2.1
Physician Labeling

3/8/2007

INFUSE® Bone Graft for Certain Oral Maxillofacial and Dental Regenerative Uses
Important Medical Information
Rx Only

DESCRIPTION:

The INFUSE® Bone Graft consists of two components – recombinant human Bone Morphogenetic Protein-2 (rhBMP-2, known as dibotermin alfa) placed on an absorbable collagen sponge (ACS). **These components must be used as a system for the prescribed indication described below. 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 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.

The 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.

The rhBMP-2 is provided as a lyophilized powder in vials delivering 4.2mg or 12 mg of protein. 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.

All the components necessary to prepare INFUSE® Bone Graft are contained in the kit: the rhBMP-2 powder; sterile water; ACS; syringes with needles; this package insert; and instructions for preparation. The number of each item may vary depending on the size of the kit.

After reconstitution, 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 surgical site. The **INFUSE® Bone Graft Instructions for Preparation and Surgical Application** contains complete details on preparation of INFUSE® Bone Graft.

Implied warranties of merchantability and fitness for a particular purpose or use are specifically excluded. See the MDT Catalog or price list for further information about warranties and limitations of liability.

INDICATIONS:

INFUSE® Bone Graft is indicated as an alternative to autogenous bone graft for sinus augmentations, and for localized alveolar ridge augmentations for defects associated with extraction sockets.

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 pregnant women.
- INFUSE® Bone Graft should not be implanted in 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 child bearing potential should be warned by their doctor of potential risk to a fetus and informed of other possible dental treatments.
- Women of childbearing potential should be advised that antibody formation to rhBMP-2 or its influence on fetal development has not been completely assessed. In the clinical trials supporting the safety and effectiveness of the INFUSE® Bone Graft for this indication, 4/184 (2.2%) patients treated with rhBMP-2/ACS and 0/91 (0.0%) patients treated with autograft bone developed antibodies to rhBMP-2. The effect of maternal antibodies to rhBMP-2, as might be present for several months following device implantation, on the unborn fetus is unknown. Additionally, it is unknown whether fetal expression of BMP-2 could re-expose mothers who were previously antibody positive. Theoretically, re-exposure may elicit a more powerful immune response to BMP-2 with possible adverse consequences for the fetus. However, pregnancy did not lead to an increase in antibodies in the rabbit study. Studies in genetically altered mice indicate that BMP-2 is critical to fetal development and that a lack of BMP-2 activity may cause neonatal death or birth defects. It is not known if anti-BMP-2 antibodies may effect fetal development or the extent to which these antibodies may reduce BMP-2 activity.
- INFUSE® Bone Graft should not be used immediately prior to or during pregnancy. Women of childbearing potential should be advised not to become pregnant for one year following treatment with INFUSE® Bone Graft.
- The safety and effectiveness of INFUSE® Bone Graft in nursing mothers has not been established. It is not known if BMP-2 is excreted in human milk.

PRECAUTIONS:

General

- INFUSE® Bone Graft has not been studied in extraction site(s) associated with molars or in the mandible.
- INFUSE® Bone Graft has not been studied in patients who are skeletally immature (<18 years of age or no radiographic evidence of epiphyseal closure).
- The safety and effectiveness of repeat applications of INFUSE® Bone Graft has not been established.
- INFUSE® Bone Graft should only be used by surgeons or dentists who are experienced in performing dental regenerative surgery.
- 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 device 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.

Bone Formation

- The safety and effectiveness of the INFUSE® Bone Graft device has not been demonstrated in patients with metabolic bone diseases.
- While not specifically observed in the clinical studies, the potential for ectopic, heterotopic or undesirable exuberant bone formation exists.

Antibody Formation/Allergic Reactions

- The safety and effectiveness of the INFUSE® Bone Graft device has not been demonstrated in patients with autoimmune disease.
- The safety and effectiveness of the INFUSE® Bone Graft device 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 a component of INFUSE® Bone Graft. The immune response to rhBMP-2/ACS components was evaluated in 184 investigational patients and 91 autogenous bone graft patients during human clinical trials of INFUSE® Bone Graft for oral maxillofacial bone grafting procedures.
    - *Anti-rhBMP-2 antibodies:* 4/184 (2.2%) patients receiving rhBMP-2/ACS component developed antibodies vs. 0/91 (0.0%) in the autogenous bone graft group.
    - *Anti-bovine Type I collagen antibodies:* 37/184 (20%) of patients receiving rhBMP-2/ACS developed antibodies to bovine Type I collagen vs. 28/91 (31%) of autogenous bone graft 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 in humans 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.

SURGEON and DENTIST NOTE: Although surgeons and dentists are the learned intermediary between the company and the patient, the important medical information given in this document should be conveyed to the patient.

[USA] FOR US AUDIENCES ONLY

POTENTIAL ADVERSE EVENTS:

The following is a list of potential adverse events which may occur with oral maxillofacial surgery using the INFUSE® Bone Graft. Some of these adverse events may have been previously reported in the adverse events table below or have been reported to the manufacturer:

- Allergic reaction
- Death
- Ectopic and/or exuberant bone formation
- Fetal development complications
- Itching
- Scar formation
- Tissue or nerve damage
- Antibodies to rhBMP-2/ACS
- Antibodies to bovine collagen
- Antibodies to human Type I collagen.

CLINICAL RESULTS:

1. Overview of Clinical Studies

There were five clinical studies that supported the approval of the PMA, three for sinus floor augmentation and two for extraction socket augmentation.

The sinus floor augmentation clinical studies were:

- Pilot Study (short term 9409 and long-term 9410)
- Dosing Study (9531)
- Pivotal Study (9730).

The extraction socket augmentation clinical studies were:

- Pilot Study (short term 9411 and long-term 9412)
- Dosing Study (9514).

A similar study protocol was followed in each of the five studies with the treatment course consisting of study device implantation followed by an osteoinduction phase, dental implant placement followed by an osseointegration phase, and prosthesis placement (functional loading) followed by functional restoration. These studies involved varying dosages of rhBMP-2/ACS and varying control groups.

A total of 312 subjects were enrolled across 5 studies. One hundred eighty four subjects received one of three concentrations of rhBMP-2/ACS (0.43 mg/mL, 0.75 mg/mL, or 1.5 mg/mL); 91 subjects received bone graft, either autogenous bone (autograft) or autogenous bone and allogeneic bone (autograft plus allograft). Two sub-groups were also treated to evaluate no treatment (20 subjects) and a placebo consisting of ACS alone, the carrier for rhBMP-2 (17 subjects).

The five studies are summarized in the tables below.

Sinus Floor Augmentation Study Summaries

Study Description	**Pilot Study (9409/9410)**		**Dosing Study (9531)**	**Pivotal Study (9730)**
	Short-Term (9409)	**Long-Term (9410)**		
Number of Subjects	12: rhBMP-2/ACS 0.43 mg/mL	(same subjects as 9409)	48 total subjects: • Autogenous bone graft: n=13 • rhBMP-2/ACS 0.75 mg/mL: n=18 • rhBMP-2/ACS 1.5 mg/mL: n=17	160 total subjects: • Autogenous bone graft: n=78 • rhBMP-2/ACS 1.5 mg/mL: n=82
Study Design	Open-label, non-randomized, four-center study	Follow-up study of subjects enrolled in 9409	Randomized multi-center trial (6 centers) of two dosage levels with ACS, or autogenous bone graft alone	Multi-center trial (21 centers) with subjects randomized to rhBMP-2/ACS or autogenous bone graft alone
Follow-Up	16 weeks post-surgery	36 months post-prosthesis	36 months post-prosthesis	24 months post-prosthesis

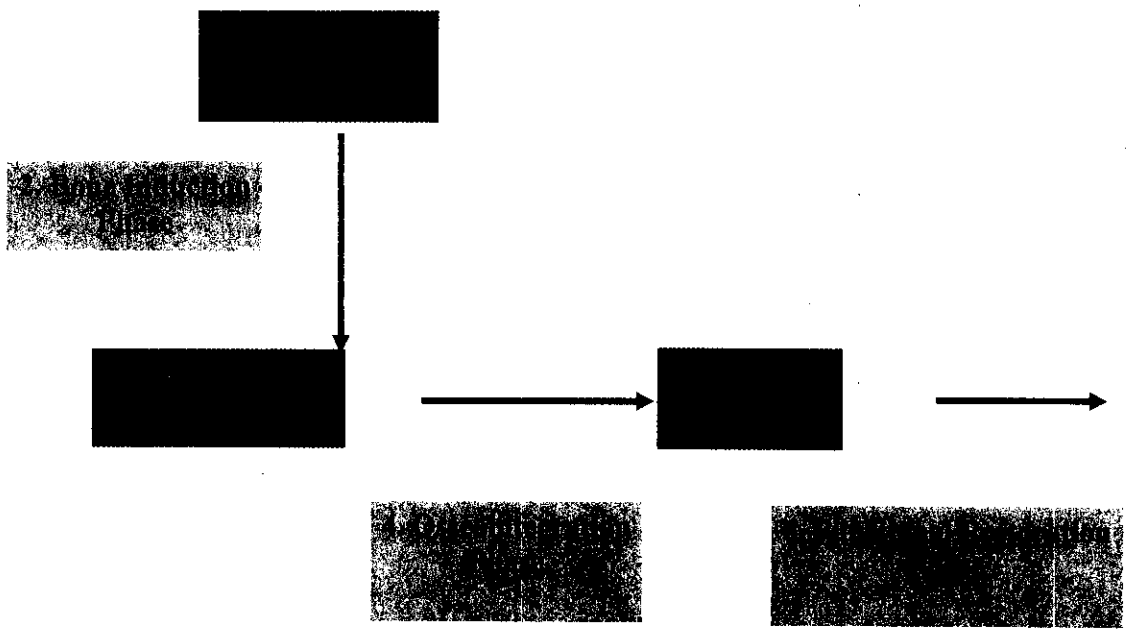
Extraction Socket Augmentation Study Summaries

