

## Literature Review: Clinical Information Relating to the Development of SureSkin® Silver Hydrocolloid Dressing and SureSkin® Silver (OTC) Bandage

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### ABSTRACT

A review of the available literature identified clinical evidence supporting efficacy and safety of silver-containing dressings on clinical wounds. Eight prospective randomized controlled trials (RCTs) support a conclusion of improved chronic wound outcomes when dressed with silver dressings. These studies reported significant ( $p < 0.05$ ) improvements in the following outcomes for chronic and acute wounds dressed for 2 to 12 weeks with silver dressings compared to non-silver gauze, foam, alginate or other best non-silver practice:

- percent of wounds healed (1 study on venous ulcers),
- reduction in wound area (3 studies on pressure, venous or mixed etiology ulcers)
- ulcer depth reduction (2 studies on diabetic foot ulcers),
- reduced slough or maceration (1 study on diabetic foot ulcers)
- reduced wound severity (1 study on mixed chronic wounds) or
- reduced bacterial burden (1 study on chronic wounds of unspecified etiology)
- less wound-related pain, trauma and time to change dressings (2 studies on acute wounds)

In addition to the above RCTs, 17 uncontrolled studies using silver-containing dressings on more than 462 chronic or acute wounds support silver wound dressing safety, but not efficacy.

Two RCTs on a total of 26 pressure ulcers, 215 venous ulcers and 26 diabetic ulcers studied Contreet® Foam\*\* dressings containing silver zeolite the active entity of which is silver ion. This silver zeolite material is the same entity used in SureSkin® Silver Hydrocolloid Dressing. Although Contreet® Foam and SureSkin® Silver Hydrocolloid Dressing differ in “base” formula, the former being a foam dressing and the latter a hydrocolloid, effects of the silver component are expected to be similar in both formulations. The relative merits of foam versus hydrocolloid would be related to the amount of wound exudate one dressing could handle versus the other. Generally foams are able to absorb more fluid than hydrocolloid adhesives over a short period while hydrocolloids generally form a more intimate adherent skin-adhesive seal, maintaining a moist wound environment more consistently than foam dressings (Bolton, Monte & Pirone, 2000). Based on the information provided here, the microbiological effectiveness reported elsewhere in the dossier for SureSkin® Silver Hydrocolloid Dressing, and the microbiological effectiveness, biocompatibility, and absence of adverse effects reported in the literature for similar wound dressings releasing bactericidal levels of silver ion, it is concluded that SureSkin® Silver Hydrocolloid Dressing is safe and effective for its intended use.

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## BACKGROUND

With the growing presence of antibiotic-resistant strains of bacteria, typical antimicrobial agents such as silver are regaining clinical favor (Jones *et al.*, 2004). Hydrocolloid dressings maintain a moist wound environment in intimate contact with the wound surface and are a two-way barrier to contaminants and bacteria (Mertz *et al.*, 1985). Adding a source of ionic silver to the hydrocolloid dressing adhesive further augments its antibacterial barrier function, conferring, substantive, broad spectrum bactericidal activity to the adhesive as it absorbs wound fluid. Clinically silver hydrocolloid dressings can confer 7-day antibacterial barrier function without the cost of frequent, traumatic dressing changes required for silver solutions or creams (Jones *et al.*, 2004).

Steenfos *et al.* (1997) reported that SureSkin® formulations are at least as effective in healing acute skin graft donor sites as classic DuoDERM® or Granuflex®. Both hydrocolloid formulations permitted faster healing than the gauze “control” dressings did. Armed with this evidence, EuroMed proposed the goal of developing a silver hydrocolloid dressing is to provide the benefits of moist wound management with sustained antimicrobial protection from the silver ion within the adhesive.

## OBJECTIVE

The objective of this clinical literature review is to relate *in-vitro* physical and antimicrobial testing for EuroMed SureSkin® Silver Hydrocolloid Dressings to published medical literature on silver-containing wound dressings currently or previously available in the worldwide market place. This study was conducted for the purpose of summarizing pre-clinical evidence on the safety and efficacy of SureSkin® Silver Hydrocolloid Dressing\* or SureSkin® Silver (OTC) Bandage in the perspective of evidence of safety, efficacy, claims and indications for typical silver-containing dressings previously approved for over-the-counter (OTC) and professional wound management.

## PROTOCOL

A systematic<sup>b</sup> literature search was conducted using the MEDLINE and Cochrane databases, internet based search engines including AltaVista.com, Google.com and Yahoo.com, NIH.gov, dynamicmedical.com, idfax.com, mednet.com medscape.com and freedmedjournals.com.

Levels of evidence were analyzed for silver dressing efficacy using evidence criteria adapted from AHRQ (Formerly AHCPR) Pressure Ulcer Treatment Guidelines for generality to all clinical wounds. Specific levels include the following evidence:

1. Level A evidence is supported by results of at least two or more randomized controlled trials (RCT) or one meta-analysis (MA) or systematic review (SR) in human wounds provide support for the claim.
2. Level B evidence is supported by results of two or more historically controlled trials (HCT) or convenience controlled trials (CCT) or a HCT or a CCT and a RCT in humans provide support for the claim.
3. Level C evidence is supported by one or more of the following types of studies:
  - (1) Results of one controlled trial, e.g. RCT or CCT or HCT
  - (2) Results of at least two case series over 20 subjects (CS) or a cohort study in humans
  - (3) Expert opinion (EO)

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<sup>b</sup> The search method followed guidelines from the University of Colorado, Health Sciences Center, Denver, CO, USA which can be seen at <http://denison.uchsc.edu/SG>. The search was limited only by financial resources.

The results of each of these searches were accomplished using the “key word” search terms including: chronic wounds, wound dressings, hydrocolloids, silver, silver ion, burns, antibacterial, hydrogels, impregnated gauze, foam dressings, infections in chronic wounds and burns, clinical study antimicrobial dressings.

A similar search was conducted of the leading medical manufacturers of chronic wound dressings, particularly hydrocolloids and dressings containing silver was also conducted with the purpose of obtaining comparative information assumed to be important and relevant on the basis that such labeling had been reviewed by regulatory agencies in Europe and the United States.

The first 200 of the relevant search “hits” not including any obvious exclusions, as for example, retail advertisements, were reviewed by abstract for suitability in this review and by availability of the citation. Those citations that were relevant to the objective were obtained in either hard copy or viewed online. Each of those citations was included in the narrative. Some citations which were indirectly relevant were included in the attached bibliography but were not cited in the body of the review. Those directly used in the narrative were cited as a footnote where the reference occurs.

Text and information was used on the basis of relevance to the subject and the objective and without regard to whether the published information could be interpreted as “positive” or “negative” with regard to EuroMed, Inc. or the commercial product viability of SureSkin® Silver Hydrocolloid Dressing or SureSkin® Silver (OTC) Bandage. Emphasis was placed on clinical information regarding chronic wound dressings containing an antibacterial agent, especially silver, and their mechanism of action and resultant safety and efficacy in clinical use. The validity of the information was further reviewed for the relevance of the author(s) and/or the institution’s experience and expertise.

**DESCRIPTION OF EuroMed SILVER-CONTAINING HYDROCOLLOID DRESSINGS AND MOST CLOSELY RELATED COMMERCIAL COUNTERPARTS**

*CONFIDENTIAL*

*SureSkin® Silver Hydrocolloid Dressing Formulation:*

**Table 1. Chemical composition of SureSkin® Silver Hydrocolloid Dressing and SureSkin® Silver (OTC) Bandage Adhesive**

Chemical Identity	Weight %
Styrene-Isoprene Linear Block Copolymer	12
Petroleum based hydrocarbon tackifier resin	17
Acrylic polymer (100% solids thermoplastic)	15.5
Mineral Oil USP	8
Sodium Salt of Carboxymethylcellulose (CMC)	46
Zeolite (ceramic) Silver Complex	1.50
TOTAL	100

There are four formulations of EuroMed SureSkin® Silver dressings, all with the same adhesive with similar capacity to absorb low to moderate amounts of wound fluid and bacteria and the same mechanism of ionic silver bactericidal action within the adhesive:

- a. SureSkin® Silver Hydrocolloid Dressing with a polyurethane film/foam laminate backing
- b. SureSkin® Silver Hydrocolloid Border Dressing with a polyurethane film backing.
- c. SureSkin® Silver Hydrocolloid Thin Dressing has a polyurethane film backing.
- d. SureSkin® Silver (OTC) Bandage. has a polyurethane film backing

All four constructions use the same silver-containing adhesive with 0.55 mg of silver content per gram of adhesive. Silver ions are delivered from the zeolite source when activated by wound fluid absorbed into the hydrocolloid adhesive. Therefore one would expect these four silver-containing hydrocolloid dressings to have similar mechanisms, spectra and duration of bactericidal activity in the adhesive, translating into similar capacity to protect the wound as an antibacterial barrier dressing.

Zeolite, a ceramic silver complex material is added to the adhesive to control the growth of bacteria in the adhesive and by extension the growth of bacteria in wound exudate that has been absorbed and trapped within the adhesive matrix of the dressing. In this sense, the dressing is similar to EuroMed's own SureSkin II dressings with changes in the formula (tackifying resin change and the addition of a medical grade acrylic) to accommodate the addition of the silver compound and still retain the tack, and fluid absorption characteristics of such hydrocolloid chronic wound dressings. The silver content of a 10cm x 10 cm SureSkin® Silver Hydrocolloid Dressing is 4.3 mg (43 micrograms per cm<sup>2</sup> of dressing; 0.55 mg/g of dressing). SureSkin® Silver (OTC) Bandage has a slightly thinner layer of adhesive, containing 34.58 micrograms of silver per cm<sup>2</sup> of dressing or 3.458 mg for a 10 cm x 10 cm dressing.

