

Determination of the Irritating and Sensitizing Propensities of Kerlix[®] AMD[™] Antimicrobial Gauze Dressing on Scarified Human Skin

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INTRODUCTION

Gauze dressings have been a mainstay for dressing wounds, which require absorption of exudate, packing, or debridement of necrotic tissue. While gauze dressings offer some physical protection of the wound from the external environment, gauze is not considered a bacterial barrier. A gauze dressing has been developed which is impregnated with 0.2% Polyhexamethylene Biguanide (PHMB) antimicrobial. At appropriate concentrations PHMB has the ability to suppress microbial growth directly on fiber when microbial contamination is present. The mechanism of action results in an irreversible instability and extensive disruption of the cytoplasmic membrane of the microorganism. The FDA has cleared PHMB's use as an antimicrobial component in wound dressings under the pre-market notification (510k) process.

Chemical sensitivity is a critical consideration when medical devices are used on compromised human tissue. The Repeated Insult Patch Test (RIPT) is a well-accepted standard method to detect a product's propensity to produce contact dermatitis. The RIPT attempts to determine whether a product is a clinically significant skin irritant and the immediacy or cumulative nature of any observed response. In addition, the RIPT is designed to characterize the nature of a product's sensitizing profile. Most forms of delayed contact dermatitis are immunological responses elicited either by prior contact with the sensitizer or by ongoing contact with the sensitizer during the study. Specific objectives included:

- To determine whether 0.2% PHMB is capable of causing visible skin damage under the conditions of the regimen used in this patch test procedure.
- To determine whether any observed skin-damage can be attributed to an irritant or sensitizing activity.
- To determine whether the results observed in the study population provide an adequate level of confidence in the safety of the test material as used by any consumer population.

METHODOLOGY

A prospective comparative study was conducted on 108 volunteer human subjects to determine the potential skin reaction to 0.2% PHMB. An intensified version of the Repeated Insult Patch Test regimen (RIPT) was conducted on scarified skin sites under double blind conditions using a bilateral design. This study design allowed subjects to serve as their own controls while comparing KERLIX[®] untreated gauze to KERLIX[®] gauze impregnated with 0.2% PHMB (Kerlix[®] AMD[™]).

Subjects were required to be at least 18 years of age or older, capable and willing to comply with the study regimen and to sign informed consent. Demographics are described in Table 1.

Table 1. Demographics

Sex	Number of Subjects (N=108)	Age
Female	87	23-81 (x=54)
Male	21	27-82 (x=56)

The regimen schedule entailed four 24-hour applications of the test product and control product conducted serially during each of the first 3 weeks followed by a one-week hiatus. Subjects who did not complete 12 applications during the Induction Phase for a valid reason were asked to return during Week 4 for completion of the Induction phase requirements. During the week 5 Challenge phase, four 24-hour applications were conducted serially on both the original induction site and a naïve site. During weeks 6 and 7, subjects were asked to communicate any information relevant to the effects of their exposure to the products as well as to express a need for treatment of any new or persistent responses. A summary of the treatment schedule is provided in Table 2.

Table 2. Treatment Schedule

		Mon	Tue	Wed	Thu	Fri	Sat	Sun
Initial Phase	WK1	E-S-P	E-P	E-P	E-P	E		
	WK2	Holiday	E-S-P	E-P	E-P	E		
	WK3	E-S-P	E-P	E-P	E-P	E		
	WK4	E-S-P	E	Hiatus or continuation of induction phase				
Challenge	WK5	E-P ^o E-S-P ⁿ	E-P ^o E-P ⁿ	E-P ^o E-P ⁿ	E-P ^o E-P ⁿ	E		
	Follow-up	WK6	E	F/U	F/U	F/U	F/U	
WK7		F/U	F/U	F/U	F/U	F/U		

E=examination/grading; S=scarification of skin; P=control and treatment patch applications; P^o=patch applications to original induction site; Pⁿ=patch applications to naïve site; F/U=follow up period

Bilateral symmetrical contact sites were prepared on each subject's back and divided into horizontal bands. During the Initial phase, the bilateral matched test skin sites were marked on the first examination day of each week and scarified in crosshatch fashion to cleave the superficial layers without eliciting capillary bleeding. The test

and control gauze were moistened with 150mL of physiologic saline and immediately applied and secured to the skin site using occlusive patches consisting of an absorbent webril pad centered on a water-impermeable plastic film. At each subsequent visit during weeks 1-3, the dressings were removed and a technician examined and graded the skin test sites according to the criteria listed in Table 3.