Study Description	**Pilot Study (9411/12)**		**Dosing Study (9514)**
	Short-Term (9411)	**Long-Term (9412)**	
Number of Subjects	12: rhBMP-2/ACS 0.43 mg/mL	(same subjects as 9411)	80 total subjects: • No treatment: n=20 • ACS alone (no rhBMP-2): n=17 • rhBMP-2/ACS 0.75 mg/mL: n=22 • rhBMP-2/ACS 1.5 mg/mL: n=21
Study Design	Open-label, non-randomized, two-center study	Long-term follow-up of subjects enrolled in 9411	Randomized multi-center trial (8 centers) of two dosage levels with ACS, ACS alone or no treatment
Follow-Up	16 weeks post-surgery	24 months post-surgery	24 months post-prosthesis

2. Study Design/Methods

The five studies used to support this PMA application were conducted in a similar manner with similar study design and methods used. The treatment course was the same for subjects enrolled in all of the five studies as shown in the Figure below.

Subject Treatment Course Across all Five Studies



Surgery and Evaluation Procedures

Subjects enrolled across the five studies were all candidates for two-stage augmentation procedures. In the first stage, the osteoinductive material is surgically implanted. The second stage is the placement of the dental implant, if applicable, after time has elapsed to allow for osseointegration.

Demographics – All Patients with INFUSE® Bone Graft (1.5mg/mL Concentration of rhBMP-2/ACS)

Demographic data for the 1.5 mg/mL (commercial concentration of INFUSE® Bone Graft) treatment group used for demonstration of effectiveness are summarized below. Age, gender, and race were categorized for all study subjects.

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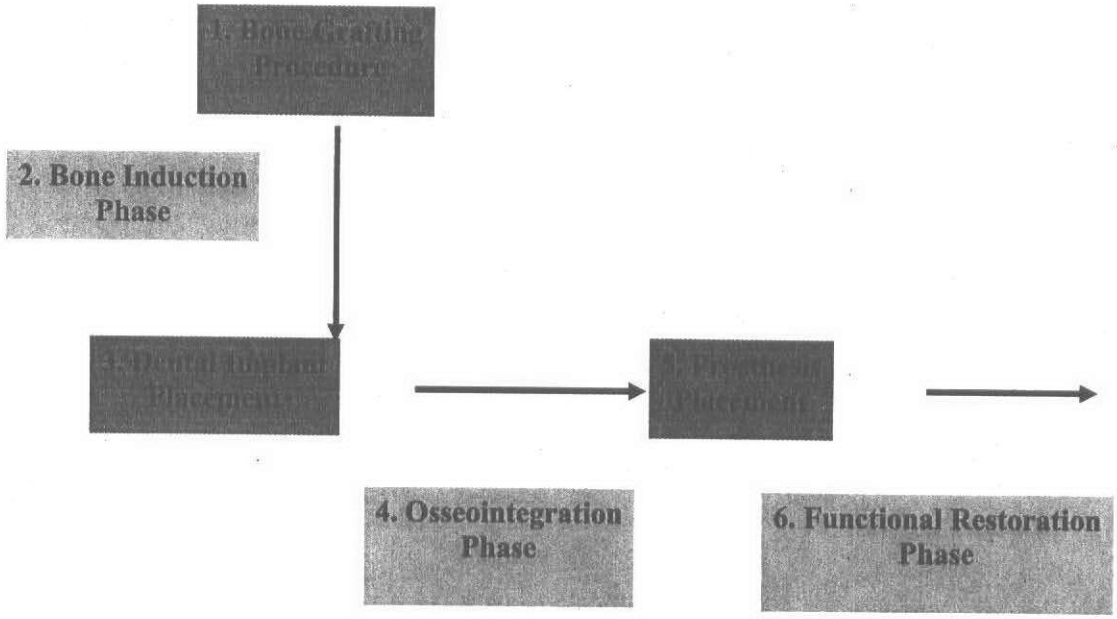

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Demographics of INFUSE® Bone Graft (1.5 mg/mL Concentration of rhBMP-2/ACS)

Characteristic	Extraction Socket Dosing Study (9514)	Sinus Dosing Study (9531)	Sinus Pivotal Study (9730)	Total
Gender				
Male	52.4%	35.3%	56.1%	52.5%
Age				
Mean	47.6	52.1	53.6	52.3
Age Category				
< 65 yrs	85.7%	88.2%	79.3%	81.7%
Race				
Black	38.1%	5.9%	6.1%	11.7%
Asian	9.5%	0.0%	1.2%	2.5%
Other	0.0%	0.0%	2.4%	1.7%
Hispanic	9.5%	5.9%	6.1%	6.7%
Caucasian	42.9%	88.2%	84.1%	77.5%

Subject Disposition of All Patients in the 5 Studies

Across all five studies, the follow-up rate was ≥85%. One death was reported during the conduct of the Extraction Socket Augmentation Dosing study. The death was determined not to be related to the study treatment. Subject withdrawals were both voluntary and withdrawn based on missed follow-ups. As per protocol, subjects who failed to complete their scheduled follow-up were withdrawn. Nine subjects withdrew. Subjects were analyzed in the groups to which they were assigned, not the groups in which they were treated.

3. Adverse Events

The assessment of safety for both indications 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.

Adverse Events for INFUSE® Bone Graft (1.5 mg/mL concentration of rhBMP-2/ACS) and Autogenous Bone Graft

The table below describes the adverse events observed in the clinical trials for the 1.5 mg/mL concentration of rhBMP-2/ACS (the commercially available concentration) used to support approval of the product. An INFUSE® Bone Graft concentration of 1.5 mg/mL was implanted in 120 investigational patients and compared to 91 autogenous bone graft patients from all the studies. 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 for INFUSE® Bone Graft (1.5mg/mL Concentration of rhBMP-2/ACS) vs. Autogenous Bone Graft Patients: Frequent Adverse Events (>5% of Patients) by Body System and COSTART Term

Body System COSTART Term	**INFUSE® Bone Graft Patients (n=120)**	**Autogenous Bone Graft Patients (n = 91)**	**p-value**
	N (%)	**N (%)**	
Body As A Whole			
Accidental Injury	10 (8.3)	4 (4.4)	0.2817
Back Pain	4 (3.3)	6 (6.6)	0.3340
Dehiscence	6 (5.0)	5 (5.5)	1.0000
Edema	2 (1.7)	34 (37.4)	<0.0001
Face Edema	81 (67.5)	52 (57.1)	0.1500
Flu Syndrome	3 (2.5)	5 (5.5)	0.2950
Headache	14 (11.7)	7 (7.7)	0.3652
Infection	30 (25.0)	39 (42.9)	0.0076
Pain	26 (21.7)	46 (50.5)	<0.0001
Peri-Implantitis	11 (9.2)	4 (4.4)	0.2793
Cardiovascular System			
Hematoma	11 (9.2)	8 (8.8)	1.0000
Hypertension	9 (7.5)	8 (8.8)	0.8011
Digestive System			
Gingivitis	7 (5.8)	5 (5.5)	1.0000
Mouth Pain	102 (85.0)	76 (83.5)	0.8489
Mouth Ulceration	4 (3.3)	6 (6.6)	0.3340
Nausea	4 (3.3)	10 (11.0)	0.0470
Oral Edema	81 (67.5)	59 (64.8)	0.7688
Oral Erythema	57 (47.5)	56 (61.5)	0.0513
Tooth Disorder	10 (8.3)	4 (4.4)	0.2817
Hemic And Lymphatic System			
Anemia	4 (3.3)	9 (9.9)	0.0797
Ecchymosis	19 (15.8)	21 (23.1)	0.2157
Metabolic And Nutritional Disorders			
Healing Abnormal	4 (3.3)	9 (9.9)	0.0797
Hyperglycemia	8 (6.7)	15 (16.5)	0.0270
Hypophosphatemia	2 (1.7)	9 (9.9)	0.0107
SGOT Increased	3 (2.5)	5 (5.5)	0.2950
SGOT Increased	6 (5.0)	6 (6.6)	0.7660
Musculo-Skeletal System			
Arthralgia	14 (11.7)	24 (26.4)	0.0069
Bone Disorder	14 (11.7)	11 (12.1)	1.0000
Nervous System			
Abnormal Gait	0 (0.0)	37 (40.7)	<0.0001
Hypesthesia	5 (4.2)	15 (16.5)	0.0036
Respiratory System			
Bronchitis	0 (0.0)	5 (5.5)	0.0140

Body System COSTART Term	INFUSE® Bone Graft Patients (n=120)	Autogenous Bone Graft Patients (n = 91)	p-value
	N (%)	N (%)	
Epistaxis	7 (5.8)	6 (6.6)	1.0000
Rhinitis	10 (8.3)	6 (6.6)	0.7944
Sinusitis	11 (9.2)	15 (16.5)	0.1390
Skin And Appendages			
Rash	9 (7.5)	34 (37.4)	<0.0001

The most frequent adverse events reported for both the INFUSE® Bone Graft (1.5 mg/mL concentration of rhBMP-2/ACS) treatment group and the autogenous bone graft group were: mouth pain (85.0% vs. 83.5%); oral edema (67.5% vs. 64.8%); face edema (67.5% vs. 57.1%); and oral erythema (47.5% vs. 61.5%). Although, not statistically significant, face edema is greater in the INFUSE® Bone Graft group and is most likely due to the recruitment of fluid and cells into the treatment area.

