# CENTER FOR DRUG EVALUATION AND RESEARCH

# APPROVAL PACKAGE FOR:

# APPLICATION NUMBER

# 21-555

# Statistical Review(s)

# Statistical Review

| | |
|---|---|
| **NDA Number:** | 20-832 (Efficacy Supplement No. 003) Now N 21-555 |
| **Product:** | Chlorhexidine Gluconate 2% (w/v) and Isopropryl Alcohol 70% (w/v) Topical Antiseptic Solution |
| **Indications Requested:** | (1) Patient preoperative skin preparation<br>(2) Preinjection skin preparation |
| **Formulation:** | One-Step Sepp® Applicator |
| **Submission Date:** | December 10, 2001 |
| **PDUFA Date:** | December 10, 2002 |
| **Review Completed:** | August 20, 2002 |
| **Statistical Reviewer:** | George Rochester, PhD |
| **Statistical Team Leader:** | Daphne Lin, PhD |
| **Document Reviewed:** | Phase III Clinical Study - Protocol 990622.MBT |
| **Sponsor:** | Medi-Flex Hospital Products, Inc.<br>8717 West $110^{th}$ Street, Suite 750<br>Overland Park, Kansas 66210 |

## Contents

# 1 Study Description

## 1.1 Study Design (Protocol Number: 990622. [illegible])

A phase III, single-center, uncontrolled, open-label, clinical trial to evaluate the safety and efficacy of SEPP applicators containing ChloraPrep for use as a patient preoperative skin preparation, and preparation of the skin prior to injection in healthy volunteers. The objective of this study was to show that ChloraPrep when packaged as a SEPP® applicator would reduce the residential microbial counts at the abdomen and groin at the respective thresholds specified in the *Tentative Final Monograph for Health-Care Antiseptic Drug products: Proposed Rule* (Federal Register, June 17, 1994).

## 1.2 Indications Requested:

1. Patient preoperative skin preparation
2. Preparation of the skin prior to injection

## 1.3 Background

ChloraPrep has been approved since 2000 as a patient preoperative skin preparation. Current packaging is a 3 mL sponge applicator. The current supplement requests approval of a new packing described as a "One-Step SEPP" applicator. The SEPP applicator is an approved device which is marketed containing a variety of antiseptics. The One-Step SEPP applicator will contain 0.67 mL of chloraPrep solution (Chlorhexidine gluconate 2% (w/v) and Isopropryl alcohol 70% w/v topical solution). An additional indication for preinjection skin preparation is also requested.

## 1.4 Subject Disposition

Healthy subjects between 18-70 years of age, free from dermatoses, dermatitis, inflammation, or injuries to the groin or abdomen, of mixed race and sex, and not currently using topical or systemic antimicrobials, steroids, or any other medication known to alter the normal microbial flora of the skin.

The study was planned to ensure 40 eligible subjects to provide 80 abdominal and 80 groin measurements. Sixty-three subjects were recruited into the "pre-test " phase of the study. Microbiological samples were collected from 45 subjects. Thirty-three (33) of the 45 subjects with microbiological samples had screening counts that were considered appropriate to enter as test subjects. Twenty-six (26) of the 33 subjects completed the study. Post-treatment samples were obtained from 50 abdominal and 40 groin sites.

## 1.5 Efficacy Parameters

### 1.5.1 Efficacy for Preoperative Skin Preparation

A product could be considered effective as a preoperative skin preparation if it reduces the number of colony forming units (CFUs) 2.0 $\log_{10}$ per $cm^2$ of skin on the abdominal sites and 3.0 $\log_{10}$ per $cm^2$ of skin on the groin sites from the average baseline counts within 10 minutes after application of the test material. Additionally, the microbial counts were not to exceed the baseline counts after 6 hours for either the abdominal or the groin sites.

### 1.5.2 Efficacy for preinjection Skin Preparation

A product could be considered effective as a preinjection skin preparation prior to injection if it reduces the number of CFUs 1.0 $\log_{10}$ per $cm^2$ of skin on the abdominal test site within 30 seconds after product use.

## 1.6 Study Procedures

At least 14 days prior to the screening period (pretest period) subjects used a specially prepared kit for personal hygiene as provided by the study coordinator and were asked to avoid certain specific hygiene products. Subjects then entered the screening period (week). Sampling sites were shaved, if necessary, and screening samples were obtained from both groins and abdominal sites (right and left) on the first day of screening. If the screening sample is not 2.2 $\log_{10}$ per $cm^2$ of skin or greater on the abdomen and 4.0 $\log_{10}$ per $cm^2$ of skin or greater on the groin the subject was not eligible to continue in the study.