SureSkin® Silver Hydrocolloid Dressing and SureSkin® Silver (OTC) Bandage are closely related to many commercial dressings containing a silver antimicrobial. It is most closely related to two Coloplast dressings containing silver that are presently being marketed throughout Europe and the United States. Coloplast's Contreet Hydrocolloid Dressing containing silver is related because both Contreet Hydrocolloid Dressing and SureSkin® Silver Hydrocolloid Dressing are "classic" hydrocolloids. On contact with wound fluid, this complex releases bactericidal silver ion (Ag<sup>+</sup>) to kill bacteria in the dressing, enhancing its microbial barrier properties. While not a hydrocolloid Coloplast's Contreet® Foam Dressings<sup>c</sup> contain the same identical silver ceramic complex, zeolite silver sodium hydrogen zirconium phosphate and have similar mechanism of antibacterial action. In chemical terms, bactericidal silver ion, Ag<sup>+</sup> is released on contact of the zeolite with fluid. This provides the antimicrobial effects of both Contreet® Foam\*\* and SureSkin® Silver Hydrocolloid Dressing. Release of the bactericidal ion Ag<sup>+</sup> is the same mechanism of action as most other commercial silver-containing wound dressings, including, but not limited to AQUACEL® Ag, Arglaes® and ACTISORB®

#### **Antimicrobial efficacy *in vitro* of similar commercially available dressings**

EuroMed's SureSkin® Silver Hydrocolloid Dressing and SureSkin® Silver (OTC) Bandage are similar in hydrocolloid construction to Coloplast's Contreet® Hydrocolloid containing silver with similar instructions for use. Both dressings are changed when clinically indicated or after a maximum of seven days. The mechanism of action for Coloplast Contreet® Hydrocolloid or Contreet® Foam silver dressings as described in product literature is similar to that for SureSkin® Silver Hydrocolloid Dressing: Silver ions (Ag<sup>+</sup>). released from the silver compound in the dressing affect bacteria by:

- Inhibiting cell division
- Interfering with the bacterial function causing the cells to die
- Destroying bacteria cells walls

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<sup>c</sup> also trademarked Contreet

Coloplast reports that the silver ion (Ag+) is effective against the following organisms:

Surface Bacteria: Bacteria	Tissue Bacteria	Resistant
Acinetobacter	anaerobics	MRSA
S. epidermidis	Streptococci	VRE
E. cloacae	Yeast	
E. coli	C. albicans	
E. faceum		
S. Aureus		
P. aeruginosa		
P. vulgaris		

Based on laboratory testing similar to that conducted for EuroMed SureSkin® Silver Hydrocolloid Dressing and SureSkin® Silver (OTC) Bandage, Coloplast claims the following actions:

- The silver is released upon interaction with the wound exudate, which can be expected when using a hydrocolloid dressing on low to moderately exuding chronic or acute wounds
- Silver ions provide antibacterial action against bacteria *within* the exudate.
- Dead bacteria are absorbed along with the exudate into the dressing

EuroMed believes that SureSkin® Silver Hydrocolloid Dressing and SureSkin® Silver (OTC) Bandage functions in the same manner as Contreet® Hydrocolloid Dressing. As wound fluid is absorbed by the hydrocolloid adhesive, silver ions released from the adhesive kill local bacteria, enhancing the previously reported (Mertz et al., 1985) bacterial barrier properties of hydrocolloid dressings. It is this mechanism and result that EuroMed claims for SureSkin® Silver Hydrocolloid Dressing. The silver material has not been included in the formulation for the purpose of delivering silver ions to the wound; the silver has been added so that exudate naturally drawn into the dressing matrix can control microbial action and reduce proliferation, similar to the mechanism of action reported for AQUACEL® Ag or Actisorb® Silver by Lansdown & Williams. (2004).

It is expected that on changing the dressing this microbially controlled exudate is discarded with the used dressing. The primary intent for SureSkin® Silver Hydrocolloid Dressing and SureSkin® Silver (OTC) Bandage use is as a microbial barrier capable of maintaining a moist wound environment typical of a hydrocolloid dressing remaining in place for up to 7 days forming a protective seal over the wound bed and absorbing fluids.

Even dry wounds or those in the final stages of healing have a higher moisture vapor transmission rate than that of intact skin (Surinchak et al, 1985). Any moisture and organisms lost through damaged skin is absorbed by the hydrocolloid adhesive where the absorbed moisture releases silver ions that kill the microbes on contact. As an example of hydrocolloid adhesive interactions with moisture from "dry" wounds or skin, very low levels of "insensate" moisture loss through intact skin are absorbed by hydrocolloid dressing adhesives sufficiently to weaken the adhesive bond with underlying skin, facilitating removal after being left in place for 48 hours or more, as described on some package insert instructions. Such adhesive-moisture interactions may render silver hydrocolloid adhesives effective as an antimicrobial barrier on OTC or professionally managed wounds with minimal exudate.

Increasing exudate is a symptom of impending wound infection. SureSkin® Silver Hydrocolloid Dressing and SureSkin® Silver (OTC) Bandage adhesive would respond to this early sign of infection by absorbing up to 187% of its weight<sup>d</sup> in excess wound fluid and killing the resident organisms on contact with silver ions in the adhesive. Thus, SureSkin® Silver Hydrocolloid Dressing and SureSkin® Silver (OTC) Bandage help absorb and manage the wound exudate bioburden while serving "double duty" alerting OTC and professional wound care-givers to progressively earlier leakage as a signal of impending infection.

### **Safety of Commercially Available Silver Dressings**

Example predicate silver wound dressing products with approved claims and indications are presented in Table 2. These products represent prior art deemed safe which is substantially equivalent to SureSkin® Silver Hydrocolloid Dressing or SureSkin® Silver (OTC) Bandage Dressings (included in the table for perspective only). These silver-containing products are currently marketed as safe for over-the-counter (OTC) and/or professional wound care use with claims and indications similar to those sought for SureSkin® Silver Hydrocolloid Dressing or SureSkin® Silver (OTC) Bandage Dressing, formulation which has passed standard pre-clinical toxicity tests.

Lansdown and Williams (2004) reviewed silver safety including potential for silver release and systemic or local absorption, concluding that "risks of lasting tissue damage or functional disorders are low." This review addressed silver absorption from products such as Contreet® Foam, silver sulphadiazine 1% cream and Acticoat® each containing more than 10 times the silver per unit area of dressing contained in SureSkin® Silver Hydrocolloid Dressing or SureSkin® Silver (OTC) Bandage (Table 2).

In order for silver to be absorbed into the human body, it must first be released from the product applied. Wound care products differ in their composition, silver content and rate of silver release or formation of ions available for absorption. Dressings may not release all the silver they contain, depending on their composition. For example SureSkin® Silver Hydrocolloid Dressing retains most of its silver within the hydrocolloid adhesive where antimicrobial activity occurs. This literature search revealed no silver-related adverse events in published literature of Contreet® Hydrocolloid Dressing, the most similar predicate product or Contreet® Foam or Avance® Foam-film which contain the same active silver moiety in the hydrocolloid adhesive of the two SureSkin® products. These findings support systemic and local safety of SureSkin® Silver Hydrocolloid Dressing and SureSkin® Silver (OTC) Bandage, providing that they are used according to package insert directions.

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<sup>d</sup> based on EuroMed laboratory tests of adhesive absorption of saline under standard conditions at room temperature.

**Table 2. Example Silver Wound Dressings Silver Content, Product Claims and Indications**

Product (Source) <sup>e</sup>	Silver-related Claims (mg silver/100 cm <sup>2</sup> dressing) <sup>f</sup> [Maximum wear time] <sup>g</sup>	Indications For Use
Acticoat™ Antimicrobial Barrier Dressing (Smith & Nephew)	Microbial barrier dressing with sustained silver release, effective against a broad spectrum of microorganisms. Acticoat™ (107-123 mg) [3 days]; Acticoat 7 (120 – 148 mg) [7 days]	<u>Professional</u> : Partial- and full-thickness wounds including decubitus ulcers, venous stasis ulcers, diabetic ulcers, first- and second-degree burns, and donor sites. May be used over debrided and grafted partial-thickness wounds.
Actisorb® Silver 220 Antimicrobial Binding Dressing / Actisorb® Plus 25 (Johnson & Johnson)	Silver ions released from elemental silver on contact with wound fluid combat wound organisms in the dressing, reducing wound bacteria and inhibiting infection. (1.2-2.4mg) [7 days]	<u>Professional</u> : The first therapeutic step in the management of all chronic wounds. It is indicated for fungating carcinomas, ulcerative, traumatic and surgical wounds where bacterial contamination, infection or odor occurs
AQUACEL® Ag Hydrofiber® Dressing with Silver (ConvaTec)	In contact with wound exudate, the highly absorbent dressing creates a soft, cohesive gel that forms an intimate contact with the wound surface and maintains a moist, wound-healing environment. Ionic silver makes it an effective barrier to bacterial penetration, which may help reduce infection. (8.3-12.0 mg) [7 to 14 days]	<u>OTC</u> : minor wounds such as minor abrasions, lacerations, minor cuts, minor scalds and burns. <u>Professional</u> : Partial thickness {second degree) burns, diabetic foot ulcers, leg ulcers (venous stasis ulcers, arterial ulcers and leg ulcers of mixed etiology) and pressure ulcers (partial- and full-thickness), surgical wounds healing by secondary intent, traumatic wounds, wounds prone to bleeding such as wounds that have been mechanically or surgically debrided and oncology wounds with exudate such as fungoides-cutaneous tumors, fungating carcinoma, cutaneous metastasis, Kaposi's sarcoma, and angiosarcoma.
Arglaes® Antimicrobial Barrier Film Dressing or Island Dressing (Maersk Medical, UnoMedical; Medline)	Sterile, clear self-adherent antimicrobial barrier dressings (Controlled release film: 15.5 mg; Island dressing which also contains alginate: 4.6 mg) [7 days]	<u>Professional</u> : Film: Pressure sores, dermal ulcers, superficial leg ulcers, incisions, burns, donor sites, lacerations abrasions and to help secure and protect intravenous catheters. Island: pressure, venous, diabetic, arterial ulcers, donor sites, other bleeding wounds, dermal wounds, trauma injuries and incisions.

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<sup>e</sup> All product names are trademarks of their source companies indicated in parentheses.

<sup>f</sup> Approximate silver content per 100 cm<sup>2</sup> of wound-dressing interface is provided only for perspective of silver dressing safety from Lansdown & Williams (2004) or Bolton (2006). These values are approximate based on information from suppliers and not intended as product claims or specifications.

<sup>g</sup> Wear times are provided from websites or package insert instructions or not stated if unavailable.

Product (Source) <sup>e</sup>	Silver-related Claims (mg silver/100 cm <sup>2</sup> dressing) <sup>f</sup> [Maximum wear time] <sup>g</sup>	Indications For Use
Avance® A or Avance® (SSL, International) foam-film dressing with (A) or without boarder.	Broad-spectrum antimicrobial protection with silver-zirconium phosphate impregnated hydropolymer in foam component (1.59 mg) [7 days]	<u>Professional:</u> Acute and chronic wounds
Contreet® Foam (Coloplast A/S) Film/silver foam adhesive or nonadhesive dressing	Moist wound healing environment, antibacterial barrier activity and exudate management. Contains zeolite silver-ceramic complex (100 mg in foam component of dressing) [7 days]	<u>Professional:</u> Moderately to highly exuding leg ulcers and pressure sores. The dressing can also be used for 2nd degree burns, donor sites, post operative wounds and skin abrasions. Contreet Foam Non-adhesive is also indicated for diabetic foot ulcers.
Contreet H or Hydrocolloid (Coloplast A/S) Hydrocolloid-silver adhesive dressing	Silver complex in hydrocolloid adhesive provides microbial barrier protection. (31.2 -32.4 mg ) [7 days]	<u>Professional:</u> low to moderately exuding leg ulcers, skin tears and pressure sores. 2 <sup>nd</sup> degree or partial thickness burns, donor sites, post operative wounds and skin abrasions.
CURAD® Silver Bandage (Beiersdorf, AG)	The bandage covers the wound to create a protected wound environment while silver ions reduce bacterial growth in the wound pad.	<u>OTC:</u> First aid to help in minor abrasions, cuts, burns, scrapes and scalds
Silverlon® Island Wound Dressings and Silverlon® Island Dressings (Argentum Medical, L. L. C.)	Silver-coated nylon fabric in direct contact with wound serves as an antimicrobial barrier (464 to 546 mg) [7 days]	<u>Professional:</u> To manage partial- and full-thickness wounds, partial-thickness burns, incisions, skin grafts, donor sites, lacerations, abrasions, and Stage I to IV dermal ulcers; not compatible with magnetic resonance imaging scanners.
Silvion Antibacterial Silver Skin & Wound Moisturizing Solution (Medical Molecular Therapeutics, L. L. C.)	Liquid bandage providing a moist wound environment, in which ionic silver protects the solution against bacterial contamination.	<u>OTC:</u> Minor bumps, abraded skin, irritated areas minor wounds. <u>Professional:</u> Stage I-IV pressure ulcers, stasis ulcers, foot ulcers, diabetic ulcers, post-surgical wounds, first and second degree bumps, abrasions and skin irritations.
Silver Shield™ Antimicrobial Skin and Wound Gel (Anacapa Technologies, Inc.)	Helps maintain a moist wound environment conducive to healing, by either absorbing wound exudate or donating moisture while delivering antimicrobial silver.	<u>OTC :</u> Abrasions and lacerations <u>Professional:</u> in management of Stage I-IV pressure ulcers, partial and full-thickness wounds, diabetic foot and leg ulcers, grafted and donor sites
SILVERSEAL®: Adhesive Strip with X-Static®, Wound Contact Dressing or Burn Contact Wound Dressing (Noble Fiber Technology)	Primary dressing (with 22% metallic silver surface containing approximately 1.5% silver oxide). In intimate wound contact, with silver providing protection against microbial contamination. .	<u>OTC:</u> used in first aid to help in minor abrasions, minor cuts, lacerations, scrapes, minor scalds and burns. <u>Professional:</u> local management of partial thickness burns, incisions, skin grafts, donor sites, lacerations, abrasions, and Stage I-IV dermal ulcers (vascular, venous, pressure and diabetic)

