Therapeutic Class Overview

Enzyme preparations and wound healing products

INTRODUCTION

- The appropriate treatment of wounds usually includes redistribution of pressure off the wound, the selection of appropriate dressings, and debridement (the removal of devitalized tissue). In addition to enzymatic debridement, other debridement options include mechanical debridement with gauze dressings, sharp surgical debridement, autolytic debridement with occlusive dressings, or application of exogenous enzymes. Treatment guidelines recommend surgical (sharp) debridement over enzymatic debridement according to the literature available (*Lipsky et al 2012, Association for the Advancement of Wound Care 2010, Stevens et al 2014*).
- Prior to a Food and Drug Administration (FDA) mandate in 2008, papain-containing products were available for the treatment of wounds. These products were withdrawn from the market due to serious safety concerns, including hypersensitivity reactions resulting in anaphylactic reactions and cardiovascular issues. After 2009, all topical papain-containing products must have FDA-approval to be manufactured or shipped (*FDA 2015*).
- This review focuses on the products that are FDA-approved for the debridement of necrotic tissue (Santyl [collagenase]) and the treatment of lower extremity diabetic ulcers (Regranex [becaplermin]). Becaplermin is a recombinant formulation of human platelet-derived growth factor.
- Medispan Therapeutic Classes: Enzymes – topical (Santyl); Wound care products (Regranex)

Table 1. Medications Included Within Class Review

Drug	Generic Availability
Regranex (becaplermin)	-
Santyl (collagenase)	-

(*Drugs@FDA 2019, Orange Book: Approved Drug Products with Therapeutic Equivalence Evaluations 2019*)

INDICATIONS

Table 2. Food and Drug Administration Approved Indications

Indication	Regranex (becaplermin)	Santyl (collagenase)
Treatment of lower extremity diabetic neuropathic ulcers that extend into the subcutaneous tissue or beyond and have an adequate blood supply. Regranex is indicated as an adjunct to, and not a substitute for, good ulcer care practices.	✔ *	
Debridement of chronic dermal ulcers and severely burned areas		✔

*Limitations of use: The efficacy of Regranex has not been established for the treatment of pressure ulcers and venous stasis ulcers. The effects of Regranex on exposed joints, tendons, ligaments, and bone have not been established in humans. Regranex is a non-sterile, low bioburden preserved product. Therefore, it should not be used in wounds that close by primary intention.

(*Prescribing information: Regranex 2018, Santyl 2016*)

- Information on indications, mechanism of action, pharmacokinetics, dosing, and safety has been obtained from the prescribing information for the individual products, except where noted otherwise.

CLINICAL EFFICACY SUMMARY

- A literature search produced limited data evaluating the efficacy of the enzyme prep and wound healing products included in this review. Head-to-head trials with becaplermin and other pharmacologic agents are not available.

