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Risk Assessment of Kerlix AMD with PHMB
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This document is written to compile information available on the toxicology and pharmacokinetics of PHMB to assess systemic toxicity of Kerlix AMD in clinical use. The information in this document is derived from the following two reports. For complete reference information, please refer to the reports.

- 1). "Risk Assessment of Kerlix MD Antimicrobial Gauze Dressing", Sharon J Northup, September 1, 1999.
- 2). "Risk Assessment of Kerlix MD Gauze Wound Dressing Utilizing PHMB, Shayne C. Gad, October 8, 1999.

Toxicology of PHMB

Toxicology studies of up to 2 years durations have been conducted with PHMB (solutions at different concentrations). The results of the studies establishing systemic toxicity of PHMB are summarized in the table below:

Table 1: Systemic toxicity of PHMB

Assay	Species	Route	Effect (amount PHMB)
Single dose (acute) systemic toxicity	Rabbit	Skin, abraded	MLD (or LD50) >400 mg/kg bw
	Rat	Oral	MLD (or LD50) = 501-549 mg/kg bw
Repeated dose (subchronic) systemic toxicity	Rat	Dermal, 6 hour/day, 5 days, 30 days, 21 total applications	NOEL = 200 mg/kg bw
		Oral, 90 days	NOEL = 84-92 mg/kg bw/day
	Dog	Oral, 6 weeks	NOEL = 90 mg/kg bw/d
Chronic toxicity	Dog	Oral, 1 year	NOEL = 45-46 mg/kg bw
	Mice	Oral, 2 years	MTD = 167-217 mg/kg bw

MLD = Median Lethal Dose LD50 = Lethal dose of 50% of a population NOEL = No Observable Effect Level
 MTD = Maximum Tolerable Dose bw = bodyweight

Pharmacokinetics of PHMB

Studies have established that PHMB is poorly absorbed through intact human skin and when administered systemically is completely and rapidly cleared from the body by excretion in the urine.

- **Absorption:** The absorption of PHMB was measured across isolated human abdominal epidermis using an *in vitro* technique at nominal concentrations of 200 g/l (20%0, 20 g/l (2%0 and 2 g/l (0.2%). The steady state absorption rates were in the range of 0.001 –0.009 micrograph/cm²/h. The results obtained in this study indicate that the absorption of PHMB through human epidermis is extremely slow and low when compared with the absorption rates of other penetrants measured using the same *in vitro* techniques. It could be concluded that dermal absorption of PHMB from normal exposure would be negligible.

- **Metabolism/Excretion:** There is negligible metabolism of PHMB as evidenced by absorption and excretion studies. Oral administration of radio labeled PHMB to rats yielded 7% or less absorption. Only low molecular weight PHMB (1230-1235 Daltons) is absorbed from the intestine and excreted intact in the urine. Kerlix AMD contains PHMB with average molecular weight of 2100-3300 Daltons.

Systemic toxicity study of Kerlix AMD

The systemic toxicity of Kerlix AMD gauze has been evaluated according ISO-10993 appropriate for a surface device contacting breached or compromised surfaces for periods of 24 hours to 30 days. In this test, Kerlix AMD samples were extracted in physiological saline and in sesame oil for 1 hour at 121⁰ C. The extracts were injected into mice and observations were made for toxic reactions for upto 72 hours. No significant acute systemic toxicity was observed.

PHMB release from AMD into wound

PHMB is applied to the gauze by immersion in an aqueous solution of PHMB. The application yields an approximately 2000 ppm PHMB per dry weight of gauze. A certain amount of total PHMB binds to the dressing substrate and is not extractable when it comes in contact with wound fluid. Testing performed on one lot of Kerlix AMD exhibited a total of 1867 ppm PHMB (i.e. microgram PHMB/g gauze). Elution studies showed that out of 1867 ppm only 1353 ppm was unbound to substrate and could be released from the gauze when totally immersed in a saline solution.

