

## **INFUSE® Bone Graft**

### **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 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 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 dibotermis 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 device is replaced by trabecular bone.

rhBMP-2 is the active agent in INFUSE Bone Graft. rhBMP-2 is 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: 1.5 mg of rhBMP-2; 5.0 mg sucrose, NF; 25 mg glycine, USP; 3.7 mg L-glutamic acid, FCC; 0.1 mg sodium chloride, USP; 0.1 mg polysorbate 80, NF; and 1.0 mL of sterile water. The reconstituted rhBMP-2 solution has a pH of 4.5, and is clear, colorless and essentially free from plainly visible particulate matter.

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 sponges, syringes with needles, this package insert and instructions for preparation. The rhBMP-2 is provided as a lyophilized powder in vials delivering 12 mg of protein. After appropriate reconstitution, the concentration of rhBMP-2 is 1.5 mg/mL. The solution is then applied to the provided absorbable collagen sponge. 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 fracture site. The Instructions for Preparation contain complete details on preparation of INFUSE Bone Graft

### **INDICATIONS:**

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.

### **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.
- INFUSE Bone Graft 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.
- INFUSE Bone Graft should not be used in patients who are skeletally immature (<18 years of age or no radiographic evidence of epiphyseal closure).
- INFUSE Bone Graft should not be used in patients with an inadequate neurovascular status, *e.g.*, high risk of amputation.
- INFUSE Bone Graft should not be used in patients with compartment syndrome of the affected limb.
- INFUSE Bone Graft should not be used in pregnant women. The potential effects of rhBMP-2 on the human fetus have not been evaluated.
- INFUSE Bone Graft should not be implanted in patients with an active infection at the operative site.

## **WARNINGS:**

- Women of childbearing potential should be advised that antibody formation to rhBMP-2 or its influence on fetal development have not been assessed. In the clinical trial supporting the safety and effectiveness of INFUSE Bone Graft in tibial fracture, 9/149 (6.0%) patients treated with INFUSE Bone Graft and 1/150 (0.7%) patients treated without exposure to rhBMP-2 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, thereby eliciting a more powerful immune response to BMP-2 with adverse consequences for the fetus. Studies in genetically altered mice indicate that BMP-2 is critical to fetal development and that lack of BMP-2 activity, as might be induced by antibody formation, may cause neonatal death or birth defects.
  - 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.
  - Women of childbearing potential should be advised not to become pregnant for one year following treatment with INFUSE Bone Graft.
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- The safety and effectiveness of INFUSE Bone Graft for non-acute fractures, with forms of internal fracture fixation other than IM nails, implanted at locations other than the tibial shaft, or used in surgical techniques other than open reduction and internal fixation after appropriate wound management have not been established.

## **PRECAUTIONS:**

### **General**

- The safety and effectiveness of repeat applications of INFUSE Bone Graft has not been established.
- Long-bone fracture and soft-tissue management procedures should be based on standard practice including control of infection. Physicians should achieve mechanical stability before implanting INFUSE Bone Graft. INFUSE Bone Graft should not be used to fill space in the presence of compressive forces.
- INFUSE Bone Graft should only be used by surgeons who are experienced in treating acute open tibial shaft fractures involving IM nail stabilization and have undergone adequate training with this device.

- A single package of INFUSE Bone Graft should be used at the fracture site.
- INFUSE Bone Graft is intended for single use only. Discard unused product and use a new device for subsequent applications. INFUSE Bone Graft must not be sterilized by the hospital.
- 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 Sofamor Danek, Inc. 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 patients with hepatic or renal impairment has not been established. Pharmacokinetic studies of rhBMP-2 indicate that the renal and hepatic systems are involved with its clearance.

#### **Geriatrics**

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

#### **Bone formation**

- The safety and effectiveness of INFUSE Bone Graft has not been demonstrated in patients with metabolic bone diseases, or in pathological fractures such as those observed in Paget's disease or in metastatic bone disease..
- While not specifically observed in the clinical study, the potential for ectopic, heterotopic or undesirable exuberant bone formation exists.

#### **Antibody Formation/Allergic Reactions**

- The safety and effectiveness of INFUSE Bone Graft has not been demonstrated in patients with autoimmune disease.
- The safety and effectiveness of INFUSE Bone Graft has not been demonstrated in patients 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. The immune response to INFUSE Bone Graft

was evaluated in 149 investigational patients and 150 control patients receiving treatment for acute open tibial shaft fractures stabilized with IM nails.