Subjects in the autogenous bone graft group showed a significantly greater amount of adverse events versus the INFUSE® Bone Graft (1.5 mg/mL concentration of rhBMP-2/ACS) treatment group. Specifically, the following adverse events occurred significantly more often in the bone graft group: pain (50.5% vs. 21.7%); infection (42.9% vs. 25%); abnormal gait (40.7% vs. 0); arthralgia (26.4% vs. 11.7%); nausea (11% vs. 3.3%), hyperglycemia (16.5% vs. 6.7%); hypophosphatemia (9.9% vs. 1.7%); edema (37. 4% vs. 1.7%); rash (erythema) (37.4% vs. 7.5%); hypesthesia (decreased sensation) (16.5% vs. 4.2%); and bronchitis (5.5% vs. 0.0%). As noted, none of the INFUSE® Bone Graft (1.5 mg/mL concentration of rhBMP-2/ACS) subjects reported abnormal gait or gait disturbance compared to 41% of bone graft subjects.

The 120 patients in the INFUSE® Bone Graft (1.5 mg/mL concentration of rhBMP-2/ACS) treatment group experienced 1184 adverse events for an average of 9.9 events/patient. 79.1% (936/1184) were mild; 18.3% (217/1184) were moderate; 2.4% (29/1184) were severe and 0.01% life threatening (1/1184).

The autogenous bone graft treatment group experienced 1249 adverse events in 91 patients for an average of 13.7 events/patient. Among the 91 subjects who received an autogenous bone graft, 1249 adverse events were reported. 82.8% (1034/1249) were mild, 14.7% (184/1249) were moderate, and 2.16 (27/1249) were severe. The increased frequencies of these events are expected in bone graft treatments because of the harvest procedure; these adverse events reflect the morbidity associated with the procedure which is not required with the INFUSE® Bone Graft treatment.

Serious Adverse Events for INFUSE® Bone Graft (1.5 mg/mL concentration of rhBMP-2/ACS)
Although there were no serious adverse events that were judged to be related to the INFUSE® Bone Graft, there were serious adverse events that occurred during the study. The 120 patients in the INFUSE® Bone Graft (1.5 mg/mL concentration of rhBMP-2/ACS) treatment group experienced 1184 adverse events for an average of 9.9 events/patient. 79.1% (936/1184) were mild; 18.3% (217/1184) were moderate; 2.4% (29/1184) were severe and 0.01% life threatening (1/1184).

Adverse Events for INFUSE® Bone Graft (any concentration of rhBMP-2/ACS) and Autogenous Bone Graft
The combined INFUSE® Bone Graft treatment group experienced 1636 adverse events in 184 patients for an average of 8.9 events/patient. 80% (1309/1636) of the adverse events were mild, 17% (286/1636) were moderate, 2% (36/1636) were reported as severe, and 0.06% (1/1636) were considered life-threatening in severity (though unrelated to rhBMP-2/ACS).

Immune Response

The presence of antibodies was assessed prior to and following use of INFUSE® Bone Graft using Enzyme-Linked ImmunoSorbent Assay (ELISA). If there was a positive response to bovine Type I collagen, the serum was also tested for antibodies to human Type I collagen.

Four of 184 (2.2%) rhBMP-2/ACS patients had a positive antibody response to rhBMP-2. While there is a theoretical possibility that antibodies to rhBMP-2 could neutralize endogenous BMP-2, thereby interfering with subsequent bone healing, this was not observed during the course of the studies. None of the autogenous bone graft patients developed these antibodies.

There were 37 of 184 (20%) rhBMP-2/ACS patients who were considered to have an authentic elevated antibody response to bovine Type I collagen. There were 28 of 91 (31%) autogenous bone graft patients who were considered to have an authentic elevated antibody response to bovine Type I collagen. No patients had positive responses to human Type I collagen.

There were seven pregnancies, in six women, reported in the clinical studies. Four pregnancies were reported in the rhBMP-2/ACS group and three pregnancies in the autogenous bone graft group. All of these pregnancies resulted in the birth of healthy babies except one in which the patient elected to terminate pregnancy for reasons unrelated to her participation in the clinical study.

Fourteen cases of cancer were diagnosed; 3 in the INFUSE® Bone Graft group, 4 at lower concentrations of rhBMP-2/ACS, and 7 in the autogenous bone graft group. Cancers in the INFUSE® Bone Graft group included 1 gastrointestinal cancer, 1 myeloma and 1 squamous cell carcinoma. Cancers noted at lower concentrations of rhBMP-2/ACS included 1 squamous cell carcinoma, 2 prostate cancers and 1 colon cancer. Cancers in the autogenous bone graft group included: 2 basal cell carcinoma, 2 squamous cell carcinomas, 1 brain cancer, 1 breast cancer, and 1 fibroadenoma. None of these cancers were considered related to the treatment.

4. Sinus Augmentation Clinical Study Summary

Evaluation of the effectiveness for the sinus floor augmentation indication is based primarily on the sinus floor pivotal study (9730). These data were analyzed in accordance with the endpoints and methodology from the sinus floor pivotal study protocol. Because of similarities between studies 9730 and 9531 (sinus floor dosing study), results based on the two studies combined are presented as well for certain endpoints.

Study Endpoints

Primary endpoint:

- Proportion of patients (within the rhBMP-2/ACS treatment group) who have successful dental implant borne restoration after 6 months of functional loading. Subjects who successfully received prosthesis but were lost to follow-up or withdrew anytime thereafter were excluded from the analysis.

Secondary endpoints:

- Proportion of patients (within each treatment group) who have successful dental implant borne restoration after 6, 12, 18 and 24 months of functional loading.
- Proportion of endosseous dental implants (within each treatment group) that once placed into the augmented maxillary sinus(es) achieve clinical osseointegration and maintain functional restoration after 6, 12, 18, and 24 months of functional loading. *(refer to the SSED for these by implant results)*

Primary Endpoint Analysis

Primary Effectiveness Endpoint Results for Sinus Augmentation Studies 9730 and 9531 with INFUSE® Bone Graft (1.5mg/mL Concentration of rhBMP-2/ACS)

Subjects	9531 (n=17)	9730 (n=82)	Combined 9730/9531 (n=99)
	N (%)	N (%)	N (%)
Received dental implants into newly induced bone without additional augmentation	15 (88.2)	67 (81.7)	82 (82.8)
Received prosthesis (functionally loaded)	14 (82.4)	65 (79.3)	79 (79.8)
After 6 months functionally loaded			
N	**17**	**81**	**98**
Success [a,b]	**14 (82.4)**	**64 (79.0)**	**78 (79.6)**
95% CI of Success[c]	**(56.6, 96.2)**	**(68.5, 87.3)**	**(70.3, 87.1)**
After 12 months functionally loaded			
N	17	80	97
Success [a,b]	14 (82.4)	63 (78.8)	77 (79.4)
95% CI of Success[c]	(56.6, 96.2)	(68.2, 87.1)	(70.0, 87.0)
After 18 months functionally loaded			
N	17	77	94
Success [a,b]	14 (82.4)	60 (77.9)	74 (78.7)
95% CI of Success[c]	(56.6, 96.2)	(67.0, 86.6)	(69.1, 86.5)
After 24 months functionally loaded			
N	17	75	92
Success [a,b]	14 (82.4)	57 (76.0)	71 (77.2)
95% CI of Success[c]	(56.6, 96.2)	(64.7, 85.1)	(67.3, 85.3)

a. Success is defined as a subject who received implant(s) into newly induced bone for any teeth under study and none required additional maxillary sinus floor augmentation.
b. For subjects who missed a functional loading visit but whose status at flanking visits was known, the known status at the last visit was imputed.
c. 2-sided 95% exact confidence interval.

Secondary Endpoint Analysis: Patient-level success rates after functional loading

Number (%) of Subjects Who Received Prosthesis and Maintained Functional Loading in the Sinus Augmentation Pivotal Study (9730)

Subjects	Autogenous Bone Graft (n=78)	INFUSE ® Bone Graft (1.5mg/mL) (n=82)	Difference[a]
Received dental implants into newly induced bone without additional augmentation	74 (94.9%)	67 (81.7%)	
Received prosthesis (functionally loaded)	72 (92.3%)	65 (79.3%)	
After 6 months functionally loaded			
N	76	81	
Success [b,c]	69 (90.8%)	64 (79.0%)	-11.8
95% CI[d]	(81.9, 96.2)	(68.5, 87.3)	(-22.8, -0.8)
After 12 months functionally loaded			
N	76	80	
Success [b,c]	69 (90.8%)	63 (78.8%)	-12.0
95% CI[d]	(81.9, 96.2)	(68.2, 87.1)	(-23.1, -1.0)
After 18 months functionally loaded			
N	76	77	
Success [b,c]	69 (90.8%)	60 (77.9%)	-12.9
95% CI[d]	(81.9, 96.2)	(67.0, 86.6)	(-24.2, -1.5)
After 24 months functionally loaded			
N	76	75	
Success [b,c]	69 (90.8%)	57 (76.0%)	-14.8
95% CI[d]	(81.9, 96.2)	(64.7, 85.1)	(-26.4, -3.1)

a. Difference = INFUSE® – autogenous bone graft.
b. Success is defined as a subject who received implant(s) into newly induced bone for any teeth under study and none required additional maxillary sinus floor augmentation.
c. For subjects who missed a functional loading visit but whose status at flanking visits was known, the known status at the last visit was imputed.
d. Exact confidence intervals for success rates in both groups; approximate confidence intervals for the difference.

