

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

20-832

CHEMISTRY REVIEW(S)

REVIEW OBJECTIVES: To determine whether the sponsor has adequate nonclinical data to support marketing of 2% chlorhexidine gluconate in 70% isopropanol in applicator devices to use for patient preoperative skin preparation.

PROPOSED DOSAGE FORM AND ROUTE OF ADMINISTRATION:

The formulation to be marketed contains:

Chlorhexidine Gluconate	2%
Isopropyl Alcohol	70%

It will be packaged in individual single-dose [redacted] applicators, then sterilized via [redacted]. The chlorhexidine gluconate/isopropanol is contained in a glass ampule enclosed in these units that is crushed at the time of use and the solution flows into a fabric plug [redacted] or sponge [redacted] for application to the skin. Both devices have been approved (510 (k)).

PROPOSED CLINICAL INDICATIONS: The sponsor requests that the product be approved as a "health care antiseptic" for reduction of "bacteria that can cause skin infection".

[redacted]

There has been extensive clinical experience with chlorhexidine gluconate. There are approved NDAs for products containing up to 4% chlorhexidine gluconate and these are in wide use as surgical scrubs, health care personnel handwashes, and patient preoperative skin preparations. There is a product containing 70% isopropanol and 0.5% chlorhexidine gluconate (Hibistat®) approved as a germicidal hand rinse for health care personnel.

PRECLINICAL PHARMACOLOGY/TOXICOLOGY: The sponsor has been given permission to cross-reference NDA 17,768. No additional preclinical studies were conducted to support this NDA and none are required. The toxicity profile of chlorhexidine gluconate has been well established and a vast quantity of data are available in the scientific literature. The sponsor has submitted a recent review article entitled "Final Report on the Safety Assessment of Chlorhexidine/Chlorhexidine Diacetate/Chlorhexidine Dihydrochloride/Chlorhexidine Digluconate" (J Am Coll Toxicol 12 (3): 201-223, 1993). Additionally, approved products containing chlorhexidine gluconate have been in clinical use for many years. 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 chlorhexidine gluconate.

SUMMARY AND EVALUATION: The sponsor has submitted an NDA for a product containing 2% chlorhexidine gluconate in 70% isopropanol. It will be used topically in a manner apparently consistent with other marketed chlorhexidine gluconate-containing products. The toxicity profile of this drug substance has been well established.

RECOMMENDATION: The pharmacologist has no objection to the approval of this NDA. The label for the drug product does not contain sections usually reviewed by pharm/tox personnel (*Carcinogenesis, Mutagenesis, Impairment of Fertility and Pregnancy Category*) as it is a cleanser for external use only and is not well absorbed through intact skin. The label does contain the appropriate warnings regarding flammability of the product and the fact that it should not be used in either eyes or ears because chlorhexidine gluconate has been reported to cause serious and permanent eye injury if allowed to remain in the eye during surgical procedures and deafness if it enters the middle ear. It may, however, be necessary to bold some of these statements and/or move them from the *Precautions* to the *Warnings* section. Additionally, the label does not mention that irritation and sensitization caused by chlorhexidine gluconate has been especially associated with application to the genital area. Other labels for chlorhexidine gluconate-containing products include this caveat.

/S/

Amy L. Ellis, Ph.D.
Pharmacologist, HFD-520

Orig. IND
cc:
HFD-520
HFD-520/Pharm Team Ldr/Osterberg
HFD-520/Pharm/Ellis
HFD-520/MO/Bostwick
HFD-520/Chem/Timper
HFD-520/CSO/Dillon-Parker
HFD-520/Micro/Sheldon

Concurrence Only:
HFD-520/REOsterberg
HFD-520/LGavrilovich

/S/ 2/7/97

/S/ 2/10/97

APPROVED FOR RELEASE
UNCLASSIFIED

DIVISION OF ANTI-INFECTIVE DRUG PRODUCTS
Review of Chemistry, Manufacturing, and Controls

NDA 20-832 **Chemistry review #2** **Review date 23 June, 2000**

<u>Submission</u>	<u>Document date</u>	<u>CDER date</u>	<u>Completed date</u>
<u>Prior Submissions</u>			
Original	1/8/97	1/15/97	7/24/97
Correspondence	2/20/97	3/21/97	7/24/97
<u>Resubmission and PDUFA starting time.</u>			
Reply to NonApp.	1/13/00	1/14/00	6/23/00
Chem. update	3/16/00	3/17/00	6/23/00
Chem. update	6/8/00	6/9/00	6/23/00

