CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

21-669

PHARMACOLOGY REVIEW

Food and Drug Administration
Center for Drug Evaluation and Research
Division of Anti-Infective Drug Products
Pharmacology and Toxicology Review

NDA 21,669

2% CHG Pre-Op Prep
Sage Products, Inc.

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EXECUTIVE SUMMARY

1. Recommendations

1.1 Recommendation on approvability

The pharmacologist has no objection to the approval of this NDA.

1.2 Recommendation for nonclinical studies

No additional nonclinical studies are recommended.

1.3 Recommendations on labeling

The label for this product should be consistent with labels for similar chlorhexidine gluconate products.

2. Summary of nonclinical findings

2.1 Brief overview of nonclinical findings

When 2% CHG Pre-Op Prep was applied to rabbit skin 4 times daily for 28 days under partial occlusion, it caused moderate dermal irritation. Over the course of the study, drug-induced erythema and edema regressed despite continued application of the product. The rabbits' skin reactions to the 2% CHG Pre-Op Prep were comparable to those caused by Hibiclens with the exception that 2% CHG Pre-Op Prep was associated with an increased incidence and severity of hair cell follicle loss at abraded skin sites.

2.2 Pharmacologic activity

Chlorhexidine gluconate exerts its antimicrobial activity by disrupting bacterial cell membranes.

2.3 Nonclinical safety issues relevant to clinical use

Repeated application of 2% CHG Pre-Op Prep under partial occlusion may be moderately irritating to human skin as it was to rabbit skin. Other products containing CHG have been demonstrated to be irritating to human skin under some conditions- particularly if the application site is occluded.

PHARMACOLOGY/TOXICOLOGY REVIEW

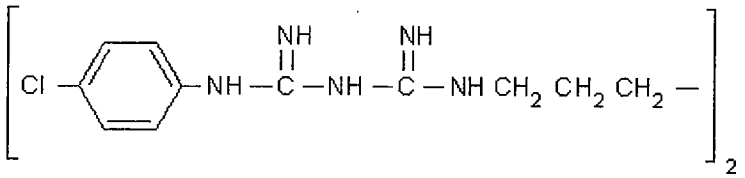
3.1 INTRODUCTION AND DRUG HISTORY

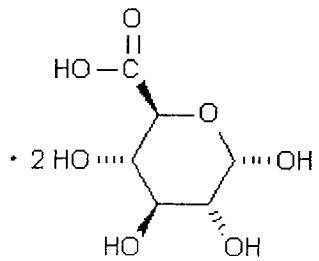
NDA number: 21,669
Review number: 1
Sequence number/date/type of submission: 000/04 Sep 2003/original NDA
Information to sponsor: Yes ( ) No (X)
Sponsor and/or agent: Sage Products, Inc. (Cary, IL)
Manufacturer for drug substance: [redacted]

Reviewer name: Amy Ellis
Division name: Anti-Infective Drug Products
HFD #: 520
Review completion date: 12/31/03

Drug:

Trade name: 2% CHG Pre-Op Prep
Generic name: Chlorhexidine gluconate [redacted]
with 2% CHG
Code name: None
Chemical name: 1,1'-Hexamethylenebis [5-(p-chlorophenyl) biguanide] di-D-gluconate
CAS registry number: 18472-51-0
Molecular formula/molecular weight: $C_{22}H_{30}Cl_2N_{10}$,$2C_6H_{12}O_7$ /897.8
Structure:





Relevant INDs/NDAs/DMFs: IND 64,143; DMFs [redacted] Additionally, there are numerous approved NDAs for patients preoperative preparations, surgical scrubs, and healthcare personnel handwashes containing CHG at concentrations up to 4%.

Drug class: Biguanide topical disinfectant

Indication: Pre-operative skin preparation [redacted]

Clinical formulation: The product consists of a package of 2 [redacted] 100% polyester washcloths, each saturated with about [redacted] of a 2% CHG solution. The composition of the solution is as follows:

USP Purified Water
Propylene Glycol
Aloe Vera [redacted]
Glycerin
Dimethicone [redacted]
Igepal [redacted]
Polysorbate 20
[redacted] Fragrance
Glucono Delta Lactone
[redacted] CHG Solution (final CHG concentration of [redacted])

Route of administration: Topical

Proposed use: Preparation of skin (cleansing and disinfecting) prior to surgery.

