CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

21-669

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW(S)

NDA#	21-669
PRODUCT	Chlorhexidine Gluconate Solution
FORMULATION	2% Chlorhexidine Gluconate Pre-Op Prep
SUBMISSION DATE	August 29, 2003
SUBMISSION TYPE	Original New Drug Application
SPONSOR	Sage Products, Inc., Cary, Illinois 60013
REVIEWER	Charles R. Bonapace, Pharm.D.
TEAM LEADER	Philip M. Colangelo, Pharm.D., Ph.D.

CLINICAL PHARMACOLOGY & BIOPHARMACEUTICS REVIEW

BACKGROUND:

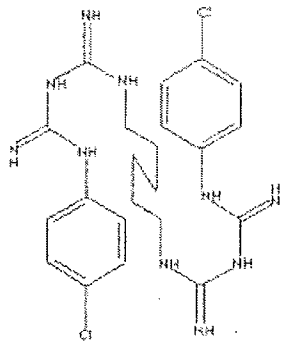
Sage Products, Inc. submitted a New Drug Application for 2% Chlorhexidine Gluconate Pre-Op Prep, an antiseptic drug product consisting of a prepackaged set of either two [redacted] 100% polyester [redacted] washcloths impregnated with an alcohol-free, no rinse surfactant solution containing chlorhexidine gluconate as the active ingredient. Each cloth measures approximately 8" × 8" and is intended for single use to cleanse the appropriate areas of skin prior to a surgical procedure.

The antibacterial activity of chlorhexidine is related to its physical properties whereby the di-cation binds to negatively charged bacterial membranes. Due to the higher negative charge on Gram-positive bacteria, the drug binds better and may be more effective against Gram-positive bacteria. After binding, the hydrophobic portion of the molecule interacts with the cell wall, disrupting its integrity. At low concentrations, chlorhexidine interferes with cell membrane function and acts as a bacteriostatic agent. At high concentrations, the cell membrane becomes leaky, causing irreversible damage and cell death.

The sponsor conducted nine clinical studies to assess safety and efficacy. Four pilot studies were uncontrolled to assess methodology and five controlled studies were performed to support the safety and efficacy of 2% Chlorhexidine Gluconate Pre-Op Prep product as a preoperative skin preparation. Data from all nine uncontrolled and controlled studies were used to support safety, whereas efficacy was based on two pivotal trials.

CHEMISTRY:

Chlorhexidine gluconate is a colorless to pale yellow solution that is a liquid at room temperature. It is miscible with water and soluble in ethanol and acetone. The molecular formula of chlorhexidine is $C_{22}H_{30}Cl_2N_{10}\bullet 2C_6H_{12}O_7$ and the structural formula is shown below.



Composition and dosage form of the bulk product (2% w/w chlorhexidine gluconate solution)

Component	Function	% w/w	Amount (kg)
Purified water, USP			
Propylene Glycol, USP			
Aloe Vera [redacted]			
Glycerin, USP			
Dimethicone [redacted]			
Igepal [redacted]			
Polysorbate 20, USP/NF			
[redacted]			
Glucono Delta Lactone, [redacted]			
2! Chlorhexidine Gluconate, [redacted]			
Total		**100.00**	

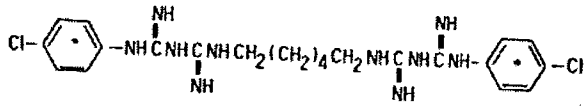
Each cloth is saturated with a target quantity of [redacted] of the 2% w/w chlorhexidine gluconate solution. Thus, the maximum exposure following the application of a single cloth is [redacted] chlorhexidine gluconate.

PHARMACOLOGY/TOXICOLOGY:

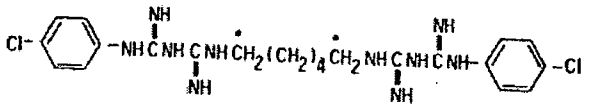
Pharmacology and toxicology studies were not performed with this submission. Instead, the sponsor provided a review of available scientific literature. Chlorhexidine is poorly absorbed following oral administration in all species tested. In animals, the small fraction of an oral dose that is absorbed is eliminated unchanged via urinary and biliary excretion.

CLINICAL STUDIES:

The percutaneous absorption of chlorhexidine gluconate was assessed in a published clinical study (D.E. Case, J. Mcainsh, A. Rushton, M.J. Winrow. 1980. Chlorhexidine: Attempts to detect percutaneous absorption in man, p. 367-374. *In* J.D. Williams, A.M. Geddes (eds.), International congress of chemotherapy, 9th edition, Plenum Press, New York). The authors assessed the percutaneous absorption of chlorhexidine gluconate using ^{14}C-labeled compound containing ^{14}C in either the aromatic ring systems or in the aliphatic carbon chain of the molecule (see diagrams below). The purity of the preparations was >98%. The sponsor's also used gas liquid chromatography (GLC) with electron capture based on degradation of p-chloroaniline. The limit of detection for this method was 0.01 to 0.05 µg/mL.