Applicant address
Medi-Flex Hospital Products, Inc.
19 Butterfield Trail
El Paso, Texas
79906

Contact
Beckloff Associates, Inc.
Commerce Plaza II, Suite 720
7400 West 110th Street
Overland Park, Kansas 66210
913-451-3955

Drug product name
Chloraprep

Pharmacological indication
Preoperative skin preparation

Dosage form
Solution and applicator

Strength
2% w/v

Route of administration
Topical

Rx/OTC
Over the counter

Supporting documents

Change from original submission:

Delete DMF [] source of drug substance
chlorhexidine gluconate (CHG). Current source of CHG is DMF []

Related documents n/a

APPEARS THIS WAY
ON ORIGINAL

Consults

Trade name consult: Acceptable, 6/5/00, HFD-400.

CMC micro for sterility controls: Acceptable, 6/6/00, HFD805.

Old site sterilizer:

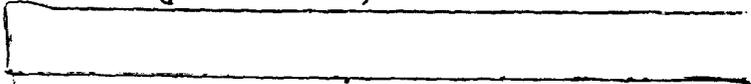
Medi Flex Hosp Products, Inc.
19 Butterfield Trail Blvd
El Paso, Tx

New site sterilizer:



Inspection request: Acceptable 6/2/00

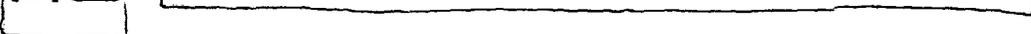
Mediflex (product manuf.):



Consult for container/applicator (to CDRH): Adequate



"This is in response to your consult for evaluation of an applicator by Med[i]flex [Hospital Products / Consultant - Beckloff Associates] to be used with a Chlorhexidine/alcohol 3ml ampule as a skin antiseptic for preop[erative] skin preparation



"The applicator as described in the 3/16/00 amendment to the NDA is to be used for the delivery of the Chlorhexidine/alcohol in the 3ml amp[o]ule. Since the applicator is intended at this time to be used only for the delivery of this specific drug (Chlorhexidine/alcohol in the 3ml amp[o]ule) it would not require a 510k. However, if the manufacturer decides to market the applicator alone it would be considered a manual surgical instrument under 21 CFR 878.4800 Manual Surgical Instruments, Class 1, 510k exempt.

Methods for analytic control: Adequate See review #1.

APPEARS THIS WAY
ON ORIGINAL

Summary

The first submission under NDA 20-832 was not approved, 2/20/98. A resubmission to the NDA 20-832 arrived in HFD-520 in January, 2000. The new amendment made changes to the applicator [redacted]

[redacted] All inspection requests were found "acceptable".

The first version of the new applicator submitted in January, 2000 for this product is defective. Examination of the new applicator revealed breaks on the pressure points of the applicator to the internal ampoule that occur on dispensing. The firm Medi-Flex Hospital Products changed the applicator [redacted]

[redacted] The current version of the applicator was addressed in a telecon with the firm on 5/22/00. The firm was requested at that time to provide the following in an amendment to the NDA 20-832:

1. Provide data on the [redacted] and its chemical impact on the container [redacted]
2. Provide DMF authorization letter for the [redacted] applicator.
3. Provide test results for the applicators subjected to the [redacted] and tested under the USP monograph <661>, Polyethylene containers: [redacted]
4. Provide justification that the current applicator will deliver adequate amount that will correlate to the applicator version used in clinical trial.

The firm has committed to reply to these items above in advance of the time deadline for PDUFA.

The firm has submitted a DMF authorization letter to DMF [redacted]

[redacted] DMF [redacted] is acceptable on 5/1/98. [redacted]

Additional chemistry review items completed and acceptable are: nomenclature review; inspection request; a CMC sterilization process review of the [redacted] process of the container/applicator.

APPEARS THIS WAY
ON ORIGINAL

Conclusions & recommendations

Recommend approval regarding the chemistry, manufacturing and controls of the Chlorhexidine gluconate, 2% solution.

APPEARS THIS WAY
ON ORIGINAL

/S/ 6/23/00

J. Timper, Review chemist
6/23/00

NDA 20-832; HFD-520/Division file;
HFD-830/Chen/DD
HFD-520/Katague/Chem-teamleader;
HFD-520/Timper/Chem;
HFD-520/Bostwick/MO;
HFD-520/Sheldon/Microbiology;
HFD-520/Dillon-Parker/Project manager

/S/ 6/30/00

APPEARS THIS WAY
ON ORIGINAL