Table 3. Criteria for Grading the Intensity of a Response

STAGES OF INFLAMMATION	VISIBLE CHANGE	CLINICAL SIGNIFICANCE	GRADE
ABSENT	None	Sub-clinical changes that are not perceptible on the skin surface.	0
VASCULAR DILATION	Redness, faint; may not involve all of contact area.	Indicates a very weak to weak inflammation-eliciting propensity.	1
	Redness, faint to moderate, all of contact area involved.	Indicates a mild to moderate inflammation-eliciting propensity.	2
	Redness, intense, all of contact area involved.	Indicates a strong inflammation-eliciting propensity, probably irritation.	3
VASCULAR LEAKAGE WITH INFILTRATION and/or INDURATION	Redness, plus edema and/or papules.	Indicates a strong inflammation-eliciting propensity, possibly sensitization.	4
	Redness, plus vesicles, blisters or bullae.	Indicates a strong inflammation-eliciting propensity, possibly sensitization.	5
	Extension of effect beyond margin of contacted area.	Indicates a strong inflammation-eliciting propensity, possibly sensitization.	6

An independent technician confirmed grading and either a supervisor or investigator resolved any disagreements in grading and validated any significant response, e.g. Grades ≥ 3 or a decrease in value > 2 grades. Grading determined whether subsequent applications should be continued on the same site, switched to a new site, or terminated. A new test skin site was used if the current skin site was graded ≥ 4 . Limit levels are detailed in Table 4. Before being dismissed for the weekends and the hiatus, subjects were given instructions to notify the investigator of a substantial increase in the intensity of a response; the spread of a response beyond the area of contact, or the outbreak of a rash on a previously unaffected site.

Table 4. Limit Levels

Grade	Qualifier	Limit Guideline
≤ 3		Continue test material on current site.
≥ 4		Abandon test material on current site.
≥ 4	within 8 days of initial contact	Pre-sensitization considered; may apply test material to alternate site or terminate in study
≥ 4	during wk 2	Applications resumed on alternate site in wk 3
≥ 4	Monday, wk 3	Applications switched to alternate site
≥ 4	after Monday, wk 3	Applications terminated for remainder of Initial Phase.

RESULTS

Two subjects dropped out before completing the required number of induction applications. Tables 5 and 6 detail the cycles completed for the Induction Phase and Challenge Phase.

Table 5

INDUCTION PHASE – (WEEKS 1, 2, 3, AND 4)					
NUMBER OF APPLICATIONS REQUIRED	NO DATA ACQUIRED		DATA ACQUIRED		
	DROP OUTS	EXCUSED	EXCUSED	NON-COMPLIANT	COMPLIANT
10	1 subject	0 subjects	0 subjects	1 subject	106 subjects

Table 6

CHALLENGE PHASE – (WEEK 5)					
NUMBER OF APPLICATIONS REQUIRED	NO DATA ACQUIRED		DATA ACQUIRED		
	DROP OUTS	EXCUSED	EXCUSED	NON-COMPLIANT	COMPLIANT
10	0 subjects	0 subjects	0 subjects	2 subjects*	106 subjects

*Dropped during Initial Phase

During the Initial Phase, there were 14 Grade 1 responses observed on 7 subjects. Two of the subjects representing 3 responses were observed in the test group; 11 of the Grade 1 responses were noted on 9 subjects in the control group. There were no additional responses observed during the remaining weeks of the Initial Phase or during the Challenge Phase. The responses obtained were insufficient to characterize either the test or control product as having clinically significant skin-irritating propensities. During the follow-up period, no subjects reported new or increased severity of responses. Maximum grades for individual subjects are presented in Table 7.

Table 7. Maximum Assigned Grades Per Individual Participant

GRADE	TYPE OF RESPONSE	INDUCTION No. of Subjects		CHALLENGE No. of Subjects	
		Test	Control	Test	Control
0	No visible change	106	103	106	106
1	Faint redness, undefined border	2	5	0	0
2	Moderate redness, defined border	0	0	0	0
3	Intense redness	0	0	0	0
4	Redness and definite edema and/or papules	0	0	0	0
	Number of responders	2	5	0	0
	Number of subjects patched	108	108	106	106
	Number of subjects providing data	106	106	106	106
	Number providing no data	0	0	2	2

CONCLUSION

The intensified version of the Repeated Insult Patch Test is an established method for detecting human skin irritation, cumulative skin irritation, and potential skin sensitizers in a medical device. This procedure effectively demonstrated that use of a new antimicrobial gauze containing 0.2% PHMB does not elicit any human skin reactions.

The absence of responses demonstrates that the test product is devoid of skin-sensitizing propensities. The test product proved to be incapable of eliciting persistent skin damage of any substantial degree. The findings suggest that the incidence of clinically significant skin damage that will be occasioned by the appropriate use of Kerlix® AMD™ will be very low ($p=0.05$).

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