
Many interbody devices are designed to be used with additional hardware, such as rods and screws, placed at the back of the spine. This supplemental fixation is used in conjunction with an interbody device to restore proper alignment and minimize movement while your back heals. By reinforcing the spine from behind, posterior supplemental fixation helps ensure that the bone graft and fusion device remain securely in place, giving the body the best chance to achieve solid bone healing and lasting stability. Some interbody fusion devices are designed to provide sufficient correction and stability without supplemental fixation. Your surgeon will advise you on which implants are necessary to achieve the goals of your surgery.

PAGE 4
[*Illustrations of interbody fusion device(s), Infuse Bone Graft, and posterior supplemental fixation*]

PAGE 5

Surgery

Infuse Bone Graft can be implanted through an opening in your abdomen (anterior or oblique lateral) with a Medtronic Interbody Fusion Device. Infuse Bone Graft with an interbody fusion device can also be implanted through an opening in your lower back (posterior or transforaminal approach) You should speak with your doctor about the risks and benefits of the various approaches prior to surgery.

During your surgery, your doctor will remove portions of the degenerated disc and vertebral body to allow the implant(s) to be inserted.

For anterior or oblique lateral approaches, the surgeon will place Infuse Bone Graft inside the hollow interbody fusion device. Depending on the type of interbody device used, your surgeon may also implant metal rods and screws (posterior supplemental fixation) to stabilize your spinal alignment until bone growth occurs.

For a posterior approach, the surgeon will place Infuse Bone Graft in front of the implant and fill the interbody device and remaining interbody space with autograft bone recovered from the surgical site. If there is not enough autograft bone to fill the remaining disc space, your doctor may also use allograft bone from a deceased donor to fill the disc space. Your surgeon will also implant metal rods and screws (posterior supplemental fixation) to stabilize your spinal alignment until new bone growth occurs.

After Surgery

Ask your doctor about your specific recovery plan following surgery. It is important to follow your doctor's instructions carefully to recover from surgery as quickly as possible and increase your chances of a successful outcome. Recovering from back pain and surgery is an ongoing process. How fast you recover depends on the type of surgery you had, your commitment to working closely with your physical therapist, and moving and exercising correctly, as recommended by your surgeon.

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In most cases, immediately after surgery, your heart and lung function will continue to be monitored, a drainage tube may have been left in your wound, and your doctor may prescribe medicines to control pain and nausea. A nurse will show you how to care for your wound before you are sent home, and your doctor will discuss a program to gradually increase your activity. You may be required to wear a back brace after surgery, and you may be told to avoid repetitive bending, lifting, stooping, twisting, and athletic activities until fusion has occurred. You may also be cautioned to avoid vibrations, like you might experience when driving a car, for a period of time after your surgery.

Contact your doctor immediately if:
» you get a fever;
» the wound starts leaking fluids;
» you have trouble swallowing or breathing;
» you have trouble urinating; or
» you have new or increased back or leg pain or numbness.

Your doctor will schedule office visits to check on how you are doing and see if anything else needs to be done. Your surgeon may refer you to a physical therapist who will teach you exercises to improve your strength and increase your mobility. The goal of physical therapy is to help you become active as soon as possible, using safe body movements that protect your back. This often includes abdominal strengthening exercises. You may also be taught different ways of standing, sitting, or lifting to avoid reinjuring your back.

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Potential Benefit

A potential benefit to using Infuse Bone Graft with a Medtronic Interbody Fusion Device in an anterior (front) or oblique lateral (side) approach is that it removes the need to collect bone graft from your hip (iliac crest autograft) to fill the inside of the device. Collecting iliac crest autograft bone involves a second or larger incision that may be painful and/or take longer to heal.

Accessing the interbody space through a posterior (back) surgical approach requires removal of bone which is processed and used as a graft material (local autograft bone). Infuse Bone Graft has been shown to improve surgical outcomes as compared to using local autograft bone alone in a posterior

approach.

