CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

21-524

PHARMACOLOGY REVIEW

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

PHARMACOLOGY/TOXICOLOGY REVIEW AND EVALUATION

NDA NUMBER:	**21-524**
SERIAL NUMBER:	**000**
DATE RECEIVED BY CENTER:	**8/5/04**
PRODUCT:	**Chlorascrub™**
INTENDED CLINICAL POPULATION:	**Anyone requiring skin antisepsis (prior to ———— , injection, or surgery)**
SPONSOR:	**Les Entreprises SoluMed, Inc.**
DOCUMENTS REVIEWED:	**Vols. 1-3**
REVIEW DIVISION:	**Anti-Infective Drug Products (HFD-520)**
PHARM/TOX REVIEWER:	**Amy L. Ellis, Ph.D.**
PHARM/TOX SUPERVISOR:	**Robert. E. Osterberg, Ph.D.**
DIVISION DIRECTOR:	**Janice Soreth, M.D.**
PROJECT MANAGER:	**Maureen Dillon-Parker**

Date of review submission to Division File System (DFS): 3/16/05

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EXECUTIVE SUMMARY

I. Recommendations

A. Recommendation on approvability

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

B. Recommendation for nonclinical studies

No additional nonclinical studies are recommended.

C. Recommendations on labeling

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

II. Summary of nonclinical findings

A. Brief overview of nonclinical findings

Nonclinical studies were not required for this drug product due to its similarity to other marketed topical antiseptics containing chlorhexidine gluconate and isopropanol.

B. Pharmacologic activity

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

C. Nonclinical safety issues relevant to clinical use

Other products containing CHG have been demonstrated to be irritating to animal and human skin under some conditions- particularly if the application site is occluded.

2.6 PHARMACOLOGY/TOXICOLOGY REVIEW

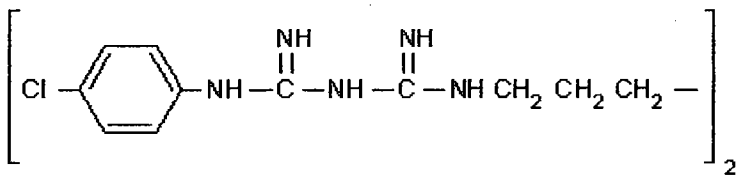
2.6.1 INTRODUCTION AND DRUG HISTORY

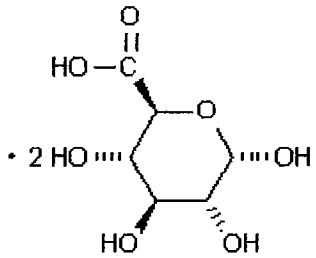
NDA number: 21,524
Review number: 1
Sequence number/date/type of submission: 000/05-AUG-04/505(b)(2) original NDA
Information to sponsor: Yes ( ) No (x)
Sponsor and/or agent: Les Entreprises SoluMed Inc. (Laval, Quebec, Canada); authorized U.S. agent Bob Reichman, Nice-Pak Products, Inc. (Orangeburg, NY)
Manufacturer for drug substance: Chlorhexidine manufactured by [redacted]; Isopropanol manufactured by [redacted]

Reviewer name: Amy L. Ellis
Division name: Anti-Infective Drug Products
HFD #: 520
Review completion date: 3/10/05

Drug:

Trade name: Chlorascrub™
Generic name: 3.15% (w/v) chlorhexidine gluconate with 70% (v/v) isopropyl alcohol
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 59,446; additionally, there are numerous approved NDAs for patients preoperative preparations, surgical scrubs, and healthcare personnel handwashes containing CHG at concentrations up to 4%. Although the sponsor does not have permission to cross reference the applications for any CHG products, it is notable that Chloraprep® contains 2% CHG in 70% isopropanol and Hibistat® germicidal hand rinse contains 0.5% CHG in 70% isopropanol. Both of these products have been found to be reasonably safe and effective for topical skin antisepsis and are on the market.

Drug class: Biguanide topical disinfectant

Intended clinical population: Anyone requiring skin antisepsis prior to injection, [redacted] or surgery.

Clinical formulation: 3.15% (w/v) chlorhexidine gluconate and 70% (v/v) isopropyl alcohol in purified water, USP. This solution will be packaged with one of three different applicators: swabsticks (1.6 ml each), maxi swabsticks (5.1 ml each), and swabs (1.0 ml each). The swabsticks are [redacted] sticks with [redacted] foam applicators at one end and the swabs are [redacted]

Route of administration: Topical

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

Data reliance : Except as specifically identified below, all data and information discussed below and necessary for approval of NDA 21,524 are owned by Les Enterprises SoluMed, Inc. or are data for which Les Enterprises SoluMed, Inc. has obtained a written right of reference. Any information or data necessary for approval of NDA 21,524 that Les Enterprises SoluMed, Inc. does not own or have a written right to reference constitutes one of the following: (1) published literature, or (2) a prior FDA finding of safety or effectiveness for a listed drug, as described in the drug's approved labeling. Any data or information described or referenced below from a previously approved application that Les Enterprises SoluMed, Inc. does not own (or from FDA reviews or summaries of a previously approved application) is for descriptive purposes only and is not relied upon for approval of NDA 21,524.]