Number (%) of Subjects Who Received Prosthesis and Maintained Functional Loading in the Sinus Augmentation Pivotal Study (9730) and Dosing Study (9531) Combined

Subjects	Autogenous Bone Graft (n=91)	INFUSE ® Bone Graft (1.5mg/mL) (n=99)	Difference[a]
Received dental implants into newly induced bone without additional augmentation	87 (95.6)	82 (82.8)	
Received prosthesis (functionally loaded)	85 (93.4%)	79 (79.8%)	
After 6 months functionally loaded			
N	89	98	
Success [b,c]	80 (89.9%)	78 (79.6%)	-10.3
95% CI[d]	(81.7, 95.3)	(70.3, 87.1)	(-20.4, -0.2)
After 12 months functionally loaded			
N	87	97	
Success [b,c]	77 (88.5%)	77 (79.4%)	-9.1
95% CI[d]	(79.9, 94.4)	(70.0, 87.0)	(-19.6, 1.4)
After 18 months functionally loaded			
N	87	94	
Success [b,c]	76 (87.4%)	74 (78.7%)	-8.7
95% CI[d]	(78.5, 93.5)	(69.1, 86.5)	(-19.5, 2.2)
After 24 months functionally loaded			
N	87	92	
Success [b,c]	76 (87.4%)	71 (77.2%)	-10.2
95% CI[d]	(78.5, 93.5)	(67.3, 85.3)	(-21.2, 0.9)

a. Difference = INFUSE® – autogenous bone graft.
b. Success is defined as a subject who received implant(s) into newly induced bone for any teeth under study and none required additional maxillary sinus floor augmentation.
c. For subjects who missed a functional loading visit but whose status at flanking visits was known, the known status at the last visit was imputed.
d. Exact confidence intervals for success rates in both groups; approximate confidence intervals for the difference.

Sinus Augmentation Clinical Data Summary

In the Pivotal Study (9730), 79.0% of patients in the INFUSE® group (95% confidence interval: 68.5% – 87.3%) successfully received dental implants without additional augmentation, received a prosthesis, and maintained functional loading for at least six months. The observed success rate at six months post-loading in the autogenous bone graft group was higher by 11.8 percentage points (95% confidence interval: 0.8% – 22.8%). Combining the Pivotal Study (9730) with the Dosing Study (9531) yielded similar results.

However, as seen in the adverse events sections, the autogenous bone graft group had a statistically significant higher number of adverse events than the INFUSE® group.

5. Extraction Socket Clinical Study Summary

The evaluation for the extraction socket augmentation procedure is based on the results of the Dosing Study (9514). The treatment groups included:

- No treatment – the extraction socket was allowed to heal on its own
- INFUSE® Bone Graft (1.5 mg/mL rhBMP-2/ACS) – ACS with commercial dose of rhBMP-2.

Study Endpoints

The protocol of study 9514 specifies the following endpoints.

Primary endpoint:

- Proportion of patients within each treatment group that have adequate bone formation to support the placement of endosseous dental implants at four months.

Secondary endpoints:

- Proportion of patients that have a prosthesis placed onto the dental implants placed into the study treatment area
- Proportion of patients that maintain a successful prosthesis at 6, 12, 18, and 24 months following loading

Primary Endpoint Analysis

Number of Patients (%) within each Treatment Group who underwent Dental Implant Placement without Additional Augmentation at 4 months

	No Treatment	INFUSE ® Bone Graft 1.5 mg/mL
Needed augmentation	8 (40%)	2 (10%)
Failed	2 (10%)	1 (5%)
Withdrew	1 (5%)	0
Succeeded	9 (45%)	18 (85%)
Total	20	21

Because of a withdrawn patient in the No Treatment group, different statistical analyses are possible depending on how this patient is handled. Counting the withdrawn patient as a failure leads to a Fisher exact p-value of 0.0088 for comparing INFUSE® Bone Graft (1.5 mg/mL rhBMP-2/ACS) to No Treatment. If the withdrawn patient is assumed to be missing completely at random, then it can be excluded from the analysis and the resulting Fisher exact p-value is 0.0171 for comparing INFUSE® Bone Graft (1.5 mg/mL rhBMP-2/ACS) to No Treatment.

Secondary Endpoint Analyses

Number of Patients (%) within each Treatment Group who underwent Prosthesis Placement without Additional Augmentation (Baseline - Time 0 Functional Loading)

	No Treatment	INFUSE ® Bone Graft 1.5 mg/mL
Needed augmentation	8 (40%)	2 (10%)
Failed	2 (10%)	3 (14%)
Withdrew	3 (15%)	0
Succeeded	7 (35%)	16 (76%)
Total	20	21

Again, different methods exist for handling the withdrawn patients. The Fisher exact p-value for comparing INFUSE® Bone Graft (1.5 mg/mL rhBMP-2/ACS) to No Treatment is 0.0122 if the patients who withdrew or missed a visit are counted as failures or 0.0458 if those patients are excluded from the analysis.

The table below shows the proportion of patients that maintain a successful prosthesis at 6 months following loading.

6-Month Functional Loading

	No Treatment	**INFUSE ® Bone Graft 1.5 mg/mL**
Needed augmentation	8 (40%)	2 (10%)
Failed	2 (10%)	3 (14%)
Withdrew	3 (15%)	0
Missed visit	1 (5%)	2 (10%)
Succeeded	6 (30%)	14 (66%)
Total	20	21

The Fisher exact p-value for comparing INFUSE® Bone Graft (1.5 mg/mL rhBMP-2/ACS) to No Treatment is 0.0294 if the patients who withdrew or missed a visit are counted as failures or 0.0442 if those patients are excluded from the analysis.

Extraction Socket Clinical Data Summary

In the Dosing Study (9514), 85% of the INFUSE® Bone Graft (1.5 mg/mL rhBMP-2/ACS) group had grown enough bone at 4 months to receive implants without additional augmentation. Sixty six percent (66%)of the patients in the INFUSE® Bone Graft (1.5 mg/mL rhBMP-2/ACS) group successfully received dental implants without additional augmentation, received a prosthesis, and maintained functional loading for at least six months. Ten percent (10%) of the patients required augmentation at the time of dental implant placement through six months, 14% of the patients failed through six months, and 10% of the patients missed their 6-month visit. The observed success rate at six months post-loading in the No Treatment group was 30%. There was a statistically significant difference between the number of patients who were successful in the No Treatment and INFUSE® groups at 6 months post-loading.

HOW SUPPLIED:

INFUSE® Bone Graft is supplied in a kit containing all the components necessary to prepare the device (a vial with the lyophilized rhBMP-2, a vial with Sterile Water for Injection to reconstitute the rhBMP-2, the ACS, syringes and needles). Packages for each of the components should be intact upon receipt. Damaged packages or products should not be used, and should be returned to MEDTRONIC.

STORAGE CONDITIONS:

Store INFUSE® Bone Graft at room temperature (15 to 30 °C, 59 to 86° F).

DOSAGE AND ADMINISTRATION:

INFUSE® Bone Graft is prepared immediately prior to use from a kit containing all necessary components. Once prepared, the 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 the solution concentration of 1.5 mg/mL and then distributed uniformly across the entire ACS.

INFUSE® Bone Graft is implanted after the surgeon or dentist prepares the implant site utilizing standard surgical techniques. The INFUSE® Bone Graft kit size is selected depending on volume requirement of the implant site.

DIRECTIONS FOR USE:

INFUSE® Bone Graft component is prepared at the time of surgery in the surgical suite by reconstituting the lyophilized rhBMP-2 with sterile water (See the **INFUSE® Bone Graft Instructions for Preparation and Surgical Application***), and then uniformly applying the reconstituted rhBMP-2 solution to the ACS. If the INFUSE® Bone Graft is not used within two hours after reconstitution, it must be discarded. The INFUSE® Bone Graft must not be sterilized by the hospital.

*To obtain a copy of the Instructions for Preparation and Surgical Application, contact your sales representative or go to www.infusebonegraft.com.

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 product quality, identity, durability, reliability, safety, effectiveness and/or performance, should notify the distributor or MEDTRONIC. If any MEDTRONIC 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(s) name and number, lot number(s), your name and address, the nature of the complaint and notification of whether a written report from the distributor is requested.

FURTHER INFORMATION:

Instructions for preparation of this product are available at no charge upon request. If further information is needed or required, please contact MEDTRONIC.

Medtronic Sofamor Danek USA, Inc.
1800 Pyramid Place
Memphis, Tennessee 38132
Telephone 800 933 2635 (In U.S.A.)
901 396 3133 (Outside of U.S.A.)
Fax 901 396 0356

Supplied by Medtronic Sofamor Danek USA, Inc.

2.2
Patient Labeling

3/8/2007
Patient Information Brochure

This brochure is designed to help you make an informed decision about your dental surgery. Your doctor has recommended that you consider surgery using INFUSE® Bone Graft.

