CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

20-832

MEDICAL REVIEW

CLINICAL REVIEW OF NDA 20-832
Resubmission

MAY - 5 2000

Date of Resubmission: January 13, 2000. Original submission dated January 8, 1997.

Date CDER Received: January 14, 2000

Date Assigned to Reviewer: January 19, 2000

Date Review Initiated: February 8, 2000

Date Review to Supervisor: April 4, 2000

Drug: ChloraPrep One-Step Antiseptic (2% chlorhexidine gluconate/70% isopropyl alcohol).

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

Related IND: [redacted]

Proposed Indication: Patient preoperative skin preparation.

Proposed Dosage and Administration:

[redacted] Dry [redacted] repeated back and forth strokes of the sponge [redacted] Completely wet the treatment area with antiseptic. [redacted] Allow the area to air-dry for approximately [redacted] (30) seconds. Do not blot or wipe away.
[redacted] Moist [redacted] repeated back and forth strokes of the sponge [redacted] Completely wet the treatment area with antiseptic. [redacted] Allow the area to air-dry for approximately one (1) minute. Do not blot or wipe away."

Packaging: The drug is packaged in a 3mL crushable glass ampule which is placed inside a plastic housing attached to a sponge. The user squeezes the ampule through the plastic housing, which breaks the ampule and releases the drug to the sponge applicator.

Related NDA's:

There are a number of NDA's approved which contain chlorhexidine gluconate in amounts from 0.5% to 4.0%. However, there is only one approved NDA for a product which is still marketed and contains both chlorhexidine gluconate (CHG) and a large (greater than 10%) amount of alcohol. This is NDA 18-300, Hibistat Germicidal Hand Rinse, which contains 0.5% chlorhexidine gluconate and 70% isopropanol (IPA). This product is marketed as a health-care personnel handwash, both as a liquid and impregnated onto a towelette.

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 This product was withdrawn from the market by the applicant because it occasionally pooled under patients when used too liberally as a preop.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 ChloraPrep 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] 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] 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.

Material Reviewed: The applicant has submitted two new studies concerning the efficacy of the product as a patient preoperative skin preparation.

Study No.	Design	No. Subjects
990326.HTR	Paired comparison of 2% CHG/IPA, IPA alone and 2% CHG alone (abdomen and groin)	106
990326.MBT	Same	74

This review will consist of the following sections:

I. Review of Pivotal Efficacy Studies and Efficacy Summary

II. Safety Summary

III. Review of Labeling

IV. Conclusions and Recommendations

Other Reviews: Reviews from other disciplines are not available at this time. It appears that only microbiology, chemistry and statistical reviews are necessary, since the pharmacology and biopharmaceutics reviews were satisfactory for the original submission.

I. Review of Pivotal Efficacy Studies and Efficacy Summary

A. Study Title: Comparison and Evaluation of a Topical Antiseptic Test Product (ChloraPrep™), and Active Control Product, and a Reference Product for Use as a Patient Preoperative Skin Preparation Drug Product (Protocol No. 990326.HTR).

Investigator: Gayle Mulberry, M.S.
Hill Top Research, Inc.
Miamiville, OH 45147

Study Dates: July 26-October 29, 1999.

Study Objectives: The following is taken directly from p. 46 of the volume 4.2 of the NDA resubmission:

> To evaluate and compare the immediate and persistent antimicrobial properties of the test product (2% chlorhexidine gluconate in 70% isopropyl alcohol) with an active control product (2% chlorhexidine gluconate) and a reference product (70% isopropyl alcohol).

To evaluate and compare potential skin irritation of all three drugs.

Method:

1. Study design: This was a single-center, randomized, paired-comparison study in normal volunteers. ChloraPrep was compared to its vehicle (70% IPA) and an aqueous 2% CHG solution, using methodology based on that recommended in the Tentative Final Monograph (TFM) for Health Care Antiseptic Drug Products for evaluating patient pre-operative skin preparations. Test subjects were required to have sufficient numbers of resident bacterial flora to permit evaluation of TFM standards for microbial reduction. One hundred six test subjects were required to obtain sufficient numbers with the required baseline microbial levels at the two test sties (abdomen and groin).

