CENTER FOR DRUG EVALUATION AND RESEARCH

APPROVAL PACKAGE FOR:

APPLICATION NUMBER

21-555

Medical Review(s)

OTC MEDICAL OFFICER'S REVIEW

Department Of Health and Human Services
Food and Drugs Administration
Center For Drug Evaluation and Research
Division of Over-the-Counter Drug Products (HFD-560)

NDA #:	**20-832/SE1-003**
Drug name:	**ChloraPrep® One-Step (Chlorhexidine Gluconate 2%/Isopropyl Alcohol 70%)**
Sponsor:	**Beckloff Associates, Inc.**
Pharmacologic Category:	**Antiseptic**
Proposed Indications:	**Patient Preoperative Skin Preparation** **Patient Preinjection Skin Preparation**
Dosage Form:	**Solution**
Route of Administration:	**Topical**
Submission dates:	**December 12, 2001** **April 19, 2002**
Review date:	**April 30, 2002**
Reviewer:	**Daiva Shetty, MD**

Introduction and Background:
This is a clinical safety review for the supplemental New Drug Application for ChloraPrep One-Step antiseptic topical solution.

The original NDA for ChloraPrep One-Step Antiseptic Topical Solution in 3-mL applicators had been submitted on January 8, 1997, and subsequently approved on July 14, 2000. In the current submission, the sponsor is requesting an approval of an additional applicator, the Sepp®, for chlorhexidine gluconate 2% (w/v) topical solution for the approved indication of patient preoperative skin preparation and for a new indication of patient preinjection skin preparation. In support of this supplemental application, the sponsor has submitted the following information:

1. Draft labeling,
2. Chemistry, manufacturing and controls information,
3. Results of the efficacy trial, and
4. Safety update.

This review will cover only the safety update data. The Division of Anti-infective Drug Products (HFD-520) will review the indications, directions for use, and efficacy for ChloraPrep One-Step Sepp Applicator.

Safety Data Review:
Since the July 14, 2000, approval and release of the One-Step 3-mL applicator containing Chlorhexidine Gluconate 2% (w/v) and Isopropyl Alcohol 70% (v/v), there have been five adverse events reported. All of the reports were limited to the site of application on the skin, and were assessed by the sponsor as non-serious. No attributable risk was reported for any of these cases. The following information has been provided by the sponsor about those events:

- One adverse event occurred due to the combination use of the Ioban dressing (i.e., a dressing that is impregnated with povidone-iodine) on a patient with known sensitive skin.
- One adverse event occurred due to shaving the insertion site where micro-abrasions were apparent on the skin surface.
- Three adverse events occurred due to aggressive irradiation treatment of cancer patients, which left the skin compromised and sensitive to alcohol and/or chlorhexidine.

The Frepp and Sepp applicators, containing Chlorhexidine Gluconate 2% (w/v) and Isopropyl Alcohol 70% (v/v), have been distributed in Canada since 1996, with no adverse events reported.

Comments:
The data provided by the sponsor shows a generally safe profile for ChloraPrep since approval over a year ago. There were no serious adverse events reported. The five adverse reports reported by the sponsor were limited to a local skin reaction.

There are no adverse events reported for ChloraPrep in the FDA's adverse event reporting system database.

Current label for the ChloraPrep One-Step 3-mL applicator, and the proposed label for the Sepp applicator already have several warnings addressing skin sensitivity to the product. The new proposed delivery device contains relatively small amount of the drug (0.67 mL). Experience with already approved higher amount of the drug containing applicator shows an acceptable safety profile of the product for OTC market. Therefore, the new proposed ChloraPrep One-Step Sepp applicator is approvable from a safety standpoint.

Recommendations:
Based on the postmarketing safety update data review, the application is approvable for OTC use. Overall approval, for the desired indication, is pending efficacy data review.

/S/

Daiva Shetty, M.D.
Medical Officer, DOTCDP
HFD-560

Concurrence:

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Clinical Consultative Review of Efficacy supplement
NDA 20-832/S-003

Date of Consult Request: January 8, 2002

Date HFD-520 Received: January 18, 2002

Date Assigned to Reviewer: January 18, 2002

Date of Submission: December 10, 2001

Date CDER Received: December 12, 2001

Date of Review Initiation: January 22, 2002

Date of Review to Supervisor: February 12, 2002

Drug: ChloraPrep (chlorhexidine gluconate 2% w/w and isopropyl alcohol 70% w/v)
One-Step Patient Preoperative Skin Preparation

Applicant: Medi-Flex Hospital Products, Inc.
Overland Park, KS 66210

Indications: Patient preoperative skin preparation

Reason for Supplement: Addition of a new packaging configuration for the product, identified as a Sepp applicator; and addition of a new indication, for patient preinjecction skin preparation (for the Sepp applicator only).

