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Subject: Irritation Potential of ChloraPrep® and FDA's Non-Allowance of ChloraPrep as a Catheter Site Maintenance Preparation

The following pages are excerpts from FDA's Medical Review of Medi-Flex, Inc.'s New Drug Application for ChloraPrep (NDA# 20-832) and address studies reviewed by the FDA consistent with those reported in the PowerPoint presentations available for download at http://www.aplicare.com/NP_ExCel-AP1.htm showing Aplicare's ExCel_{AP}® formulation being significantly less irritating than ChloraPrep.

The entire Medical Review document can be downloaded from the FDA web site at http://www.fda.gov/cder/foi/nda/2000/20-832_CHLORAPREP%20ONE-STEP%20ANTISEPTIC_medr.pdf. All documents published by FDA associated with this application can be found at http://www.fda.gov/cder/foi/nda/2000/20-832_CHLORAPREP.htm

On page 2, paragraph 3 (below), the reviewer states:

“When this NDA was originally submitted in 1997, it was indicated for use as [redacted]. In the resubmission, the requested indication is patient preoperative skin preparation.”

As explained below, the redacted indication sought but not allowed was for catheter site maintenance. As indicated in FDA's statements below, in spite of Medi-Flex's statements in their literature and oral presentations to the contrary, ChloraPrep is only approved by the FDA for use as a single use, Patient Preoperative Skin Preparation and **not** as a repeated use product.

Under item #3 in the Background section, the reviewer goes on to say:

“3. The combination product appears to be too irritating to be used under occlusive dressings. In any resubmission of this application, information/data must be presented which establish the safety of such use, given that the irritancy and sensitisation testing suggest that the product would be unacceptable to the patient when used under occlusion.”

At the bottom of page 14 under Section II (Safety Summary) of this Medical Review, the reviewer states:

“The safety data presented in support of this NDA establish that ChloraPrep is acceptably safe for its intended use.”

It's important to note that from the reviewer's perspective, the intended use is as a single use Patient Preoperative Skin Preparation and **not** as a repeated use product – see below.

In that same section, the reviewer goes on to say:

"The following comments are pertinent:

1. In the Clinical Review of this NDA dated December 23, 1997, the Safety Summary noted that ChloraPrep demonstrated a relatively high potential to cause irritation and sensitization reactions in predictive skin testing. It scored much higher in irritancy testing than Hibiclens [redacted]. Concern was also voiced that repeated use could exacerbate the irritation/sensitization possibilities."

At the top of the following page (15), the reviewer goes on to say:

"These concerns have been satisfied by the decision to indicate the product for use as a patient preoperative skin preparation. This is a one time use [redacted]. Thus, while the product is irritating, its intended indication does not prohibit its use. The margin of safety available to the patient under these conditions is acceptable."

Conclusions:

1. As evidenced by Aplicare's ExCel_{AP}® formulation passing the FDA-prescribed 21-Day Cumulative Skin Irritation Test for repeated use products (see pages 3 and 4 of the ExCel_{AP} Technical Bulletin available at www.aplicare.com/library and data presented in the PowerPoint presentations available at www.aplicare.com/NP_ExCel-AP1.htm) and the fact that ChloraPrep was not able to pass similar tests submitted to the FDA (see above), it can be concluded that ExCel_{AP} is significantly less irritating than ChloraPrep.
2. ChloraPrep is only approved by the FDA for use as a single use, Patient Preoperative Skin Preparation and **not** as a repeated use product.

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RESEARCH**

APPLICATION NUMBER:
20-832

MEDICAL REVIEW

A similar formulation was marketed under NDA 18-049. This product was marketed as Hibitane Tincture, and was used as a patient preoperative skin preparation. This product was withdrawn from the market by the applicant because it occasionally pooled under patients when used too liberally as a preop. When electrocautery equipment was employed in proximity to the pooled product, it ignited and caused serious burns to the patients involved.

The small amounts of material contained in the ChloroPrep packaging configuration makes accidental ignition of the drug unlikely. The labeling should still bear warnings about the flammability of the product.