Approximately 40 evaluable test sites (abdomen) and 25 evaluable test sites (groin) were treated with each of the test products. These numbers of test sites have been shown in the past to be sufficient to statistically demonstrate the effect of drugs of this type.

2. Inclusion criteria: The following is taken directly from p. 55 of volume 4.2 of the NDA submission:

Healthy subjects between 18 – 70 year of age with no evidence of dermatoses, dermatitis, inflammation, or injuries to the drug application sites on the abdomen or groin who are not excluded by the criteria listed below will be admitted into the study.

3. Exclusion criteria: The following is taken directly from p. 55 of volume 4.2 of the NDA submission:

Subjects with the following conditions will be excluded from 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 the past 30 days
- Receipt of systemic or topical antibiotic medication, steroids, or any other product known to affect the normal microbial flora of the skin
- Insulin-dependent 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

Subjects will not be enrolled in the study if the screening sample on the right or left abdomen does not contain at least 2.2 $\log_{10}$ CFU/cm^2 of skin or the screening sample on the right or left groin does not contain at least 4.0 $\log_{10}$ CFU/cm^2 of skin.

4. Dosage and duration of therapy: This study was performed using a modified protocol for patient preoperative skin preparations suggested in the TFM. Test subjects were screened for minimum bacterial counts as outlined in exclusion criteria, above. On the first test day, patients were evaluated for baseline skin irritation scores (see Safety evaluation below for scoring scales). Each test subject was assigned 2 of the 3 test materials. One material was applied to one side of the abdomen or groin and one to the other side in a randomized fashion. Each treatment area (right or left) was approximately 130 cm^2 and was divided into 4 subsites, for microbial sampling at baseline and 10 minutes, 6 hours and 24 hours after drug application. The test sites were covered with a gauze bandage after the 10 minute sample to minimize contamination from external sources. Information concerning the microbial sampling procedure [redacted] may be found in the Microbiology Review for this NDA. Skin irritation was also scored at the various sampling times.

The scrub procedures used were as follows:

Abdomen: [redacted] back-and-forth strokes of the sponge [redacted] for approximately **30 seconds**. Completely [redacted] wet the treatment area with antiseptic [redacted] Allow the [redacted] area to air dry for approximately 30 seconds. [redacted]

Groin: [redacted] back-and-forth strokes of the sponge [redacted] for approximately **2 minutes**. Completely [redacted] wet the treatment area with antiseptic [redacted] Allow the area to air dry for approximately 1 minute. [redacted]

5. Effectiveness parameters: The TFM standards for patient preoperative skin preparations are a decrease of 2 logs in the baseline microbial counts at a dry test site (abdomen) within 10 minutes 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. There is no TFM standard for microbial counts at 24 hours after drug application.

6. Safety evaluation: Adverse events were recorded and compared between the treatment groups. In addition, skin irritation was evaluated using the following scale:

Erythema	0	No reaction
	1	Mild and/or transient redness limited to sensitive area
	2	Moderate redness persisting over much of the product-exposed area
	3[a]	Severe redness extending over most or all of the product-exposed area
Edema	0	No reaction
	1	Mild and/or transient swelling limited to sensitive areas
	2	Moderate swelling persisting over much of the product-exposed area
	3[a]	Severe swelling extending over most or all of the product-exposed area
Rash	0	No reaction
	1	Mild and/or transient rash limited to sensitive area
	2	Moderate rash persisting over much of the product-exposed area
	3[a]	Severe rash extending over most or all of the product-exposed area
Dryness	0	No reaction
	1	Mild and/or transient dryness, limited to sensitive area
	2	Moderate dryness persisting over much of the product-exposed area
	3[a]	Severe dryness extending over most of the product-exposed area

[a] = Represents significant irritation and requires subject's removal from study

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: The values in the following tables (except for baseline) represent log reduction seen at the various time points. That is, the baseline log count minus the log count measured is shown. The number of observations in each case is 42. Standard deviations are also given [in the table, STD = standard deviation].

