



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

MEMORANDUM

Food and Drug Administration
1350 Piccard Drive
Rockville, MD 20850

Date: June 18, 2004

From: Janie Fuller, Product Evaluation Branch I
Division of Postmarket Surveillance (DPS)
Office of Surveillance and Biometrics (OSB)

Subject: Analysis of adverse event reports
Calcium phosphate-containing bone fillers (Procode LYC and LPK) and
Becaplermin (a drug used as a component in some calcium phosphate-
containing bone fillers)

To: Chiu Lin, Director, Division of Anesthesiology, General Hospital, Infection
Control, & Dental Devices (DAGID), Office of Device Evaluation (ODE)
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Through: Suzanne Rich, Chief Product Evaluation Branch I, DPS, OSB _____
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Purpose

This report provides information on adverse events (AE) reports in the:

- Manufacturer and User Facility Device Experience (MAUDE) database (contains all voluntary reports received since June 1993, user facility reports since 1991, distributor reports since 1993, and manufacturer reports since August 1996) associated with calcium phosphate-containing bone fillers; and
- Center for Drug Evaluation and Research Adverse Event Reporting Systems (AERS) database associated with Becaplermin.

This analysis was requested by the ODE Dental Devices Branch as background information for an FDA Advisory Panel meeting at which a PMA will be considered for GEM 21S of BioMimetic Pharmaceuticals, Inc.

Background

GEM 21S of BioMimetic Pharmaceuticals, Inc. is a combination product composed of two individually marketed components, VitOss, an osteoconductive, biocompatible and resorbable synthetic β -tri-calcium phosphate sterile porous bone void filler for repair of bony defects (supplied by Orthovita, Inc.), and Becaplermin (Rh PDGF-BB) a highly-purified recombinant human platelet derived growth factor (supplied by Chiron Corporation) in a non-sterile, low-bioburden preparation.

This combination product, falls under the jurisdiction of CDRH and CBER, with the two Centers agreeing for CDRH to take the lead in premarket reviews and for CBER to provide consultation. An IDE was approved April 24, 2002, and after study completion the PMA was submitted March 12, 2004. Presentation before the Dental Products Panel is set for July 13, 2004.

Becaplermin, originally approved by CDER for topical treatment of diabetic foot ulcers, was intended in that application to promotion of the growth of mesenchymal cells to promote normal healing and enhance wound closure.

Methods

CDRH MAUDE database search: The MAUDE database was searched for product codes LYC and LPK. A text search of the resulting reports was performed for the terms "tricalcium," "calcium," or "phosphate." MAUDE queries were also performed for the relevant manufacturers BioMimetic Pharmaceuticals, Inc. and Orthovita, Inc. and for the brand name VitOss.

CDER AERS search: The AERS database was searched for any reactions listed under product names Becaplermin and Regranex.

Results

MAUDE data: The MAUDE database search on product codes LYC and LPK yielded 31 reports. The text search among these reports for "tricalcium," "calcium," or "phosphate" located one report. Manual review of the device information (e.g., brand name, generic device) contained in these reports revealed no other reports associated with calcium phosphate devices. Additional MAUDE searches on relevant manufacturers yielded no reports on calcium phosphate devices.

The one MAUDE report on a calcium phosphate-containing bone filler reported observation of (1) thrombus formation when injected into the venous circulation of a pig and (2) decreased *in vitro* clotting time when tested on the blood of one human subject.

CDER AERS search:¹ A search of the AERS database on product names Becaplermin and Regranex yielded 324 cases. Among these, 128 reported a serious outcome, including 74 deaths. The relationship of these events to Becaplermin is not known.

A cursory examination of the reports suggests that some deaths may be due to underlying medical conditions such as pneumonia, lung neoplasm, leg amputation, and sepsis. The typical patient who receives Becaplermin for diabetic foot ulcers has multiple medical problems and experience a wide variety of complicating events unrelated to Becaplermin during the course of their treatment.

The most frequently reported terms were skin hypertrophy (54), pain (40), death (31), skin disorder (29), granuloma (28), condition aggravated (25), drug effect decreased (25), paresthesia (23), infection (20), rash erythematous (16), skin discoloration (12) and impaired healing (11). With the exception of death, these conditions are fairly consistent with events expected for a topically administered product. These terms are consistent with those observed during clinical studies that supported the approval of Becaplermin for this indication, and in clinical trials of Becaplermin in other chronic ulcers (pressure and venous stasis). The CDER review of these reports on Becaplermin raised no concerns that led to further investigation into these events.

Conclusions:

Relevance of MAUDE and AERS data reviewed are of questionable relevance to the use of GEM 21S due to the different conditions of use and because the events reported may be attributed to the patients' underlying medical condition.

¹ Information on Becaplermin adverse events data was taken from a June 14, 2004, teleconference with Libero Marzella, CDER; and from a May 24, 2004, email message from Susan Lu, CDER.

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