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Possible Complications

Spinal surgery carries risks, including complications from the approach or implants used. These may be serious and could require further surgery. Possible complications from spine surgery performed using Infuse Bone Graft with an Interbody Fusion Device include:

Potential complications associated with any surgery include:
» Allergic reaction to the implant materials;
» Bleeding, which may require a blood transfusion;
» Bowel, bladder, or gastrointestinal problems;
» Damage to nearby tissues, blood vessels and/or nerves;
» Death;
» Infection;
» Localized swelling (edema) or collection of fluid near the implant site;
» Pain or discomfort (itching);
» Psychological complications;
» Respiratory (breathing) problems;
» Scar formation or other problems with the surgical incision;
» Side effects from anesthesia or the surgical approach;
» Vascular problems other than bleeding.

Potential complications associated with an instrumental ALIF, OLIF or one- and two-level TLIF surgery:
» Bending, breakage, loosening, and/or migration of the implants;
» Bone fracture or failure to fuse;
» Bone formation that is abnormal, excessive, or in an unintended location;
» Bone resorption, which may not be permanent;
» Loss of spinal mobility or function, and hastened adjacent level degeneration
» Paralysis or other neurological problems;
» Postoperative changes in spinal curvature or loss of correction or disc height;
» Sexual dysfunction;
» Spinal cord or nerve damage;
» Tears of the dura (a layer of tissue covering the spinal cord); or

Potential complications associated with the use of Infuse™ Bone Graft include:
» Fetal development complications;
» Allergic reaction to the components of Infuse Bone Graft

These potential complications underscore the importance of thorough discussion with your doctor when considering spinal surgery. Understanding both the possible risks and the anticipated benefits can help you make an informed decision about surgery.

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Indications for Use – Anterior or Oblique Lateral Approach

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. DDD is defined as discogenic back pain with degeneration of the disc confirmed by patient history and radiographic studies. These DDD patients may also have up to Grade 1 spondylolisthesis or Grade 1 retrolisthesis at the level involved. Patients receiving the Infuse™ Bone Graft/Medtronic Interbody Fusion Device should have had at least six months of nonoperative treatment prior to treatment.

Indications for Use – Posterior (Transforaminal) Approach

Infuse™ Bone Graft with an FDA cleared intervertebral body fusion device and metallic screw-and-rod system is indicated for use in a transforaminal lumbar interbody fusion (TLIF) surgical approach at one or two adjacent levels from L2-S1 in the treatment of symptomatic degenerative disc disease (DDD) confirmed by patient history and radiographic studies and having at least six months of nonoperative treatment attempted prior to treatment with Infuse™ Bone Graft.

Contraindications

The Infuse Bone Graft with an Interbody Fusion Device should not be used if:

- you are pregnant or suspect that you might be pregnant;
- you are sensitive to titanium, titanium alloy, polyetheretherketone (PEEK), bovine (cow) Type I collagen, or recombinant human Bone Morphogenetic Protein-2;
- you have an infection near the area of the operative site;
- you have a tumor or had a tumor removed from the area of the implantation site;
- you have or are currently being treated for cancer; or
- your bones have not stopped growing.

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Warnings and Precautions

This device has not been tested in pregnant women to determine if there is any effect on a developing fetus. This device has also not been studied in nursing mothers.

When tested in female rabbits that received rhBMP-2, a component of the device, developed an immune response, and later became pregnant, the following was seen:

- The antibodies developed by the mother were able to reach the developing rabbit fetus. The effect of these antibodies on the developing rabbit fetus is not currently known.
- Some bone formation abnormalities were observed in a small number of the rabbit fetuses tested. It is not known if these changes would disappear as the rabbit fetus continued to develop or at some time after birth.

This device should not be used immediately prior to or during pregnancy. Women of childbearing potential should be advised not to get pregnant for one year following treatment with the device. Women of childbearing potential should be warned of potential risk to a fetus and should discuss other possible orthopedic treatments with their surgeon.