Disclaimer: Tabular and graphical information are constructed by the reviewer unless cited otherwise.

Studies reviewed within this submission:

28 Day Repeat Dose Dermal Irritation/Toxicity Study in Rabbits ([redacted] Report No. 02-2778-G1)

Studies not reviewed within this submission: All were reviewed.

3.2 PHARMACOLOGY

3.2.1 Brief summary

Chlorhexidine gluconate exerts its antimicrobial activity by binding to bacterial cell membranes, leading to leakage. It binds to skin and thus exerts residual antimicrobial activity. CHG is not significantly absorbed through intact skin and, if swallowed, is not efficiently absorbed by the GI tract.

3.2.2 Primary pharmacodynamics

Mechanism of action: CHG binds to bacterial cell membranes.

Drug activity related to proposed indication: Antimicrobial

3.2.3 Secondary pharmacodynamics

Nothing to report.

3.2.4 Safety pharmacology

Not relevant for this product. Significant absorption does not occur when product is used on intact skin as directed.

3.2.5 Pharmacodynamic drug interactions

Not relevant.

3.3 PHARMACOKINETICS/TOXICOKINETICS

3.3.1 Brief summary

Significant absorption does not occur when CHG is applied to intact skin.

3.3.3 Absorption

Significant absorption does not occur when CHG is applied to intact skin. CHG is poorly absorbed via the GI tract.

3.3.4 Distribution

Not relevant for this product.

3.3.5 Metabolism

Not significant.

3.3.6 Excretion

If a small amount of CHG is absorbed (e.g., accidental ingestion), it is eliminated unchanged via urinary and biliary excretion.

3.3.7 Pharmacokinetic drug interactions

Not relevant for this product.

3.3.10 Tables and figures to include comparative TK summary

Not relevant for this product.

3.4 TOXICOLOGY

3.4.1 Overall toxicology summary

As one would expect for a product containing CHG, 2% CHG Pre-Op Prep caused moderate dermal irritation when repeatedly applied to rabbit skin under partial occlusion. CHG has been used for decades at concentrations up to 4% as a surgical scrub, healthcare personnel handwash, and a patient preoperative skin preparation. CHG has proven to be very safe for these dermal uses.

3.4.2 Single-dose toxicity

No single-dose toxicity studies were performed with this product. Reports from the literature indicate that large single oral doses of CHG (>3 g/kg) can be given to rats without causing significant toxicity. However, significant lethality was observed in a group of rats after 20 mg/kg IV doses of CHG were given.

3.4.3 Repeat-dose toxicity

28 Day Repeat Dose Dermal Irritation/Toxicity Study in Rabbits-OECD

Key study findings: [redacted] was a moderate dermal irritant when applied to rabbit skin (intact or abraded) 4 times daily for 28 days under partial occlusion. Despite continued application of the product, drug-induced erythema and edema regressed during the study after peaking at around days 10-11. Hibiclens and [redacted] had similar effects on rabbit skin under the conditions of this study with the exception that [redacted] was associated with an increased incidence and severity of hair cell follicle loss at abraded skin sites.

Study No.: [redacted] Report No. 02-2778-G1
Volume 5, pp 1605-1683
Conducting laboratory and location: [redacted]
Date of study initiation: 6/3/02
GLP compliance: Yes (US and OECD)
QA report: yes (X) no ( )
Drug, lot #, and % purity: [redacted] Lot # 201-2022-01 (test article); Hibiclens, Lot # 3102F (control article)

Methods

Doses: The full strength clinical formulations of [redacted] and Hibiclens were used.

Species/strain: New Zealand White Rabbits

Number/sex/group or time point (main study): 5/sex/group

Route, formulation, and volume: 0.5 ml of test substance (both were the clinical formulations) was applied to an absorbent pad, placed on each dermal application site, and covered with a semi-occlusive dressing. Dosing occurred 4 times daily, approximately 2 hours apart for 28 days.

