INTRODUCTION

Augment is intended to be used as an alternate to autograft in foot and ankle procedures, including fusion and fracture repair, where the use of supplemental bone graft is indicated.

Augment is a combination drug/device product being developed for use in bone repair and regenerative procedures. The product eliminates the need for a second surgery to harvest autologous bone, therefore there is no donor site morbidity (e.g. pain, infection, etc.) and anesthesia time is reduced.

Augment combines recombinant human platelet-derived growth factor B homodimer (rhPDGF-BB) with a biodegradable synthetic bone matrix (beta-tricalcium phosphate or β-TCP). Augment can only achieve its intended use when its two functional components are combined. These two components are packaged together and sold as a system. They are physically combined immediately prior to use.

The β-TCP scaffold fills the defect and provides an osteoconductive matrix for the formation of new bone the combination of rhPDGF-BB with the β-TCP enhances bone growth. rhPDGF-BB is a well characterized endogenous protein, with a scientifically established mode of action that is known to enhance connective tissue formation, bone formation, cell proliferation and angiogenesis.

Pharmacology

Brief Summary

Augment is intended for use in the treatment of bone fusions of the foot and ankle in patients with chronic inflammation or tissue degeneration in these joints. A positive outcome for the patient requires bone formation stimulated by Augment across the decorticated junction of two or more bones in the foot and ankle. The preclinical studies demonstrate the safety and efficacy of rhPDGF-BB in combination with β-TCP for bone fusion and accelerating fracture healing using models that mimic the osseous healing required following foot-and-ankle fusion surgery. The studies utilize matrices containing chemically identical β-TCP products.

The first and second studies describe the results of fracture healing conducted to evaluate rhPDGF-BB combined with a β-TCP/collagen matrix in two rat models of delayed or impaired bone repair (aged, ovariectomised or diabetic). In both models, treatment with rhPDGF-BB combined with β-TCP/collagen resulted in acceleration of fracture healing at either the tibia or the femur, demonstrating also that rhPDGF-BB at a dose of 0.3 mg/mL is as efficacious as or better than at a dose of 1.0 mg/mL. The third study describes results from a canine partial...
arthrodesis model in which rhPDGF-BB combined with a β-TCP matrix equivalent to Augment’s β-TCP or a β-TCP/collagen matrix leads to improved bone fusion compared to the matrices alone. In addition, bone fusion with rhPDGF-BB combined with β-TCP appeared to be equivalent to or better than autograft. The fourth study is an evaluation of rhPDGF-BB combined with β-TCP for treatment of rabbit tibial osteotomies. Although there were no differences in the amount of bone formation at osteotomies treated with or without rhPDGF-BB, the combination of rhPDGF-BB and β-TCP did not interfere with bone formation at the sites and led to increased bone remodeling after 4 weeks.

Finally, animal studies have been conducted that provide additional support for the safety and efficacy of rhPDGF-BB for bone healing, and involve combinations of the protein with matrices composed of β-TCP or other materials.

Overall, the preclinical data in these animal models support the safety and efficacy of rhPDGF-BB combined with β-TCP matrix for the healing of bone defects and fractures in a variety of animal backgrounds that model the bone healing taking place following a foot-and-ankle fusion procedure. The data support the use of Augment for the clinical treatment of foot-and-ankle fusions in which the product enhances the healing and formation of new bone at the fusion sites.

Pharmacokinetics

Brief Summary

A critical aspect for the use of Augment treatment to enhance fracture repair is the release characteristics of rhPDGF-BB from the matrix with which it is combined. BioMimetic has conducted a series of in vivo and in vitro studies assessing the release characteristics of 125I-labeled rhPDGF-BB from multiple types of matrices, all of which contain β-TCP as an osteoconductive scaffold.

Two in vivo studies assessed the release of 125I-rhPDGF-BB when implanted in a rat calvarial bone defect. This model was selected to mimic the placement of rhPDGF-BB at the site of a bone defect containing bleeding bone, as occurs with the use of Augment for the treatment of foot and ankle fusions. Additionally, a series of in vitro studies were conducted to demonstrate that combining the rhPDGF-BB with β-TCP has no impact on the chemical stability or biological activity of the protein. The methods used to assess chemical and biological stability are procedures that are routinely used as part of our ongoing program to monitor stability of formulated rhPDGF-BB.
Toxicology

Brief Summary

The extensive history of use of β-TCP as a bone void filler and bone cement has demonstrated that this material is biocompatible and nontoxic. Implantation of β-TCP in animal bone repair models is not associated with any detectable increases in serum calcium, or serum phosphate, nor any calcification of the kidneys arising from resorption of the implant (for example, Cameron et al., 1977; reviewed in Rawlings, 1993). The conclusion that β-TCP lacks significant toxicity is supported by over 25 years of safe use in the clinic for dental, maxillofacial and orthopaedic indications.

rhPDGF-BB based products have been on the market for over 10 years, initially in Regranex®, a product for the treatment of diabetic foot ulcers (marketed in the US and in the EU) and GEM 21S, a product for the treatment of periodontal defects (marketed in the US and Canada). Augment has been used to treat approximately 471 patients in both pilot and pivotal clinical studies with no report of any serious adverse event. Over 80,000 units of GEM 21S have been distributed over the past three years with no reported serious adverse events resulting from the use of the product, including no known cases of cancer. Regranex has been used in over 750,000 cases to date.

BioMimetic has worked in collaboration with the FDA to develop a program of preclinical safety and toxicology studies that are intended to provide additional data to support the safety of Augment, among these a GLP study to evaluate the long-term chronic toxicity and carcinogenic potential of rhPDGF-BB combined with Augment β-TCP matrix following surgical implantation adjacent to the femur, in a rat model. The results of these studies demonstrate that Augment is biocompatible, nontoxic, and noncarcinogenic.

The results of pharmacokinetics analyses demonstrate that rhPDGF-BB administration leads to brief and minimal systemic exposure with a systemic half-life of 2.3 min.

Single and repeated dose toxicity of rhPDGF-BB has been characterized in intravenous and intramuscular studies in rats. rhPDGF-BB has also been evaluated in one reproductive toxicity study in rats and in one in vitro genotoxicity study. These studies did not show any adverse reactions or findings, which again support the conclusion that rhPDGF-BB is safe both alone and in combination with the Augment matrix.