- *Anti-rhBMP-2 antibodies:* 9/149 (6%) patients receiving the InFUSE™ Bone Graft component developed antibodies vs. 1/150 (0.7%) in the control group.
  - *Anti-bovine Type I collagen antibodies:* 29/149 (20%) of patients receiving the InFUSE™ Bone Graft component developed antibodies to bovine Type I collagen vs. 9/150 (6%) of control patients. No patients 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 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:**

The table below describes the adverse events observed in the clinical trial used to support approval of the product. Two INFUSE Bone Graft doses, 0.75mg/ml and 1.5mg/ml, were evaluated. INFUSE Bone Graft with IM nail stabilization was implanted in 300 investigational patients (149 in the 1.50 mg/ml and 151 in the 0.75 mg/ml groups) compared to IM stabilization alone in 150 control patients. Adverse event rates presented are based on the number of patients having at least one occurrence for a particular adverse event divided by the total number of patients in that treatment group.

**Adverse events reported for patients enrolled in clinical trial supporting approval**

	Total Adverse Events														
	1 <sup>st</sup> quarter postop			2 <sup>nd</sup> quarter postop			3 <sup>rd</sup> quarter postop			4 <sup>th</sup> quarter postop			# (%) of Patients		
	Control (n=150)	low dose (n=151)	Inves. (n=149)	Control (n=147)	low dose (n=144)	Inves. (n=144)	Control (n=144)	low dose (n=144)	Inves. (n=144)	Control (n=138)	low dose (n=142)	Inves. (n=141)	Control (n=150)	low dose (n=151)	Inves. (n=149)
<b>Number of patients</b>	150	150	149	147	144	144	144	144	138	142	141	150	150	149	
<b>Abnormal healing</b>															
surgical site	64	60	53	19	19	13	7	4	4	2	3	65 <sup>a</sup>	62	57	
other locations	9	13	23	0	1	0	1	0	0	0	2	10	10	13	
<b>Abnormal lab tests</b>															
Alkaline phosphatase increased	8	8	3	0	0	0	0	0	0	0	0	8	8	3	
Amylase increased	5	23	11	0	0	0	0	0	0	0	0	5	20	10	
Bilirubinemia	8	9	11	0	0	0	0	0	0	0	0	7	9	11	
BUN increased	0	3	1	0	0	0	0	0	0	0	0	0	0	1	
Creatinine clearance decreased	2	1	2	0	0	0	0	0	0	0	0	2	1	2	
Gamma glutamyl transpeptidase increased	0	1	2	0	0	0	0	0	0	0	0	0	1	2	
Hypocalcemia	2	1	0	0	0	0	0	0	0	0	0	2	1	0	
Hypokalemia	2	3	3	0	0	0	0	0	0	0	0	2	3	3	
Hypokalemia	7	9	17	1	0	0	0	0	1	0	0	9	9	17	
Hypomagnesemia	3	11	3	0	0	0	0	0	0	0	0	2	11	3	
Hypocalcemia	54	63	55	0	0	0	0	0	0	0	0	50	60	53	
Lactic dehydrogenase increased	30	34	32	0	1	0	0	0	0	0	0	29	33	26	
SGOT increased	43	47	42	0	1	0	0	0	0	0	0	39	46	42	
SGPT increased	26	28	23	0	0	0	0	0	0	0	0	24	26	21	
Other	134	119	117	0	0	0	0	1	0	0	0	80	82	77	
<b>Accidental injuries</b>	1	2	4	1	0	2	0	0	0	0	2	2	2	6	
<b>Cardiovascular</b>	3	0	2	0	0	0	0	0	0	0	2	3	0	4	

<sup>a</sup> No. of patients with event  
<sup>b</sup> Percent of patients with event  
<sup>c</sup> Total number of events