Table 1. Mean Log_{10} Reductions in Bacterial Counts (CFU/cm^2) (Abdomen)

	Treatment Group					
Time Point	**ChloraPrep**	**STD**	**IPA**	**STD**	**2% CHG**	**STD**
Baseline	3.06	0.56	2.92	0.57	2.94	0.41
10 minutes	2.52	0.71	2.54	0.66	2.30	0.92
6 hours	2.37	0.84	2.23	1.04	2.40	0.63
24 hours	2.69	0.72	1.79	1.59	2.12	1.11

All p-values for statistically significant reduction from baseline were 0.0001. There were fewer observations per treatment group for the groin. In the following table, there were 26 observations for the ChloraPrep group, 28 for the IPA group, and 20 for the 2% CHG group.

Table 2. Mean Log_{10} Reductions in Bacterial Counts (CFU/cm^2) (Groin)

	Treatment Group					
Time Point	ChloraPrep	STD	IPA	STD	2% CHG	STD
Baseline	5.04	0.77	4.96	0.68	4.95	0.78
10 minutes	3.54	1.10	3.26	1.37	2.73	1.18
6 hours	3.74	1.28	3.30	1.57	3.67	1.67
24 hours	3.82	1.22	2.62	2.35	3.65	1.70

All p-values for statistically significant reductions from baseline were 0.0001.

Reviewer's Comment: These results indicate that all three test compounds meet the TFM requirements of a 2 log reduction in baseline microbial counts (abdomen) or a 3 log reduction (groin) within 10 minutes with the counts not to exceed baseline for at least 6 hours, with one exception: the 2% CHG product did not achieve a 3-log reduction at the groin site at 10 minutes. Since the 2% product was formulated only for the purpose of this study, this is not a surprising result. CHG is notoriously difficult to formulate due to its tendency to bind selectively to various chemicals so a purely aqueous formulation may not be optimal.

It is not surprising that 70% IPA performed so well in the 6 hour portion of the study, since the TFM found 70-91% IPA to be effective as a patient pre-op. However, its performance at 24 hours is interesting, since it is often presumed that alcohols have limited ability to continue killing microbes over extended time periods.

The following tables present the p-values for the differences between ChloraPrep, IPA and 2% CHG at the designated time internals. The log reduction difference represents the difference seen between the log reductions achieved by ChloraPrep and the reductions achieved by the other two preparations at the indicated time interval. A negative figure indicates that IPA or 2% CHG was superior to ChloraPrep at that point.

Table 3. Between Groups Difference in Log Reductions from Baseline Bacterial Counts (CFU/cm^2) (Abdomen)

	Log Reduction Difference		Log Reduction Difference	
Time Point	ChloraPrep – IPA	p-value	ChloraPrep-CHG	p-value
10 minutes	-0.02	0.61	0.22	0.09
6 hours	0.14	0.83	-0.03	0.59
24 hours	0.90	0.0003	0.57	0.028

Table 4. Between Groups Difference in Log Reductions from Baseline Bacterial Counts (CFU/cm^2) (Groin)

Time Point	Log Reduction Difference ChloraPrep – IPA	p-value	Log Reduction Difference ChloraPrep-CHG	p-value
10 minutes	0.28	0.64	0.81	0.27
6 hours	0.44	0.04	0.07	0.83
24 hours	1.20	0.028	0.17	0.65

Reviewer's Comment: These results indicate that the combination product is superior to both individual components of the product at the abdomen test site at the 24 hour observation. The combination is also superior to IPA at the groin test site at 24 hours. The remainder of the groin data is puzzling in that the sponsor's data indicate that the combination is statistically better than IPA at 6 hours with a difference in log reductions of 0.44, but is not statistically better than CHG at 10 minutes with a difference in log reductions of 0.81. This apparent anomaly may have to do with the relatively small number of observations at the groin site and/or data variability.

