

# Section X – Device Labeling

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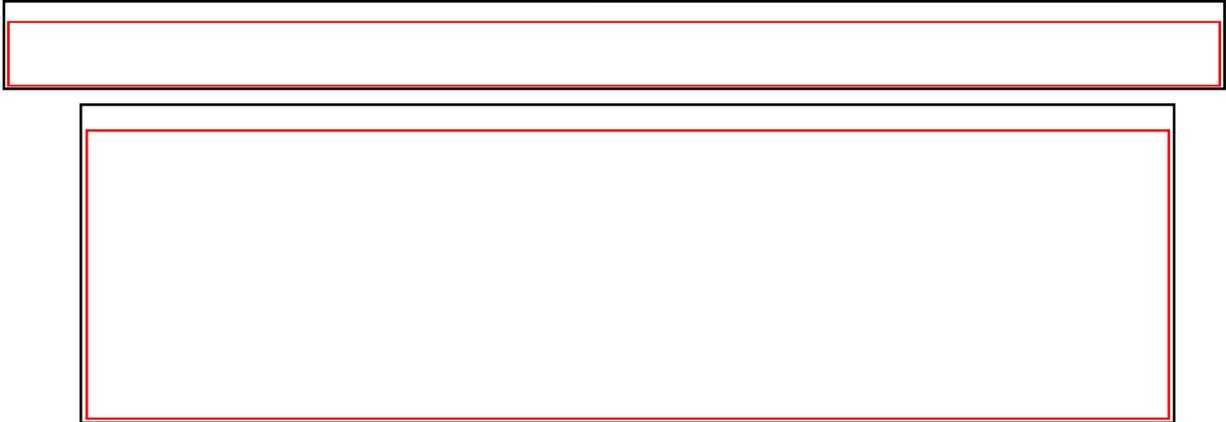
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## X. Device Labeling

### X.A. Device Description

INFUSE<sup>®</sup> BONE GRAFT, the subject of this Premarket Approval application is identical to that currently commercially available in the United States through P000054 (INFUSE<sup>®</sup> BONE GRAFT) and P000058 (INFUSE<sup>®</sup> BONE GRAFT/LT-<sup>®</sup>



INFUSE<sup>®</sup> BONE GRAFT consists of recombinant human Bone Morphogenetic Protein-2 (rhBMP-2, known as dibotermis alfa) placed on an absorbable collagen sponge (ACS). The INFUSE<sup>®</sup> BONE GRAFT component induces new bone tissue at the site of implantation.

rhBMP-2 is the active agent in the INFUSE<sup>®</sup> BONE GRAFT component. 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.

Each INFUSE<sup>®</sup> BONE GRAFT Kit (See Figure X.A-1 INFUSE<sup>®</sup> BONE GRAFT Kit) contains vial(s) of rhBMP-2, absorbable collagen sponge(s) (ACS), and the necessary materials to reconstitute the lyophilized rhBMP-2 and place the reconstituted rhBMP-2 on the ACS.

Figure X.A-1 INFUSE<sup>®</sup> BONE GRAFT Kit



Four kit sizes are available, depending on the size of the implant site and the amount of bone growth required. The kits are designated as Small, Medium, Large, and Large II. At least one kit is required for each procedure. INFUSE<sup>®</sup> BONE GRAFT kits are stored at room temperature.

Kits come with vial(s) containing either 4.9 or 12.7 mg of lyophilized rhBMP-2. ACS for use with rhBMP-2 is provided in packages containing two, four or six 1" x 2" pieces or a single 3" x 4" piece depending upon the size and configuration of the kit. Prior to implantation, rhBMP-2 is reconstituted with Sterile Water for Injection and the solution is then uniformly applied to the ACS.

Note that 12 mg of the 12.7 mg of rhBMP-2 in the larger vial is applied to the ACS following reconstitution. Likewise, 4.2 mg of the 4.9 mg of rhBMP-2 in the smaller vial is applied to its ACS following reconstitution. As a result, the larger vial is sometimes referred to as the 12 mg vial and the smaller vial is sometimes referred to as the 4.2 mg vial.