**Adverse events reported for patients enrolled in clinical trial supporting approval**

# (%) of Patients  
Total Adverse Events

	1 <sup>st</sup> quarter postop				2 <sup>nd</sup> quarter postop				3 <sup>rd</sup> quarter postop				4 <sup>th</sup> quarter postop				Control (n=150) (%)		low dose (n=151) (%)		Inves. (n=149) (%)	
	Control		Inves.		Control		Inves.		Control		Inves.		Control		Inves.		Control	low dose	Inves.	Control	Inves.	
	low dose	Inves.	low dose	Inves.	low dose	Inves.	low dose	Inves.	low dose	Inves.	low dose	Inves.	low dose	Inves.								
altered function	3	10	19	2	1	1	0	0	0	0	1	2	0	0	0	6	3	0	6	4	4	
altered rhythm	2	2	1	0	0	0	0	0	0	0	0	0	0	0	0	7	2	11	7	10	7	
hypercoagulability, surgical site	3	5	2	0	0	1	0	0	0	0	0	0	0	0	0	2	3	2	2	1	1	
hypercoagulability, general	7	10	6	2	2	0	0	0	0	1	0	2	0	0	0	8	3	12	5	3	3	
hypertension/hypotension	1	3	2	0	0	0	0	0	0	0	1	0	0	0	0	1	11	3	13	6	6	
other, surgical site	1	1	8	0	1	1	0	0	0	0	0	0	0	0	0	1	1	3	3	3	3	
other, general	11	5	9	1	1	2	0	0	0	0	0	0	0	0	0	10	2	6	7	8	5	
<b>Digestive system</b>																						
altered function	0	1	0	0	0	0	0	0	0	0	0	0	0	0	0	0	20	2	29	27	31	
bleeding episodes	2	2	3	0	0	0	0	0	0	0	1	0	0	0	0	2	2	2	2	4	0	
constipation	5	4	2	2	2	3	2	0	1	1	0	2	0	0	0	8	2	7	7	5	6	
dyspepsia	34	30	30	5	11	4	1	2	3	3	0	2	3	4	4	26	42	30	30	24	16	
irritation & inflammation	9	6	14	1	1	3	0	0	0	0	0	1	0	0	0	10	11	7	7	14	17	
nausea & vomiting	85	85	86	2	1	0	0	1	1	1	0	1	0	1	1	79	88	75	75	74	50	
other	14	20	14	1	0	0	0	0	0	0	0	0	0	0	0	12	15	17	20	12	14	
<b>Hematic/lymphatic system</b>																						
anemia	12	11	7	0	4	5	1	4	2	2	1	1	1	2	2	12	14	16	20	11	16	
allergic reactions, surgical site	13	13	24	3	2	1	0	0	0	0	0	0	1	0	0	14	16	12	16	16	25	
allergic reactions, systemic	1	0	0	0	0	0	0	1	0	0	0	0	0	0	0	1	1	1	1	0	0	
autoimmune disorders	24	20	17	4	3	3	1	5	1	3	1	2	2	1	1	25	31	22	30	20	22	
surgical site, superficial	15	10	14	2	3	0	1	2	1	1	1	0	1	1	1	16	18	13	13	14	16	
surgical site, deep	8	9	18	4	0	1	2	0	1	1	1	3	1	1	1	13	17	8	16	15	16	
general	64	74	78	6	5	5	2	0	4	4	2	0	0	0	0	47	53	53	35	56	39	
<b>Inflammation</b>																						

Adverse events reported for patients enrolled in clinical trial supporting approval

# (%) of Patients  
Total Adverse Events

	1 <sup>st</sup> quarter postop		2 <sup>nd</sup> quarter postop		3 <sup>rd</sup> quarter postop		4 <sup>th</sup> quarter postop		Control (n=150) (%)	low dose (n=151) (%)	Inves (n=149) (%)
	Control	Inves.	Control	Inves.	Control	Inves.	Control	Inves.			
	low dose		low dose		low dose		low dose				
systemic											
surgical site	72	67	30	16	6	10	8	5	78	79	87
Kidney	0	4	0	0	0	0	0	0	116	114	98
Liver, other	0	3	0	0	0	0	0	0	0	1	4
Metabolic & nutritional	12	10	1	0	0	0	1	0	0	0	3
Neuromuscular/skeletal									11	14	10
altered mental status	63	70	1	4	1	1	1	3	47	40	41
altered sensory status, general	10	11	0	3	1	1	0	0	66	58	78
altered sensory status, surgical site	16	27	2	6	2	0	3	1	11	10	15
altered motor status, general	4	4	1	0	0	0	0	0	5	8	4
altered motor status, surgical site	13	11	2	1	0	0	1	0	10	10	11
other, surgical site	160	158	127	86	33	37	41	33	121	111	109
other, general	68	71	9	19	14	8	11	7	54	43	44
Respiratory system	31	39	0	1	0	0	0	0	30	38	32
Skin and appendages									31	49	40
surgical area	2	3	1	1	0	0	0	0	3	2	4
general	3	1	0	1	1	0	0	1	4	0	3
Urogenital									7	7	8
dysfunction	6	10	1	2	1	1	0	0	8	9	13
hematuria	0	3	0	1	0	0	0	0	0	2	4
infection	1	4	0	2	0	1	0	0	1	4	6

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### Potential Adverse Events:

The following is a list of potential adverse events which may occur with treatment of open tibial fractures requiring stabilization with an IM nail. Some of these adverse events may have been previously reported in the adverse events table. As with any surgery, surgical treatment of a fracture is not without risk. A variety of complications related to surgery or the use of INFUSE Bone Graft can occur. These may occur singly or in combination. Some of these may be severe, affecting patient outcome.