Why is bone important for dental restoration?
Teeth are anchored into the jaw in an area of bone called the alveolar ridge. The alveolar ridge bone surrounds tooth roots to secure teeth, and allows for normal tooth use such as chewing.

Without enough alveolar ridge bone, the jaw cannot support either natural teeth or dental implants. There are many reasons why you may have lost bone in your jaw. For example, you may have had either a tooth knocked out and bone was lost with the tooth, or you may have periodontal (gum) disease. For whatever the reason, you may not have enough bone in your jaws to anchor your natural teeth or to support the successful placement of dental implants.

If you have lost alveolar ridge bone, and need to re-grow the bone to place dental implants, your surgeon may recommend that you have a bone graft surgery. INFUSE® Bone Graft may be an option.

What is INFUSE® Bone Graft?
INFUSE® Bone Graft consists of two parts: a protein that is found in everyone's body, plus a natural carrier for delivery. The protein ingredient in INFUSE® Bone Graft is rhBMP-2 (recombinant (engineered) human bone morphogenetic protein-2), a synthetic version of a protein everyone's body produces naturally in small amounts to regulate bone growth and healing. The natural carrier is made of a material found in tendons. It releases the protein over time where it is placed, provides a scaffold (framework) for new bone to grow into, and is absorbed and replaced by bone.

Using INFUSE® Bone Graft eliminates the need for a second surgery to "harvest," or remove surgically, bone from your body ("autogenous" bone) for placement at the oral surgery site. Autogenous bone harvest has the risk of pain, complications, longer surgical time and more anesthesia. Choosing INFUSE® Bone Graft eliminates the need for the harvest surgery avoiding the pain and bodily harm associated with the bone harvest procedure. For procedures where autogenous bone is not typically used, INFUSE® Bone Graft can also be used.

How does INFUSE® Bone Graft work?
INFUSE® Bone Graft is surgically placed where new bone growth is needed. It attracts your body's own bone building cells to the site and over time, new bone is formed. Bone grows where the INFUSE® Bone Graft is placed, for predictable bone growth results.

Who is INFUSE® Bone Graft for and how will it fit into my doctor's prescribed course of treatment?
INFUSE® Bone Graft is now approved for two oral procedures: in sinus augmentation, and for localized alveolar ridge augmentation following tooth extraction. INFUSE® Bone Graft gives you and your surgeon a choice for growing bone where it is needed for the support of dental implants or other dental restoration. You and your doctor should discuss the benefits and risks of INFUSE® Bone Graft versus autogenous bone or other treatments.

S2

- **A sinus augmentation**, or "sinus lift," is a surgical bone grafting procedure that is performed in the maxillary (upper jaw) sinus cavity (above the area that anchors your teeth) to prepare the patient for dental restoration. Some patients have such small amounts of existing bone in these areas that dental restoration simply cannot occur without sufficient formation of new bone. Your surgeon may feel that autogenous bone or INFUSE® Bone Graft is needed to form the necessary bone in this area for reliable and functional dental restoration. In this case INFUSE® Bone Graft or autogenous bone harvested from another site in your body may be placed into your upper jaw to promote bone growth in the floor of the sinus cavity to anchor the dental implants to allow for dental restoration.

- **A localized alveolar ridge augmentation after tooth extraction,** or "ridge augmentation," involves placing INFUSE® Bone Graft directly into the empty socket where a tooth's roots used to be, to help create the natural shape of the gums and jaw that may have been lost following tooth extraction. Patients usually need a ridge augmentation procedure after losing one or more teeth, to prepare for a future dental restoration.

Please discuss these procedures with your surgeon, and whether INFUSE® Bone Graft is right for you.

Who should not receive it?
INFUSE® Bone Graft should not be used if:

- you are pregnant, or suspect that you might be pregnant
- you are hypersensitive (highly 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 are being treated for cancer.

What are some warnings for using INFUSE® Bone Graft?
This product has not been tested in pregnant women to determine if it could harm a developing fetus. This product has also not been studied in nursing mothers.

It is not known if a woman who gets pregnant after receiving the product could have a second immune reaction to the BMP-2. BMP-2 is normally found in a developing fetus and an immune reaction to it may result in harm to the mother and/or the fetus. In a rabbit pregnancy study, no increase in the immune reaction to BMP-2 was observed.

Women of child bearing age should not become pregnant for one year following treatment with the product. Women of child bearing age should be warned of potential risks to a fetus and should discuss other possible dental treatments with their doctor.

If I become pregnant after having treatment with INFUSE® Bone Graft, could there be problems for the fetus?
This issue was not studied in humans. However, in a rabbit pregnancy study, an immune reaction to INFUSE® Bone Graft developed by the mother crossed into the fetus; the effect of this immune reaction on the fetus is unknown. In addition, the rabbit study showed some bone formation abnormalities in a small number of 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.

What are some precautions for using INFUSE® Bone Graft?
This product has not been tested:

- in the lower jaw (mandible) or in extracted molar tooth sites
- in patients under 18 years of age whose facial bones are growing
- to see if there are side effects by using it more than once in the same person
- in people with liver or kidney problems
- in people with bone-weakening diseases
- in people with autoimmune (self immunity) or immunosuppressive (decreased immunity) disease, such as lupus or HIV/AIDS
- in people with immune deficiency (lacking immunity) due to other treatments, such as radiation therapy, chemotherapy or steroid therapy.

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

What are the potential complications of INFUSE® Bone Graft?
As with any surgery, surgical treatment to promote bone growth in the jaw 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
- bleeding, which may require a blood transfusion
- bone formation that is not normal, in excess or in an unintended location
- damage to nearby tissues or nerves
- death
- fetal development complications
- infection
- pain or discomfort
- skin swelling or irritation
- respiratory (breathing) problems
- scar formation or other problems with the surgical incision
- side effects from anesthesia or the surgical approach
- (short-term) mild to severe swelling.

What can I expect after surgery?
Your doctor will have a specific recovery plan for you to follow after your procedure. It is important that you follow your doctor's instructions carefully, so you can recover as quickly as possible and increase your chances of a successful outcome.

Contact your doctor immediately if:

- you get a fever
- you do not feel well after your surgery
- you experience pain
- you experience tenderness or swelling of the skin or surgery site
- you experience itching, redness at surgery site
- you experience nausea and vomiting
- you experience anything else that is making you feel unwell even if it is not on this list.

Are there clinical data for INFUSE® Bone Graft?
Multiple studies were conducted on approximately 312 patients who did not have enough bone in their upper jaw to place implants. These patients received either INFUSE® Bone Graft or autogenous bone graft. INFUSE® Bone Graft grew bone without the need of a bone harvest procedure that is necessary for autogenous bone grafting. Both the INFUSE® Bone Graft and autogenous bone graft formed new bone that allowed for the placement of dental implants into patients who otherwise would not have been able to have implants placed. These implants were retained by the majority of patients for 2 years.

In the sinus lift clinical studies, most patients grew enough bone to place a dental implant regardless of whether they had autogenous bone or INFUSE® Bone Graft. However, the patients who received autogenous bone graft had a higher success rate of dental implant placement without additional augmentation and a higher rate of significant adverse events, such as limping, pain, and infection.

Complications were reported for both INFUSE® Bone Graft and autogenous bone graft patients. Patients who received INFUSE® Bone Graft had less complications than those patients who had autogenous bone graft. However, one adverse event, face swelling, was reported more often in the INFUSE® Bone Graft group. "What are the potential complications of INFUSE® Bone Graft?" and "What can I expect after surgery?" sections above to see the types of complications that can occur.

Please speak with your doctor concerning potential complications associated with your procedure, as well as for more information on these clinical studies.

What are my bone grafting alternatives?
Grafting options are different for different procedures. Before INFUSE® Bone Graft, surgeons relied on autogenous bone harvesting from the patient's own body for reliable and safe sinus lift procedures.

In the sinus lift clinical studies comparing the safety and effectiveness of INFUSE® Bone Graft to autogenous bone, most patients grew enough bone to place a dental implant regardless of whether they had autogenous bone or INFUSE® Bone Graft. However, the patients who received autogenous bone graft had a higher success rate of dental implant placement without

additional augmentation and a higher rate of significant adverse events, such as limping, pain, and infection.

Other grafting options are available. However, these options may not have been studied in the highest level of clinical trials as INFUSE® Bone Graft has. These options include allograft (bone from a human donor), xenograft (bone from another animal species, usually a cow), and synthetic or man-made grafting materials, all of which have their own considerations.

Questions To Ask Your Doctor

1. Why do I need a bone graft (or bone augmentation)?

2. Please describe the procedure to me.

3. What medications will be prescribed?

4. How long will my entire course of treatment take?

5. Who may I contact in your office if I have more questions, and how can I reach them?

Talk to your Doctor

While this brochure is meant to provide you with 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 about INFUSE® Bone Graft, please call or see your doctor, who is the only one qualified to diagnose and treat your condition. As with any surgical procedure, you should find a surgeon who is experienced in performing the specific surgery that you are considering.