### **X.C. Contraindications**

INFUSE<sup>®</sup> BONE GRAFT is contraindicated in the following:

- For patients with a known hypersensitivity to recombinant human Bone Morphogenetic Protein-2, bovine Type I collagen or to other components of the formulation.
- In the vicinity of a resected or extant tumor or any active malignancy or patients undergoing treatment for a malignancy.
- In patients who are skeletally immature (<18 years of age or no radiographic evidence of epiphyseal closure).
- In pregnant women. The potential effects of rhBMP-2 on the human fetus have not been evaluated.
- In patients with an active infection at the operative site.

## X.D. Warnings and Precautions

### X.D.1. Warnings

Note that Medtronic Sofamor Danek has recently completed testing required as a condition of approval for INFUSE<sup>®</sup> BONE GRAFT PMAs P000054 and P000058 which address the following fetal development warning.

- Women of childbearing potential should be advised that the influence of rhBMP-2 on fetal development has not been assessed. In the clinical trials supporting the safety and effectiveness of INFUSE<sup>®</sup> BONE GRAFT for oral maxillofacial bone grafting procedures where space maintenance is present,  (2.2%) patients treated with INFUSE<sup>®</sup> BONE GRAFT and  (0.0%) patients treated with bone graft 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 did not cause fetal abnormalities in rabbit studies. Additionally, it is known from rabbit studies that fetal expression of BMP-2 which could re-expose mothers who were previously antibody positive, did not elicit a more powerful immune response to BMP-2 with adverse consequences for the fetus.
- The safety and effectiveness of INFUSE<sup>®</sup> 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<sup>®</sup> BONE GRAFT.

## **X.D.2. Precautions**

### **X.D.2.a. General**

- The safety and effectiveness of repeat applications of INFUSE<sup>®</sup> BONE GRAFT has not been established.
- INFUSE<sup>®</sup> BONE GRAFT should only be used by surgeons or dentists who are experienced in oral maxillofacial 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 Sofamor Danek representative.
- Do not use after the printed expiration date on the label.

### **X.D.2.a.1. Hepatic and Renal Impairment**

- The safety and effectiveness of INFUSE<sup>®</sup> 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.

### **X.D.2.a.2. Bone formation**

- The safety and effectiveness of INFUSE<sup>®</sup> BONE GRAFT 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.

### **X.D.2.a.3. Antibody Formation/Allergic Reactions**

- The safety and effectiveness of INFUSE<sup>®</sup> BONE GRAFT has not been demonstrated in patients with autoimmune disease.
- The safety and effectiveness of INFUSE<sup>®</sup> 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.

#### **X.D.2.a.4. Immunogenicity**

- As with all therapeutic proteins, there is a potential for immune responses to be generated to a component of INFUSE<sup>®</sup> BONE GRAFT. The immune response to INFUSE<sup>®</sup> BONE GRAFT components was evaluated in  investigational patients and  control patients during human clinical trials of INFUSE<sup>®</sup> BONE GRAFT for oral maxillofacial bone grafting procedures where space maintenance is present.
  - *Anti-rhBMP-2 antibodies:* 2.2% patients receiving INFUSE<sup>®</sup> BONE GRAFT component developed antibodies vs. 0.0% in the control group.
  - *Anti-bovine Type I collagen antibodies:* 20% of patients receiving INFUSE<sup>®</sup> BONE GRAFT developed antibodies to bovine Type I collagen vs. 31% 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<sup>®</sup> BONE GRAFT with the incidence of antibodies to other products may be misleading.

**X.E. Draft Labeling**

**X.E.1. Package Insert**

See Appendix X-1

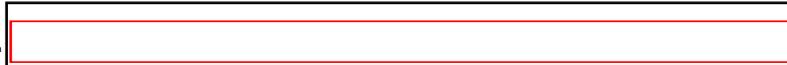
**X.E.2. Preparation Instructions**

See Appendix X-2

**X.E.3. Surgical Technique**

See Appendix X-3

**X.E.4.**



See Appendix X-4

**X.E.5. rhBMP-2 Vial Label**

See Appendix X-5

**X.E.6. ACS Labels**

See Appendix X-6

**X.E.7. Patient Labels**

See Appendix X-7

**X.E.8. Patient Brochure**

See Appendix X-8