- In the clinical use, although a wound would be covered with multiple layers of gauze, only the inner most layer of the gauze would have contact with the skin or wound. For example, if a wound is covered with 6 layers (6-ply) of gauze, only one-sixth of the total PHMB on the gauze dressing would have direct skin or wound contact and as indicated previously, only a part of this PHMB would be released in wound fluids.
- Given the protein and biomembrane binding nature of PHMB, an even smaller proportion of this reduced released amount would be expected to gain systemic distribution.
- High molecular weight could also prevent diffusion across cell membranes limiting systemic absorption.

Clinical use – Potential Exposure Scenario

Case:

- **Patient description:** Male, 40 years old, 6 feet, 205 pounds, Generally healthy
- **Wound description:** 35% total burn surface area wound covering the back and arms
- **Treatment:**
 - Stabilize patient per hospital protocol
 - Wounds are dressed with Kerlix AMD and Silver Sulfadiazine (SSD)
 - Dressing changes with 6 rolls of product twice daily for 7 days, then daily for 14 more days. Kerlix AMD rolls are used for the entire 21 days of treatment

Worst case Assumptions: (To demonstrate theoretical maximum exposure)

- Each Kerlix roll used in packing the wound is in direct contact with the wound.
 - In reality, overlap and outer layers might not have body contact
- The volume of wound exudates is high and it wets all of the dressing rolls (i.e. scenario where the dressing is totally immersed in solution)
- The 100% of possible PHMB released into wound gains complete systemic absorption
 - In actual case, the release of PHMB would be limited based on the volume of wound fluid and determined by absorption rate and duration of exposure.

- In actual case out of total released PHMB significantly less PHMB would pass into systemic distribution for the reasons discussed in previous sections on pharmacokinetics and PHMB release.

Exposure Calculations:

- PHMB elution potential: 1353 microgram/g of gauze
- One Kerlix roll: 37 g weight

1-day exposure: (First 7 days – higher exposure)

1353 microgram/g of gauze **X** 37 g gauze/1 Roll **X** 2 Dressing changes/Day **X** 1 day **X** 6 rolls/Dressing change:

$$= 600732 \text{ micrograms} = 601 \text{ milligrams PHMB}$$

601-mg/92.97 Kg body weight

$$= 6.46 \text{ mg PHMB/Kg body wt/day}$$

Referring to systemic toxicity study results:

- Acute toxicity MLD was found to be >400 mg PHMB/Kg body wt/day. The calculated worst-case exposure of 6.46-mg/kg body wt. is 60X lower.
- The lowest identified dermally applied no observable effect level from a preclinical study of length equivalent to or longer than the proposed potential human exposure was 200 mg/kg in a 30 day rat study which is more than 30X the worst case calculated total exposure.

1-day exposure: (Last 14 days)

1353 microgram/g of gauze **X** 37 g gauze/1 Roll **X** 1 Dressing change/Day **X** 1-day **X** 6 rolls/Dressing change:

$$= 300366 \text{ micrograms} = 300 \text{ milligrams PHMB}$$

300-mg/92.97 Kg body weight

$$= 3.22 \text{ mg PHMB/Kg body wt/day}$$

Average daily exposure

(6.46 X 7 + 3.22 X 14)/21 days

$$= 4.3 \text{ mg PHMB/Kg body wt/day}$$

Referring to systemic toxicity study results:

- The lowest identified dermally applied no observable effect level from a preclinical study of length equivalent to or longer than the proposed potential human exposure was 200 mg/kg in a 30 day rat study which is more than >45X the worst case calculated total exposure (4.3 mg PHMB/kg body wt).
- The lowest identified oral or systemic no observable biologic effect levels for preclinical studies of a length equivalent to or longer than the proposed longest human exposure were 90 mg/kg in a six week dog study (more than 20 X the highest possible human exposure, if complete dermal absorption were to occur) and 84 mg/kg in a 90 day rat oral study (more than 19 X the highest potential human exposure)

Conclusion:

As illustrated the worst-case systemic level is significantly less than the established systemic toxicity level. If the above data is utilized in conjunction with low absorption rates a safety margin of >130 for application to typical surface wounds and a most likely safety margin of >1800 for wounds up to 70% of total body surface area could be calculated. It should therefore be expected that PHMB as a component in this device would not be expected to have any pharmacologic or systemic biologic effect.