On test Day 1 a single dose of test material was applied to the right and left abdomen, and either the right or left groin as randomized. Subjects were sampled after 30 seconds, 10 minutes and 6 hours at the abdominal sites, and at 10 minutes and 6 hours for the groin sites.

## 1.7 Results

The average combined screened and baseline $\log_{10}$ CFUs will be compared to the $\log_{10}$ CFU at 30 seconds for the abdominal sites, and 10 minutes and 6 hours for both the abdominal and groin sites utilizing the Student's t-test for paired data.

Table 1 shows the distribution of the $\log_{10}$ CFUs for the abdominal counts at three time points. The median and mean counts were similar at all time points. The standard deviation at the 30 second time point was slightly larger than those at either 10 minutes or 6 hours. The maximum counts were similar for all time points. The two-sided 95% confidence intervals (C.I.) are also

shown. These data suggest that the test material reduced the average microbial counts of 2 $\log_{10}$ reductions (2.24, 3.02) at 30 seconds and 2 $\log_{10}$ reductions (2.45, 3.08) at 10 minutes. At six hours the CFU were at least 1.77 $\log_{10}$ unit reduction below the average baseline microbial counts.

Table 1. $\text{Log}_{10}$ Reductions of Colony Forming Units of Microbial Counts from Average Baseline Counts at the Abdominal Sites

| Time Point | Min. | Median | Mean | Max. | Std. Dev. | t-test (95% C.I.) |
|---|---|---|---|---|---|---|
| N=50 Samples | | | | | | |
| 30 Seconds | -0.86 | 2.52 | 2.63 | 4.31 | 1.37 | (2.24, 3.02)[a] |
| 10 Minutes | 0.06 | 2.22 | 2.55 | 4.31 | 1.11 | (2.45, 3.08)[a] |
| 6 Hours | -0.15 | 2.26 | 2.11 | 4.30 | 1.17 | (1.77, 2.44)[b] |

[a] *One sample t-test against a null hypothesis of 2 $\log_{10}$ reductions.*

[b] *One sample t-test against an null hypothesis of no change from baseline.*

Table 2 shows the distribution of the $\log_{10}$ CFUs for the counts from the groin sites at two time points. The median and mean counts were similar at both time points. The standard deviation at the 6 hour time point was slightly larger that at 10 minutes. The two-sided 95% confidence intervals (C.I.) are also shown. These data suggests that at 10 minutes the test material achieved a 3 $\log_{10}$ (3.48, 4.26) reduction in CFUs and maintained a $\log_{10}$ reduction of at least 2.61 $\log_{10}$ units below the average baseline counts at 6 hours after ChloraPrep was applied to the groin.

Table 2. $\text{Log}_{10}$ Reductions of Colony Forming Units of Microbial Counts from Average Baseline Counts at the Groin Sites

| Time Point | Min. | Median | Mean | Max. | Std. Dev. | t-test (95% C.I.) |
|---|---|---|---|---|---|---|
| N = 40 Samples | | | | | | |
| 10 Minutes | 0.50 | 4.18 | 3.87 | 4.57 | 1.21 | (3.48, 4.26)[a] |
| 6 Hours | 0.43 | 3.22 | 3.10 | 5.77 | 1.53 | (2.61, 3.58)[b] |

[a] *One sample t-test against a null hypothesis of 3 $\log_{10}$ reductions.*

[b] *One sample t-test against a null hypothesis of no change from baseline.*

## 1.8 Safety

An adverse reaction scoring form was used to record indicators of skin irritation. No adverse experiences were reported in this study.

# 2 Conclusion

## 2.1 Preoperative Skin Preparation

Based on the data from this clinical study, the test product meets the criteria for preoperative skin preparation of reduction in CFUs of 2.0 $\log_{10}$ per $cm^2$ of skin on the abdominal sites and 3.0 $\log_{10}$ per $cm^2$ of skin on the groin sites from the average baseline counts within 10 minutes after application of the test material. The microbial count after 6 hours for either the abdominal or groin sites were less than the average baseline counts.

## 2.2 Preinjection Skin Preparation

As a preinjection skin preparation it reduces the number of CFUs 1.0 $\log_{10}$ per $cm^2$ of skin on the abdominal test site within 30 seconds after product use.

## 2.3 Comment

While the criteria for both the patient preoperative skin preparation and preinjection skin preparation appear to be met this was a non-comparative, open-label, single-center, clinical study. The study does not provide a basis for interpretation of the results without a comparison group. Without a control group the internal validity of the study is not assured. This study design does not meet the standards usually applied to antiseptic drug products.

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/s/

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8/21/02 05:46:53 PM
BIOMETRICS

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No
Biopharmcological
review requested.

DSI not consulted for this application.