BMP-2 plays a critical role during fetal development in humans and other animals. It is not known whether a pregnant woman, previously exposed to BMP-2 by implantation with the device, might develop a second immune response to BMP-2 from the developing fetus with adverse effects for the woman or baby. In a rabbit pregnancy study to investigate this issue, no increase in anti-BMP-2 antibodies was observed.

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In addition, this device has not been tested:

- to see if there are side effects by using it in more than one surgical procedure in the same person;
- in people with liver or kidney problems (this might be important because these organs are involved in removing any by-products of the device);
- in people with metabolic bone diseases, such as osteoporosis;
- in people with autoimmune or immunosuppressive disease, such as lupus or HIV/AIDS; or
- in people with immune deficiency due to other treatments, such as radiation therapy, chemotherapy, or steroid therapy.

Sufficient numbers of patients 65 years and older have not been studied to determine whether they respond differently from younger people.

If this device is implanted using the anterior surgical approach, some males may experience retrograde ejaculation (a form of sexual dysfunction). Male patients should consider this potential risk.

There is a possibility that too much bone may form at the implantation site (exuberant bone formation), bone may form at a location away from the implantation site (heterotopic bone formation), or the bone that is formed may be abnormal.

Some patients may have an allergic reaction to the Infuse Bone Graft component. Please talk with your doctor about any of the above warnings and precautions.

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While this brochure has hopefully provided you with information you need to make an informed decision about your treatment options, it is not intended to replace professional medical advice. As with any surgical procedure, you should find a surgeon who is experienced in performing the specific surgery that you are considering.

If you have any questions or need additional information about Infuse Bone Graft, please contact your doctor.

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Clinical Results (anterior or oblique lateral approach)

A total of 413 patients participated in clinical studies of Infuse Bone Graft with the LT-Cage Lumbar Tapered Fusion Device (one of the devices approved for use with Infuse Bone Graft). An anterior open surgical approach was used for 143 patients, and an anterior laparoscopic (minimally invasive) surgical approach was used for 134 patients. A group of 136 control patients were implanted with the LT-Cage Lumbar Tapered Fusion Device filled with bone taken from their hip, an alternative procedure.

The tables below compare the success rates at 24 months after surgery for the three groups of patients:

Anterior Open Surgical Approach Groups (24-month Evaluation)

	nce the Investigational Patients Had a Successful Outcome	Chance the Control Patients Had a Successful
Fusion	93%	88%
Pain and Function	71%	71%
Neurologic Status	81%	82%
Overall Success	57%	57%

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Anterior Laparoscopic Surgical Approach Groups (24-month Evaluation)

	nce the Investigational Patients Had a Successful Outcome	Chance the Control Patients Had a Successful
Fusion	93%	88%
Pain and Function	83%	71%
Neurologic Status	89%	82%
Overall Success	68%	57%

The overall success rate describes the number of patients who had successful outcomes in fusion, pain and function, and neurologic status. Also, to be considered an overall success, a patient could not have a serious complication associated with the device or have a second surgery because the first surgery was not successful.

Two years after their surgery, 82% of the investigational patients and 80% of the control patients said that it was definitely true or mostly true that they were satisfied with the results of their surgery.

All the patients in the study had blood collected to see if they generated antibodies (a type of protein that your body's immune system produces when it detects an unknown substance, such as bacteria, a virus, or a foreign object, such as a device) to specific parts of the device – rhBMP-2 and bovine Type I collagen – as well as to human Type I collagen. Three patients had a response to rhBMP-2, 66 patients had a response to bovine Type I collagen, and none had a response to human Type I collagen. When these results were compared to whether or not these patients had a successful outcome, no connection was seen between the antibody response and outcome.

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A total of 145 investigational subjects were evaluated out to six years (72 months) after the initial surgery in a post-approval study. The patient population was obtained from participants in both the open and laparoscopic arms of the original clinical trial. Control subjects were not followed in the post-approval study. Using the same criteria from the clinical study, the table below summarizes the success rates at four and six years after the initial surgery.