Studies reviewed within this submission: Nonclinical studies were not required. The sponsor submitted an annotated summary of the publicly available toxicology data for chlorhexidine gluconate as directed by the Division.

Studies not reviewed within this submission: none

2.6.2 PHARMACOLOGY

2.6.2.1 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.

2.6.2.2 Primary pharmacodynamics

Mechanism of action: CHG binds to bacterial cell membranes.

Drug activity related to proposed indication: Antimicrobial

2.6.2.3 Secondary pharmacodynamics

Nothing to report.

2.6.2.4 Safety pharmacology

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

2.6.2.5 Pharmacodynamic drug interactions

Not relevant.

2.6.4 PHARMACOKINETICS/TOXICOKINETICS

2.6.4.1 Brief summary

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

2.6.4.2 Methods of Analysis

Not relevant.

2.6.4.3 Absorption

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

2.6.4.4 Distribution

Not relevant for this product.

2.6.4.5 Metabolism

Not significant.

2.6.4.6 Excretion

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

2.6.4.7 Pharmacokinetic drug interactions

Not relevant for this product.

2.6.6 TOXICOLOGY

2.6.6.1 Overall toxicology summary

The sponsor did not conduct any nonclinical toxicity studies to support the IND and NDA for this product and none were necessary. The toxicity profile of chlorhexidine gluconate has been well established and a vast quantity of data are available in the scientific literature. Approved products containing chlorhexidine gluconate have been in clinical use for many years and the vehicle, 70% isopropanol, also has a long history of clinical use. Additional preclinical testing is not likely to add significant information to the body of knowledge that has been accumulated regarding these substances. The Division requested that the sponsor submit an annotated summary of toxicity information on chlorhexidine gluconate, particularly when used topically. The sponsor has done so.

2.6.6.2 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 rats and mice after 20 mg/kg IV doses of CHG were given.

2.6.6.3 Repeat-dose toxicity

No repeat-dose toxicity studies were performed with this product. Reports from the literature indicate that the NOAEL in rats receiving CHG in their drinking water for up to 3 months was at least 200 mg/kg/day. Larger doses were not feasible by this dosing method due to the unpalatable taste.

2.6.6.4 Genetic toxicology

Genotoxicity studies were not performed with this product. Reports from the literature describe a variety of assays for mutagenicity and clastogenicity conducted with CHG. A mouse micronucleus test using male Swiss mice was negative using CHG doses up to 30 mg/kg. CHG did not induce chromosome aberrations in CHO cells at concentrations up to 100 μg/ml. Positive results have been reported in bacterial mutagenesis assays (*Salmonella* and *E. coli*), but many of these results occurred at highly cytotoxic concentrations of CHG and thus are likely to be secondary to bactericidal activity.

2.6.6.5 Carcinogenicity

Carcinogenicity studies were not performed with this product. A report from the literature stated that no evidence of carcinogenicity was seen in rats given up to 50 mg/kg of CHG via their drinking water.

2.6.6.6 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 cited 2 rat CHG reproduction toxicity studies from the literature. Pregnant rats received oral doses of CHG up to 68.5 mg/kg/day during organogenesis and no harm to their offspring was observed. Oral doses of CHG up to 50 mg/kg/day did not affect the reproductive performance of male or female rats or cause embryofetal harm.

2.6.6.7 Local tolerance

Topical disinfectants containing CHG are considered eye irritants and the label cautions against eye contact. Additionally, deafness have been observed in a variety of animal species and humans following instillation of CHG into the middle ear. Cochlear damage was seen in the animals.

2.6.6.8 Special toxicology studies

None were performed.

OVERALL CONCLUSIONS AND RECOMMENDATIONS

Conclusions: The safety of Chlorascrub™ would not be expected to differ significantly from several other CHG products being marketed. 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. Chlorascrub™ is expected to be safe for its intended use as a topical skin antiseptic prior to injection, [redacted] or surgery.

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 Chlorascrub™ should be consistent with those for similar CHG products. It contains appropriate statements cautioning that the product is flammable, potentially irritating, and should not be used in the eyes, ears, mouth, or mucous membranes or for lumbar puncture or in contact with the meninges.

Signatures (optional):

Reviewer Signature _____

Supervisor Signature_____ Concurrence Yes ___ No ___

Deputy Director Signature_____ Concurrence Yes ___ No ___

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
3/16/05 04:32:21 PM
PHARMACOLOGIST
The pharmacologist has no objection to the approval of the Chlorascrub NDA.
Bob- You signed the paper copy of this review on 3/15/05.

Robert Osterberg
3/21/05 11:07:42 AM
PHARMACOLOGIST

Lillian Gavrilovich
3/21/05 07:14:45 PM
MEDICAL OFFICER