- For collagenase, 2 small head-to-head trials are available: one comparing collagenase to papain/urea ointment (which is no longer commercially available), and 1 comparing collagenase to silver sulfadiazine (SSD) ointment (*Alvarez et al 2002, Ostlie et al 2012*).
  - An open-label, multicenter, randomized clinical trial (RCT) with 28 patients evaluated collagenase ointment once daily compared to papain/urea ointment once daily (no longer commercially available) until complete debridement or 4 weeks (*Alvarez et al 2002*). The papain/urea ointment was significantly more effective in reducing the amount of non-viable, necrotic tissue at each evaluation compared to the collagenase ointment ($p < 0.0167$). Development of granulation was significantly enhanced in the papain/urea group compared to the collagenase group (P value not reported). Epithelialization generally correlated with the development of a granulating wound bed, but the increase in the amount of epithelial tissue did not predict a significantly different rate of reduction in the wound area.
  - In an open-label, single-center, RCT, 100 children with partial thickness burns were treated with initial debridement followed by SSD for 2 days (*Ostlie et al 2012*). Patients continued to receive daily debridement with either collagenase ointment plus polymyxin (n = 50) or SSD daily (n = 50). Debridement continued for 10 days or until wound healing. Grafting occurred after 10 days if the wound did not heal. The need for skin grafting did not differ between the collagenase group (32%) and the SSD group (36%) ($p = 0.68$). There were no significant differences between the collagenase and SSD groups for time to skin grafting (12.9 ± 2 vs 13.5 ± 4.6 days) or length of hospitalization (11.3 ± 5.8 vs 11.2 ± 5.2 days). Seven of 50 patients in the collagenase group and 1 of 50 patients in the SSD group experienced a burn wound infection, but this difference did not reach statistical significance ($p = 0.06$).
- There are conflicting clinical data for becaplermin regarding efficacy. Several meta-analyses have been completed with each noting the difficulty in comparing the available data due to heterogeneity and clinical trial methodological issues (*Wieman 1998, Smiell et al 1999, Perry et al 2002*).
  - A meta-analysis by Wieman described the results of 4 clinical trials (n = 922) of becaplermin and demonstrated a significantly higher incidence of complete healing in the patients receiving becaplermin 30 µg and/or 100 µg gel in 2 studies (only the 100 µg gel is commercially available) (*Wieman 1998*). The other 2 studies either showed no significant difference between active treatment group and placebo or good ulcer care, or were not powered to detect a difference between becaplermin and standard care. Pooled safety data for becaplermin showed that erythematous rash was more common than placebo (2 vs 1%) (*Smiell 1998*). Mortality rates did not differ between becaplermin treatment and other therapy groups.
  - In a similar analysis, the efficacy and safety of becaplermin were evaluated in the same 4 RCTs enrolling 922 patients with nonhealing, lower extremity diabetic ulcers (*Smiell et al 1999, Steed et al 1995, Wieman 1998, Wieman et al 1998, d'Hemecourt et al 1998*). Studies 1 through 3 were double-blind; however, study 4 was evaluator-blinded and compared becaplermin to good ulcer care alone. In all studies, becaplermin or placebo gel were applied once daily and kept in place for 12 hours with saline moistened gauze and then rinsed away before the second dressing change with saline moistened gauze. Becaplermin gel was administered at 30 mcg/g in studies 1 and 2 and 100 mcg/g (FDA-approved strength) for studies 3 and 4. The primary endpoint was complete healing within 20 weeks. The meta-analysis determined that patients with baseline ulcer area of ≤ 10 cm^2 (95% of the population) were the focus of the analysis due to homogeneity of treatment responses (*Smiell et al 1999*). The estimated probability of complete healing was significantly higher ($p = 0.007$; logistic regression model) with becaplermin 100 mcg/g gel vs placebo gel.
  - A post hoc analysis evaluated the same 4 clinical trials for efficacy rates of becaplermin on ulcer healing rates (*Perry et al 2002*). Authors suggested that the size (area) of the baseline ulcer should be taken into account when comparing the overall efficacy of becaplermin to placebo.
  - An open-label, multicenter study by Embil et al showed that complete healing of ulcers of chronic, neuropathic, lower extremity diabetic ulcers was achieved in 57.5% of patients receiving becaplermin 100 µg gel with once daily dressing changes; all patients (n = 134) in this study received active treatment for 20 weeks or until complete wound healing (*Embil et al 2000*).