2. Safety: There were seven adverse events reported in six subjects. All adverse events were located at the test sites, and included macular rash (2), papular rash (2), a rash later identified as fungal in origin, an accidental cut of the skin by a technician, and a small blister. All events were evaluated as moderate in severity except the macular rashes and one of the papular rashes, which were rated as mild in severity. The investigator rated only one event (macular rash moderate in severity) as being possibly related to drug testing, but it seems possible that all the reactions (except the accidental cut and fungal rash) could have been drug related.

No erythema or edema were seen in the skin irritation evaluations planned in the protocol. One IPA subject and two CHG (alone) subjects developed moderate rashes, and one CHG (alone) subject had mild dryness.

Reviewer's Summary of Study No. 990326.HTR

This study was intended to accomplish two objectives: the first was to see whether ChloraPrep, which is to be labeled as a patient preoperative skin preparation, meets the standards for such products as stated in the TFM. The second was to establish that both active ingredients make a contribution to the overall effect of the product.

The first objective was met. ChloraPrep, and its individual ingredients, all meet the TFM standard at the abdomen site, and all three preparations were able to keep microbial counts below baseline for 24 hours, rather than the 6 hours required by the TFM. At the groin site, the 2%

CHG product failed to achieve a 3 log reduction after 10 minutes, but otherwise all three preparations met the TFM standard and in addition kept counts below baseline for 24 hours.

The interpretation of the data concerning the second objective is more difficult. The results indicate that ChloraPrep is more effective than IPA at the 6 hour timepoint at the groin site, but as noted above, the reviewers regard that result with some caution. ChloraPrep is not statistically more effective at maintaining microbial reductions at 6 hours, the end of the TFM recommended timepoints, than its individual components for the abdomen test site or than CHG at the groin test site.

However, ChloraPrep is statistically more effective than its individual ingredients at the 24 hour time point for both test sites. It is noted that the 2% CHG product performed as well as ChloraPrep at the groin site at 24 hours, but it is also true that 2% CHG failed to meet the TFM requirement at the 10 minute time observation at this site.

Since ChloraPrep was submitted as an NDA, its review is not bound by TFM requirements, even though the TFM methodology was used. Therefore the key issue here is whether the difference shown at 24 hours is clinically relevant (or more accurately, whether it is relevant to the use of the product). The endpoint for the TFM method was presumably set because it was felt that most surgical procedures would not take longer then 6 hours. However, there are occasional procedures which take longer (e.g., vascular surgery). Therefore, the ability of ChloraPrep to suppress microbial growth over this longer time period could be useful.

The adverse events seen were not unexpected for this product. It did prove to be irritating in predictive patch testing (see Safety Summary, below).

One final comment concerning study design is relevant. Since most drug sponsors who have proposed combination CHG/alcohol products have found it difficult to formulate an aqueous CHG formulation, HFD-520 has waived the requirement to include an aqueous CHG product in studies of the effect of the individual components of the combination. Usually, a reference product (commonly Hibiclens, containing 4% CHG) is included in place of the aqueous CHG formulation. Since Medi-Flex was able to manufacture the aqueous CHG, inclusion of the approved reference product is not necessary.

B. Study Title: Comparison and Evaluation of a Topical Antiseptic Test Product (Chlora Prep™), an Active Control Product, and a Reference Product for Use as a Patient Preoperative Skin Preparation Drug Product (Protocol No. 990326.MBT).

Investigator: Judith DeJoseph
Micro Bio Test, Inc.
Sterling, VA 20164

Study Dates: June 29 – September 23, 1999

Study Objectives: These were the same as for Study A, above.

Method:

1. Study design: This was the same as for Study A, above. Seventy four test subjects were required to obtain sufficient numbers with the required baseline microbial counts at the two test sites (abdomen and groin). Forty evaluable test sites (abdomen) and 45 evaluable test sites (groin) were treated with each of the test products. These numbers of test sites have been shown in the past to be sufficient to statistically demonstrate the effect of drugs of this type.