Success Rates in Investigational Patients

	4-Year Evaluation	6-Year Evaluation
Fusion	98%	99%
Pain and Function	82%	79%
Neurologic Status	73%	81%
Overall Success	61%	60%

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Clinical Results (posterior approach)

A total of 480 patients participated in a clinical study of Infuse Bone Graft in a one or two level transforaminal lumbar interbody fusion (TLIF) procedure in the treatment of symptomatic degenerative disease of the lumbosacral spine. Study participants were randomly assigned to receive either Infuse Bone Graft at 2.1 mg per treated level (163 patients), Infuse Bone Graft at 4.2 mg per treated level (160 patients), or no Infuse bone graft (control group; 157 patients). All patients were treated with a Medtronic spinal interbody system, a Medtronic posterior supplemental fixation system, and local autograft bone supplemented with allograft (cadaver) bone as needed. A total of 379 patients were treated at one level and 101 patients were treated at two levels.

The primary assessment made in this study was a composite measure termed “Overall Success”, which included key safety and effectiveness considerations. The table below compares the success rates at 24 months after surgery for the three groups of patients.

	% of Patients Had a Successful Outcome					
	One-Level Subjects			Two-Level Subjects		
	24 Months			24 Months		
Variable	2.1 mg	4.2 mg	Ctrl	2.1 mg	4.2 mg	Ctrl
ODI Success	94.4%	96.9%	92.9%	89.5%	77.8%	87.5%
Fusion Success	87.5%	90.5%	61.8%	78.9%	86.7%	43.8%
Neurological Success	84.5%	90.5%	90.0%	84.2%	84.2%	80.0%
Overall Success	**68.6%**	**70.1%**	**53.6%**	**57.9%**	**60.0%**	**20.0%**

The percentage of patients achieving Overall Success at the 24-month visit was higher in the Infuse 2.1 mg/level and 4.2 mg/level groups compared with the Control group. Patients in the three groups had similar rates of reoperation over the two years following surgery.

Patients were also assessed for whether their treated levels were fused successfully, as evaluated with CT and conventional X-ray scans. The percentage of patients achieving Fusion Success at the 24-month visit was also higher in the Infuse 2.1 mg/level and 4.2 mg/level groups compared with the Control group.

The Infuse Bone Graft groups were found to be at least as safe as the control treatment, with no statistical differences in serious complications between the groups two years after surgery.

The safety and effectiveness results in this study demonstrated that Infuse Bone Graft performed as well or better than the control treatment in terms of overall success and fusion success and is at least as safe as the control treatment when using Infuse Bone Graft at 2.1 mg or 4.2 mg per level treated.

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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
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.
- 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.
- The Clydesdale™ Spinal System, implanted via an OLIF approach at a single level from L2-L5.
- The Divergence-L™ Anterior/Oblique Lumbar Fusion System implanted via an ALIF approach at a single level from L2-S1 or an OLIF approach at a single level from L5-S1.
- 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, the Clydesdale™ Spinal System, the Divergence-L™ Anterior/Oblique Lumbar Fusion System, the Pivox™ Oblique Lateral Spinal System, the Anteralign™ Spinal System with Titan nanoLOCK Technology 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™ Bone Graft kit. An electronic version of the package insert may be found at manuals.medtronic.com.

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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BRIEF SUMMARY OF INDICATIONS, CONTRAINDICATIONS, AND WARNINGS FOR: Infuse™ Bone Graft

Infuse™ Bone Graft with an FDA cleared intervertebral body fusion device and metallic screw-and-rod system is intended for use in a transforaminal lumbar interbody fusion (TLIF) surgical approach at one or two adjacent levels from L2-S1 in the treatment of symptomatic degenerative disc disease (DDD), confirmed by patient history and radiographic studies and having at least six months of nonoperative treatment attempted prior to treatment with Infuse™ Bone Graft.

Infuse™ Bone Graft consists of two components – a recombinant human bone morphogenetic protein 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 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).

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BACK COVER
[*Contact information*]