CLINICAL GUIDELINES

- The American Diabetes Association (ADA) 2018 Diabetes standards of care recommend a foot evaluation at least annually for patients with diabetes to identify risk factors for ulcers and amputations (*ADA 2018*).
- For diabetic wound infections, the Infectious Diseases Society of America notes that sharp or surgical methods of debridement are best, and clinicians may consider growth factors as 1 of several adjunctive therapies for selected diabetic foot wounds that are slow to heal (*Lipsky et al 2012*).
- The International Diabetes Federation (IDF) recommends offloading of pressure, using various modalities such as debridement, surgery, or negative pressure wound therapy. Adjunctive therapies such as topical antimicrobials or wound dressings may also be used. For diabetic foot ulcers that fail to demonstrate improvement (> 50% wound area reduction) after ≥ 4 weeks of standard wound therapy, adjunctive therapies such as platelet-derived growth factor, living cellular therapy, extracellular matrix products, negative pressure therapy, or amnionic membrane products may be used. There are no recommendations with regard to the efficacy or effectiveness of these therapeutic options (*IDF 2017*).
- The International Working Group on the Diabetic Foot (IWGDF) guidance recommends that local wound care include debridement of the ulcer (with a scalpel), dressings to control excess exudation and maintaining a moist environment, and to consider negative pressure therapy to heal post-surgical wounds and systemic hyperbaric oxygen in poor healing wounds to hasten wound healing (*Schaper et al 2017*). Routine wound management using biologically active products such as collagen, growth factors, and bio-engineered tissue in neuropathic ulcers and the use of silver or other antimicrobial dressings are not well supported by available evidence. More specifically, the IWGDF do not recommend agents to improve wound healing by altering the biology of the wound, including growth factors, bioengineered skin products and gases, in preference to accepted standards of good quality care (strength of recommendation: strong; level of evidence: low) (*Game et al 2016*). This includes the use of recombinant platelet-derived growth factor. Six trials have shown either no improvement in healing between the intervention and control group or there were significant methodological issues with the clinical trials.
- The Wound Healing Society updated guidelines for the management of diabetic foot ulcers in 2016. In addition to increasing oxygenation, nutrition and promotion of wound healing, several adjuvant agents are recommended for the promotion of wound healing. Topical platelet-derived growth factors reduce the time to healing and increase the proportion of ulcers that heal (Level I: meta-analyses of multiple RCTs or at least 2 RCTs supporting the intervention). Wound debridement is necessary to remove devitalized tissues, reduce bacterial burden and remove dead cells. Maintenance debridement is required to maintain the appearance and readiness of the wound. Methods of debridement include surgical, enzymatic, mechanical, biological, or autolytic; there is little evidence to support that one method is superior to another (*Lavery et al 2016*).
- The Agency for Healthcare Research and Quality (AHRQ) completed a comparative effectiveness review on pressure ulcer treatment strategies (*Saha et al 2013*). Debriding enzymes, including collagenase, had insufficient evidence about their effectiveness due to the differences in the enzymes studied and the outcomes measured. No recommendation regarding collagenase was included.
- The American College of Physicians released guidelines in 2015 for the treatment of pressure ulcers. Clinicians should use protein or amino acid supplementation in patients with pressure ulcers to reduce wound size (Grade: weak recommendation, low-quality evidence). Hydrocolloid or foam dressings are useful in patients with pressure ulcers (Grade: weak recommendation, low-quality evidence). Use of electrical stimulation in addition to standard treatment has been shown to accelerate the healing rate of stage 2 to 4 ulcers (Grade: weak recommendation, moderate-quality evidence) (*Qaseem et al 2015*).
- The Association for the Advancement of Wound Care (AAWC) 2010 guidelines recommend debridement of pressure ulcer areas with eschar and/or devitalized tissue to manage bacterial load (*AAWC 2010*). Selection of autolytic, enzymatic, mechanical, surgical, larval, or other debridement depends on the pressure ulcer status, patient's condition, and goals of care. These guidelines note that autolytic debridement is effective and possibly more effective than enzymatic debridement with collagenase. Efficacy of enzymatic debridement varies with different enzymes. Collagenase has been shown to be more effective than placebo. Growth factors are not indicated in pressure ulcers.
- Guidelines from the Infectious Diseases Society of America for the management of skin and soft tissue infections recommend surgical debridement but do not mention enzymatic debridement (*Stevens et al 2014*).

SAFETY SUMMARY

- In November 2018, the Regranex label had the boxed warning and a warning from the Warning and Precautions section for increased rate of mortality secondary to malignancy removed.
- Contraindications
  - Regranex is contraindicated in patients with known neoplasm(s) at the site(s) of application.
  - Santyl is contraindicated in patients who have shown local or systemic hypersensitivity to collagenase.
- Warnings and precautions
  - Regranex
    - If application site reactions occur, the possibility of sensitization or irritation caused by parabens or m-cresol should be considered. Consider interruption or discontinuation and further evaluation (e.g., patch testing) as dictated by clinical circumstances.
  - Santyl
    - The optimal pH range of collagenase is 6 to 8. Higher or lower pH conditions will decrease the enzyme's activity, and appropriate precautions should be taken.
    - The enzymatic activity is also adversely affected by certain detergents, and heavy metal ions such as mercury and silver, which are used in some antiseptics.
    - Debilitated patients should be closely monitored for systemic bacterial infections because of the theoretical possibility that debriding enzymes may increase the risk of bacteremia.
    - A slight transient erythema has been noted in the surrounding tissue, particularly when Santyl Ointment was not confined to the wound.
- Adverse effects
  - Regranex
    - Erythematous rashes and burning sensations have been reported post-marketing. In trials, erythematous rashes occurred equally between patients treated with Regranex Gel and placebo (2% in each group).
  - Santyl
    - No allergic sensitivity or toxic reactions noted when used as directed. One case of systemic manifestations of hypersensitivity to collagenase was reported in a patient treated for more than 1 year with a combination of collagenase and cortisone.

