



Omnicare

Date: October 2, 2008

To: Omnicare Nursing Facility Clients
Directors of Nursing
Medical Directors and Prescribers

From: Barbara J. Zarowitz, Pharm.D.
Chief Clinical Officer

Subject: Papain-Containing Wound Care Products

Memorandum

Effective January 21, 2009, no papain-containing wound care products will be available in the U.S. The attached communication from HealthPoint outlines that papain products are being withdrawn from the market due to reports of adverse events and allergic reactions.

A list of papain-urea and papain-urea-chlorophyll-copper products follows.

Papain-urea
(Debrider)

Accuzyme- All formulations
AllanEnzyme – All formulations
AllanZyme Topical Spray
Ethezyme – All formulations
Gladase Debriding Topical Ointment
Kovia – All formulations
Papain-urea
Paptase

Papain-Urea-Chlorophyll-Copper-
Complex (Debrider-Healer)

AllanfilEnzyme – All formulations
Allanfil Spray
Gladase-C
Panafil - All formulations
Papfyl
Ziox – All formulations

There are few options remaining. All residents prescribed a papain-containing product should be evaluated to determine whether topical debridement should be continued. Collagenase (Santyl®) is an FDA-approved product indicated for the debridement of chronic dermal ulcers- e.g. pressure ulcers, vascular ulcers, diabetic foot ulcers and severely burned areas. Collagenase (Santyl®) may be an appropriate alternative for papain products. Becaplermin (Regranex® Gel) is another FDA-approved alternative for the treatment of diabetic foot ulcers that extend into the subcutaneous tissue or beyond and have an adequate blood supply. Regranex® is significantly more expensive than Santyl®.

Omnicare will continue to supply papain-containing products **while supplies last**, up to January 21, 2009.

- Consultant pharmacists will provide patient-specific recommendations for prescribers in November and December in preparation for papain-containing product withdrawal.
- For prescriptions for papain-containing products after this date, Omnicare will suggest Santyl® using a therapeutic interchange process.

Please feel free to contact your Omnicare pharmacy if you have any questions.



September 29, 2008

Dear Customer,

On September 23rd, the FDA announced that companies marketing topical drug products containing papain must stop manufacturing these products on or before November 24, 2008 and that no such products may be shipped in interstate commerce after January 21, 2009. As this action affects two Healthpoint products, Accuzyme[®] and Panafil[®], we want to take this opportunity to explain some of the background related to these products, as well as actions Healthpoint will be taking to comply with this notice.

Background

Like thousands of other prescription drugs, topical papain products entered the US market prior to 1962, predating current FDA requirements for drug approval applications. Provided that certain characteristics such as labeling, formulation, etc., were not materially altered, the Agency, consistent with its Compliance Policy Guide,¹ historically allowed pre-1962 drugs to remain on the market pending a final determination by FDA as to whether new drug approval requirements were applicable.

In June 2006, the Agency confirmed that pre-1962 drugs required approval based upon current Federal requirements and encouraged manufacturers to contact the Agency about seeking approval. Otherwise, FDA indicated it would pursue a risk-based approach to removing pre-1962 drugs from the market in a manner that would not adversely affect public health, impose undue burdens on consumers, or unnecessarily disrupt the market.

Healthpoint has long recognized the importance of natural enzymes as a necessary therapeutic option for the treatment of wounds. Accordingly, Healthpoint contacted the Agency about approval requirements for Accuzyme[®] and Panafil[®], while continuing to proactively share information about the safety of the products with FDA. At about the same time, Healthpoint acquired the only FDA-approved enzyme for debridement, Collagenase SANTYL[®] Ointment (*FDA Application No. (BLA) 101995*), which, at the time, was available only in limited supply. In order to ensure sufficient availability of enzymatic therapy, Healthpoint continued to make Accuzyme[®] and Panafil[®] available, while exploring its options for pursuing their approval and working to increase the production of SANTYL[®] Ointment.

Factors Cited in FDA's September 23rd Communications

In its notice, FDA cited 37 reports of serious adverse events associated with the use of products containing papain since 1969, some of which included allergic hypersensitivity reactions. Papain is derived from papaya, a tropical fruit. Allergic reactions to papain—an ingredient also found in multiple everyday products, including meat tenderizer, contact lens solution, and adhesive removers in the beauty industry—have been reported in the medical literature. A patient's history of anaphylaxis on exposure to papaya, or antigenically related substances (notably, *Ficus* tree, banana, fig, avocado, cassava, pineapple, or kiwi fruit), should alert prescribers to the possibility of similar reactions to papain.

FDA also noted that patients may be at increased risk for adverse reactions to papain if they have allergic sensitivity to latex. "Latex" is a generic term referring to the milky fluid from various

plants, including the rubber tree. Sensitization to tropical fruit latex has been reported in 2.5% of atopic individuals and mostly occurs independently of allergy to rubber latex.ⁱⁱ

Further, the FDA stated that, in addition to general standard care of wounds, there are two approved topical products that are effective alternatives to papain products for many types of wounds: Regranex[®] Gel (indicated for the treatment of diabetic foot ulcers) and Collagenase SANTYL[®] Ointment (indicated for the debridement of chronic dermal ulcers-e.g., pressure ulcers, vascular ulcers, diabetic foot ulcers, etc. -and severely burned areasⁱⁱⁱ). The Agency recommended that patients consult a healthcare professional for detailed guidance on the treatment options that are right for them.

Healthpoint's Actions

Healthpoint will fully comply with FDA's notice by ceasing the manufacture and shipment of Accuzyme[®] and Panafil[®] by the dates specified in FDA's notice. In the interim, these products will be available to healthcare professionals for their patients.

We at Healthpoint remain committed to providing patients with safe and effective wound care products that contribute to improved clinical and quality-of-life outcomes. Moreover, we intend to work with our customers to ensure the smoothest transition possible during this period.

To that end, should you have questions regarding the FDA notice and how it might affect your practice, please contact our Medical Affairs department at (866) 932-6390. If you have inquiries related to product availability or other general questions, please call our Customer Service department at (800) 441-8227.

Sincerely,



Michael Steadman
Group President and Chief Operating Officer
Healthpoint, Ltd.

i See Guidance for FDA Staff and Industry Marketed Unapproved Drugs — Compliance Policy Guide, Sec. 440.100, Marketed New Drugs Without Approved NDAs or ANDAs (CPG 7132c.02), in effect prior to June 9, 2006.

ii Hemmer W, Focke M, Gotz M, Jarisch R. Sensitization to Ficus benjamina: relationship to natural rubber latex allergy and identification of foods implicated in the Ficus-fruit syndrome. Clin Exp Allergy 2004; 34(8):1251-1258.

iii Occasional slight transient erythema has been noted in surrounding tissue when applied outside the wound. One case of systemic hypersensitivity has been reported after 1 year of treatment with collagenase and cortisone. See complete prescribing information online at: [http://www.healthpoint.com/divisions/tm/images/Santyl-PI-Update\(Final-Client-11Dec07\).pdf](http://www.healthpoint.com/divisions/tm/images/Santyl-PI-Update(Final-Client-11Dec07).pdf)