Satellite groups used for toxicokinetics or recovery: None

Age: at least 11 weeks old

Weight: 2.03-2.24 kg

Study design and methodology: Application sites were clipped free of hair 24 hours before dosing. Subsequently, hair was removed as needed. Two application sites were used on each animal. One was intact skin. The other skin site was abraded-shallow incisions were made to the stratum corneum, not deep enough to draw blood. Rabbits were sacrificed on day 29 of the study, the day after the final doses of test articles were administered.

Observation times and results

Mortality: There were no unscheduled deaths.

Clinical signs: Rabbits were observed for clinical signs of toxicity each day after the last dose. No signs of clinical toxicity were seen.

The sites of application were examined for skin irritation twice each day before the first dose and following the last. They were graded for erythema and edema on a 0-4 point scale. Erythema: 0= none; 1= barely perceptible; 2= well defined; 3= moderate to severe; 4= severe (beet red) to slight eschar formation. Edema: 0= none; 1= barely perceptible; 2= slight (edges well-defined); 3= moderate (raised approximately 1 mm); 4= severe (raised >1 mm and extending beyond exposure area).

By the second day of application, grade 1 erythema began to be seen at most application sites. Slight edema was observed in some Hibiclens animals at abraded application sites. At the end of the first week of application, varying degrees of erythema were seen at all sites, mostly grades 2-3. The severity of erythema peaked at around days 10-11 of treatment with a few animals in each treatment group reaching grade 4. Edema was not seen in every animal and did not exceed grade 2. It did not correlate with the severity of erythema. By day 15, the severity of erythema began to regress in both treatment group despite continued application of the test articles. In general, the severity of erythema and edema were similar between the [redacted] and Hibiclens groups.

Body weights: The rabbits were weighed weekly. Body weight gain did not differ significantly between the 2 treatment groups.

Food consumption: Animals were given [redacted] Rabbit Diet [redacted]) and tap water *ad libitum*. Food consumption was assessed weekly. There was no difference in food consumption between the 2 groups.

Ophthalmoscopy: Not done.

EKG: Not done.

Hematology: Performed at the end of dosing; all parameters were within normal ranges with no biologically significant differences between groups excluding data from one male in the [redacted] group. All values for this animal were very low (e.g., a hematocrit of 1.6%) and it appeared as though the sample may have been excessively diluted (perhaps with anticoagulant), although the report did not discuss the discrepancy in the hematology data from this animal.

Clinical chemistry: Performed at the end of dosing; all parameters were within normal ranges with no biologically significant differences between groups.

Urinalysis: Not done

Gross pathology: Included the external surface of the body, all orifices, the cranial, thoracic, and abdominal cavities with their contents. No treatment-related changes beyond local effects on the skin were observed.

Organ weights (specify organs weighed if not in histopath table): Not done.

Histopathology: Adequate Battery: yes (X), no ( )
Peer review: yes ( ), no (X)

The test sites, brain, liver, kidneys, adrenals, spleen, stomach, small and large intestines, heart, and lungs were fixed in 10% neutral buffered formalin. Slides of these tissues were prepared and stained with H&E before evaluation by a board-certified veterinary pathologist.

Test article-related microscopic changes were not observed in any tissue distant from the site of application. Histopathologic observations at the sites where test articles were applied to the skin included superficial dermal cellular infiltrate, hyperkeratosis, acanthosis, superficial dermal fibroplasia, periadnexal mononuclear cell infiltrate and hair follicle loss. The pathologist believed that some of these changes were likely to have been related to repeated clipping for hair removal as opposed to a direct effect of either test article. In general, the findings (mostly mild to moderate in severity) were similar between the Hibiclens and [redacted] groups. Severity tended to be greater at compound-treated abraded sites compared to compound-treated intact skin. The incidence and severity of hair follicle loss was greatest at abraded skin sites treated with [redacted] compared with intact skin sites treated with the same substance or with abraded sites exposed to Hibiclens.

Toxicokinetics: Not done.