- Bone fracture.
- Bowel, bladder or gastrointestinal problems.
- Change in mental status.
- Damage to blood vessels, bleeding (which may require a blood transfusion) or cardiovascular system compromise.
- Damage to nearby tissues.
- Death.
- Development of respiratory problems.
- Disassembly, bending, breakage, loosening, and/or migration of IM nail components.
- Ectopic and/or exuberant bone formation.
- Fetal development complications.
- Foreign body (allergic) reaction.
- Incisional complications.
- Infection.
- Neurological system compromise.
- Nonunion (or pseudarthrosis), delayed union, mal-union.
- Pain or discomfort.
- Rash or allergic reaction.
- Scar formation.
- Side effects from anesthesia or the surgical approach.
- Swelling.
- Tissue or nerve damage.

Note: Additional surgery may be necessary to correct some of these potential adverse events.

### CLINICAL RESULTS:

Safety and effectiveness of INFUSE Bone Graft were evaluated as part of a prospective, randomized, controlled, multinational (11 countries), multi-center (49 sites) study. Subjects were randomized into one of three groups – control or one of two investigational groups (0.75 or 1.50mg/ml rhBMP-2). All subjects received wound management and fracture stabilization with an IM nail, while the investigational subjects also received INFUSE Bone Graft at the fracture site. No restrictions were placed on the type of IM nail used or whether it was reamed or non-reamed. The use of bone wax, Gelfoam, or other collagen hemostatic agents, corticosteroids, bone growth stimulators (electrical, ultrasound, or magnetic) was specifically prohibited.

Only the subjects and an independent radiology panel were blinded with respect to treatment. The investigators were aware of the treatment assignment.

The enrolled patients had been diagnosed with an acute, open tibia fracture of Gustilo Grade I, II, IIIA or IIIB with the major component of the fracture being diaphyseal. Patients with isolated tibia fractures and those with multiple injuries were included.

#### **Clinical and radiographic effectiveness parameters**

Subjects were followed for 12 months after definitive wound closure (DWC). Evaluations were performed postoperatively at 6, 10, 14, 20, 26, 39 and 50 weeks. Adverse events, device-related or not, were evaluated over the course of the clinical trial. At each evaluation timepoint, the primary and secondary clinical and radiographic outcome parameters were evaluated. Success was determined from data collected during the initial 12 months of follow-up. Antibodies to rhBMP-2 and bovine Type I collagen were assessed preoperatively and at timepoints post-operatively. Antibodies to human Type I collagen were assessed if the antibody response to bovine Type I collagen was positive.

Clinical and radiographic fracture assessments were performed at each postoperative visit, however the protocol did not provide the specific objective criteria that were used to determine fracture healing. The "Assessment of Fractured Limb" case report form provided for the documentation of the following parameters, but did not indicate how these were to be used to determine fracture status or how many needed to be present in order for a complete evaluation to have occurred:

- wound (healed, not healed, not evaluated)
- pain (absent, present, not evaluated)
- swelling (absent, present, not evaluated)
- tenderness (absent, present, not evaluated)
- neurovascular status (intact, impaired, not evaluated)
- infection (absent, present, not evaluated)
- weight-bearing status (non-, touch down, partial, full, not evaluated).

Radiographic assessments (AP and lateral radiographs) were performed at each post-op visit. Oblique radiographs were to be used if the standard views did not adequately visualize the fracture. The radiographs were evaluated by the investigator and the radiology panel.

Investigators were to evaluate radiographic healing by assigning a score of "united", "not united", "uncertain union" or "uninterpretable". No definitions for these terms were provided in the protocol.

The protocol for the independent radiology panel stated that "...fracture union was determined if there was cortical bridging and/or disappearance of the fracture lines were visible on 3 of the 4 bone aspects (anterior, posterior, medial, and lateral)...". These definitions were not available to the investigators. The first visit at which these criteria were met was considered the time of union radiographically. The independent radiographic evaluation protocol called for the review of each radiograph by all three members of the panel. An agreement of 2 of the 3 reviewers was necessary for a determination of fracture union. The independent radiographic evaluation was performed on all available radiographs. Adverse events were assessed for relatedness to the device and severity was based on the WHO recommendations.

Investigators were provided with the following definitions:

"...*Nonunion* – considered to be established when a minimum of 9 months have elapsed since injury and the fracture site showed no visibly progressive signs of healing for a minimum of 3 months (no change of fracture callus).

*Delayed union* – insufficient fracture healing determined by radiographic and clinical assessment. A specific time point at which delayed union was defined was not provided.