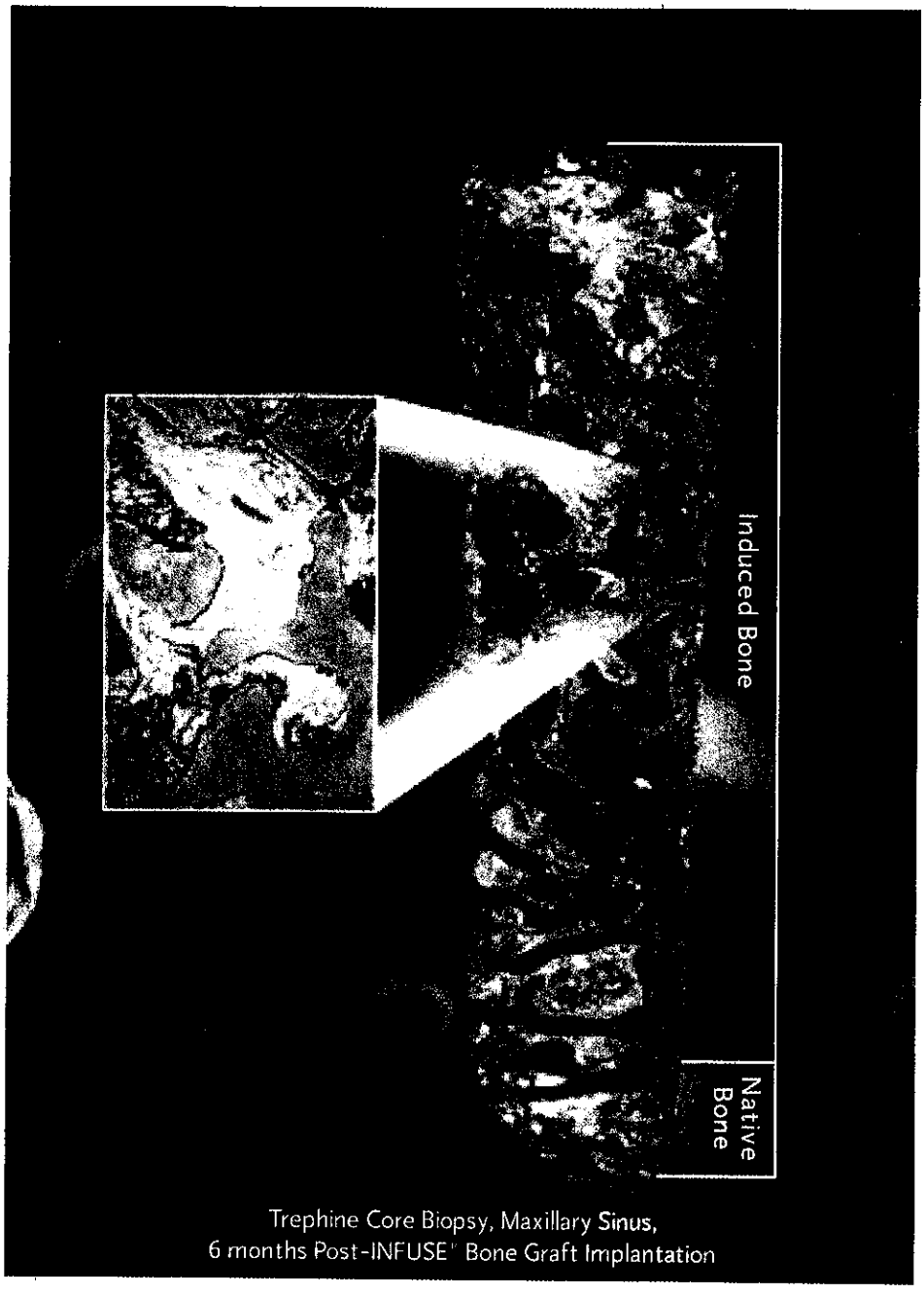
For additional information visit our website at: www.infusebonegraft.com or contact your doctor.

2.3
Operator's Manual

Medtronic

INFUSE® Bone Graft

Instructions for Preparation and Surgical Application



Trephine Core Biopsy, Maxillary Sinus,
6 months Post-INFUSE® Bone Graft Implantation

- Sinus Augmentation
- Alveolar Ridge Augmentation Associated with Extraction Sockets

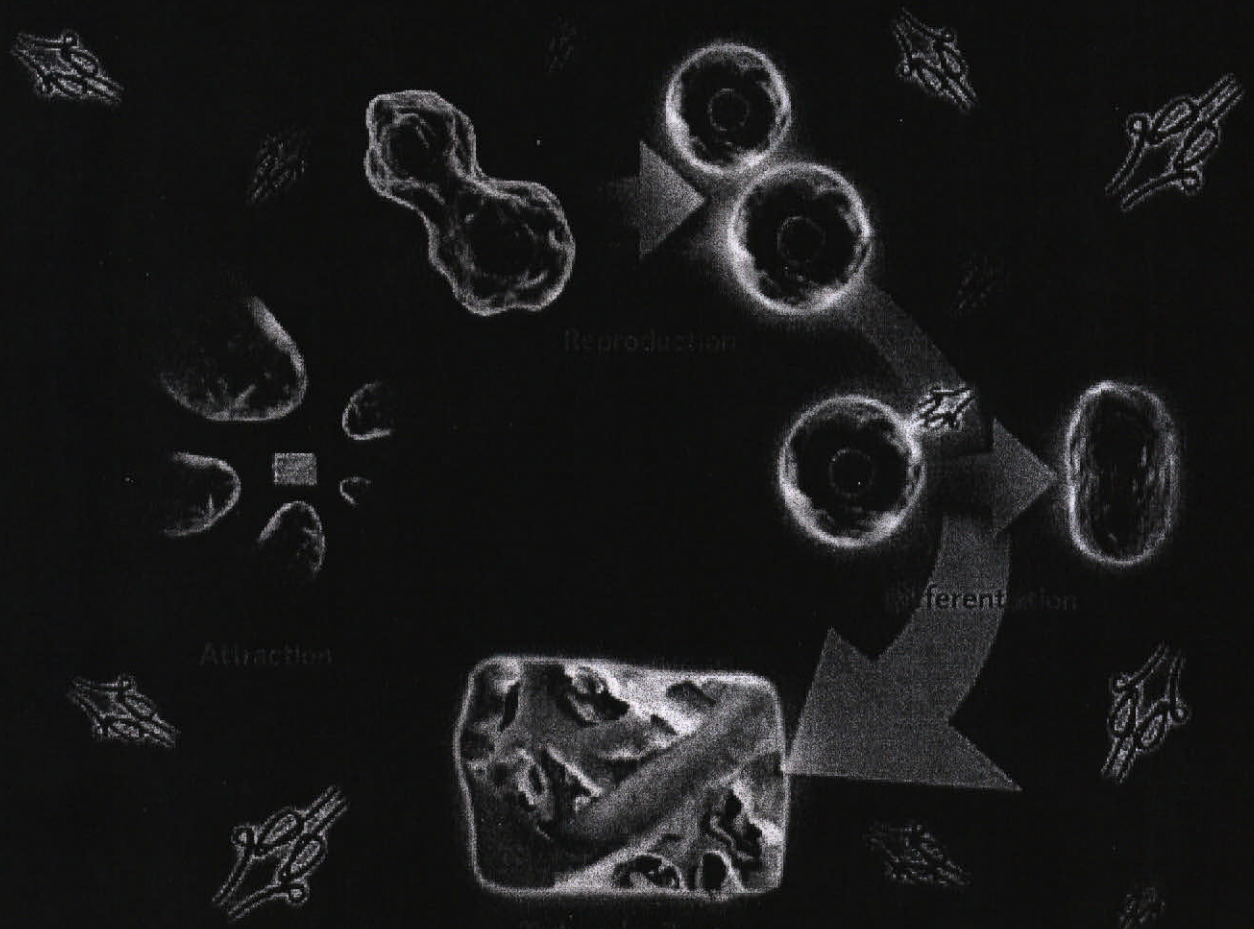
DRAFT

"BMP is destined to bring osteogenesis under the control of surgeons..."

Marshall R. Urist, MD 1997

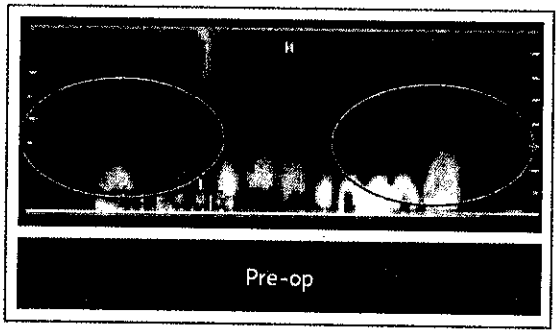
MECHANISM OF ACTION

INFUSE® Bone Graft induces new bone formation for dental implant placement

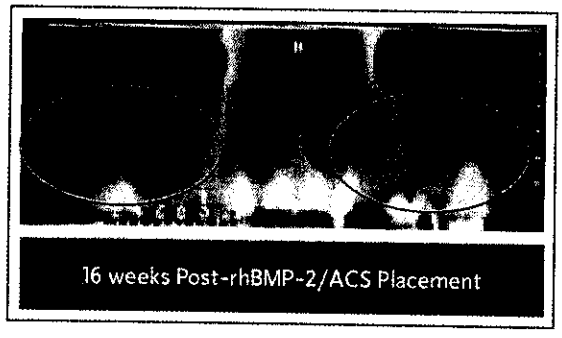


Sinus Augmentation

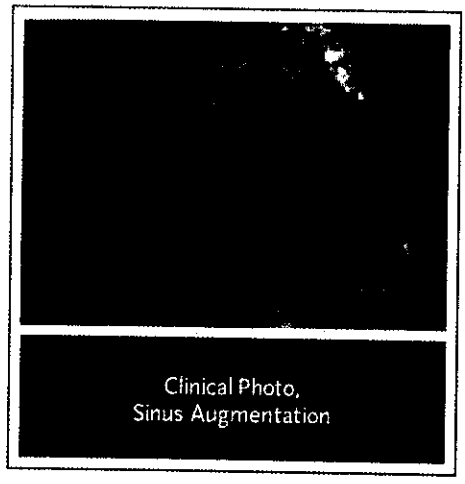
Placement of INFUSE® Bone Graft into the sinus regenerates new bone in the maxilla to permit the placement of dental implants that can be used to support either fixed or removable dental prostheses.