Product (Source) <sup>e</sup>	Silver-related Claims (mg silver/100 cm <sup>2</sup> dressing) <sup>f</sup> [Maximum wear time] <sup>g</sup>	Indications For Use
SureSkin® Silver (OTC) Bandage Dressing	Moist wound environment, waterproof barrier against external contamination and bacteria. Absorbs small amounts of exudate, reduces dressing change pain (3.458 mg)[7 days]	<u>OTC</u> : First aid to help minor cuts, scrapes, abrasions, lacerations, blisters and scalds.
SureSkin® Silver Hydrocolloid Dressing	Supports healing, reduces odor, facilitates autolytic debridement provides functional barrier to external contaminants and bacteria. (zeolite silver-ceramic complex in hydrocolloid adhesive: 4.3 mg) [7 days]	<u>Professional</u> : Chronic and acute partial- and full-thickness wounds with low to moderate exudate such as pressure ulcers, leg ulcers, second degree burns, donor sites, post-operative wounds and skin abrasions or wounds where risk of infection is suspected or exists. Suitable for use under compression on low to moderately exuding venous ulcers.

The mechanism of action of SureSkin® Silver Hydrocolloid Dressing and SureSkin® Silver (OTC) Bandage is similar to that of the predicate products in Table 2. Each dressing provides a bacterial barrier for wounds by releasing ionic silver into the adhesive layer of the wound dressing as it absorbs wound fluid. Silver ions kill microorganisms as they are absorbed with wound exudate into the SureSkin® Silver Hydrocolloid Dressing or the SureSkin® Silver (OTC) Bandage adhesive.

Safety of the levels of silver in the two EUROMED silver dressings is further supported by the fact that the total dose of silver delivered per 100 cm<sup>2</sup> is between the silver content of products with evidence of efficacy that have been marketed globally for more than 10 years: Actisorb® (Johnson & Johnson) and Acticoat® (Smith & Nephew). The level of silver is less than one tenth the dose of silver delivered per unit area from clinically used Silverlon or Acticoat 7 dressings and more than twice the lower limit of Actisorb® silver dose per 100 cm<sup>2</sup>.

SureSkin® Silver Hydrocolloid Dressing or SureSkin® Silver (OTC) Bandage have the same mechanism of antibacterial action through release of ionic silver and similar claims and indications to other commercially available dressings with higher and lower doses of silver compared to the two EuroMed silver dressings. Prolonged clinical usage of other silver dressings exceeding silver dosages per 100 cm<sup>2</sup> of wound-dressing interface further supports clinical safety of the EuroMed dressings. Therefore we conclude that SureSkin® Silver Hydrocolloid Dressing and SureSkin® Silver (OTC) Bandage may be deemed clinically safe and effective as an antibacterial barrier for use in wound management.

## CRITICAL EVALUATION OF THE LITERATURE: Safety and Efficacy of Silver-Containing Wound Dressings

### Efficacy of Silver Wound Dressings

Earlier Cochrane reviews have concluded that there is insufficient evidence of complete healing outcomes to recommend using silver dressings on infected or contaminated wounds (Vermeulen *et al.*, 2007) or diabetic foot ulcers (Bergin. & Wraight, 2006) However more recent RCT evidence not yet included in Cochrane reviews adds perspective to a critical analysis of best available evidence on a variety of clinically relevant outcomes (Table 2).

One limitation of this critical analysis is that clinical outcomes differed sufficiently to prevent a meta-analysis of efficacy on wounds of any specific etiology. Nonetheless, the evidence systematically reviewed can inform clinical decisions regarding silver-containing dressing efficacy and safety when these dressings are used as bacterial barriers on chronic wounds.

Comparators in the controlled studies often vary in aspects other than silver content, limiting the capacity to conclude that all improvements in outcome measures of wounds dressed with silver dressings are due solely to their silver content. Despite the disparity of control protocols in the literature, consistently significant beneficial effects of silver-containing dressings are reported compared to same-study controls for the following clinical outcomes:

- Improved % wound area reduction of pressure, venous or diabetic ulcers (3 RCTs: Level A evidence)
- Improved depth reduction of diabetic foot ulcers (2 RCTs: Level A evidence)
- Reduced maceration and wound severity for ulcers of mixed etiology (1 RCT: Level C Evidence)
- Reduced odor, leakage, pain and discomfort for venous ulcers (1 RCT: Level C Evidence)
- Reduced bacterial burdens of various chronic wound etiologies (1 RCT: Level C Evidence).

Additional safety support on a variety of chronic and acute wounds is provided in uncontrolled clinical studies described in Table 3. Combined with this additional safety evidence these clinical effects support the cautious conclusion of earlier reviews that most silver dressings are safe (Lansdown & Williams, 2004; Lansdown *et al.*, 2005; Hermans & Bolton, 2004), with *in vitro* antibacterial efficacy sufficient to provide a microbial barrier. Evidence from controlled studies of predicate silver dressings supports a conclusion of consistently positive effects on aspects of chronic wound healing such as autolytic debridement, depth reduction and bacterial burden (Bolton, 2006).

To optimize safety using any wound dressing one should avoid use on patients sensitized to any dressing component. Frequent dressing changes should be avoided when possible to minimize discomfort, wound trauma, exposure and external contamination. Ideally hydrocolloid dressings should be changed at 48 hour or longer intervals, after peak adhesion to the skin. If earlier removal is required, the dressing may be stretched in place on the skin up to 50 percent beyond its normal length to release the adhesive bond to the skin before gently peeling the dressing away from the skin from one corner.

Wounds dressed with hydrocolloid dressings are reported to experience sterling healing rates (Chaby *et al.*, 2007) autolytic debridement and economic outcomes (Kerstein *et al.*, 2001; Bolton *et al.*, 2004) with reduced pain and likelihood of infection compared to gauze (Hutchinson & McGuckin, 1991). Clinical research measured outcomes during up to 20 dressing changes on 1080 acute and chronic dermal wound patients (Gallego *et al.*, 2005) managed with non-silver containing EuroMed hydrocolloid dressings. Healing, autolytic debridement and pain alleviation on dressing changes were comparable to those reported for similar wounds in prior peer-reviewed hydrocolloid publications.

. The historical effectiveness of hydrocolloids in managing chronic and acute wounds and comparable results on similar wounds dressed with SureSkin® Hydrocolloid Dressing combine with the proven *in-vitro* antimicrobial effectiveness of silver-containing dressings in general and SureSkin® Silver Hydrocolloid Dressing in particular, to support a conclusion of safety and efficacy of the family of SureSkin® Silver Hydrocolloid Dressings for professionally treated wounds and SureSkin® Silver (OTC) Bandage for minor wounds managed by consumers.

EuroMed, Inc.

**Table 3. Controlled Clinical Studies Supporting Safety and/or Efficacy of Silver Wound Dressings on Chronic Ulcers and Burns.**

Etiology Reference	Patients Enrolled		Study Design	Clinical Outcomes Measured	Significant Results (Reported only if p<0.05)		Wounds for which safety is supported Reviewer's comments are highlighted.
	Test (N) Silver Source	Control (N)			Test Result	Control Result	
<b>Pressure Ulcers (PU)</b>							
Munter <i>et al.</i> 2006	Contreet® Foam (26) 100 mg / 100 cm <sup>2</sup> Silver-ceramide complex	Local Best Practice (21) with gauze or other dressings	Prospective open-label parallel, block randomized 4-week study	Healing, pain at or between dressing changes, malodor	58.5% reduction in wound area	33.3% reduction in wound area	Mixed arterial-VU and other wounds also studied which are not reported here.
<b>Venous Ulcers (VU)</b>							
Jorgenson <i>et al.</i> , 2005	Contreet® Foam (65) 100 mg / 100 cm <sup>2</sup> Silver-ceramide complex	Allevyn® Hydrocellular (64)	Prospective Multi-center 4-week RCT of delayed-healing VU	Healing, area, odor, maceration absorption, leakage,	At 4 weeks, 45% healed; 19% had odor; 19% leakage; 37% maceration; comparable AEs	At 4 weeks 25% healed; 39% had odor; 49% leakage; 48% had maceration; comparable AEs	Groups initially comparable. All results except healing also significant at week 1.
Munter <i>et al.</i> 2006	Contreet® Foam (150) 100 mg / 100 cm <sup>2</sup> Silver-ceramide complex	Local Best Practice (146) with gauze or other dressings	Prospective multi-center open-label parallel, block randomized 4-week study	Healing, pain at or between dressing changes, malodor, slough	46.2% reduction in wound area; less pain and discomfort than in control group.	26.9% reduction in wound area; more pain and discomfort than in test group	Mixed arterial-VU and other wounds also studied are not listed here.
<b>Diabetic Foot Ulcers (DU)</b>							
Jude E <i>et al.</i> 2006	AQUACEL® Ag (67) 1.2% ionic silver salt	Algosterile® (67)	Prospective Multi-center 8-week RCT	Healing, area and depth reduction, infection	Depth reduction 2.5 mm after 8 weeks (n=50) 31% healed (p not significant for % healed)	Depth reduction 1.3 mm after 8 weeks (n=50) 22% healed.	Test and control comparable at baseline and on safety and infection results.