*Secondary intervention for delayed union* – any intervention, surgical or non-surgical, that was performed to induce or accelerate fracture union after DWC. Examples included use of autograft, allograft or bone graft substitutes; IM nail dynamization; exchange nailing; or noninvasive modalities, e.g., ultrasound, magnetic field, or electrical stimulation...." The decision to perform a secondary intervention for delayed union was dependent on the definition of delayed union above.

Investigators determined fracture union based on clinical judgement. The protocol did not provide the specific objective criteria that were used to determine fracture healing or deciding whether to recommend secondary interventions to promote fracture healing.

#### **Patient demographics and accountability**

The sample size estimation called for 150 subjects per treatment group. A total of 149 investigational and 150 control patients were enrolled in the study and received treatment. Only the results from the control patients and investigational patients receiving the 1.5mg/ml dose device are described below.

The demographics of the patient population were similar across all study groups except for the parameter of age, specifically the mean and range. The subjects in the investigational group were younger (mean = 33.4 years, range 18-77 years) compared to the control group (mean = 36.8 years, range = 17-87 years). Patients in the control group had a slightly larger percentage of nails that were unreamed and/or less than 9mm, while the investigational group had a higher percentage of reamed nails and /or nails that were greater than 11mm. Nail type did affect the number of secondary interventions, i.e., patients with unreamed nails had a higher incidence of secondary interventions compared to patients receiving reamed nails.

#### **Clinical and radiographic effectiveness evaluation**

The primary efficacy endpoint was defined as the proportion of subjects who required a secondary surgical intervention to promote fracture healing within 12 months of DWC. The secondary efficacy endpoints included the following:

- the proportion of subjects healed at 6 months without a secondary intervention as determined by the investigator's clinical and radiographic assessment;
- the independent radiology panel's assessment of time to fracture union; and
- the pharmaco-economic impact of the treatment.

#### **Primary effectiveness endpoint**

The rate of secondary interventions was significantly lower in the INFUSE Bone Graft group ( $p=0.001$ ) as described in the table below. Interventions were categorized in one of three ways – recommended by the investigator and performed, recommended by the investigator and not performed, or not recommended by the investigator but performed anyway. If any of these occurred, the patient was considered to have failed the primary endpoint and, therefore, was considered a study failure. In addition, patients who experienced screw breakage resulting in self-dynamization were also considered treatment failures.

Number of patients with secondary interventions <sup>a</sup>		
	control (n = 150)	investigational (n = 149)
Recommended/performed	38	19
Recommended/not performed	3	5
Not recommended/performed	6	7

Self-dynamizations	19	7
Total failures/patients (%)	66/150 (44)	38/149 (26)

<sup>a</sup>Includes bone grafting, fibula osteotomies, exchange nailing, plate fixation, Ilizarov frame removal, external fixation placement, bone transport, IM nail dynamizations, exchange to a functional brace and electrical stimulation

### Safety and immune response evaluation

The assessment of safety consisted of an evaluation of the reported adverse events, as well as an evaluation of antibodies to rhBMP-2, bovine Type I collagen and human Type I collagen. The complete list of adverse events is described in the Adverse Events section above. Refer to this section for a description of the rates associated with infection and abnormal clinical lab values. Adverse events of special interest are discussed below.

#### *fracture healing*

The rates of hardware failure in the investigational and control groups were 18/149 (14%) and 32/150 (24%), respectively. Delayed union was the most frequent serious adverse event reported at one year; occurring in 39 (26%) control and 26 (17%) investigational patients.

The rate of nonunion was lower in the investigational group as compared to control. A total of 80/150 (53.3%) control and 56/149 (37.6%) investigational patients did not require a secondary intervention and were not radiographically healed at 12 months as determined by the independent radiology panel. For the control patients who required a secondary intervention, 18/66 (27%) reported nonunions at 12 months compared to 19/38 (50%) investigational patients. Investigational patients who required a secondary intervention were considered healed *later* than control patients.

#### *abnormal bone formation*

Heterotopic ossification (HO) was not a significant concern and no ectopic ossification was reported. Because only the involved tibia was evaluated radiographically, it is not clear if abnormal bone formation occurred in other anatomical locations. Although twice as many investigational patients reported hypertrophic callus formation compared to controls (8 vs. 4), no action was required to treat any of these events. A total of 12 patients experienced at least one event classified as hypertrophic callus, with the investigational group having the highest number (8) and percentage (6%) of patients with HO. No interventions were required to treat any of the HO-related events.

#### *infections*

The combined rate of deep and superficial infections of the injured limb was lower in patients with Gustilo IIIA and B fractures of the investigational group as compared to the control group [16/66 (24%) and 26/61 (43%), respectively].