Aromatic ring system



* denotes position of ^{14}C

Aliphatic carbon chain

This study assessed the absorption of chlorhexidine gluconate after a single application, repeated applications, and among hospital staff. In the single application portion of the study, chlorhexidine gluconate (containing 18 μCi of ^{14}C) was applied as either a 5% aqueous solution or a 4% formulated hand wash to 50 cm^2 of the forearm skin of five adult male subjects. The formulations were left on the skin for 3 hrs under a non-occluding guard. Five blood samples were collected in the first 6 hrs and a further sample at 24 hrs. Urine and feces were collected up to 10 days. Only two fecal samples (from two different subjects) contained detectable ^{14}C-levels that were close of the limit of detection and represented less than 0.009% of the applied dose. None of the blood or urine samples contained any detectable radioactivity; the limit of detection was 0.005 μg/mL.

A repeated application study was performed to simulate conditions more comparable to those in general use. Fifteen healthy adults (eight female and seven male) used 'Hibiclens' (4% chlorhexidine gluconate preparation) in a hand-scrubbing regimen five times a day, five days each week, for three weeks. The hands and forearms were scrubbed with a bristle brush for 3 min with 5 mL of chlorhexidine gluconate. Nails were cleaned with a disposable cleaner, the hand and forearms rinsed with water, and then finally washed for 3 min, again using 5 mL of chlorhexidine gluconate.

Blood samples were obtained on days 0, 5, 12, 16, and 19 one-half hour after hand scrubbing, after one, three, or five scrubbing procedures, and assayed by the GLC method. No detectable level of chlorhexidine or chlorhexidine-derived material was found in any samples from any of the 15 subjects. Urine and fecal samples were not collected from subjects.

A hospital study was also carried out among UK hospital staff using 'Hibiscrub' surgical hand cleanser (5% digluconate preparation). The 25 subjects from three hospitals who participated in the study had been regular users of chlorhexidine for at least 6 months as a pre-operative antiseptic for hand disinfection. On average, the preparation had been used 5 times a day, washing for one minute with 5 mL of the 5% digluconate preparation, rinsing with water and repeating the wash for a further two minutes. Blood samples were obtained from subjects one to two hours after scrubbing. Concentrations of chlorhexidine could not be detected in any of the samples (limit of detection was 0.01 μg/mL).

Sage Products, Inc. is requesting a waiver of evidence of in vivo bioavailability or bioequivalence based on the currently marketed products containing chlorhexidine gluconate as the active ingredient. Based on 21 CFR 320.22(b), the sponsor meets the requirements for a waiver of evidence of in vivo bioavailability or bioequivalence if (1) the product is a solution for application to the skin; (2) contains an active drug ingredient in the same concentration and dosage form as a drug product that is the subject of an approved full new drug application or abbreviated new drug application; and (3) contains no inactive ingredient or other change in formulation from the drug product that is the subject of the approved full new drug application or abbreviated new drug application that may significantly affect absorption of the active drug ingredient or active moiety for products that are systemically absorbed, or that may significantly affect systemic or local availability for products intended to act locally.

The bulk drug product in the NDA is 2% chlorhexidine gluconate solution and is impregnated in [redacted] washcloths. Numerous topical solutions are currently marketed with chlorhexidine gluconate as the active ingredient with concentrations ranging from 0.5% to 4%; the proposed product is within this range. The sponsor has provided data to support the minimal absorption of chlorhexidine gluconate from intact skin when used as a hand cleanser following a single application as well as with multiple applications. Although the inactive ingredients of the 2% Chlorhexidine Gluconate Pre-Op Prep may differ from marketed products, it is unlikely that they will impact the bioavailability of chlorhexidine. Thus, the data submitted supports granting a waiver of evidence of in vivo bioavailability or bioequivalence. No further studies are necessary to support the in vivo bioavailability of 2% Chlorhexidine Gluconate Pre-Op Prep.

LABELING:
The sponsor submitted the proposed package labeling for 2% Chlorhexidine Gluconate Pre-Op Prep pre-packaged set of two washcloths. The package labeling is shown below.

The reviewer has no comments for the 2% Chlorhexidine Gluconate Pre-Op Prep package labeling. However, the sponsor has not submitted the package insert that will be included with each package of washcloths and is encouraged to do so when it is available.

RECOMMENDATIONS:
This application was reviewed by the Office of Clinical Pharmacology and Biopharmaceutics, Division of Pharmaceutical Evaluation III and found to be acceptable from a clinical pharmacology point of view.

Charles R. Bonapace, Pharm.D.
Office of Clinical Pharmacology/Biopharmaceutics
Division of Pharmaceutical Evaluation III

RD/FT Initialed by Philip M. Colangelo, Pharm.D., Ph.D.
Team Leader

cc:
Division File: NDA 21-669
HFD-520 (CSO/Dillon-Parker)
HFD-520 (MO/Mulinde, Bostwick)
HFD-880 (Division File, Lazor, Selen, Colangelo, Bonapace)
CDR (Clin. Pharm./Biopharm.)

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/s/

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10/20/03 02:17:33 PM
BIOPHARMACEUTICS

Phil Colangelo
11/7/03 04:46:48 PM
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