<b>Etiology Reference</b>	<b>Patients Enrolled</b>		<b>Study Design</b>	<b>Clinical Outcomes Measured</b>	<b>Significant Results (Reported only if p&lt;0.05)</b>		<b>Wounds for which safety is supported Reviewer's comments are highlighted.</b>
	<b>Test (N) Silver Source</b>	<b>Control (N)</b>			<b>Test Result</b>	<b>Control Result</b>	
Munter <i>et al.</i> 2006	Contreet® Foam (26) (100 mg / 100 cm <sup>2</sup> ) Silver-ceramide complex	Local Best Practice (23) with gauze or other dressings	Prospective multi-center open-label parallel, block randomized 4-week study	Healing, wound pain, malodor, slough, maceration	Less slough in wound bed than control; less maceration; median odor 1	◆ More slough and maceration in wound bed than test; median odor 2	Mixed arterial-VU and Other wounds also studied are not reported here.
Reyzelman <i>et al.</i> 2005	AQUACEL® Ag (52) 1.2% ionic silver salt	Saline-moistened Gauze (45)	Prospective Multi-center 12-week RCT	Healing, area and depth reduction, infection	Overall depth reduction 4.0 mm 42% healed (NS)	Overall depth reduction 1.0 mm 42% healed (NS)	Test and control were comparable at baseline and on safety and infection results
<b>Mixed Pressure Ulcers, Venous Ulcers or Other Chronic Wounds</b>							
Meaume <i>et al.</i> 2005	Silvercel® (51) Nylon fibers coated with 8% elemental silver	Algosteril® Alginate without silver (48)	Prospective RCT 4-week multi-center stratified by wound type	Rate of wound closure; infection rate wound severity score	0.32 cm <sup>2</sup> /day 32% reduction in wound severity score(40)	0.16 cm <sup>2</sup> /day 23% reduction in wound severity score (38)	0% (test 40) and 10.5% (control 38) required antibiotics at final visit (p=0.053)
<u>Chronic Wound Etiology Unspecified</u> Verdu-Soriano <i>et al.</i> 2004	Actisorb® Plus 25 (67) Activated charcoal cloth + nylon coated with 0.15% elemental silver	Tielle® (58)	Prospective multi-center 2-week RCT	Contaminated-≤ 10 <sup>3</sup> CFU <sup>h</sup> Colonized - ≤ 10 <sup>4</sup> CFU Infected - ≥ 10 <sup>5</sup> CFU	After 2 weeks 85.1% of ulcers reduced wound bacterial count; 1 of 14 (7.1%) ≥ 10 <sup>5</sup> CFU persisted	After 2 weeks 62.1% of ulcers reduced wound bacterial count; ; 9 of 12 (75%) ≥ 10 <sup>5</sup> CFU persisted	Healing or adverse events were not described.
<b>Acute Wounds</b>							

<sup>h</sup> CFU means Colony Forming Units per gram of tissue

<u>Etiology</u> Reference	Patients Enrolled		Study Design	Clinical Outcomes Measured	Significant Results (Reported only if p<0.05)		Wounds for which safety is supported Reviewer's comments are highlighted.
	Test (N) Silver Source	Control (N)			Test Result	Control Result	
<u>Burns</u> Caruso et al. 2006	AQUACEL® Ag (42) with gauze cover, dressing	SSD gauze (42) optional cover dress.	Prospective RCT to healing	Healing, pain, infections, adverse events medications	Less pain, nursing time, procedural medications compared to control	No outcomes favored control.	
<u>Surgical open wounds</u> Jurczak et al. 2007	AQUACEL® Ag (35) No cover dressing	Povidone .Iodine gauze (32)	Prospective RCT to healing	Healing, pain, trauma, ease of use	Less pain, trauma, easier use than control	No outcomes favored control	

EUROMED

**Table 4. Uncontrolled clinical studies supporting safety of silver-containing modalities on chronic wounds**

<b>Etiology Reference</b>	<b>Modality (number of patients studied)</b>	<b>Study Design</b>	<b>Clinical Safety Outcomes Measured</b>	<b>Results</b>	<b>Comments</b>
<b>Pressure ulcer</b>					
<b>Total 54 patients</b>					
Hermans, 2004	AQUACEL® Ag (54, 38% clinically infected on enrollment)	Prospective ≤ 4 week standardized multi-center clinical evaluation	Healing /improvement of wound and peri-wound skin	At study end 6% of wounds healed and 81% showed some or marked improvement. 56% of subjects showed significant or moderate peri-wound skin improvement.	Convenience sample of patients deemed appropriate for this dressing; no adverse events were reported.
<b>Venous ulcer</b>					
<b>Total 200 patients</b>					
Hermans, 2004	AQUACEL® Ag (113)	Prospective ≤ 4 week standardized multi-center clinical evaluation	Healing /improvement of wound and improvement of peri-wound skin	At study end, 12% of wounds healed completely, 73% showed some or marked improvement. 61% of subjects showed peri-wound skin improvement.	Convenience sample of patients deemed appropriate for this dressing; no adverse events were reported.
Karlsmark <i>et al.</i> 2003	Contreet Foam (23) moderately to highly exuding VU	Prospective 4-week standardized study	Clinical infection, healing, odor, pain Serum silver levels	No ulcer infections reported. 56% reduction in VU area. Serum silver levels in safe range.	Wound odor reduced after one week (p<0.05)
Jorgensen <i>et al.</i> 2006	Physiotulle-Ag® (30)	Prospective open 4-week standardized study	Healing; area reduction; granulation tissue; fibrin; odor; adverse events	One (3%) healed. There was an average 55% reduction in area. Granulation tissue, fibrin and odor all improved. There were no device-related adverse events.	Incidence and severity of maceration, erythema, and eczema decreased.
Lantis <i>et al.</i> 2006	Prisma® in combination with Regranex® (23)	6-month prospective case series of VU of duration > 4 years in HIV+ patients	Healing; decrease in area	8 (35%) healed. Wounds decreased in size by an average of 38 cm <sup>2</sup>	

<b>Etiology Reference</b>	<b>Modality (number of patients studied)</b>	<b>Study Design</b>	<b>Clinical Safety Outcomes Measured</b>	<b>Results</b>	<b>Comments</b>
Vanscheidt W. <i>et al.</i> 2003	AQUACEL® Ag (11 + 5 mixed etiology, 1 arterial and 1 other ulcer)	Prospective 4-week standardized multi-center clinical evaluation	Adverse events, including infection and pain	Two mild adverse events: 1. related to dressing: pain 3 h post application 2. Possibly related: ulcer discolored day 18 spontaneously resolved day 20. Infection resolved in 2 of 11 subjects infected at baseline.	Pain with dressing in place and on dressing removal decreased from baseline to study end (p < 0.05).
<b>Diabetic foot ulcer</b>	<b>Total 134 patients</b>				
Bohanon <i>et al.</i> 2006	Silverlon® (30) Iodosorb® mixed 50:50% with Curasol® (30)	Retrospective chart review of 85 to 154 days duration or to healing	Wound healing	Comparable healing rates, with 83% of the wounds healing	
Hermans, 2004	AQUACEL® Ag (47, 60% judged neuropathic)	Prospective ≤ 4 week standardized multi-center clinical evaluation	Healing /improvement of wound and improvement of peri-wound skin	At study end, 10% of wounds healed completely, 71% showed some or marked improvement. 49% of subjects showed peri-wound skin improvement.	Convenience sample of patients deemed appropriate for this dressing; no adverse events were reported.
Carson <i>et al.</i> , 2005	Silverlon® over Dermagraft® (30 candidates for limb salvage with diabetes, lower leg ischemia and a lower extremity ulcer colonized with MRSA, VRE or other pathogens)	13-month case series of patients who failed to heal during 5-60 weeks with moist wound care. After ischemia correction ulcer was debrided dressed with a dermal substitute under a silver dressing	Healing outcome with or without grafting during 12 weeks on study.	Seventeen patients healed during 12 weeks. (average heal time 46 days; range 32-94 days). Eight patients required skin grafts then healed. Five patients did not heal and required amputation.	Author concluded that this study supports safety and performance of silver dressings within a protocol addressing the causes of lower limb tissue ischemia in diabetic patients
Rayman <i>et al.</i> , 2005	Contreet® Foam (27 Wagner Grade I or II) plus "good diabetic wound care	Prospective 4-week treatment after 1 week Biatain® dressing	Healing Clinical infection	Healed: 4 of 27 (15%) Infected: 2 of 27 (7.4%)	Six non-study controls all became infected (100%).
<b>Variety of Etiologies of Acute Wounds or Chronic Ulcers</b>			<b>Total 71 patients</b>		

<b><u>Etiology Reference</u></b>	<b><u>Modality (number of patients studied)</u></b>	<b><u>Study Design</u></b>	<b><u>Clinical Safety Outcomes Measured</u></b>	<b><u>Results</u></b>	<b><u>Comments</u></b>
Conway-Salerno, 2005	SilvaSorb® Hydrogel dressings (4 geriatric home care patients with chronic infected wounds)	Wounds were cleansed with a commercial wound cleanser then dressed with primary silver dressing covered with a gauze dressing	Wound improvement or closure	Improvement was noted over three weeks.	Author noted that the silver dressing was adopted as the standard of care of the
Coutts & Sibbald, 2005; Sibbald <i>et al.</i> 2006	AQUACEL® Ag (30 recalcitrant ulcers: 13 VU; 4 PU; 4 neuropathic DU, 9 other ulcers)	Prospective single-center 4-week trial	Wound size; quantitative bacterial biopsies; exudate; peri-wound temperature	Wound size decreased in 16 (62%) of patients. Bacterial burden decreased in 22 (85%) of shallow biopsies and 19 (73%) of deep biopsies.	Higher bioburden was associated with delayed ulcer healing at week 2 (p=0.01) and elevated peri-wound temperature.
Gibbins et al., 2000	AcryDerm® Silver Antimicrobial Dressing covered by a thin film dressing (3 surgical incisions; 3 skin tears; 7 PU; 3 DFU; 5 VU)	Prospective case series ranging in duration of dressing use from 1.2 weeks for skin tears to 3 weeks (surgical incisions), 4 weeks for VU, 10 weeks for DFU or 12.8 weeks for PU.	Incidence of adverse reactions or skin or wound staining.	The only adverse event recorded was pain occurring in one venous leg ulcer patient.	Adverse event not necessarily related to study dressing.
Lee, 2003	AQUACEL® Ag (4 patients: 1 with diabetes and a heel ulcer, 1 cancer patient with abdomen wound dehiscence, 1 VU, 1 DFU.	The silver dressing was left in place for 7 days while changing the outer non-silver AQUACEL® dressing as needed.	Tolerability, pain healing progress capability of management in home care settings	One patient went home where healing occurred in 2 weeks. In the dehisced wound healing progressed during the first week. Leaving the silver dressing in place for 7 days improved wound pain ease of dressing use.	VU patient required compression and systemic antibiotics to work in synergy with the topical antibacterial dressing.

