

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

Laura Bolton, Ph.D^a, Adjunct Associate Professor, Department of Surgery (Bioengineering)
University of Medicine and Dentistry of New Jersey and President, BoltonSCI, L. L. C.

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^b 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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^b 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 cm² 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 cm² 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⁺) to kill bacteria in the dressing, enhancing its microbial barrier properties. While not a hydrocolloid Coloplast's Contreet® Foam Dressings^c 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⁺ 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⁺ 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⁺). 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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^c 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^d 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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^d 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) ^e	Silver-related Claims (mg silver/100 cm ² dressing) ^f [Maximum wear time] ^g	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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^e All product names are trademarks of their source companies indicated in parentheses.

^f Approximate silver content per 100 cm² 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.

^g Wear times are provided from websites or package insert instructions or not stated if unavailable.