DOSING AND ADMINISTRATION

Table 3. Dosing and Administration

Drug	Available Formulations	Route	Usual Recommended Frequency	Comments
Regranex (becaplermin)	Gel, 0.01%	Topical	Once daily	The amount of Regranex gel to be applied will vary depending upon the size of the ulcer area. The greatest length and width of the ulcer should be measured and a formula should be used to calculate the length of gel to apply. Spread over the entire ulcer area to yield a thin continuous layer of approximately 1/16 of an inch thickness.
Santyl (collagenase)	Ointment 250 units/gram	Topical	Once daily	Santyl may be applied directly to the wound or to a sterile gauze pad which is then applied to the wound. Use should be terminated when debridement of

Drug	Available Formulations	Route	Usual Recommended Frequency	Comments
				necrotic tissue is complete and granulation tissue is well established.

See the current prescribing information for full details

CONCLUSION

- One enzyme preparation agent (Santyl) and 1 wound healing product (Regranex) are FDA-approved for the debridement of necrotic tissue and treatment of diabetic neuropathic ulcers, respectively.
- The 2016 Wound Healing Society guidelines for the management of diabetic foot ulcers recommend increasing oxygenation, nutrition and promotion of wound healing (*Lavery et al 2016*). The guidelines also suggesttopical platelet-derived growth factors to reduce the time to heal and increase the proportion of ulcers that heal. Wound debridement is also suggested to remove devitalized tissues, reduce bacterial burden, and remove dead cells. Methods of debridement include surgical, enzymatic, mechanical, biological, or autolytic; however, there is little evidence to support that 1 method is superior to another.
- The IWGDF guidance recommends debridement of the ulcer, wound dressings to control excess exudation, and maintaining a moist environment (*Schaper et al 2017*). Routine wound management using biologically active products such as collagen, growth factors, and bio-engineered tissue in neuropathic ulcers and the use of silver or other antimicrobial dressings are not well supported by available evidence. More specifically, the IWGDF does not recommend agents to improve wound healing by altering the biology of the wound, including growth factors including the use of recombinant platelet-derived growth factor, bioengineered skin products and gases, in preference to accepted standards of good quality care (strength of recommendation: strong; level of evidence: low) (*Game et al 2016*). Six trials have shown either no improvement in healing between the intervention and control group or there were significant methodological issues with the clinical trials.
- Regranex should be reserved for use in treating diabetic neuropathic ulcers.

REFERENCES

- Alvarez O, Fernandez-Obregon A, Rogers R, et al. A prospective, randomized, comparative study of collagenase and papain-urea for pressure ulcer debridement. Wounds. 2002;14(8):293-301.
- American Diabetes Association. Microvascular Complications and Foot Care: Standards of Medical Care in Diabetes – 2018. *Diabetes Care* 2018;41(1):S105-S118. Available at: http://diabetesed.net/wp-content/uploads/2017/12/2018-ADA-Standards-of-Care.pdf. Accessed March 22, 2019.
- Association for the Advancement of Wound Care. AAWC Guideline of Pressure Ulcer Guidelines (2010). Available: https://s3.amazonaws.com/aawc-new/memberclicks/AAWCPressureUlcerGuidelineofGuidelinesAug11.pdf. Accessed March 22, 2019.
- d'Hemecourt PA, Smiell JM, Karim MR. Sodium carboxymethylcellulose aqueous-based gel vs. becaplermin gel in patients with nonhealing lower extremity diabetic ulcers. Wounds 1998;10:69–75.
- Drugs@FDA: FDA approved drug products. Food and Drug Administration Web site. https://www.accessdata.fda.gov/scripts/cder/daf/. Accessed March 22, 2019.
- Embil J, Papp K, Sibbald G, et al. Recombinant human platelet-derived growth factor-BB (becaplermin) for healing chronic lower extremity diabetic ulcers: an open-label clinical evaluation of efficacy. Wound Repair Regen. 2000;8(3):162-8.
- Game FL, Apelqvist J, Attinger C, et al for he International Working Group on the Diabetic Foot. IWGDF guidance on the use of interventions to enhance the healing of chronic ulcers of the foot in diabetes. Diabetes/Metabolism Research and Reviews. 2016;32(Suppl 1):75-83.
- International Diabetes Federation. IDF Clinical practice recommendations on the diabetic foot – 2017. https://www.idf.org/e-library/guidelines/119-idf-clinical-practice-recommendations-on-diabetic-foot-2017.html. Accessed March 22, 2019.
- Lavery LA, Davis KE, Berriman SJ, et al. Wound Healing Society (WHS) guidelines update: Diabetic foot ulcer treatment guidelines. Wound Repair Regen. 2016;24(1):112-126.
- Lipsky B, Berendt A, Cornia P, et al. 2012 Infectious Diseases Society of America clinical practice guideline for the diagnosis and treatment of diabetic foot infections. Clin Infect Dis. 2012;54(12):132-173. Available at: http://cid.oxfordjournals.org/content/54/12/e132.full.pdf+html. Accessed March 22, 2019.
- Orange Book: Approved drug products with therapeutic equivalence evaluations. Food and Drug Administration Web site. https://www.accessdata.fda.gov/scripts/cder/ob/default.cfm. Accessed March 22, 2019.
- Ostlie DJ, Juang D, Aguayo P, et al. Topical silver sulfadiazine vs collagenase ointment for the treatment of partial thickness burns in children: a prospective randomized trial. J Pediatr Surg. 2012;47(6):1204-7.
- Perry BH, Sampson AR, Schwab BH, et al. A meta-analytic approach to an integrated summary of efficacy: a case study of becaplermin gel. Controlled Clinical Trials. 2002;23:389-408.