<b><u>Etiology Reference</u></b>	<b><u>Modality (number of patients studied)</u></b>	<b><u>Study Design</u></b>	<b><u>Clinical Safety Outcomes Measured</u></b>	<b><u>Results</u></b>	<b><u>Comments</u></b>
Nametka, 2002	Acryderm® Silver Antimicrobial dressing (12 patients 62-93 years of age, 8 with recurrent infected wounds.	Case series dressing wounds with the silver study dressing for 8 weeks. Historic control data was abstracted from patient records.	Incidence of infection and dressing change frequency before and after silver dressing use began	Silver dressing extended time between dressing changes by 235% as compared to prior dressings on the same wounds, reducing wound care costs. 8 of 12 patients had an infected wound before silver dressing use compared to 0 of 12 patients with the silver dressing	One multiple sclerosis patient with a Stage IV PU of 2 years duration healed in 8 weeks with ionic silver. A wheelchair bound patient with a PU for 4 months healed in 4 weeks.
<b>Acute Burns or Trauma</b>		<b>Total 15 patients</b>			
Argentum Medical 2006	Silverlon® with antibiotics, repeated debridement (1)	Case study with subject evaluated day 49, 60 and 129	Infection resolution	Infection resolving by day 60. Wound judged healed by day 120.	Relative contribution of silver product to outcome is unclear.
Chen <i>et al.</i> 2005	AQUACEL® Ag (12 2 <sup>nd</sup> degree burn patients mean body surface area 15.9%)	Case series of patients with silver dressing applied after debridement.	Healing or grafting outcome, time to close, infections, allergies	All but 2 patients healed completely with AQUACEL® ag left on for 15 days. One healed in 21 days. one was grafted. No infections or allergy	
Ermer-Seltun & Leninger, 2005	AQUACEL® Ag 1.2% w/w ionic silver Hydrofiber® dressing (2 second degree burn patients started ionic silver dressing. Day 1 post burn)	Case series. One subject initially managed with 1% silver sulfadiazine cream. One with a blistered hand burn initially dressed with antibiotic ointment.	Healing time	Complete re-epithelization occurred on day 14 for both patients	

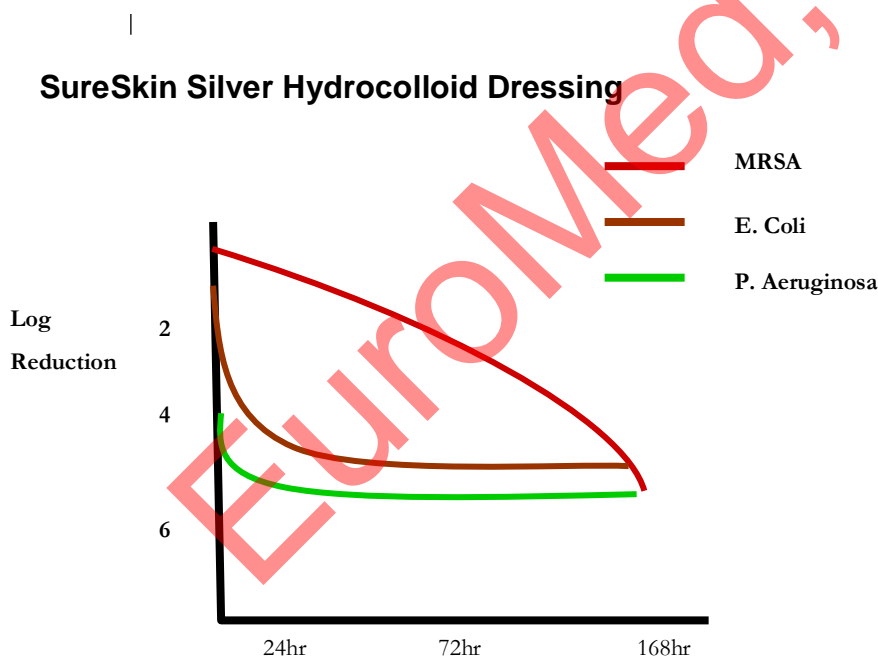
**SUPPLEMENTAL PRECLINICAL EVIDENCE ON EUROMED SILVER DRESSINGS**

**Antimicrobial Efficacy in *Vitro* of SureSkin® Silver Hydrocolloid Dressing**

EuroMed supported independent laboratory studies (Gibraltar Laboratories, 2007) confirming antibacterial efficacy of SureSkin® Silver Hydrocolloid Dressing *in-vitro* against pathogenic clinical isolates of *Aspergillus niger*, *Candida albicans*, *Escherichia. coli*, *Methicillin-Resistant Staphylococcus aureus (MRSA)*, and *Pseudomonas aeruginosa*. Figure 1 displays smooth bactericidal curves fitted<sup>9</sup> to the data for the latter three important pathogens. Inocula of 10<sup>6</sup> to 10<sup>7</sup> colony forming units (CFU) of each organism suspended in 2 ml bovine serum broth were placed on the dressing adhesive pad, incubated under standard conditions. After 24, 72 or 168 hours (7 days) the inoculated pad was harvested and immediately mixed with fluid thioglycolate medium to neutralize silver. Serial dilutions of viable organisms were recovered and plated onto appropriate media for CFU counts. Bactericidal (kill) activity was reported as reduction in numbers of CFU below original inoculum levels:

- *A. niger*: more than 4 log kill after 7 days (99.99% )
- *C. albicans*: more than 3 log kill after 7 days (99.9%)
- *E. coli*: more than 4 log kill after 24 hours (99.99%)
- *MRSA*: more than 2 log kill after 72 hours; more than 5 log kill after 7 days (99.999%)
- *P. aeruginosa*: more than 4 log kill after 24 hours (99.99%)

**Figure 1. Bactericidal effects of SureSkin® Silver Hydrocolloid Dressing *In Vitro***



SureSkin® Silver Hydrocolloid Dressing has the same formulation with a slightly thinner adhesive layer so it contains about 25% more silver per cm<sup>2</sup> of interface area between dressing adhesive and bacterial-laden fluid than SureSkin® Silver (OTC) Bandage. The similarity between formulations would lead one to expect a similar duration and spectrum of bactericidal activity for the two EuroMed dressings.

19 \_\_\_\_\_  
<sup>9</sup> Using Microsoft EXCEL® and POWERPOINT®

**Wound Healing Study in Rats**

EuroMed authorized an independent laboratory to conduct a 13 day study of dressing performance as well as wound healing and surrounding skin responses on rats (NAMSA, 2005). Sterile sections of one lot each of three dressings were placed adhesive side down in eight 2 cm x 2 cm full-thickness excision wounds, one excision per rat for each of the following dressings:

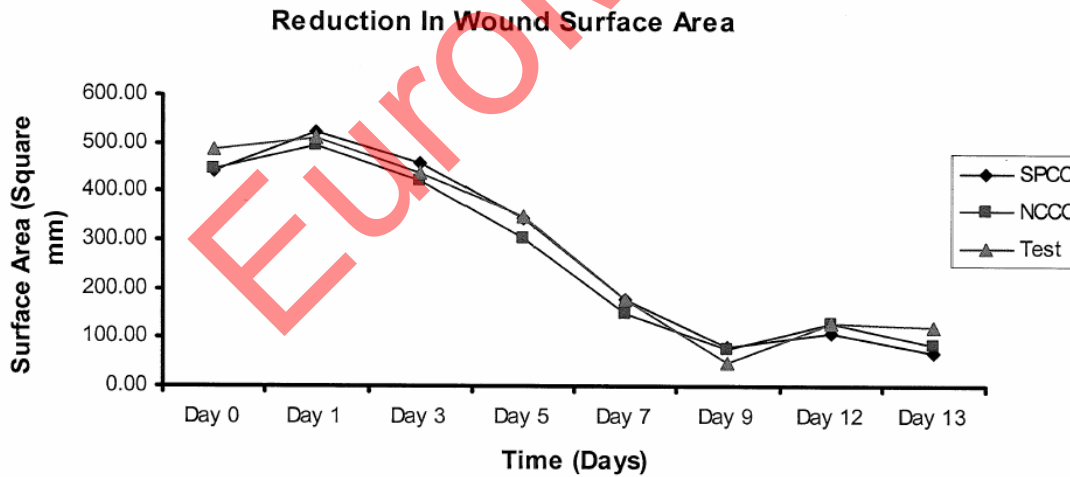
- EuroMed SureSkin® Silver Hydrocolloid Dressing (Test Silver Hydrocolloid Dressing)
- Coloplast Contreet® Hydrocolloid containing silver (Silver Hydrocolloid Dressing Control)
- SureSkin II (EuroMed’s hydrocolloid dressing – Non-silver Control)

Each study dressing was covered with gauze and an occlusive top dressing. All dressings were changed on study days 1, 3, 5, 7, 9 and 12. Standardized evaluations on days 5, 7, 9 and 12 recorded:

- rat general health and body weight,
- macroscopic ratings of wound bed, wound edge and surrounding skin appearance,
- healing parameters including granulation, length and width,
- dressing leakage, wetness and adherence,
- at study end, standardized microscopic wound observations by a trained pathologist.

Under the conditions of this study the test group (SureSkin® Silver Hydrocolloid Dressing) was comparable on all parameters evaluated to the non-silver control (SureSkin II) and the silver hydrocolloid dressing control (Contreet® Hydrocolloid with silver) with no statistically significant differences on any parameter evaluated. Overall healing as measured by reduction in wound surface area was similar for all three groups with no statistically significant dressing effects as shown in Figure 2.

**Figure 2. Rat full-thickness excision healing response to silver and non-silver hydrocolloid dressings (Legend: SPCC: Contreet Hydrocolloid Dressing with Silver; NCCC: SureSkin® Hydrocolloid Dressing without silver; Test: SureSkin® Silver Hydrocolloid Dressing)**



**CONCLUSION**

The clinical literature reviewed supports the conclusion that silver dressings in general are safe on chronic and acute wounds, including minor OTC wounds treated by consumers, and may confer significant wound healing benefits.

The formula for the SureSkin® Silver Hydrocolloid Dressing line and SureSkin® Silver (OTC) Bandage is essentially equivalent to those of existing silver hydrocolloid dressing formulations. Its active silver ceramide moiety is identical to that of Contreet® Foam dressing, which has Level A RCT support for healing efficacy on chronic wounds.

*In vivo* rat full-thickness excisional wound healing was similar to that of Contreet® Hydrocolloid Dressing with silver, as well as SureSkin® Hydrocolloid Dressings without silver further supporting the conclusion that SureSkin® Silver Hydrocolloid Dressing should have a clinical safety profile similar to these two predicate dressings.

*In vitro* microbiology studies support bactericidal efficacy of the SureSkin® Silver Hydrocolloid Dressing line and SureSkin® Silver (OTC) Bandage for up to 7 days. The spectrum and duration of bactericidal activity reported for the SureSkin® Silver Hydrocolloid Dressing adhesive are similar to *in vitro* antimicrobial efficacy results reported for Contreet® Foam.

Essential equivalence of the SureSkin® Silver Hydrocolloid Dressing line of products to currently marketed products with proven safety and antimicrobial barrier efficacy plus preclinical safety on mammalian excisions and up to 7-day bactericidal efficacy on a spectrum of recognized pathogenic bacteria supports the conclusion that Standard, Thin and Border SureSkin® Silver Hydrocolloid Dressings and SureSkin® Silver (OTC) Bandage are safe and effective for use as an antimicrobial barrier dressing on full- and partial-thickness human wounds.

