



Indiana Medicaid Therapeutics Committee Therapeutic Class Review Summary

Therapeutic Class:

Wound Care Products

Overview:

The goals of wound care are to prevent infection and promote tissue growth. Necrotic tissue, which often occurs in stage III and stage IV wounds, delays healing, promotes infection, and must be removed for proper tissue growth. The methods of necrotic tissue removal include surgical, sharp, mechanical, and enzymatic debridement. Enzymatic debridement involves application of enzymatic products to dissolve necrotic tissue. The process of enzymatic debridement is slow, and it should be considered for patients who are not candidates for surgical debridement.

The available enzymatic agents are the following:

- 1) **Papain/Urea Combination:** Papain is a proteolytic enzyme, which digests nonviable tissue with no effect on viable tissue. However, it is relatively ineffective when used alone. Papain requires the presence of activators to stimulate its digestive potency. Urea exposes the sulfhydryl groups in the nonviable tissue, which allows papain to attach to those tissues and perform degradation. Therefore, papain is often used in combination with urea. The available products are EtheZyme™-650 Ointment and Gladase™ Ointment.
- 2) **Chlorophyllin Copper Complex/Papain/urea Combination:** In addition to papain and urea, chlorophyllin copper complex is added to the combination to promote healing, control local inflammation, and reduce wound odor. The available product is Gladase™-C Ointment.
- 3) **Collagenase:** Collagenase digests collagen in necrotic tissue, which facilitates granulation. The available product is Santyl.

The above products are designed to remove necrotic tissue. The indications are mainly for pressure ulcers (decubitus) and burns. Papain and urea combinations have also been used in diabetic foot ulcer. Although some products have the same active ingredients, they are different in concentration or formulation (ointment, gel, or spray). Most of the agents are not rated in the orange book for their interchangeable status. Published data for comparative studies of these products are also limited. However, in general, products that contain papain and urea seem to have a similar effect when compared to the collagenase products, and ointments are more efficient than sprays. Of note, FDA has determined the castor oil/peru balsam/trypsin combination products to be DESI (less than effective); therefore, the following products are no longer under consideration for PDL inclusion: Allanderm T, Granulderm, Granulex, Optase, TBC Aerosol, and Xenaderm ointment.

On September 23, 2008, the FDA announced that it has ordered companies to stop marketing unapproved drug products that contain papain in a topical dosage form. Under this notice, firms marketing any unapproved topical papain products must stop manufacturing these products by



November 24, 2008. Companies or others engaged in shipping these products must stop shipping them by January 21, 2009. After these dates, all topical products containing papain must have FDA approval to be manufactured or shipped interstate. Topical drug products containing papain have historically been marketed without approval; there are no approved topical drug products containing papain. FDA is taking this action because adverse events with use of topical papain drug products reported to the agency raise serious safety concerns regarding these products. These drugs can produce harmful or near fatal effects including hypersensitivity resulting in anaphylactic reactions. Hypersensitivity manifestations have also resulted in cardiovascular symptoms such as hypotension and tachycardia. Furthermore, the effectiveness of these products is not supported by scientifically sound studies in the medical literature. Very few papain containing products continue to be available.

A relatively new wound care agent, becaplermin (Regranex), was developed to promote tissue growth. Becaplermin has biological activity similar to that of endogenous platelet-derived growth factor. It is indicated for the treatment of lower extremity neuropathic diabetic ulcers. However, its effects diminish when used in areas without adequate blood supply. Although becaplermin has been used in the management of pressure ulcers, it is not an FDA approved indication. Recently, an increased rate of mortality secondary to malignancy was observed in patients treated with three or more tubes of Regranex Gel in a postmarketing retrospective cohort study. As a result, Regranex should only be used when the benefits can be expected to outweigh the risks, and should be used cautiously in patients with known malignancy.

GENERIC NAME	BRAND NAME	MANUFACTURER	GENERIC
Papain; Urea	EtheZyme™-650 Ointment, Gladase™ Ointment	Smith&Nephew, Ethex Corp.	No information
Chlorophyllin Copper Complex; Papain;Urea	Gladase™-C Ointment	Smith&Nephew,	No information
Collagenase	Collagenase Santyl®, Santyl®	Healthpoint Ltd	N
Becaplermin, rh- PDGF	Regranex®	Ortho-McNeil	N

Summary:

In clinical practice, products containing papain and urea seem to have a similar effect when compared to products containing collagenase; products containing castor oil, peru balsam and trypsin are milder debriding agents; and ointments are more efficient than sprays.

Becaplermin promotes tissue growth, which is different from enzymatic debridement agents. Becaplermin should be reserved for the treatment of diabetic ulcer of lower extremities and with adequate blood supply.