2. Inclusion criteria: These were the same as for Study A, above.

3. Exclusion criteria: These were the same as for Study A, above.

4. Dosage and duration of therapy: These were the same as for Study A, above.

5. Effectiveness parameters: These were the same as for Study A, above.

6. Safety evaluations: These were the same as for Study A, above.

Results: As noted above, the critical analyses of the bacterial reduction results are to be performed by the microbiologist. Therefore, the following results are identical to those presented by the applicant.

1. Efficacy: The values in the following tables (except for baseline) represent the log reduction seen at the various time points. That is, the baseline log count minus the log count measured is shown. The number of observations in each case was 40. Standard deviations are also given in the table.

Table 5. Mean Log_{10} Reductions in Bacterial Counts (CFU/cm^2) (Abdomen)

	Treatment Group					
Time Point	**ChloraPrep**	**STD**	**IPA**	**STD**	**2% CHG**	**STD**
Baseline	3.24	0.80	3.23	0.68	3.31	0.74
10 minutes	2.56	0.99	2.84	0.78	2.37	1.16
24 hours	2.15	1.29	2.08	1.29	1.80	1.31
6 hours	2.18	1.15	1.86	1.26	2.10	1.41

All p-values for statistically significant reductions from baseline were 0.0001. The number of observations in each case for the groin test site was 45.

Table 6. Mean Log_{10} Reductions in Bacterial Counts (CFU/cm^2) (Groin)

	Treatment Group					
Time Point	ChloraPrep	STD	IPA	STD	2% CHG	STD
Baseline	4.94	0.70	4.81	0.56	4.82	0.62
10 minutes	4.20	1.30	3.96	1.24	3.86	1.29
6 hours	3.50	1.45	3.14	1.53	3.35	1.66
24 hours	2.67	1.56	2.54	1.82	2.86	1.84

All p-values for statistically significant reductions from baseline were 0.0001.

Reviewer's Comment: These results indicate that all three test compounds meet the TFM requirements of a 2 log reduction in baseline microbial counts (abdomen) or a 3 log reduction (groin) within 10 minutes with the counts not to exceed baseline in 6 hours. All 3 preparations also kept counts well below baseline for 24 hours.

The following tables present the p-values for the differences between ChloraPrep, IPA and 2% CHG at the designated time intervals. The log reduction difference represents the difference seen between the log reductions achieved by ChloraPrep and the reductions achieved by the other two preparations at the indicated time intervals. A negative figure indicates that IPA or 2% CHG was superior to ChloraPrep at that point.

Table 7. Between Group Differences in Log Reductions from Baseline Bacterial Counts (CFU/cm^2) (Abdomen)

	Log Reduction Differences		Log Reduction Differences	
Time Point	ChloraPrep-IPA	p-value	ChloraPrep-CHG	p-value
10 minutes	-0.28	0.54	0.19	0.19
6 hours	0.07	0.25	0.35	0.22
24 hours	0.32	0.39	0.08	0.70

Table 8. Between Group Differences in Log Reductions from Baseline Bacterial Counts (CFU/cm^2) (Groin)

	Log Reduction Differences		Log Reduction Differences	
Time Point	ChloraPrep-IPA	p-value	ChloraPrep-CHG	p-value
10 minutes	0.24	0.01	0.34	0.006
6 hours	0.36	0.11	0.15	0.38
24 hours	0.13	0.53	0.19	0.88

Reviewer's Comment: These results indicate that the combination product is superior to both individual components of the product at the groin test site at the 10 minute observation. Thus, the results of the two pivotal studies indicate that the combination

product is superior to its individual components for at least one test site and time observation in both studies.

It is noted the results of the pivotal studies are not consistent in that they demonstrated superiority of the combination product at different times and test sites. If a theoretical set of results were to be constructed, one would expect that the combination would be better than CHG alone at the 10 minute time frame because the IPA in the combination provides a more rapid killing effect than does CHG alone. Similarly, one would expect that the combination would be better than IPA alone at the later times (6 and 24 hours) because the CHG in the combination has more residual activity than IPA alone.