Pre-op



16 weeks Post-rhBMP-2/ACS Placement



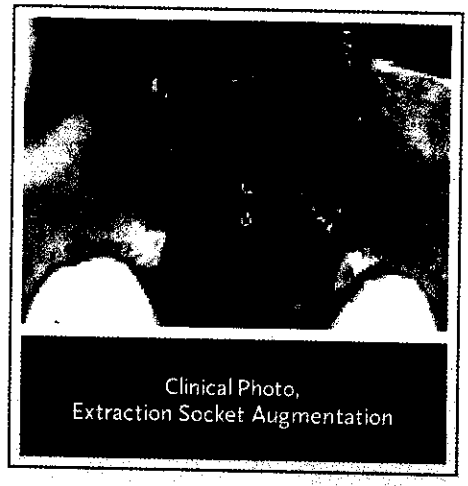
Clinical Photo,
Sinus Augmentation

Alveolar Ridge Augmentation Associated With Extraction Sockets

Augmenting the alveolar ridge by placing INFUSE® Bone Graft into the recently extracted sockets generates new bone of adequate dimension that permits placement of dental implants that can be used to support fixed dental prostheses.

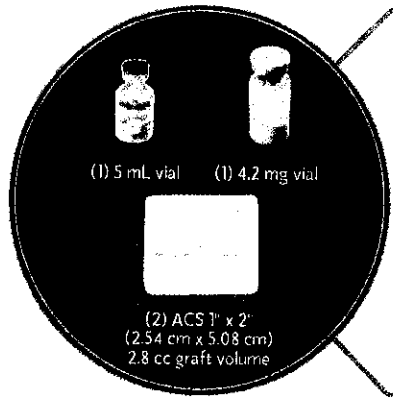
Pre-operative CT

De novo Bone Formation at
4 months Post-operative

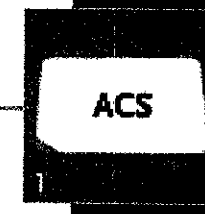


Clinical Photo,
Extraction Socket Augmentation

7510200 SMALL KIT



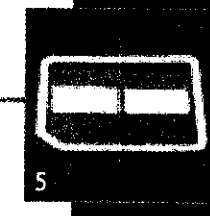
IN NON-STERILE FIELD



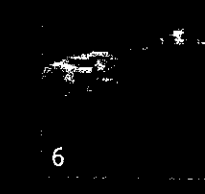
Observing proper sterile technique, open the outer ACS package and place the inner package containing the two 1" x 2" collagen sponges in the sterile field. Open and place one of the two 5 mL syringes/needles into the sterile field.

Using the othe needle, withdr water for injec

IN STERILE FIELD



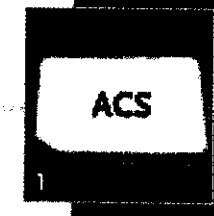
Open the inner ACS package leaving all collagen sponges in the plastic tray.



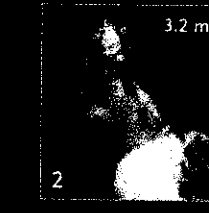
In the sterile fi syringe/needle of reconstitute the vial held by non-sterile fiel

[illegible] KIT

IN NON-STERILE FIELD



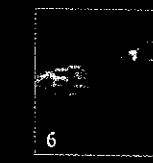
Observing proper sterile technique, open the outer ACS package and place the inner package containing the four 1" x 2" collagen sponges in the sterile field. Open and place two of the four 5 mL syringes/needles into the sterile field.



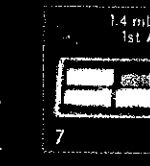
Using one of th 5 mL syringes/ withdraw 3.2 m water for injec

IN STERILE FIELD

Open the inner ACS package leaving all collagen sponges in the plastic tray.



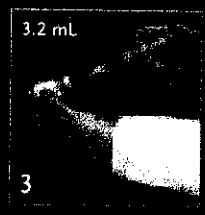
In the sterile field use the 5 mL syringe/needle to withdraw 1.4 mL of reconstituted rhBMP-2 from the vial held by the person in the non-sterile field.



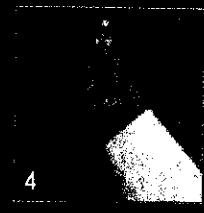
Uniformly distribute 1.4 m of reconstitute rhBMP-2 on one of the 1" x 2" collagen sponge

Allow wetted collagen sponges to stand for a minimum of 15 minutes. Use within 2 hours.
DO NOT use irrigation or suction near implanted device. Note: During handling avoid excessive squeezing of the wetted sponge.

yringe/
L of sterile

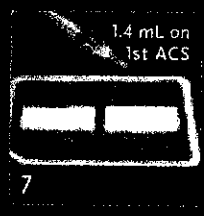


Reconstitute the rhBMP-2 with 3.2 mL of sterile water.

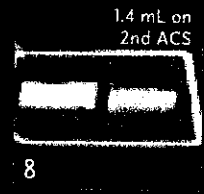


Gently swirl (do not shake) the rhBMP-2 vial to ensure adequate mixing.

he 5 mL
draw 1.4 mL
P-2 from
rson in the



Uniformly distribute 1.4 mL of reconstituted rhBMP-2 on one of the 1" x 2" collagen sponges.



Using the same 5 mL syringe/needle, repeat steps 6 & 7 for the remaining 1" x 2" collagen sponge.

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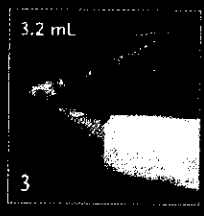
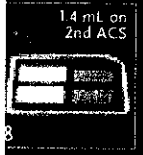
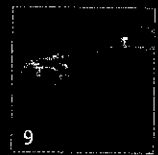


Reconstitute one vial of the rhBMP-2 with 3.2 mL of sterile water.

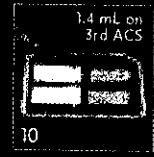
Gently swirl (do not shake) the rhBMP-2 vial to ensure adequate mixing. Using a second 5 mL syringe/needle, repeat steps 2 & 3 with the remaining vial of sterile water and vial of rhBMP-2.



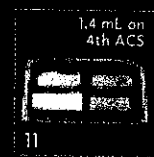
Using the same 5 mL syringe/needle, repeat steps 6 & 7 for the second 1" x 2" collagen sponge.



In the sterile field use the second 5 mL syringe/needle to withdraw 1.4 mL of reconstituted rhBMP-2 from the second vial held by the person in the non-sterile field.



Uniformly distribute 1.4 mL of reconstituted rhBMP-2 on the third 1" x 2" collagen sponge.

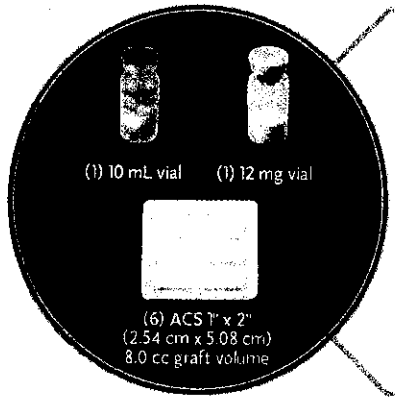


Using the second 5 mL syringe/needle, repeat steps 9 & 10 for the fourth 1" x 2" collagen sponge.

Remember: To achieve 1.5 mg/mL concentration, hydrate 4.2 mg of protein and apply to 2.8 cc of sponge volume. (2.8 cc sponge graft volume = two 2.54 cm x 5.08 cm wetted sponges)

602

7510600 LARGE KIT

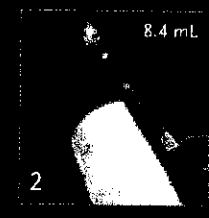


IN NON-STERILE FIELD

ACS

1

Observing proper sterile technique, open the outer ACS package and place the inner package containing the six 1" x 2" collagen sponges in the sterile field. Open and place one of the two 10 mL syringes/needles into the sterile field.



2

Using the othe
needle, withdr
water for injec

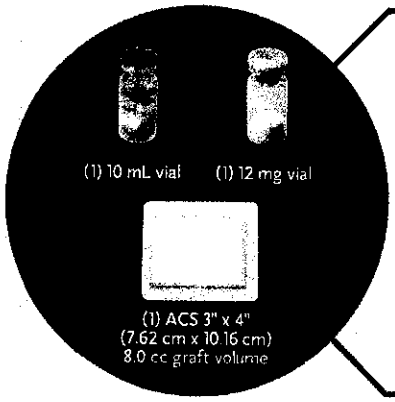
5

Open the inner ACS package leaving all collagen sponges in the plastic tray.

6

In the sterile fi
mL syringe/ne
4.0 mL of reco
from the vial h
the non-sterile

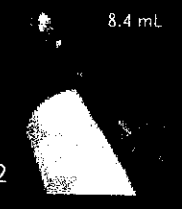
7510800 LARGE II KIT



ACS

1

Observing proper sterile technique, open the outer ACS package and place the inner package containing the 3" x 4" collagen sponge in the sterile field. Open and place one of the two 10 mL syringes/needles into the sterile field.