Background: When this NDA was originally submitted in 1997, it was indicated for use as [redacted] [redacted] In the resubmission, the requested indication is patient preoperative skin preparation. The original application was made not approvable on February 20, 1998 for a variety of reasons, principally in the areas of microbiology and clinical studies. The deficiencies in each submitted clinical study were detailed in the not approvable letter. For the purposes of this review, the following points which have been taken directly from the letter, summarize the principal clinical deficiencies for the product as originally labeled:

1. There is no study to establish the contribution of each active ingredient (CHG and IPA) to the effect of the product. Specifically, no study contains a CHG alone arm.
2. There is no study which establishes the efficacy of the product at a "dry" skin site. Studies have been submitted using forearm, chest or clavicle sites, but they are flawed by artificial elevation of resident bacteria, small numbers of subjects, or failure to test for the contribution of each active component to the total effect of the product. This is especially important because the testing submitted to date (i.e., with 24 hour evaluation points) indicates that the product is intended for use in conjunction with [redacted] which are commonly placed at "dry" sites.
3. The combination product appears to be too irritating to be used under occlusive dressings. In any resubmission of this application, information/data must be presented which establish the safety of such use, given that the irritancy and sensitization testing suggest that the product would be unacceptable to the patient when used under occlusion. Specifically, the resubmission should discuss the possibilities for sensitization and/or irritancy reactions under the proposed conditions of use [redacted]

Subsequently, the sponsor, in conjunction with their CRO, Beckloff Associates [redacted] [redacted] Instead, a new clinical program was designed to establish the effectiveness of the product as a patient preoperative skin preparation, which is one of the standard uses for topical antiseptics. Please refer to the earlier clinical review of this NDA dated December 23, 1997 for further background on this product.

**Table 11. Differences Between ChloroPrep and 2% CHG
in Log Reductions from Baseline Bacterial Counts (CFU/cm²)**

Time Point/Site	Study 990326.HTR		Study 990326.MBT	
	Difference	p-value	Difference	p-value
Abdomen				
10 minutes	0.22	0.09	0.19	0.19
6 hours	-0.03	0.59	0.35	0.22
24 hours	0.57	0.028	0.08	0.70
Groin				
10 minutes	0.81	0.27	0.34	0.006
6 hours	0.07	0.83	0.15	0.38
24 hours	0.17	0.65	-0.19	0.88

In both studies, ChloroPrep easily met the requirements for patient preoperative skin preparations as outlined in the TFM. Further, the product kept microbial counts well below baseline for 24 hours (though it must be mentioned that the individual components of the combination also maintained some reduction at 24 hours).

When compared to its individual components, ChloroPrep was superior to IPA alone at 24 hours at both the groin and abdomen sites in the Hill Top Research study and at 10 minutes at the groin site in the Micro Bio Test study. Also, ChloroPrep was superior to 2% CHG alone at 24 hours at the abdomen in the Hill Top Research study and at 10 minutes at the groin in the Micro Bio Test study. Though the results of the studies were not consistent, it is seen that at some time and test site, ChloroPrep was shown to be superior to its ingredients in both studies.

II. Safety Summary

The safety data presented in support of this NDA establish that ChloroPrep is acceptably safe for its intended use. The following comments are pertinent:

- In the Clinical Review of this NDA dated December 23, 1997, the Safety Summary noted that ChloroPrep demonstrated a relatively high potential to cause irritation and sensitization reactions in predictive skin testing. It scored much higher in irritancy testing than Hibiclens.

Concern was also voiced that repeated use could exacerbate the irritation/sensitization possibilities.

These concerns have been satisfied by the decision to indicate the product for use as a patient preoperative skin preparation. This is a one time use [redacted]

Thus, while the product is irritating, its intended indication does not prohibit its use. The margin of safety available to the patient under these conditions is acceptable. However, the labeling should bear a statement concerning the irritancy potential of the drug, and warn against its repeated use in the same subject.

2. This product is flammable. While the immediate container label has adequate warnings concerning this, other components of the labeling should include flammability statements (see Review of Labeling, below).
3. There were five adverse events in the Hill Top Research study and four adverse events in the Micro Bio Test study which in the opinion of the reviewers could have been associated with drug use. These were all localized at the test site and consisted of rashes (at the Hill Top Research site) or redness/drying/irritation (at the Micro Bio Test site). These reactions are consistent with use of an irritating topical product especially when occlusion takes place (as in these studies after the 10 minute reading).
4. No pediatric data has been submitted with this application. It is reasonable to expect that this product will be used in children who require surgery. There is no reason to expect that the drug will be more or less efficacious in children than in adults, and the efficacy data may therefore be extrapolated to the pediatric population. Because of the irritancy potential of ChloroPrep, there is concern that it may be more hazardous to the pediatric population than to adults. Dr. Martin Okun, a Team Leader in the Division of Dermatologic and Dental Drug Products was asked at what age the skin of the infant becomes as competent as that of the adult in terms of resistance to irritants, absorption rates, etc. His reply, which is consistent with answers to similar questions the reviewers have posed in the past, states [in part]:

“ In summary, I would think that the permeability of > 2 month old skin is essentially that of adult skin, remembering that there is tremendous regional variability [i. e., face skin more permeable than palm skin].”

On this basis, it seems prudent to warn against using ChloroPrep in children less than 2 months of age due to its irritancy potential and the