However, there is no requirement that theoretical expectations must be met. The broad requirement that the combination product must in some way be demonstrably superior to the individual components has been demonstrated. In this case, the Hill Top study demonstrated superiority of the combination to both individual components at 24 hours at the abdomen test site and to IPA alone at the groin test site, while the Micro Bio Test study demonstrated superiority of the combination to both individual components at 10 minutes at the groin test site.

2. Safety: There were four adverse events reported in four subjects. All adverse events were located at the test sites, and are presented as redness and/or drying and/or irritation "due to the removal of the Tegaderm Patch". There is no attribution of relationship between drug use and adverse events by the investigator, nor was a severity rating assessed. It is possible that all the reactions could have been drug related.

The skin irritation evaluations made by protocol found no irritation in any subjects.

Reviewer's Summary of Study No. 990326.MBT

This study had the same objectives as the study described above (990326.HTR).

The first objective of meeting the TFM standards for patient preoperative skin preparations was met by all 3 test products, and in addition all 3 products were able to keep resident organisms below baseline for 24 hours.

The second objective of establishing that both active ingredients contribute to the effect of the product was met in that the combination product was superior to both of the components in lowering baseline bacterial counts at the groin test site at the 10 minute observation.

The adverse events seen were not alarming for this product. It did prove to be irritating in predictive patch testing (see Safety Summary, below).

C. Efficacy Summary

The studies presented here contain adequate evidence to support the approval of ChloraPrep as a patient preoperative skin preparation, pending satisfactory reviews from the microbiologist and statistician assigned to this NDA.

The following table presents the log reductions in bacterial counts found in the two pivotal studies at the time points measured. Only values for ChloraPrep are given, along with standard deviations.

Table 9. Log Reductions in Bacterial Counts (CFU/cm^2)

Time Point/Site	Study 990326.HTR	STD	Study 990326.MBT	STD
Abdomen				
10 minutes	2.52	0.71	2.56	0.99
6 hours	2.37	0.84	2.15	1.29
24 hours	2.69	0.72	2.18	1.15
Groin				
10 minutes	3.54	1.10	4.20	1.30
6 hours	3.74	1.28	3.50	1.45
24 hours	3.82	1.22	2.67	1.56

In both studies, the difference in log reduction achieved by ChloraPrep and its two active ingredients tested separately was measured in order to assure that FDA's policy of requiring that each active ingredient in a drug contribute to the total effect of the product was met. The following tables present those results.

Table 10. Differences Between ChloraPrep and IPA in Log Reductions from Baseline Bacterial Counts (CFU/cm^2)

	Study 990326.HTR		Study 990326.MBT	
Time Point/Site	Difference	p-value	Difference	p-value
Abdomen				
10 minutes	-0.02	0.61	-0.28	0.54
6 hours	0.14	0.83	0.07	0.25
24 hours	0.90	0.003	0.32	0.39
Groin				
10 minutes	0.28	0.64	0.24	0.01
6 hours	0.44	0.04	0.36	0.11
24 hours	1.20	0.028	0.13	0.53

Table 11. Differences Between ChloraPrep and 2% CHG in Log Reductions from Baseline Bacterial Counts (CFU/cm^2)

	Study 990326.HTR		Study 990326.MBT	
Time Point/Site	**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, ChloraPrep 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, ChloraPrep 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, ChloraPrep 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, ChloraPrep 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 ChloraPrep is acceptably safe for its intended use. 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.

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 ChloraPrep, 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 ChloraPrep in children less than 2 months of age due to its irritancy potential and the

possibility of enhanced absorption of the drug in younger infants. The safety and efficacy data from the adult test population may be extrapolated to the remainder of the pediatric population.