#### ACKNOWLEDGMENT

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#### FOOTNOTES

\* SureSkin® is a registered trademark of EuroMed Incorporated in Austria, Spain, Sweden, Denmark, France and Germany.

EuroMed Incorporated has pending trademark applications in other foreign jurisdictions.

\*\* Contreet® is a registered trademark of Coloplast Corporation, Humlebæk, Denmark.

\*\*\* AQUACEL®, DuoDERM® and Hydrofiber are registered trademarks of ConvaTec, Skillman, New Jersey, United States.

† SILVERCEL®, ACTISORB®, PRISMA® and Regranex® are registered trademarks of Johnson & Johnson Wound Management, a division of ETHICON, Inc., Somerville, New Jersey, USA.

All other product names indicated registered trademark sign (®) or by the trademark (™) are registered or pending registration by the company marketing the respective product.

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- Vanscheidt W, Lazareth I, Routkovsky-Norval C. Safety evaluation of a new ionic silver dressing in the management of chronic ulcers. *WOUNDS* 2003; 15(11): 371-378.
- Verdu Soriano J, Lopez JR, Martinez Cuervo F, Soldevilla Agreda J. Effects of an activated charcoal dressing on chronic wounds with no clinical signs of infection. *J Wound Care* 2004; 13(10):419-423.
- Vermeulen H, van Hattem JM, Storm-Versloot MN, Ubbink DT. Topical silver for treating infected wounds. *Cochrane Database Syst Rev*. 2007 Jan 24;(1):CD005486.

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## APPENDIX A: THE AUTHOR'S CURRICULUM VITAE

Laura Lee Bolton, Ph.D.  
Adjunct Associate Professor, Surgery (Bioengineering), Univ. Medicine & Dentistry of New Jersey  
President, *BoltonSCI, L.L.C.*  
15 Franklin Place, Metuchen, NJ 08840  
Tel or Fax: 732-548-0344 E-mail: llbolton@gmail.com

**Education:**

	<u>Undergraduate:</u>
1962-1966	B.A. Psychology - University of Illinois Minor: Mathematics
	<u>Graduate:</u>
1967-1968	M.S. Psychology (Memory) - Stanford University
1970-1975	Ph.D. Psychobiology (Hyperactivity) - Rutgers University
	<u>Professional:</u>
1977	Managerial Skills - Rutgers University
1979	Mechanisms of Growth Control - SUNY at Syracuse
1980	Immunochemistry & Immunobiology - Center for Professional Advancement
	Continuing Medical Education Courses at UMDNJ: Chronic Wound & Therapy
1983	Pressure Sores
1985	Current Test Methods, Clinical Therapies
1986	CME/CEU Lecturer
1987-present	Good Clinical Practices: Center Professional Advancement
1990	Leadership for Excellence (Darden)
1991	Managing Business Performance (Carnegie Mellon)
1992	Cochrane Medical Literature Review Training
1995	Earned ~ 24 hours CME credit annually (Wound care)
1995-present	

**University Appointments:**

2000-2002	Lecturer: La Salle University Wound Ostomy Continence Nursing Education Program: Wound Healing
1990-present	UMDNJ - Robert Wood Johnson Medical School, Dept of Surgery (Bioengineering) Adjunct Assoc. Professor
1981-1989	" Adjunct Assistant Professor
1972-1973	Instructor, Douglas College, Rutgers University, UMDNJ
1970	Teaching Assistant, Department of Psychiatry, UMDNJ
1967-1968	Research Asst, Psychology Dept., Stanford University

**Industrial Experience:**

2007-present	<u>Derma Sciences, Inc.</u> Chief Scientific Advisor
2006-present	<u>BoltonSCI, L. L. C.</u> President,.
1987-2006	<u>ConvaTec - A Bristol-Myers Squibb Company</u>
2003-present	Director, Scientific Affairs & Clinical Communications
2001-2003	Director, Scientific Affairs /Global Medical Affairs

1995-2001	Director, Scientific Affairs / Global Strategic Marketing
1992-1995	Director, Scientific Affairs / Global Business Development
1991-1992	Director, Wound Care Research & Development
1987-1991	Manager, Wound Care Research & Development, led team that developed DuoDERM® CGF® family of dressings
1973-1987	<u>Johnson &amp; Johnson Products, Inc.</u>
1982-1987	Principal Scientist, Project Team Leader
1976-1982	Senior Scientist, Project Team Leader
1974-1976	Scientist
1973-1974	Assistant Scientist
1969-1970	<u>Child Welfare League of America: Research Assistant</u>

**Professional Societies:**

1984-1995	Surgical Infection Society Membership Committee
1988-present	Society for Investigative Dermatology
1985-present	Inflammation Research Association
1976-1983	American Society of Zoologists
1975-1977	Association of Advancement of Medical Instrumentation
1988-2005	New York Academy of Science
1989-2002	Academy of Surgical Research
1994-2001	National Pressure Ulcer Advisory Panel
1995-present	Wound Healing Society (currently on Education Committee)
1997-present	Association for the Advancement of Wound Care (AAWC)
2002-2006	Co-chair Regulatory & Government Task Force
2007-present	Co-chair Guideline Sub-committee
	WHO Collaboration for Under-resourced Countries
1999-present	<i>Wounds</i> Editorial Board
2001-2007	Amer. Prof. Wound Care Assn. (Fellow)
2001-present	<i>Advances in Skin &amp; Wound Care</i> Editorial Board
2005-2007	<i>Skin Med</i> Editorial Board

**Awards and Citations:**

1966-1967	Fulbright Scholar to Belgium
1966	Woodrow Wilson fellow (declined to accept Fulbright)
1966	Phi Beta Kappa, Phi Lambda Delta
1980-present	American Men and Women of Science
1978-1999	Sigma Xi - President of J&J Chapter, 1985, 1986
1995-present	Who's Who In Science and Engineering
Sep 21, 2001	Sharon Baronoski Founder's Award Clin. Symp. Skin & Wound Care
April 25, 2003	AAWC Distinguished Member Award, Co-chair Gov. & Reg. Task Force
October, 2004	<i>Advances in Skin &amp; Wound Care</i> , Distinguished Journal Reviewer Award.
June 13, 2005	<i>Journal of Wound Ostomy Continence Nursing</i> 2005 Manuscript Award
April 20, 2007	RADM Faye G. Abdellah Publication Award for Nursing Research with DL Bernato (recipient on behalf of AAWC G&R Task Force)

**Graduate Student Advisor or Mentor:**

1986 Vanderstar, J. "Effect of electrical stimulation on bacterial sterilization", Ph.D., Rutgers University - UMDNJ - Rutgers Medical School Joint Program in Bioengineering

1987 Bolecek-Skaggs, C. "Effect of electrical stimulation on soft tissue repair", M.S. Rutgers University - UMDNJ - Rutgers Medical School Joint Program in Bioengineering.

1990 Bates-Jensen, B. "Assessment Tool for Pressure Ulcers", Ph.D. UCLA School of Nursing.

2002-6 Smitten, A. "Burden of Wound Care" Harvard University Business School, Ph.D. Candidate.

### **Selected Appointments**

1995-Present	Reviewer, <i>Journal of Investigative Dermatology</i>
1995-2000	Corporate Representative, National Pressure Ulcer Advisory Panel-- Co-founded NPUAP Research Foundation
1998-2002	Abstract Reviewer: Symposium for Advanced Wound Care
2000-Present	Editor, <i>Wounds; Evidence Corner</i> and Outcomes Sections
2000-Present	Board Member, Assoc. for Advancement of Wound Care
2000-2002	Abstract Reviewer: American Diabetic Association
	Co-Chair Biotechnology Section, TechTrends, 2001
2002-2004	Editorial Board, <i>Women's Dermatology Society Newsletter</i>

### **Publications in Peer-Reviewed Journals**

1. Renner, K.E. and Specht, L.L. The relative desirability or adversiveness of immediate and delayed food shock. J Exp Psychol 1967;75:586-570.
2. Cattell, R.B. and Bolton, L.L. What pathological dimensions lie beyond the normal dimensions of the MMPI and 16PF factor domains? J Cons Clinical Psychol 1969;33:18-29.
3. Bower, G.H. and Bolton, L.L. Why are rhymes easy to learn? J Exp Psychol 1969;82:453-462.
4. Bolton, L.L., Bullard, R., Squibb, R.L., Pierotti, R., Collier, G.H. Effects of prior and current activity and deprivation on body composition. Proceedings: Eastern Psychological Association Convention, New York, April 1971.
5. Bolton, L.L., Squibb, R.L., Collier, G.H. Lysine deficiency and voluntary exercise in the albino rat. J Nutrition 1979;109:1313-1320.
6. Bolton, L.L., Foleno, B., Means, B., Petrucelli, S. Direct current bactericidal effect of intact skin. Antimicrobial Agents Chemother 1980;18:137-141.
7. Bolton, L.L., Constantine, B.E., Rovee, D.T. The kinetics of ornithine decarboxylase activity as a function of wounding in guinea pig ear epidermis. J Inv Dermatol 1981;76:480-483.
8. Bolton, L.L. TENS electrodes irritation. J Amer Acad Dermatol 1983;8:134.
9. Constantine, B.E., Bolton, L.L. A wound model for ischemic ulcers in guinea pig. Arch Dermatol Res 1986;278:429-431.
10. Bolton, L.L. (1) Dressing affects on healing (2) Debridement. Nursing '89, Consult. November 1989.
11. Bolton, L.L., Pirone, L.A. Letter to Editor: Effects of dressings on return of barrier function to transepidermal water loss in standardized human wounds. J Amer Acad Dermatol 1990.