#### *immune response*

The presence of antibodies was assessed using ELISA. If there was a positive response to bovine Type I collagen, the serum was also tested for antibodies to human Type I collagen. The screening ELISA cutpoint for positive antibody responses was set to 2 times the signal generated by pooled normal human sera in each ELISA. Subjects were considered to have an elevated immune response if the preoperative test was negative (titer < 50) and postoperative test was positive (titer ≥ 50) or if the preoperative test was positive and the postoperative test was positive with a three-fold higher titer than the preoperative test.

There were detectable rhBMP-2 antibodies in 1 control patient and 9 investigational patients after treatment. Of the 9 investigational patients with elevated post-treatment antibody titers, 2 were elevated at visit 6 (20 weeks), the last planned assessment and data from 1 patient were unavailable for visit 6. An additional sample from 1 of these patients was collected and tested. following the positive test at

visit 6, and the titers decreased to <50 (No follow-up data were available for the other patient. Anti-rhBMP-2 antibody responses were determined to be transient in 6/9 patients by 20 weeks, and in 7/9 patients after follow-up testing (samples from 2 patients were unavailable to confirm transience of the antibody response). Because of the small numbers involved, it was not possible to determine if a correlation existed between the immune response and clinical outcome.

There were 38 patients who developed antibodies to bovine Type I collagen - 9 (6%) control and 29 (20%) investigational patients. Approximately half of the patients had persistently elevated antibody titers at evaluations 20 weeks and more after DWC. Thirty categories of adverse events that may have been manifestations of an immune response were identified and all were observed to have a comparable incidence across all groups. Although there were 4 patients with an adverse event termed "allergic event", the investigators believed that there was no evidence of allergic response to the investigational treatment.

Immune response		
	control [n (%)]	investigational [n (%)]
anti-rhBMP-2 antibodies	1 (1)	9 (6)
anti-bovine Type I collagen antibodies	9 (6)	29 (20)
anti-human Type I collagen antibodies	0 (0)	0 (0)
# healed patients with antiBMP-2 antibody response (successes)	1	6
# secondary intervention patients with antiBMP-2 antibody response (failures)	0	3

The rates of authentic antibody response to rhBMP-2 were higher than that observed for another application of rhBMP-2/ACS. When rhBMP-2/ACs was placed inside of a metallic spinal fusion cage for anterior interbody fusion treatment of degenerative disc disease, the antiBMP-2 antibody response in the investigational group was 0.7%. This compares to a 6% rate in the investigational group in the trauma study. The contribution of the trauma setting to this outcome is unknown, as is the clinical significance of the antibody response.

**HOW SUPPLIED:**

INFUSE Bone Graft is supplied in a kit containing all the components necessary to prepare the device (*i.e.*, the collagen sponge, a vial with the lyophilized rhBMP-2, a vial with the sterile water for reconstituting the rhBMP-2, syringes and needles).

**STORAGE CONDITIONS:**

Store INFUSE Bone Graft at room temperature [15 – 25 degrees Centigrade ( 59 to 77° F)].

**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 1.5 mg/mL. The instructions for preparation must be followed and the rhBMP-2 must be reconstituted to this solution concentration of 1.5 mg/ml and then distributed uniformly across the entire ACS

Only a single INFUSE Bone Graft kit should be used for each patient.

INFUSE Bone Graft is implanted after the completion of IM nail fracture stabilization and wound management, *i.e.*, at the time of soft tissue coverage. The number of INFUSE Bone Graft kits and the volume of INFUSE Bone Graft to be implanted are determined by the fracture anatomy. Generally, the fracture is treated with one kit. The accessible surface area of the fracture (fracture lines and defects) should be covered with INFUSE Bone Graft. Because very few patients in the clinical trial received more than one INFUSE Bone Graft kit (specifically, 2 kits) the response to the use of more than one kit is unknown. When determining the specific volume and placement for INFUSE Bone Graft, the potential to induce compartment syndrome should be considered.

**DIRECTIONS FOR USE:**

For directions for using the INFUSE Bone Graft for tibia fractures, see the brochure entitled "Instructions for Preparation and Surgical Application."

**PRODUCT COMPLAINTS:**

Any health care professional (e.g., customer or user of this system of products), who has any complaints or who has experienced any dissatisfaction in the quality, identification, durability, reliability, safety, effectiveness and/or performance of this product, should notify the distributor, Medtronic Sofamor Danek, Inc.. Further, if any of the implanted INFUSE Bone Graft ever "malfunction," (i.e., do not meet any of their performance specifications or otherwise do not perform as intended), or are suspected of doing so, the distributor should be notified immediately. If any Medtronic Sofamor Danek, Inc. product ever "malfunctions" and may have caused or contributed to the death or serious injury of a patient, the distributor should be notified immediately by telephone, fax or written correspondence. When filing a complaint, please provide the component name and number, lot number, your name and address, the nature of the complaint and notification of whether a written report from the distributor is requested.