- Qaseem A, Humphrey LL, Forciea MA, et al, Clinical Guidelines Committee of the American College of Physicians. Treatment of pressure ulcers: a clinical practice guideline from the American College of Physicians. Ann Intern Med. 2015 Mar 3;162(5):370-9.
- Regranex prescribing information. Smith & Nephew, Inc. Fort Worth, TX. December 2018.
- Saha S, Smith MEB, Totten A, et al. Pressure Ulcer Treatment Strategies: Comparative Effectiveness. Comparative Effectiveness Review No. 90. (Prepared by the Oregon Evidence-based Practice Center under Contract No. 290-2007-10057-I.) AHRQ Publication No. 13-EHC003-EF. Rockville, MD: Agency for Healthcare Research and Quality; May 2013. Available at: https://effectivehealthcare.ahrq.gov/sites/default/files/related_files/pressure-ulcer-treatment_executive.pdf. Accessed March 22, 2019.
- Santyl prescribing information. Healthpoint. Fort Worth, TX. December 2015.
- Schaper NC, Van Netten JJ, Apelqvist J, et al for the International Working Group on the Diabetic Foot (IWGDF). Prevention and management of foot problems in diabetes: A Summary Guidance for daily practice 2015, based on the IWGDF guidance documents. Diab Res Clin Pract. 2017;124:84-92.
- Smiell JM, Wieman J, Steed DL, et al. Efficacy and safety of becaplermin (recombinant human platelet-derived growth factor-BB) in patients with nonhealing, lower extremity diabetic ulcers: a combined analysis of four randomized studies. Wound Repair Regeneration. 1999;7:335-346.
- Smiell JM. Clinical safety of becaplermin (rhPDGF-BB) gel. Am J Surg. 1998;176(2 Suppl 1):68S-73S.
- Steed DL, the Diabetic Ulcer Study Group. Clinical evaluation of recombinant human platelet-derived growth factor for the treatment of lower extremity diabetic ulcers. J Vasc Surg 1995;21:71–81.
- Stevens DL, Bisno AL, Chambers HF, et al. Practice guidelines for the diagnosis and management of skin and soft-tissue infections: 2014 update by the Infectious Diseases Society of America. Clin Infect Dis. 2014. 59(2):e10-e52. Available at: http://cid.oxfordjournals.org/content/59/2/e10. Accessed March 22, 2019.
- U.S. Food and Drug Administration. Questions and answers about FDA's enforcement action regarding unapproved topical drug products containing papain. Maryland: U.S. Food and Drug Administration: December 2015. Available at: https://www.fda.gov/drugs/guidancecomplianceregulatoryinformation/enforcementactivitiesbyfda/selectedenforcementactionsonunapproveddrugs/ucm119646.htm. Accessed March 22, 2019.
- Wieman T, et al. Clinical efficacy of becaplermin (rhPDGF-BB) gel. Am J Surg. 1998;176(2A):74S-79S.
- Wieman T, Smiell JM, Su Y. Efficacy and safety of a topical gel formulation of recombinant human platelet-derived growth factor-BB (becaplermin) in patients with chronic neuropathic diabetic ulcers: a phase III, randomized, placebo-controlled, double-blind study. Diabetes Care 1998;21:822–7.
- Drugs@FDA: FDA approved drug products. Food and Drug Administration Web site. https://www.accessdata.fda.gov/scripts/cder/daf/. Accessed March 22, 2019.

Publication Date: April 2, 2019