3.4.4. Genetic toxicology

The labels for Peridex® and Periogard® chlorhexidine gluconate oral rinses state that a mouse dominant lethal assay was negative at doses up to 1000 mg/kg/day and a hamster cytogenetic test was negative at doses up to 250 mg/kg/day. The oral route of administration was used in both studies, however, so it is unlikely that large amounts of CHG would have reached the target tissues. A report from the literature indicated that CHG induced mutations in *S. typhimurium* TA 1535 and TA 1538 at 280 µg/l, with or without metabolic activation. It also induced DNA damage in a DNA-polymerase-deficient strain of *E. coli*, but was not clastogenic to CHO cells at concentrations up to 100 µg/ml, regardless of metabolic activation.

3.4.5. Carcinogenicity

No evidence of carcinogenicity was observed in rats that received up to 50 mg/kg/day of CHG in their drinking water for approximately 2 years.

3.4.6. Reproductive and developmental toxicology

The labels for Peridex® and Periogard® chlorhexidine gluconate oral rinses state that no impairment of fertility was observed in rats that received up to 100 mg/kg/day of CHG and no evidence of fetal harm was seen in rats or rabbits at doses of 300 mg/kg/day or 40 mg/kg/day, respectively. The route of administration used in the reproduction toxicity studies is not specified in these labels, but the compound was likely to have been given orally. The sponsor of the current NDA also cited a study from the literature where pregnant rats received oral doses of CHG up to 50 mg/kg/day during organogenesis and no harm to their offspring was observed.

3.4.7 Local tolerance

Topical disinfectants containing CHG are considered eye irritants and are labeled as such. Additionally, deafness have been observed in guinea pigs, cats, sand rats and humans following instillation of CHG into the middle ear. Cochlear damage was seen in the animals.

3.4.8 Special toxicology studies

None were performed.

3.6 OVERALL CONCLUSIONS AND RECOMMENDATIONS

Conclusions: The 2% CHG Pre-Op Prep appears similar to comparable patient preoperative skin preparation products containing CHG, although it is not rinsed off of the skin. This product did not cause excessive dermal irritation when repeatedly applied to rabbit skin under partial occlusion for 28 days. Chlorhexidine gluconate, at concentrations up to 4%, has been used as a surgical scrub, healthcare personnel

handwash, and patient preoperative skin preparation for decades. It is not significantly absorbed through intact human skin and absorption is poor following oral administration. CHG, at lower concentrations, is also used as an oral rinse and as a preservative in cosmetics and contact lens solutions. Sage 2% CHG Pre-Op Prep is expected to be safe for its intended use as a patient preoperative skin preparation product.

Unresolved toxicology issues (if any): None

Recommendations: The pharmacologist has no objection to the approval of this NDA.

Suggested labeling: Labels for topical skin disinfectants containing CHG use an OTC drug label format. They do not contain several sections usually reviewed by the pharmacologist that are found in prescription drug labels (e.g., *Carcinogenesis, Mutagenesis, Impairment of Fertility* and *Pregnancy Category*). The label for Sage 2% CHG Pre-Op Prep should be consistent with those for other CHG products. It contains appropriate precautionary statements regarding the potential for eye injury if allowed to remain in the eye during surgical procedures, that the product should not come in contact with the meninges, and that irritation and sensitization have been associated with CHG-containing products. Some CHG products also have cautionary statements that deafness can occur if the product enters the middle ear, but that may not be necessary in this case because the [redacted] dispensing unit would not lend itself to middle ear instillation.

Signatures (optional):

Reviewer Signature _____

Supervisor Signature_____ Concurrence Yes ___ No ___

3.7. APPENDIX/ATTACHMENTS

None.

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

Amy Ellis
1/15/04 01:48:02 PM
PHARMACOLOGIST
The pharmacologist has no objection to the approval of this NDA.
Bob- You signed the paper copy of this review on 1/12/04.

Robert Osterberg
1/15/04 01:56:35 PM
PHARMACOLOGIST

Lillian Gavrilovich
1/16/04 04:18:43 PM
MEDICAL OFFICER