PRODUCT MONOGRAPH

SANTYL OINTMENT

(Collagenase)

Topical Enzymatic Debriding Agent

Smith & Nephew Inc.
Mississauga, Ontario
L5N 6H8

Date of Authorization:
December 12, 2014

Control number: 179002

NAME OF DRUG

SANTYL OINTMENT
(Collagenase)

THERAPEUTIC CLASSIFICATION

Topical enzymatic debriding agent

STRUCTURAL FORMULA AND CHEMISTRY

Collagenase is a large protein molecule of biologic origin, being derived from the fermentation of Clostridium histolyticum. The enzyme may be obtained in two forms, one a protein of 105,000 molecular weight, collagenase A and a molecule of 57,000 molecular weight, collagenase B. SANTYL contains a mixture of these two forms in an indeterminable ratio. Both collagenase A and collagenase B require free sulfhydryl groups for formation of enzyme substrate complex. Collagenase also requires enzyme bound zinc for activity. The optimal pH range for enzymatic activity is 7 to 8. Like all enzymes having sulfhydryl groups at the active site, inactivation with heavy metals, such as mercury, silver, cobalt, magnesium, and manganese can occur. The specific substrate for collagenase is collagen. However, minimal amounts of other amidase and esterase activity may be found in the collagenase enzyme preparation.

DESCRIPTION

Each gram of SANTYL Ointment contains 250 units of collagenase enzyme per gram of white petrolatum U.S.P. The potency assay of collagenase is based on the digestion of undenatured collagen (from bovine Achilles tendon) at pH 7.2 and 37°C for 24 hours. The number of peptides cleaved are measured by reaction with ninhydrin. Peptides released by a trypsin digestion control are subtracted. One net collagenase unit will solubilize ninhydrin reactive material equivalent to 4 micromoles of leucine.

ACTION

Collagenase digests collagen in the physiologic pH and temperature range. Since collagen accounts for 75% of the dry weight of skin tissue, collagenase is useful in the removal of detritus from the craters of dermal ulcers or skin burns. Rapid debridement contributes toward the formation of granulation tissue and subsequent epithelization of these lesions.

INDICATIONS AND CLINICAL USES

SANTYL Ointment is a sterile ointment indicated for the debridement of dermal ulcers [3,4,5,6,7,25,26,27,28,30,31,32] or severely burned areas.[8,9,0,12,13,29]

CONTRAINDICATIONS

Application is contraindicated in patients who have shown local or systemic hypersensitivity to collagenase.

WARNINGS

Debilitated patients should be closely monitored for systemic bacterial infections because of the theoretical possibility that debriding enzymes may increase the risk of bacteremia.

PRECAUTIONS

The enzyme's optimal pH range is 7 to 8.[14,15] Significantly lower pH conditions have a definite adverse effect on the enzyme's activity and appropriate precautions should be taken.

The enzymatic activity is also adversely affected by detergents and hexachlorophene[11,17] and heavy metal ions[14,16] such as mercury and silver which are used in some antiseptics and by cobalt, magnesium and manganese. When it is suspected such materials have been used, the site should be carefully cleansed by repeated washings with normal saline before SANTYL Ointment is applied. Soaks containing metal ions or acidic solutions such as Burow's (aluminium acetate) solution should be avoided because of the metal ion and low pH. Cleansing materials such as hydrogen peroxide or Dakin's (dilute sodium hypochlorite) solution do not interfere with the activity of the enzyme.

The ointment should be confined to the area of the lesion in order to avoid the risk of irritation or maceration of normal skin; however, the enzyme does not damage newly forming granulation tissue.[30,31] A slight erythema has been noted occasionally in the surrounding tissue particularly when the enzyme ointment was not confined to the lesion. This can be readily controlled by more careful application or by protecting the healthy skin with a material such as Lassar's (zinc oxide - 25%) paste.

Since the enzyme is a protein, sensitization may develop with prolonged use although this has not been observed to date.

ADVERSE REACTIONS

Irritation, maceration or erythema have been noted where prolonged contact of normal skin with SANTYL has been allowed, either by application of the ointment to areas of normal skin or by excessive application of ointment to the wound crater with subsequent spread to normal skin when bandages are applied. The reported incidence for this type of reaction was 1.8%. No systemic adverse effects have been reported due to SANTYL.