12. Bolton, L.L., Pirone, L., Chen, J., Lydon, M. Dressings' effects on wound healing. Wounds July/August 1990;2(4): 126-134.
13. Pirone, L.A., Monte, K.A., Shannon, R.J., Bolton, L.L. Wound healing under occlusion and non-occlusion in partial-thickness and full-thickness wounds in swine. Wounds 1990;2:74-78.
14. Bolton, L.L., van Rijswijk, L. Wound Dressings: Meeting clinical and biological needs. Dermatol Nurs 1990; 2(3): 146-161 (Continuing Education Feature).
15. Bolton, L.L., Johnson, C.L., van Rijswijk, L. Occlusive dressings: Therapeutic agents and effects on drug delivery. Clinics Dermatol 1992;9:573-583.
16. Pirone, L.A., Bolton, L.L., Monte, K.A., Shannon, R.J. Effect of Calcium Alginate Dressings on Partial-Thickness Wounds in Swine. J Invest Surg 1992;5:149-153.
17. Bolton, L.L., Montagna, W. Mast cells in human ulcers. Amer J Dermatol 1993;15(2):133-138.
18. Bolton, L. Article on enzymatic debridement inspires literature search of controlled studies. Letter to the editor, Ostomy/Wound Management 1993.
19. Hermans, M.H.E., Bolton, L.L. Air exposure versus occlusion: merits and disadvantages of different dressings. J Wound Care, November 1993;2(6):362-365.
20. Smith, D.J., Thompson, P.D., Bolton, L.L., Hutchinson, J.J. Microbiology and healing of the occluded skin-graft donor site. Plast Reconstr Surg 1993;91:1-4.
21. Bolton, L., Fattu, A.J. Topical Agents and Wound Healing. Clinics in Dermatology 1994;12:95-120.
22. Bolton, Laura. Clinical studies and product evaluations: How to maximize their value. Ostomy/Wound Management 1995;41(7A)Suppl:88S-96S.
23. Bolton L. Hydrocolloid dressings clarified. Dermatol Nurs 1995; 7(5):294.
24. Tur, Ethel, Bolton, Laura, Constantine, Barry E. Topical hydrogen peroxide treatment of ischemic ulcers in the guinea pig: Blood recruitment in multiple skin sites. Journal of the American Academy of Dermatology 1995;33:217-221.
25. Bolton LL. Kudos to authors at the community leg ulcer clinic in London. Ostomy/Wound Management, 1996; 43(6):6-7.
26. Hermans, M.H.E., Bolton, L.L. The Influence of Dressings on the Costs of Wound Treatment. Dermatology Nursing 1996;8(2):93-100.
27. Cevera, J.J. Bolton, L.L., Kerstein M.D. Options for diabetic patients with chronic heel ulcers. Journal of Diabetes and Its Complications, November, 1997;11:358-366.
28. Boulton, A.J.M, Knowles, A., Laing, P., Jones, R., Hunt, A., Bolton, L., Eberhardt, D., Westwood, B. A hydrocolloid dressing in wound care in diabetic patients. Advances in Wound Care 1997;10(2):10-12.
29. Bolton L., van Rijswijk L., Shaffer, F. Quality wound care equals cost effective wound care: a clinical model. Nursing Management, 1996: 27(7):30, 32033,37. Also published in Advances in Wound Care, 1997: 10(4):33-38.

30. Bolton L, Zaki, G. Monte, K, Durham, S., Monticello T., Hudak, J., Shannon, R., Wilfinger W. Tissue Repair in Space. *Wounds* July, 1997; 9(4):127-142.
31. Morris, DE., Wu, L., Zhao, LL, Bolton, LL, Roth, SI, Ladin, DA,, Mustoe, TA. Acute and chronic animal models for excessive dermal scarring: quantitative studies. *Plastic and Reconstructive Surgery*, September, 1997; 100(3): 674-681.
32. Bolton, L. Believe it or not. Letter to the editor, *Ostomy/Wound Management*, 1997; 44(9): 1.
33. Lyon R, Veith FJ, Bolton L, Machado F, and the Venous Ulcer Study Group Clinical benchmark for healing of chronic venous ulcers. *Amer J Surg*, 1998; 176:172-175.
34. Bolton, LL, Monte K, Pirone LA. Moisture and healing: Beyond the jargon. *Ostomy Wound Management* 2000; 46 (Suppl 1A): 51S-64S.
35. Hermans MHE, Bolton LL, Establishing a skin integrity program. *Remington Report*, 2001; 9(6) Suppl. 1:6-8
36. McGuckin M, Goldman R, Bolton L, Salcido R. The clinical relevance of microbiology in acute and chronic wounds. *Adv. Skin Wound Care* 2003; 16(1):12-23; CME Quiz: 24-25.
37. Bolton L, McNees P. Wound healing outcomes using standardized care. *J WOCN* 2003; 30(3): S24. (Abstract selected for presentation Merit Award Recipient)
38. Bolton L. Healing acute and chronic wounds. *Hospital Management International* April, 2003: 175-176.
39. Bolton L, McNees P, van Rijswijk L et al. Wound healing outcomes using standardized care *JWOCN* 2004; 31(3):65-71. (Received 2005 JWOCN Award for Best Research Article)
40. Bolton L. Introduction (Guest Editor for May issue dedicated to "Outcomes in Wound Management") *Wounds*, 2004; May 2004; 15.
41. Hermans MHE, Bolton LL. Clinical Consultation: How do we manage critically colonized wounds? *Rehabilitation Nursing* 2004; 29(6):187-194.
42. Smitten A, Bolton L. Burden of pressure ulcer care. In Ayello E. Research Forum. *Advances in Skin & Wound Care* 2005; 18(4):192-193.
43. Bolton L. Modern wound dressings: Yesterday, today and tomorrow. *Expert Nurse* 2005, 12(15):116-119.
44. Bolton LL. What is...Evidence-based medicine? *Advances in Skin & Wound Care*, 2005; 18(3):126.
45. Parish LC, Bolton LL. Evidence-based dermatology and wound healing: Let's get real *SkinMed: Dermatology for the Clinician* 2006; 5(1):6-7.
46. Bolton LL, Corbett L, Bernato DL, Dotson P, Laraus S, Merkle D, Patterson G, Phillips T, McNees P, Porter Riedesel P, Sheehan P and the AAWC Government and Regulatory Task Force. Development of a content-validated venous ulcer guideline. *Ostomy/Wound Management* 2006; 52(11):32-48.
47. Bolton LL. Evidence-based Report Card: Are silver products safe and effective for chronic wound management. *JWOCN* 2006; 33(5): 469-477.
48. Bolton LL. Evidence-based Report Card: Operational definition of moist wound healing. *JWOCN* 2007;

34(1):23-29.

49. Parish LC, Bolton LL. Wound infection: Facts to face. *SkinMed: Dermatology for the Clinician* 2007; 6(1): (in press).
50. Bolton LL. Evidence-based Report Card: Which pressure ulcer risk assessment scales are valid for use in the clinical setting? *JWOCN* 2007; 34(4):368-381.
51. Bolton LL. Evidence-based Report Card: Venous ulcer compression *JWOCN* (in press, Jan 2008)

**Publications: Non-Peer-Reviewed**

- 1 Bolton, L.L., Collier, G.H., Squibb, R.L. Dietary components affecting activity. Proceedings: Eastern Psychological Association Convention, New York, April 1972.
- 2 Bolton, L.L. The behavioral and biochemical effects of lysine deficiency on active and inactive rats. Proceedings: Eastern Psychological Association Convention, Philadelphia, April 1974.
- 3 Bolton, L.L. Effects of bioelectric fields on regenerating systems. Invited panel discussant, American Society of Zoologists Convention, Montreal, December 1977.
- 4 Bolton, L.L., Foleno, B., Means, B. The effects of direct current stimulation on microorganisms in repairing wounds. Proceedings: First Annual Bioelectric Repair and Growth Society, Philadelphia, November, 1981.
- 5 Bolton, L.L. The bioelectrochemical effects of direct current on soft tissue. Invited address, Philadelphia Section, the Electrochemical Society, September 29, 1982.
- 6 Bolton, L.L., Oleniacz, W., Constantine, B., Kelliher, B.O., Jensen, D., Means, B., Rovee, D. Repair and antibacterial effects of topical antiseptic agents. In H. Maibach & N. Lowe (Eds) Models in Dermatology, Vol. 2, Karger, Basel, 1985, pp.145-158.
- 7 Bolton, L.L., Constantine, B. Partial-thickness wound models in small animals. In H. Maibach and N. Lowe (Eds) Models in Dermatology, Vol. 3, Karger, Basel, 1986, pp.190-195.
- 8 Bolton, L.L., Pines, E, Rovee, D.T. Wound Healing and Integumentary System. Experimental Surgery and Physiology: Induced Animals Models of Human Disease, Swindle, M. Michael/Adams, Roberg, J. 1988:1-9.
- 9 Tur, E., Bolton, L.L. Follow-up of the healing process of ischemic ulcers in the guinea pig. Proceedings 13th National Scientific Convention of the Israel Dermatologic Society. Haifa, Israel, October 19-21, 1988.
- 10 Bolton, L., Chen, J., Lydon, M. Occlusive dressings: Expanding Role in Wound Healing-Poster Session: Advanced Wound Healing Symposium. Health Management Publications, April 23, 1989, New Orleans, LA.
- 11 Mulder, G, Bolton L, Lydon M. Resolution of pericapillary fibrin in venous leg ulcers treated with hydrocolloid dressing. Poster. *Symposium for Advanced Wound & Skin Care*, 1992.
- 12 Bolton, L. Wound healing. Invited Chapter section on Wound Healing for Textbook on Dermatologic Surgery, Ron Moy (ed), 1995.
13. Bolton, L.L., Pirone, L. A., Monte, K.A., Shannon, R.J. Swine donor site healing as a function of dressing moisture barrier (MVTR). Proceedings: Wound Healing Society, San Diego, CA, April 1994.

14. Bolton, L., Zaki, G., Monte, K., Shockley, J., Shannon, R., Durham, S., Monticello, T., Fattu, A.J., Wilfinger, W. Spaceflight and Environment Effects on Incision Repair on Rats. Poster: Presented at the Gordon Conference on Wound Healing, New Hampshire, July 1995.
15. Bolton, L., Zaki, G., Monte, K., Shockley, J., Shannon, R., Durham, S., Monticello, T., Fattu, A.J., Wilfinger, W. Spaceflight and Environment Effects on Incision Repair on Rats. Poster: Presented at the American Academy of Dermatology, New Orleans, February 1995.
16. Bolton, L.L., Johnson, C.L., Fattu, A.J. Topical Medications and Pharmacological Agents in Wound Healing. In Prem Gogia (ed) Clinical Wound Management, 1995:SLACK, Inc., Thorofare, NJ, pp.55-72.
17. Allen, R.B., Friedman, P.S., Pryce, C.F.H., Kerstein, M., Klassen, H.J., Lawrence, J.C., Monafu, W., Smith, D., Stanley, J., Thomson, P., Swartz, W. Twomey, J., Vloemans, A.F.J.M., Hutchinson, J., Hermans, M., Bolton, L. Prospective Study of Clinical Infections in Wounds Dressed With Hydrocolloid Versus Conventional Dressings. Poster.
18. Bolton, L., Pirone, L., Monte, K., Hancock, A., van Rijswijk, L. Occlusion and Wound Healing. Poster. Proceedings, Society of Investigative Dermatology, Washington, D.C., May 4, 1996.
19. Bolton, L.L., van Rijswijk, L.. Cost Effective Wound Care. Monograph: *Wound Care: A Clinical Update*. Kerstein, M., ed. May 1996. (CME credit sponsored by Medical College of Pennsylvania/Hahnemann University).
20. Bolton, L.L., van Rijswijk, L. Occlusive dressings. *The Decubitus Ulcer in Clinical Practice*, Springer, September, 1997. L.C. Parish, J.A. Witkowski, J.T. Chrissey (Eds.). Chapter 13. Pages 131-144.
21. Roma, A., Bolton L, McNally A. Controlled clinical evaluations vs case studies: Why wound care professionals need to know the difference. In D. Krasner , D. Kane (Eds) *Chronic Wound Care, Second Edition*, Wayne, PA, Health Management Publications, Inc., December, 1997; pp 373-382.
22. Bolton L, Vasko A, Monte K. Quantification of wound healing. Chapter 17 in Doris Schwindt & Howard Maibach (Eds.) Cutaneous Biometrics, Kluwer Academic/Plenum Publishers, New York, 2000, pp 205-219.
23. Roma-Moore A, Bolton L, McNally A. Controlled clinical evaluations vs. case studies: Why wound care professionals need to know the difference. Chapter 7 in: Krasner DL, Rodeheaver GT, Sibbald RG (Eds.) *Chronic Wound Care: A Clinical Source Book for Healthcare Professionals. Third Edition*, HMP Communications, Wayne, Pennsylvania, 2001, pp 51-61.
24. NPUAP. *Pressure Ulcers in America: Prevalence, Incidence and Implications for the Future*. April 1, 2001. Acknowledged contributor.
25. Evidence Corner Department Editor for the peer-reviewed journal *Wounds* August 2002-Present. 2-page Section summarizing state of the art randomized controlled trial evidence on modalities or techniques in wound care:
  - August, 2002: Outcomes from growth factors, gauze, hydrocolloid dressings
  - September, 2002: Appropriate treatment for pressure ulcers
  - November, 2002: Compression bandaging for venous insufficiency ulcers.
  - January, 2003: Wound measurement
  - March, 2003: Wound pain management
  - May, 2003: Debridement of diabetic foot ulcers
  - July, 2003: Scar alleviation
  - September, 2003: Predicting healing