III. Review of Labeling

Four pieces of labeling have been submitted with the resubmission. They are:

1. A "package insert" which is to be included with each carton of 25 individual packages of the product.
2. The immediate container label.
3. An intermediate packaging label which is to be included with the carton of 25 individual packages.
4. An outer shipper label, which is to be applied to a larger carton containing 4 of the 25 package cartons.

It appears that the most critical labeling piece from the use standpoint is the individual container label, since this is the unit which will be present in the operating theater. This piece does not bear directions for use or most of the standard warnings concerning chlorhexidine use. It is not clear whether this is due to lack of space. The product is packaged in a sponge attached to a handle which appears to be large enough to require a container which would hold all the necessary labeling. Therefore, it is recommended that all 3 principal labeling pieces (package insert, immediate container and intermediate carton) all bear the same information, as follows:

Chloraprep™ One-Step
Chlorhexidine gluconate 2% w/v and isopropanol 70%, v/v
Patient Preoperative Skin Preparation
Antiseptic
3.0 mL Applicator

(The following statements should be in capital letters and in a contrasting color from the rest of the label. Red print is preferred).

WARNING. FLAMMABLE. KEEP AWAY FROM FIRE OR FLAME.
DO NOT USE WITH ELECTROCAUTERY PROCEDURES.

Do not use

- In children less than 2 months of age, because of the potential for excessive skin irritation and increased drug absorption
-
- For lumbar puncture or in contact with the meninges.
- On open skin wounds or as a general skin cleanser.

When using this product

- [redacted]
- Keep out of eyes, ears and mouth. May cause serious and permanent [redacted] injury if permitted to enter and remain [redacted]
- If contact occurs, rinse with water right away.

Stop use and ask a doctor if

- Irritation, sensitization or allergic reaction occurs. These may be signs of a serious Condition

Keep out of reach of children. If swallowed, get medical help or contact a Poison Control Center right away.

Directions for Use:

Pinch the wings on the [redacted] to break the ampoule and release the antiseptic. Do not touch the sponge. Wet the sponge by repeatedly pressing and releasing the sponge against the treatment area until liquid is visible on the skin.

[redacted] Dry Surgical Sites (such as the abdomen or arm):

Use repeated back and forth strokes of the sponge for **approximately 30 seconds**. Completely wet the treatment area with antiseptic. Allow the area to air dry for **approximately 30 seconds.** Do not blot or wipe away.

[redacted] Moist Surgical Sites (such as the [redacted]

Use repeated back and forth strokes of the sponge for **approximately 2 minutes**. Completely wet the treatment area with antiseptic. Allow the area to air dry for **approximately one (1) minute.** Do not blot or wipe away.

[redacted] maximum treatment area for one applicator is approximately 130 cm^2. Discard the applicator after a single use.

Other information

[redacted].

IV. Conclusions and Recommendations

ChloraPrep One-Step Patient Preoperative Skin Preparation is recommended for approval. This product meets the standards set in the TFM for products of this type. Additionally, information has been submitted which establishes that both CHG and isopropanol contribute to the effect of the product as active ingredients (please see the Efficacy Summary for details).

The product is safe for its intended use, though it is one of the most irritating topical products which has been seen in this Division when evaluated by standard predictive patch tests. It is felt that the one-time use of the drug, combined with the recommended labeling warnings against use in children under 2 months of age, permit its use as a patient pre-op.

Labeling revisions are necessary to assure that the user has all the necessary information for the safe and effective use of the product. In addition, satisfactory reviews from the microbiologist and statistician are necessary prior to approval.

A request for consultation on the structure and function of the device has been forwarded to the Center for Devices and Radiological Health.

Original NDA
HFD-520/Div. File
HFD-340
HFD-520/Clin/Bostwick
HFD-520/TL Clin/Rakowsky
HFD-520/PM/Dillon-Parker
HFD-520/Micro/Sheldon

/S/
David Bostwick

/S/ 5-2-00
Alexander Rakowsky, M.D.

Concurrence : G. Chikami/Div. Dir./HFD-520
/S/ 5/5/2000

APPEARS THIS WAY
ON ORIGINAL