**SUPPLIED BY**

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# INFUSE® Bone Graft

## PATIENT INFORMATION BROCHURE

**Read this entire document carefully .**

- Keep this document. You may want to read it again.
- If you have further questions, please ask your doctor.

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This Patient Guide is designed to help you decide whether or not to have surgery using INFUSE Bone Graft to treat your broken tibia (lower leg).

There are alternative treatments to this surgery that do not involve the use of INFUSE Bone Graft. You should discuss these other options with your doctor before you make your decision.

Please read this booklet completely and discuss your questions with your doctor. Only your doctor can determine whether INFUSE Bone Graft is appropriate for you.

### **WHAT IS INFUSE BONE GRAFT?**

INFUSE Bone Graft consists of two parts – a solution containing rhBMP-2 (recombinant human bone morphogenetic protein 2) and the ACS (absorbable collagen sponge). The protein is a manufactured (genetically engineered) version of a natural protein normally found in small quantities in the body. The purpose of the protein is to stimulate bone formation. During surgery, the protein solution is soaked into the ACS. The ACS is a sponge manufactured from bovine (cow) Type I collagen. It is designed to resorb (disappear) over time. The ACS keeps the solution from moving away from your broken bones and acts as a scaffold for the formation of the new bone that the protein stimulates.

### **WHAT IS INFUSE BONE GRAFT USED FOR?**

INFUSE Bone Graft was designed to aid in the treatment of fresh, open tibial shaft (lower leg) fractures. INFUSE Bone Graft is used in addition to wound management (cleaning the wound, treating any infections and preparing the wound to be closed) and using an intermedullary nail (also known as an IM nail, a metal rod placed inside of your broken lower leg bone) to stabilize your fracture. INFUSE Bone Graft must be applied within 14 days after you break your leg. INFUSE Bone Graft should only be used in patients that are skeletally mature (have stopped growing).

### **WHO IS NOT A CANDIDATE FOR INFUSE BONE GRAFT?**

INFUSE Bone Graft should not be used if:

- you are pregnant or suspect that you might be pregnant
- you are sensitive to bovine (cow) Type I collagen or recombinant human Bone Morphogenetic Protein-2
- you have an infection near the area of the surgical incision
- you had a tumor removed from the area of the implantation site
- you have or had cancer
- your bones have not stopped growing

## **WHAT ARE SOME PRECAUTIONS AND WARNINGS FOR USING INFUSE BONE GRAFT?**

This product has not been tested in pregnant women to determine if it could harm a developing fetus.

In addition, it is not known if a woman who got pregnant at some time after receiving the product could have a second immune reaction to the BMP-2 normally found in a developing fetus and harm the mother and/or the fetus.

Women of child-bearing age must not get pregnant for one year following treatment with the product.

This product has also not been studied in nursing mothers.

In addition, this product has not been tested:

- to see if there are side effects by using it more than once 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 product)
- in people with bone-weakening diseases
- in people with autoimmune or immunosuppressive disease, such as lupus or HIV/AIDS
- 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.

Although not seen in the studies performed by the manufacturer, there is a possibility that too much bone may form at the fracture site (exuberant bone formation), bone may form at a location away from the fracture site (ectopic bone formation) or the bone that is formed may be abnormal.

Some patients may have an allergic reaction to INFUSE Bone Graft.

Please talk with your doctor about any of the above warnings and precautions.

## **WHAT WILL HAPPEN BEFORE SURGERY INVOLVING INFUSE BONE GRAFT?**

Before you can be treated with INFUSE Bone Graft, your doctor must provide appropriate wound management. This includes cleaning out the opening in your skin, treating any infections that might be present and making preparations to close the wound. Your doctor will also have stabilized your fracture to prevent the different pieces of bone from moving relative to each other.

## **WHAT WILL HAPPEN DURING SURGERY?**

Within 14 days after you have broken your leg, your doctor will perform the final treatment of your fracture. This may include additional cleaning of your wound and restabilization of the fracture. If you have not received an IM nail yet, it will be implanted at this time. Before your incision is closed, your doctor will prepare INFUSE Bone Graft and place it inside of your leg around the broken bones.