- November, 2003: Post-operative and rehabilitative nutrition
- January, 2004: Hyperbaric oxygen and healing
- March 2004: Laser stimulation
- May 2004: Surgical Infection diagnosis & prediction
- July 2004: Exudate: matrix metallo-proteases
- September 2004: Sensitization
- November 2004: Spinal Cord Injury
- January 2005: Silver dressings
- March 2005: Negative pressure therapy
- May 2005: Tubular compression for venous ulcers
- July 2005: Surgical and sharp debridement
- September 2005: Radiant heat therapy
- November 2005: Team approach to wound management
- January 2006: Effect of psychological stress on wound healing
- March 2006: Effect of exercise on wound healing
- May 2006: Infection control in burn patients
- July 2006: Preventing surgical infections
- September, 2006: Maggots for debridement
- November, 2006: Ultrasound in wound care
- February, 2007: Venous ulcer dressings
- April, 2007: Diabetic foot ulcer treatment
- June, 2007: Pressure ulcer risk assessment
- August, 2007: Swab or biopsy to diagnose infection.
- October, 2007: Wound closure techniques
- December, 2007: Negative pressure wound therapy

26 Bolton LL. Moist wound healing from past to present. In D Rovee, H Maibach (Eds.) *The Epidermis in Wound Healing Dermatology: Clinical & Basic Science Series*. CRC Press, Boca Raton, FL, 2004.

27 Bolton LL. Letter to Editor responding to query about July 2006 *Evidence Corner* on clipping versus shaving to prevent infections. *Wounds* 2006; 18(10):A19.

28 Bolton LL, Dotson P, Kerstein M. Controlled clinical trials versus case studies: Why wound care professionals need to know the difference. Chapter 7 in: Krasner DL, Rodeheaver GT, Sibbald RG, eds. *Chronic Wound Care: A Clinical Source Book for Healthcare Professionals. 4<sup>th</sup> Edition* Malvern, PA, HMP Communications, 2007, pp 57-66.

**Continuing Education Lecture Topics**

1. Controversies in topical wound management: "Current Concepts on Tissue Trauma Therapy". New York, Woodhull Memorial Hospital, April 1994
2. Advances in Wound Healing using Moisture-Retentive Dressings. *Nursing Rounds* Saratoga, NY, Aug. 1994
3. Pathophysiology of wound healing and basic wound care: *Grand Rounds*, North Carolina Academy of Physicians Assistants. October, 1994.
4. TLC for Leg Ulcers. *Nursing Grand Rounds*, Cleveland Clinic, March 1995.
5. Clinical studies and product evaluations: How to maximize their value. *First Short Hills Symposium*, Short Hills, NJ, April 1995.
6. Wound Management: Updating the Science of Healing. *Dermatology Grand Rounds*, Stanford University, October, 1994.
7. Measuring outcomes in wound management. *Clinical Symposium on Wound Management*, September 1995. (Also *Canadian Association of Wound Care*, 1996; *Western Canadian Association of Wound Care*, May, 14, 1998; *Advanced Wound Care*, San Jose, Costa Rica, July 20-24, 1998)
8. Cost-effective wound management with predictable outcomes. *Advances in Wound Care* Visiting Nurse Service of New York, Brooklyn, NY, June, 1996. (Also *Advanced Wound Care*, San Jose, Costa Rica, July 20-24, 1998)
9. Cost effectiveness in wound management. *7<sup>th</sup> Annual Dermatology Teaching Day for Nursing Staff*, Department of Veterans Affairs, VA Medical Center, Brooklyn, NY, Sept. 18, 1996.
10. State of the art of wound healing: Science or Fiction? *Advances in Wound Therapy for the 21st Century: Continuing Education Symposium*, Virginia Beach, VA, November 7, 1997
11. Wound Healing--The Changing Market Place. *New Technologies, Regulatory Requirements and Reimbursement Strategies*. IBC, San Diego, CA, December 15-16, 1997.
12. Hydrocolloid Dressings in Diabetic Ulcer Care. *Canadian Association of Wound Care*, 1997; *Western Canadian Association of Wound Care*, Winnipeg, May 15, 1998.
13. Moist Wound Healing: Striving for the Optimal Milieu. *American Diabetic Association*, Chicago, June 13, 1998.
14. Moist Wound Healing--March 10, 1999, Grand Rounds, RedBank Medical Center
15. Cost Effectiveness of Modern Wound Care with the Diabetic Patient—May 8, 1999, Grand Rounds, St. Michael's Hospital, Toronto, Ontario
16. Moist Wound Healing—Sept. 24, 1998, Phelps Memorial Hospital Center, Terrytown, NY
17. Wound Healing Physiology—Oct 6, 1998, LaSalle University WOCNEP
18. Don't just cover it, heal it—May 27, 1999, Grand Rounds, Dept of Surgery, University of Calgary, Alberta, Canada, also May 28, Burnaby, BC, Canada
19. Wound care management based on objectives of care—May 26, 1999, Edmonton, Alberta, Canada
20. Optimizing wound care outcomes—September 16, 1999, Halifax, Nova Scotia, Canada
21. Writing your results—*CE Lecture: Clinical Symposium on Wound Management* October 8, 1999
22. Evidence-based wound care outcomes—October 16-19, 1999, Edmonton, Alberta; Winnipeg, Manitoba; Vancouver, British Columbia
23. Wound and skin care management by objectives—October 24, 1999, Lansdale, Pennsylvania
24. Animal models of wound care—CE Lecture: *Symposium for Advanced Wound Care*, April 8, 2000.
25. Pressure ulcer prevention and care. July 6, 2000, San Jose, Costa Rica.

26. Moist wound healing. July 6, 2000, Grand Rounds, San Jose, Costa Rica.
27. Diabetic foot ulcer diagnosis and care. July 7, 2000, Grand Rounds, San Jose, Costa Rica.
28. Cost Effective Wound Care, Sept 29, 2000, Maritime Provinces Wound Care Symposium, St. Johns, Newfoundland
29. Physiology of wound healing: Factors promoting and hindering wound healing. October 9, 2000, Wound, Ostomy and Continence Nursing Education Program, La Salle University Graduate School of Nursing.
30. Moist wound healing, October 31,2000, Friendship Hospital, Beijing, China
31. Physiology of wound healing, November 6, 2000, LaSalle Graduate School of Nursing, Philadelphia, PA
32. Science of Moist Wound Healing, *Burn/Trauma Unit Grand Rounds*, Friendship Hospital, October 27, 2000, Xi'an, China.
33. Cosmetic aspects of the occlusive dressing, November 10, 2000, International Academy of Cosmetic Dermatologists, Rio de Janeiro, Brazil.
34. Biometrics and cosmetic dermatology, November 11, 2000, International Academy of Cosmetic Dermatologists, Rio de Janeiro, Brazil.
35. Cost Effective Wound Management, June 13, 2001, The Greater New York Hospital Assn. Supply chain Services Clinical Update Series (Approved for CEU).
36. Role of Moist Wound Healing in Chronic Wounds, August 16,2001, Cedar Lane Rehabilitation Center, Waterbury, CT (Grand Rounds)
37. New Technologies: Truth and Myth about Outcomes, Nov. 8, 2001, CEU: Southwest WOCN
38. Keynote Address: Synergy in Academia and Industry, December 14, 2001, CME Lecture for Hospital for Joint Diseases, New York University Post Graduate Medical School, St. Thomas--US Virgin Islands
39. *Wound Care and Industry*, CME: First Annual Amer. Prof. Wound Care Assn., St. Mary Medical Center, April 12, 2002, Langhorne, PA
40. Science of Wound Healing, CEU: NYU Medical Center , May 30, 2002, New York, NY.
41. *Integrating Wound Care Research Into Clinical Practice and May the Force be With You: Physical stimuli for wounds*. CEU/CME Aug 16, 2002, Cleveland Clinic Symposium, Cleveland, OH.
42. *Wound Healing: Biology, Evidence & Outcomes* Surgical Grand Rounds: UMDNJ, New Brunswick, NJ October 2, 2002.
43. *Making Cost Effectiveness work for you and your patients*. CME: American Professional Wound Care Association 2<sup>nd</sup> Annual National Symposium, "Wound Care and the Related Sciences" Hilton Philadelphia Airport Hotel, March 27-29, 2003.
44. *Addressing The Wound Care Environment* CEU: Massachusetts General Hospital Annual "Skin and Wound Care Update" May 23, 2003.
45. *Wound Healing Outcomes Using Standardized Care* CEU: 35<sup>th</sup> Ann. WOCN, Cincinnati, OH Convention Center, June 16, 2003.
46. *Research: Adventure with a Purpose* Keynote Address: University of Pennsylvania Department of Rehabilitation Medicine, Third Annual Research Day, June 25, 2003.
47. *Attacking the Icon: The Great Debate on Evidence-Based Medicine*, 7<sup>th</sup> Annual Wound Care Congress, San Antonio, Texas, October 4, 2003.
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### Patents

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**HISTORY PAGE**

OLD REVISION	NEW REVISION	DATE OF CHANGE	CHANGES	DCR
UNRELEASED	A	2/24/2005	1. add reports Clinical Information Leading to the Development of SureSkin® Silver Hydrocolloid Dressing	3249
A	B	2/14/2006	1. The revision will be written by Richard Bradley. The current bibliography will be reviewed and only those papers that directly reference silver ion and its action on wounds and wound microbiology will be used. Only competitive literature that most closely resembles our modality will be used (similar to the predicate device "test" of FDA). Additional references not included when this report was written in July of 2004 will also be added.. Specific footnotes related to the exact citation will be added to various parts of the narrative. The draft of this new revision "B" will be posted here on completion.	4500
B	C	7/6/2006	1. Clinical data review (Report) PLEASE DO NOT REFORMAT DOCUMENT IN ANY WAY 2. Add the revision history page at the end of the document.	5324
C	D	5/13/2008	References were added and tabulated and evidence summary was analyzed for basis of safety and efficacy conclusions. Product safety was summarized relative to currently available silver dressings.	

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