2

Using the othe
needle, withdr
water for injec

5

Open the inner ACS package. Using sterile scissors, cut the 3" x 4" collagen sponge into two 1 ½" x 4" strips. Return the cut collagen sponges to the plastic tray.

6

In the sterile fi
syringe/needle
4.0 mL of reco
from the vial h
the non-sterile

Allow wetted collagen sponges to stand for a minimum of 15 minutes. Use within 2 hours.
DO NOT use irrigation or suction near implanted device. Note: During handling avoid excessive squeezing of the wetted sponge.

syringe/
nL of sterile

Reconstitute the rhBMP-2 with 8.4 mL of sterile water.

Gently swirl (do not shake) the rhBMP-2 vial to ensure adequate mixing.

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withdraw
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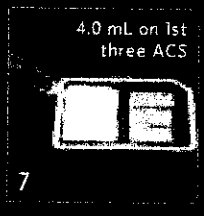
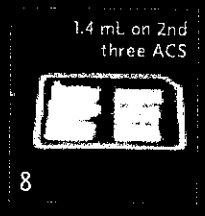
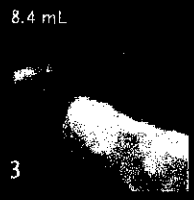


Uniformly distribute 4.0 mL of reconstituted rhBMP-2 on three of the 1" x 2" collagen sponges.



Using the same 10 mL syringe/needle, repeat steps 6 & 7 for the remaining 1" x 2" collagen sponges.

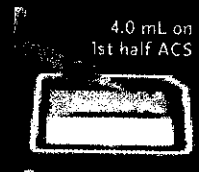
syringe/
nL of sterile



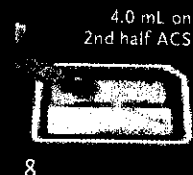
Reconstitute the rhBMP-2 with 8.4 mL of sterile water.

Gently swirl (do not shake) the rhBMP-2 vial to ensure adequate mixing.

he 10 mL
draw
d rhBMP-2
ne person in



Uniformly distribute 4.0 mL of reconstituted rhBMP-2 on one of the 1 ½" x 4" collagen sponges.



Using the 10 mL syringe/needle, repeat steps 6 & 7 for the remaining 1 ½" x 4" collagen sponge.

Remember: To achieve 1.5 mg/mL concentration hydrate 4.2 mg of protein and apply to 2.8 cc of sponge volume.
(2.8 cc sponge graft volume =two 2.54 cm x 5.08 cm wetted sponges)

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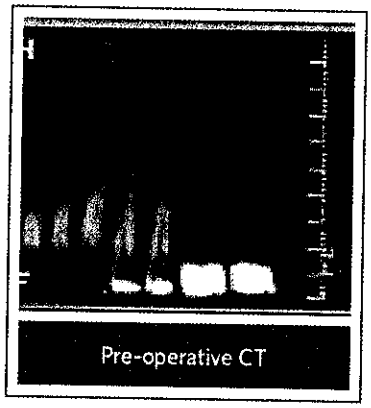
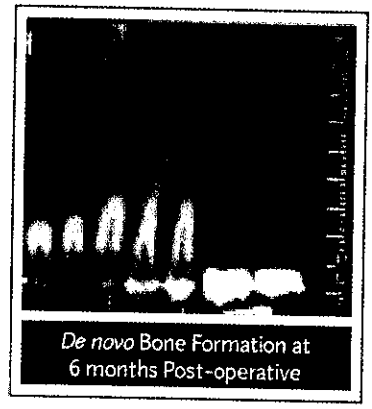
INSTRUCTIONS FOR SINUS AUGMENTATION SURGICAL APPLICATION



Pre-operative CT



De novo Bone Formation at 6 months Post-operative

Pre-implantation

- Create an adequate window via osteotomy and removal of the lateral maxillary wall.
- Elevate the sinus membrane to provide space for INFUSE® Bone Graft in the desired location. This includes elevation of the membrane along the medial wall, but take care not to reflect beyond the ostium.
- Achieve hemostasis prior to INFUSE® Bone Graft implantation in order to provide a relatively dry implantation site.
- The volume of INFUSE® Bone Graft implanted is determined by the sinus anatomy, the desired amount and location of augmentation and the ability to fill the surgical void created by the surgeon.
- After preparing the entire ACS according to the Instructions for Preparation, cut the INFUSE® Bone Graft into sizes that allow for easy and precise placement, evenly distributed within the lower third of the sinus where bone growth is desired.

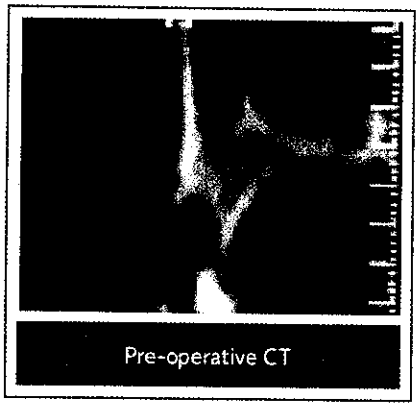
Implantation

- During implantation, use forceps to handle INFUSE® Bone Graft to avoid excessive loss of fluid.
- Place INFUSE® Bone Graft so that it extends to the medial wall and fills the void created by the surgeon.
- INFUSE® Bone Graft should be evenly distributed into the sinus as the geometry of the sinus requires.
- Proper surgical technique should be employed to minimize compressive forces on the INFUSE® Bone Graft.

Post-implantation

- Once INFUSE® Bone Graft is implanted, do not irrigate the wound.
- Achieve complete soft tissue coverage of INFUSE® Bone Graft following its implantation.
- Place dental implants after adequate bone has been induced (typically 6 months post-op.)

INSTRUCTIONS FOR ALVEOLAR RIDGE AUGMENTATION ASSOCIATED WITH EXTRACTION SOCKETS



Pre-operative CT

De novo Bone Formation at 4 months Post-operative

Pre-implantation

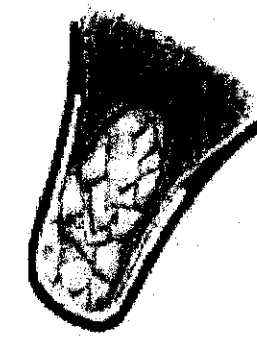
- Release full-thickness periosted flaps by utilizing sulcular and vertical incisions.
- Extract teeth and debride sockets.
- Create four to eight perforations on the socket wall using a 1/2 round burr.
- Achieve hemostasis prior to INFUSE® Bone Graft implantation in order to provide a relatively dry implantation site.
- The volume of INFUSE® Bone Graft implanted is determined by the socket anatomy and the ability to fill the surgical void created by the surgeon.
- After preparing the entire ACS according to the Instructions for Preparation, fold or cut the INFUSE® Bone Graft as needed prior to implantation.

Implantation

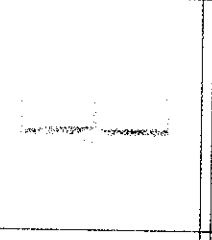
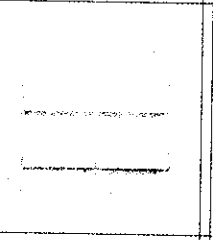
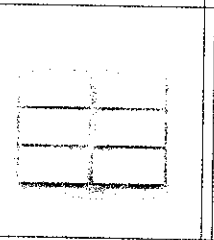
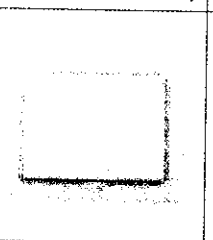
- During implantation, use forceps to handle INFUSE® Bone Graft to avoid excessive loss of fluid.
- Cut INFUSE® Bone Graft as the geometry of the site requires, leaving enough room to place a large strip of INFUSE® Bone Graft over entire site.
- INFUSE® Bone Graft may be placed into the socket (loosely packed), folded, rolled, or wrapped, as the geometry of the socket requires.
- Proper surgical technique should be employed to minimize compressive forces on the INFUSE® Bone Graft.

Post-implantation

- Establish a tension-free soft tissue wound closure environment.
- Once INFUSE® Bone Graft is implanted, do not irrigate the wound.
- Achieve complete soft tissue coverage of INFUSE® Bone Graft following its implantation.
- Place dental implants after adequate bone has been induced (typically 6 months post-op.)



AVAILABLE KIT SIZES

INFUSE® Bone Graft Kits				
Sterile Absorbable Collagen Sponge (ACS)	(2) ACS 1" x 2" (2.54 cm x 5.08 cm)	(4) ACS 1" x 2" (2.54 cm x 5.08 cm)	(6) ACS 1" x 2" (2.54 cm x 5.08 cm)	(1) ACS 3" x 4" (7.62 cm x 10.16 cm)
				
Total Graft Volume	2.8 cc	5.6 cc	8.0 cc	8.0 cc
mg rhBMP-2	4.2 mg	8.4 mg	12.0 mg	12.0 mg
Concentration rhBMP-2	1.5 mg/mL	1.5 mg/mL	1.5 mg/mL	1.5 mg/mL

listen. respond. deliver.

The surgical technique shown is for illustrative purposes only. The technique(s) actually employed in each case will always depend upon the medical judgment of the surgeon exercised before and during surgery as to the best mode of treatment for each patient. Please see the package insert for the complete list of indications, warnings, precautions, and other medical information.

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