TREATMENT OF OVERDOSAGE

SANTYL Ointment can be rendered inert by the application of Burow's Solution U.S.P. (pH 3.6-4.4) to the treatment site. If this should be necessary, reapplication should be made only with caution.

PHARMACOLOGY

Since collagen accounts for 75% of the dry weight of skin tissue, the ability of collagenase to digest insoluble fibrous collagen by peptide bond cleavage under physiological conditions of pH and temperature, makes it particularly effective in the removal of detritus. Collagenase thus contributes towards the formation of granulation tissue and subsequent epithelization[3,4] of dermal ulcers and severely burned areas.

Hot water burns, being resistant to enzymatic debridement and approximating the conditions at the periphery of contact burns and other lesions, present a suitable basis for testing the efficacy of the debriding action of collagenase. In a study of these burns on guinea pigs, the average debridement of the collagenase treated animals was 83%, while that of the placebo was 8%. This demonstrates the ability of collagenase to debride a refractory type of burn and to provide a healthy base for the healing process.[18]

TOXICOLOGY

1. Investigation of the enzyme collagenase, derived from Clostridium histolyticum, began in 1949 with the work of MacLennan, Mandl and Howes.1 They had selected the strains H4 and 230-2 from 80 strains of *C. histolyticum* because of their high enzyme yields and low toxicity. MacLennan et al. established that H4 and 230-2 strains of C. histolyticum elaborated no or relatively minute amounts of the lethal neurotoxin (toxin). The complete or almost complete absence of toxin was later confirmed by Howes, Mandl and Zaffuto[33]. In the same publication, the pharmacological effects of collagenase were also described.

It is important to note that the enzyme incorporated into SANTYL (collagenase) Ointment, is derived from a subculture of the H4 strain described in the paper by Howes, Mandl and Zaffuto. As described in the paper, the enzyme displays a low order of toxicity.

2. Acute Systemic Toxicity of Collagenase Powder[19]

The acute toxicity of four lots of collagenase powder, administered intravenously to male mice, was determined. The results of these studies are presented below:

Collagenase Lot	LD_{50} (mg/kg)	Confidence Limits (mg/kg)	LD_1 (mg/kg)	Slope Function of Curve
551	320	308 - 333	283	1.07
552	290	266 - 316	239	1.23
553	306	231 - 333	251	1.21
550	532	488 - 539	412	1.21

3. Toxicity Study of Collagenase Powder Administered Intravenously to Rabbits

As a result of reports that high daily intravenous doses of collagenase produced a drop in platelet counts, three intravenous toxicity studies in rabbits were carried out. The results of these studies are described below:

a) Collagenase powder in dosages of 0.25 mg/kg/day and 2.5 mg/kg/day was administered five times a week for three weeks to rabbits. The powder in a dosage of 7.5 mg/kg/day was administered five times a week to rabbits for a total of seven days.

Rectal temperatures taken before and one hour after collagenase administration indicated the collagenase solutions, as used, were pyrogenic.

The data collected indicated that collagenase powder, when administered daily, 5 days a week intravenously, in doses of 0.25 mg/kg/day for 3 weeks, 2.5 mg/kg/day for 3 weeks and 7.5 mg/kg/day was non-toxic to rabbits. No toxic symptoms were noted in any of the treated animals and all remained in good condition during the course of the study. None showed any evidence of bleeding from body orifices, hyperemia of the eye or hemorrhage in the tissues and viscera examined on the post mortem examination. No gross or histopathology was noted in any of the animals. The dose regimens of 2.5 and 7.5 mg/kg/day produced a decrease in blood platelets. This

effect, however, was reversible at the 2.5 mg/kg/day dose level but was not followed in the animals treated with the 7.5 mg/kg/day for reversibility. Alterations in the platelet count were not associated with any toxic manifestations in the animals.[22]

b) In a second study, the effect of intravenous administration of collagenase powder at a dose of 0.25 mg/kg/day, 5 times a week for 3 weeks was studied in rabbits. It was concluded from the experimental data, that collagenase powder was non-toxic to rabbits when administered in this manner. No toxic symptoms were noted in any of the treated animals. All remained in good condition during the course of the study. None showed any evidence of bleeding from the body orifices, hyperemia of the eye or hemorrhage in any tissues and viscera examined on post mortem examination. Further, no gross pathology or histopathology was noted in the animals.