## **WHAT WILL HAPPEN 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 your fracture and surgery is an ongoing process. During the recovery period, the duration and type of activities that you will be allowed to participate in will slowly increase. How fast you recover depends on the type of fracture you had, your commitment to working closely with your physical therapist, and moving and exercising correctly, as recommended by your doctor.

Contact your doctor immediately if:

- you get a fever
- the wound starts leaking fluids
- you get a rash, redness or increased swelling occurs in the area of the surgery
- you have trouble swallowing or breathing
- you have trouble urinating

Your doctor will schedule office visits to check on how you are doing and see if anything else needs to be done.

## **WHAT ARE SOME POSSIBLE SIDE-EFFECTS AND ADVERSE EVENTS OF USING INFUSE BONE GRAFT?**

As with any surgery, surgical treatment of a fracture is not without risk. A variety of complications related to surgery or the use of INFUSE Bone Graft can occur. These may occur singly or in combination. Some of these may be severe, affecting your outcome. You may also need to have additional surgery to correct these complications. Some of the possible complications include:

- allergic reaction to the implant materials;
- bending, breakage and/or loosening migration of the implant;
- bleeding, which may require a blood transfusion;
- bone fracture or failure to heal;
- bone formation that is abnormal, excessive or in an unintended location;
- bowel, bladder or gastrointestinal problems;
- damage to nearby tissues;
- death;

- fetal development complications;
- infection;
- pain or discomfort;
- paralysis or other neurological problems;
- rash;
- respiratory (breathing) problems;
- scar formation or other problems with the surgical incision;
- side effects from anesthesia or the surgical approach;
- swelling;
- vascular problems other than bleeding.

You should tell your doctor immediately if you do not feel well after your surgery, particularly if you experience pain, fever, nausea and vomiting, infection, inflammation, redness or rash, itching, tenderness or swelling of the skin or surgery site. Tell your doctor or nurse if you notice anything else that is making you feel unwell, even if it is not on this list.

### **HAS INFUSE BONE GRAFT BEEN STUDIED IN HUMANS?**

Yes. The safety and effectiveness of INFUSE Bone Graft were evaluated in a clinical study. Three groups of patients were evaluated:

- a group of 149 patients were treated with INFUSE Bone Graft after wound management and fracture stabilization using an IM nail;
- a group of 151 patients were treated with a lower dose of INFUSE Bone Graft after wound management and fracture stabilization using an IM nail; and
- a group of 150 control patients were treated with just wound management and fracture stabilization using an IM nail, an alternative procedure.

The goal of the study was to see if the use of INFUSE Bone Graft combined with wound management and fracture stabilization using an IM nail reduced the number of patients who needed another treatment to cause their fracture to heal if it had not healed by 12 months after the first treatment. The patients receiving the recommended higher dose required fewer additional medical procedures to promote healing after implantation of the product compared to the group of patients who did not receive the product (38/149 [26%] of the patients who received the product required an intervention compared to 66/150 [44%] of the patients in the control group). The types of additional medical procedures included the following:

- having surgery to:
  - place a bone graft (often taken from their hip) at the fracture site;
  - make a cut in one of their lower leg bones;
  - remove the broken IM nail or screws;
  - implant a new IM nail;

- implant a different fracture treatment device;
- having their leg placed into a brace; or
- having an electrical bone growth stimulator applied to their lower leg.

Patients who received the product and required an additional medical procedure, however, healed at a slower rate compared to patients who did not receive the product.

All the patients in the study had blood collected to see if they generated antibodies (had an allergic reaction) to specific parts of the product - rhBMP-2, bovine (cow) Type I collagen and human Type I collagen. Nine patients who were treated with INFUSE Bone Graft had a response to rhBMP-2 compared to 1 control patient. Because of the small numbers of patients who developed an allergic reaction, it was not possible to determine if there was a connection between the allergic reaction and the need for additional treatment to heal their fracture. There were 38 patients who developed antibodies to Type I bovine collagen - 9 (6%) control and 29 (20%) INFUSE Bone Graft patients. None of these patients had an allergic reaction to human Type I collagen.

### **WHAT ELSE SHOULD I KNOW?**

While this brochure has hopefully provided you with the information you need to make an informed decision about your treatment options, it is not intended to replace professional medical care or provide medical advice.

If you have any questions or need additional information about INFUSE Bone Graft, please call or see your doctor, who is the only one qualified to diagnose and treat your fracture. As with any surgical procedure, you should find a doctor who is experienced in performing the specific surgery that you are considering.

### **WHO DO I CONTACT FOR ADDITIONAL INFORMATION?**

For additional information about this product, please contact Medtronic Sofamor Danek USA, Inc., Memphis, Tennessee 1-800-933-2635.

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Printing date xx/xx/xx  
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