CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

21-524

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW(S)

Clinical Pharmacology and Biopharmaceutics Review
Division of Pharmaceutical Evaluation III

NDA:	21-524
Drug:	Chlorascrub™ Swabstick, Maxi Swabstick and Swab (3.15% (w/v) chlorhexidine gluconate and 70% (v/v) isopropyl alcohol)
Sponsor:	Les Enterprises Solumed Inc.
Date of Submission:	6/26/04
Type of Submission:	Original NDA (505(b)(2) application)
Reviewer:	Venkateswar R. Jarugula, Ph.D.

EXECUTIVE SUMMARY

Chlorascrub™ is a topical antiseptic solution which contains two active ingredients, 3.15% (w/v) chlorhexidine gluconate (CHG) and 70% (v/v) isopropyl alcohol (IPA). This NDA is a 505(b)(2) application and it relies on the Agency's previous findings of safety of Chloraprep® (Medi-Flex, Inc., NDA 20-832), a topical antiseptic containing 2% (w/v) chlorhexidine gluconate and 70% (v/v) isopropyl alcohol.

The proposed indications for Chlorascrub are: skin antiseptic, skin preparation prior to surgery and skin preparation prior to injection [redacted] Chlorascrub is dosed as a Swab applicator containing 1.0 mL of Chlorascub applied over a 2.5 x 2.5 inch treatment area for approximately 30 seconds and dried for 30 seconds; a Swabstick applicator containing 1.6 mL of Chlorascrub applied over a 3 x 5 inch (moist) or 4 x 4 inch (dry) treatment area for approximately 1.5 minutes and dried for 1.5 minutes; and a Maxi Swabstick applicator containing 5.1 mL of Chlorascrub applied over a 3 x 7.5 inch (moist) or 7 x 7 inch (dry) treatment area for approximately 2 minutes and dried for 2 minutes.

Three pivotal clinical trials were submitted to evaluate the antimicrobial efficacy of Chlorascrub™ in comparison to product vehicle and a reference product. In addition, two safety/dermal studies were also conducted to evaluate the human skin irritation and sensitization potential of Chlorascrub.

No new bioavailability or pharmacokinetic studies were conducted for Chlorascub. The sponsor's request for waiver for bioavailability and pharmacokinetic studies on Chlorascrub is acceptable based on the published literature information that indicates the dermal absorption of CHG in presence and absence of IPA is negligible.

RECOMMENDATION

NDA 21-524 has been reviewed by the Office of Clinical Pharmacology and Biopharmaceutics/Division of Pharmaceutical Evaluation III and it is acceptable from clinical pharmacology and biopharmaceutics perspective.

Venkateswar R. Jarugula, Ph.D.

RD/FT initialed by Arzu Selen, Ph.D., Deputy Director, HFD-880 _____

cc: NDA , HFD-520 (), HFD-880 (Lazor, Selen, Jarugula), CDR (B.Murphy for Drug).

Question Based Review

1. Biopharmaceutics

1.1 What is the bioavailability (systemic absorption) of chlorhexidine gluconate following the application of Chlorascrub on the skin?

The sponsor did not conduct any pharmacokinetic study to determine the systemic absorption of chlorhexidine gluconate (CHG) and isopropyl alcohol (IPA) from Chlorascrub (marketed as three products: Swab, Swabstick and Maxi Swabstick based on the size of the application area). Based on the previous agreement with FDA in the preNDA meeting, the sponsor is requesting waiver of bioavailability or pharmacokinetic studies for Chlorascrub.