Background: ChloraPrep has been approved since 2000 as a patient preoperative skin preparation. The product is presently packaged in a 3 mL sponge applicator. The Sepp applicator has already been approved as a medical device and is marketed containing a variety of antiseptics, including alcohol. It consists of a crushable glass ampule which is filled with 0.67 mL of the ChloraPrep solution. The ampule is sealed and placed in a plastic tube which is sealed at one end. At the other end of the plastic tube is an polyester applicator tip. To use, the ampule is broken through the plastic tube and the drug flows onto the application tip.

Material submitted: The sponsor has submitted a description of the device, along with a patient preoperative skin preparation study which follows the procedure in the Tentative Final Monograph (TFM) for Heath Care Antiseptics. This study includes evaluation of the product both as a patient preoperative skin preparation and as a skin preinjection preparation. The study is uncontrolled. Labeling for the new dosage form and indication are also enclosed.

This review will consist of the following sections:

I. Review of Efficacy Study
II. Review of Labeling
III. Conclusions and Recommendations

I. Review of Efficacy Study

Study Title: Evaluating the Safety and Efficacy of Sepp Applicators Containing ChloraPrep for Use as a Patient Preoperative Skin Preparation and Sepp Applicators Containing ChloraPrep for the Preparation of the Skin Prior to Injection (Protocol No. 990622. —

Investigator:

Study Dates: November 12, 1999 – January 21, 2000

Study Objectives: The following is taken directly from p. 3 of the study summary:

> To evaluate the safety and the immediate and persistent antimicrobial properties of a test preoperative skin preparation drug product (2% chlorhexidine gluconate in 70% isopropyl alcohol), and to evaluate the test product for preparation of the skin prior to injection.

Method:

1. Study design: This was a single-center, open-label, uncontrolled study during which the ability of ChloraPrep packaged in the Sepp device to lower residential bacterial counts at the abdomen and groin was measured. The methodology was based on that recommended in the TFM for evaluating patient pre-operative skin preparations and preparations for use on the skin prior to an injection. Test subjects were required to have sufficient numbers of resident bacterial flora to permit evaluation of TFM standards for microbial reduction. Thirty-three test subjects had baseline counts sufficient for study entrance. Although not specifically stated in the summary, it appears that 25 test subjects completed the abdomen portion of the study, and 20 test subjects completed the groin portion of the study.

2. Inclusion criteria: Healthy subjects between the ages of 18 and 70 years who had no evidence of dermatological conditions or injuries to the drug application sites were entered. In order to participate, the subject must have had a baseline level of at least 2.2 $\log_{10}$ Colony Forming Units (CFU) per cm^2 at the abdomen site and /or at least 4.0 $\log_{10}$ CFU/cm^2 at the groin site.

3. Exclusion criteria: The following is taken directly from p. 5 of the protocol for the study:

   - Allergies or sensitivities to alcohol, adhesive tape, latex gloves, or chlorhexidine gluconate.
   - Pregnant or nursing females
   - Active skin rash or a break in the skin at the test sites
   - Contact dermatitis
   - Participation in a clinical study where treatments were applied to the abdomen or groin within 14 days prior to treatment application for this study
   - Receipt of systemic or topical antibiotic medication, steroids, or any other product known to affect the normal microbial flora of the skin
   - Insulin-dependant diabetics or individuals taking medication that may interfere with the study results
   - Immunocompromised or HIV –infected individuals
   - Subjects with a history of alcohol abuse and/or illicit drug use
   - Individuals with heart murmur or mitral valve prolapse
   - Individuals not willing or not able to fulfill protocol requirements

4. Dosage and duration of therapy: Test subjects were screened for minimum bacterial counts as outlined in inclusion criteria, above. On the first test day, patients were evaluated for baseline skin irritation scores (see Safety evaluation below). Each subject was treated on both sides of the body (e.g. left and right abdomen) so the total number of test readings is twice the number of subjects. Each treatment area was approximately 6 x 7 cm. Sampling sites for the various sampling times were designated randomly within the larger 6 x 7 cm site. Sampling was done at baseline and at 30 seconds, 10 minutes and 6 hours after drug application at the abdomen site and at baseline and 10 minutes and 6 hours after drug application at the groin site. The test sites were covered with a gauze bandage after the 30 second and 10 minute sample to minimize contamination from external sources. Information concerning the microbial sampling procedure may be found in the Microbiology Review for this supplement. Skin irritation was also scored at the various sampling times.

   The scrub procedures used were: application at the abdomen site with the Sepp device for 30 seconds, followed by 30 seconds of air drying; and application at the groin site with the Sepp device for 2 minutes, followed by 1 minute of air drying.