c) In a third study rabbits were injected with collagenase powder at a concentration of 0.25 mg/kg/body weight, 2.5 mg/kg/body weight and 7.5 mg/kg/body weight. The rabbits were on the intravenous injection schedule for a total of three weeks. All three dose levels caused a pyrogenic reaction to occur in some of the test animals. After the first and second days of injections, increased vascularization was noted until at the twelfth day after the onset, when the condition almost disappeared. No gross pathological conditions were noted throughout the experiment except for the unexplained death of one rabbit eight days after the start of the experiment.

It was concluded that in the dosages used, the enzyme was pyrogenic in some instances. The high dose level seemed to cause a temporary loss of weight or a very slow increase in weight during the experiment. It would seem that the consistent I.V. injection of the higher dosage levels resulted in a relative decrease in platelet counts and hematocrit values but that this alteration has a tendency towards self correction after a short rest period of two to five days.

Toxicity Studies of the Final Product

1. Subacute Dermal Toxicity

The backs of twenty rabbits were closely clipped to compare areas of skin measuring about 7x7 inches. The denuded areas of half of the animals in both groups were scarified.

For 15 consecutive working days, the test (250 units collagenase per gram of petrolatum) or control (petrolatum) material was gently inuncted into the backs of the animals at a daily dosage level of 3.5 grams per kilogram of body weight.

A usually mild and transient erythema that subsided even before the end of the study was the only sign of local toxicity.

There were no remarkable findings with respect to possible toxic effects exerted by the formulation under study based on clinical laboratory findings.

No evidence of systemic toxicity was noted based on histopathologic criteria.[19]

2. Draize Eye Test (Primary Irritation to Eye Mucosa)

It was established that SANTYL Ointment is not irritating when 100 mg is instilled into the eyes of rabbits.[21]

3. Treatment of Infected Scalds in Rabbits

The influence of collagenase on the incidence of bacteremia associated with infected lesions of the skin was studied.

The results obtained support the conclusion that collagenase does not affect the likelihood of infection or predispose the animal to bacteremia.[23]

4. Debridement with SANTYL (collagenase)

Hot water burns were artificially produced on six guinea pigs. Three animals were treated with SANTYL Ointment 0.3% and three with white petrolatum for three days. There was significant debridement in each group (80% collagenase, 68% white petrolatum).[24]

DOSAGE AND ADMINISTRATION

SANTYL Ointment should be applied once daily in the following manner:

1. Prior to application, the lesions should be gently cleansed with a gauze pad saturated in normal saline, (buffered to pH 7.0-7.5) or hydrogen peroxide to remove any film and digested material.
2. Whenever infection is present, as evidenced by positive cultures, pus, inflammation or odour, it is desirable to use an appropriate topical antibacterial

agent. Neomycin-Bacitracin-Polymyxin B (Neosporin) has been found compatible with SANTYL Ointment. This antibiotic should be applied to the lesion in powder form or solution prior to the application of SANTYL Ointment. Should the infection not respond, therapy with SANTYL Ointment should be discontinued until remission of the infection.

3. SANTYL Ointment should be applied (using a wooden tongue depressor or spatula) directly to deep wounds. When dealing with shallow wounds, SANTYL Ointment should be applied to a sterile gauze pad which is then applied to the wound. The wound is covered with sterile gauze pad and secured with clear tape or Kling bandage.

4. Crosshatching thick eschar with a #11 blade is helpful in speeding up debridements. It is also desirable to remove as much loosened detritus as can be done readily with forceps and scissors.

5. All excess ointment should be removed each time dressing is changed.

6. Use of the ointment should be terminated when sufficient debridement of necrotic tissue has occurred and granulation is well underway.

DOSAGE FORMS

SANTYL Ointment is available as a sterile ointment in a white petrolatum base packaged in 15, and 30 gram tubes.

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