Chlorhexidine gluconate was first synthesized in 1950 and shown to have antibacterial and antifungal properties. CHG was used as degerming agent in Europe and Canada for several decades prior to its approval for use in the USA in the 1970's. The following formulations of CHG have been approved by the FDA:

Hibiclens® (4% CHG in a detergent base) approved in 1976
Hibitane (0.5%CHG, 70% IPA) approved in 1978
Hibitane was withdrawn from the market in 1984 because of safety issues associated with alcohol fire hazard resulting from improper use of the product.
Hibistat (0.5% CHG, 70% IPA) approved in 1979
Chloraprep (2% CHG, 70% IPA) approved in 2000

In the preNDA meeting held on 3/11/2002, the Agency agreed to grant the sponsor a biowaiver for Chlorascrub if the following criteria are met:

- If the total quantity of CHG to be applied and the total surface area that the drug product will be applied to in clinical use conditions are no greater than those for the approved CHG products with the same indications;
- If the literature does not suggest that there is increased percutaneous absorption of CHG in the presence of IPA.

Chlorhexidine has been widely used as an antiseptic as well as preservative for over 30 years. Several studies have been conducted to evaluate the systemic absorption of CHG through skin. Dermal absorption of CHG has been reported to be negligible as shown by pharmacokinetic studies in adults, neonates and animals (*Denton GW. Chlorhexidine. In: Block S, editor. Disinfection, Sterilization and Preservation. 4th ed. Philadelphia 1991; 274-289*).

Comparison of Chlorascrub and Chloraprep

A comparison of Chlorascrub and Chloraprep in terms of the total quantity of CHG applied and the total surface area that the drug product will be applied in clinical use conditions is summarized in the following table.

Table 1. Comparison of Chlorascrub and Chloraprep

Description	Chlorascrub[#] 3.15%(w/v) CHG, 70% (v/v) IPA			Chloraprep[@] 2%(w/v) CHG, 70%(v/v) IPA	
	Swabstick	Maxi Swabstick	Swab	One-Step Frepp 3.0mL/unit	One-Step Frepp 1.5mL/unit
Treatment surface area (in^2)	a) 16.0 Dry site b) 15.0 Moist site	a) 49.0 Dry site b) 22.5 Moist site	6.25	20.0[$]	6.25[$]
Quantity of product (mL)	1.6	5.1	1.0	3.0[$]	1.5[$]
Quantity per unit surface area (mL/in^2)	a) Dry site b) 0.11 Moist site	a) Dry site b) 0.23 Moist site			
Amount of CHG per unit surface area (g/in^2)	a) Dry site b)0.0035 Moist site	Dry site b)0.0071 Moist site			

from Chlorascrub proposed package insert,
@ from Chloraprep One-Step Frepp Applicators package insert,
$ http://www.medi-flex.com/new_site/chlora_applicators.shtml; June 15, 2004

As noted in the above Table, Chlorascrub does not apply more CHG per square inch of skin than Chloraprep with the exception of the Swab applied on the forearm (minor difference, 0.005 vs. 0.0048 g/in^2) and the Maxi Swabstick applied on the groin. However, higher concentrations of CHG are applied on the skin with Hibiclens (4%CHG in a detergent base) and may result in higher exposures than Chlorascrub.

Absorption of CHG in the presence of IPA:

For transdermal absorption of small molecules, stratum corneum is known as the main barrier. Several factors such as the condition of the skin, the age of the skin, temperature, permeation enhancers, solubility and physicochemical properties of the molecule influence the percutaneous absorption.

Dermal absorption of CHG has been reported to be negligible based on the literature articles. There are no published articles that show that CHG absorption is increased in the

presence of IPA. Studies that have been conducted to date have shown that CHG has a very slow diffusion rate in human skin as a result of its strong affinity for skin proteins and its large molecular size irrespective of the medium that it is dissolved in. Biowaiver was granted for previous products containing CHG and IPA because the published data showed minimal percutaneous absorption of CHG (see Clinical Pharmacology and Biopharmaceutics reviews for Chloraprep (NDA 20832) containing 2% CHG and 70% IPA, and 2% CHG solution (NDA 21669)). Therefore, a biowaiver can be granted for the current NDA also as the available information indicates that the percutaneous absorption of CHG from Chlorascrub will be minimal.

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/s/

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