5. Effectiveness parameters: The TFM standard for patient preoperative skin preparations are a decrease of 2 logs in the baseline microbial counts at a dry test site (abdomen) within 10 minute of drug application, with the count not to exceed baseline for at least 6 hours. The requirement is similar for a "wet" test site (groin), though the 10 minute reduction is to be 3 logs, rather than 2.

The TFM standard for preparation of the skin prior to an injection is a decrease of one log in the baseline microbial count at a dry test site within 30 seconds of drug application.

6. Safety evaluation: Adverse reactions were recorded, and skin irritation was evaluated at each time point. The protocol provided a scoring scale for skin irritation, but since no irritation was noted at any point in the study, the scale will not be reproduced here.

Results: By prior agreement between the supervisory microbiologist/HFD-520 and the clinical review team, the critical analyses of the bacterial reduction results for topical antiseptics are to be performed by the microbiologist. Therefore, the following results are identical to those presented by the applicant.

1. Efficacy:

   a. Abdominal site. A total of 49 test values were obtained at the abdomen site. The mean log reductions were as follows:

Mean Log_{10} Reduction (n =49)

30 seconds	10 minutes	6 hours
2.63	2.77	2.11

   b. Groin site. A total of 40 test values were obtained at the groin site. The mean log reductions were as follows:

Mean Log_{10} Reduction (n=40)

10 minutes	6 hours
3.87	3.10

2. Safety: No adverse events or irritation were observed during the study.

Reviewer's Comment: These results indicate that the product meets the TFM requirements for both patient preoperative skin preparation (10 minute and 6 hour results) and for patient preinjection skin preparation (30 second results). This study is flawed in that it does not include a control product. The control product (typically Hibiclens, which contains 4% chlorhexidine gluconate) is necessary to validate the conduct of the study. This is possible because the activity of Hibiclens in studies of this type is well-known. However, the reviewers are prepared to accept this study because ChloraPrep contains 70% isopropyl alcohol, (IPA) which is included in the TFM as effective for both patient preoperative skin preparation and patient preinjection skin preparation. The principal reason for conduct of this study was to establish that the Sepp device did not interfere with the already

known effectiveness of IPA alone and in combination with chlorhexidine. This objective has been accomplished. It must be noted that the open, uncontrolled design of this protocol is not acceptable for most studies of this type.

II. Review of Labeling

The sponsor has submitted labeling which is identical to that previously approved for this product, with the following exceptions:

1. The "Use" section now includes preparation of the skin prior to injection.

2. The Directions section provides information on breaking the ampule which is appropriate to the Sepp device, rather than the winged device which was originally approved.

3. The maximum treatment area covered by one drug/device system is 2.5 by 2.5 inches (rather than 4 x 5 inches covered by the 3mL applicator already marketed). This information should be included in the "Use" section of the labeling, as follows:

   Use: for the preparation of the patient's skin prior to surgery or injection. The maximum treatment area for one applicator is approximately 2.5 by 2.5 inches.

   Please see the discussion of coverage area below.

4. Because the individual Sepp package is small, it bears only the trade name, ingredients of the product, company name, lot number and the following statements: "Warning. Flammable. Keep away from fire or flame. Do not use with electrocautery procedure. Applicator sterile unless seal is broken". This is acceptable.

Reviewer's Comment: **The proposed labeling is acceptable, with the revision noted in item number 3 above. Because the area covered by one Sepp device is so small, there is some question concerning whether any surgical procedure is small enough to justify approval of the product as a patient preoperative skin preparation. A CDER employee who is also a surgeon (Wiley Chambers, M.D.) was consulted on this matter. Dr Chambers states that punch biopsies would be performed by cleaning an area this small. Therefore, there is no objection to approval of the Sepp device for the patient preop indication, though it is felt that the coverage area for the product should be emphasized in the labeling.**

III. Conclusions and Recommendations

This supplemental application may be approved from a clinical standpoint. It should be understood that the microbial reduction study submitted in support of this supplement would not be acceptable in most circumstances because it is uncontrolled. However, since one of the active ingredients, 70% isopropyl alcohol, is acceptable under the TFM for both requested indications, it is felt that the requirements for a positive control in this study may be waived.

The following comments are pertinent:

1. This is a combination product. If the product were unapproved, it would be necessary to do studies which establish that both active ingredients contribute to the total effect of the product. Since these studies were done in support of the original NDA, it is not necessary to repeat them.

2. It may be useful to point out that the immediate (30 second) antimicrobial effect of this drug is supplied exclusively by the IPA. Chlorhexidine gluconate takes longer to act.

A favorable review from HFD-520 microbiologist is necessary prior to the approval of this product.

/S/

David C. Bostwick

/S/

Jean Mulinde, M.D.

CC: HFD-520/Soreth
HFD-560/Katz
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