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June 8, 2005

Division of Dockets Management
Food and Drug Administration (HFA-305)
Department of Health and Human Services
5630 Fishers Lane, Room 1061
Rockville, MD 20852

CITIZEN PETITION

Dear Sir or Madam:

The undersigned submits this petition, in quadruplicate, pursuant to Section 505(j)(2)(C) of the Federal Food, Drug and Cosmetic Act and in accordance with 21 CFR 10.30 requesting the Commissioner of the Food and Drug Administration declare the drug product, Chlorhexidine Gluconate 2% w/v and Isopropyl Alcohol 70% v/v Patient Preoperative Skin Preparation 3 mL, in a different dosage form suitable for consideration as an abbreviated new drug application (ANDA).

A. Action Requested

The petitioner requests the Commissioner of the Food and Drug Administration declare the drug product Chlorhexidine Gluconate 2% w/v and Isopropyl Alcohol 70% v/v Patient Preoperative Skin Preparation 3 mL suitable for submission in an ANDA. The petitioner seeks a change to the dosage form from that of the reference listed drug product. This petition is based on the reference listed drug (RLD) Chloraprep® (Chlorhexidine Gluconate 2% w/v and Isopropyl Alcohol 70% v/v Patient Preoperative Skin Preparation) indicated for the preparation of the skin prior to surgery. Medi-Flex, Inc. is the sponsor of the RLD under NDA 20-832 and marketing exclusivity expired July 14, 2003. A copy of the listing from the Electronic Orange Book (<http://www.fda.gov/cder/ob/default.htm>) is included in Attachment 1.

B. Statement of Grounds

The RLD is currently available in product volumes of 1.5 mL, 3 mL, and 10.5 mL. Aplicare proposes to submit an ANDA for the 3.0 mL product using a modified applicator. Therefore, only the 3.0 mL dosage form is discussed in this petition. The approved 3.0 mL product consists of a dry polyurethane foam sponge applicator located on the end of a plastic applicator handle with wings. The drug product solution is contained within a sealed glass ampule located inside the applicator handle. Pinching the wings of the handle breaks the ampule and saturates the foam sponge. The drug product is applied directly to the skin via the foam sponge to prepare the skin for surgery in accord with the labeled directions.

The petitioner seeks to submit an ANDA for a product using one (1) presaturated sponge on the end of a plastic applicator handle. As the sponge of the proposed product would be presaturated, the user simply opens the package and applies the antiseptic directly to the skin without having to break a glass ampule in preparation for skin application. One (1) presaturated applicator saturated with a total volume of three (3) mL of the solution would be packaged within one (1) foil pouch. The foam sponge material used to apply the drug product would be identical to the RLD sponge material for the three (3) mL dosage form; i.e., 100 PPI white polyurethane foam. Therefore, the user would administer the same

2005P.0224

CP1

amount of the same drug product in accord with the method of use identical to that of the RLD (apply saturated foam sponge containing the drug product directly to skin in accord with labeled directions), using the identical foam material.

To illustrate the approved 3.0 mL RLD product as well as the proposed product, the following images are provided. Image #1 is a rendering of the RLD obtained from the Medi-Flex, Inc. web site (www.medi-flex.com); Image #2 is a photograph of the RLD (right) and the proposed product (left).

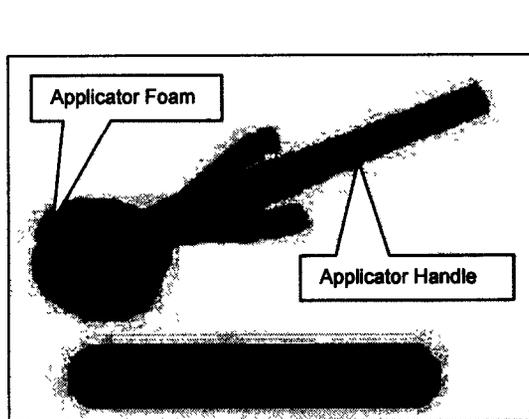


Image #1 – rendering of RLD

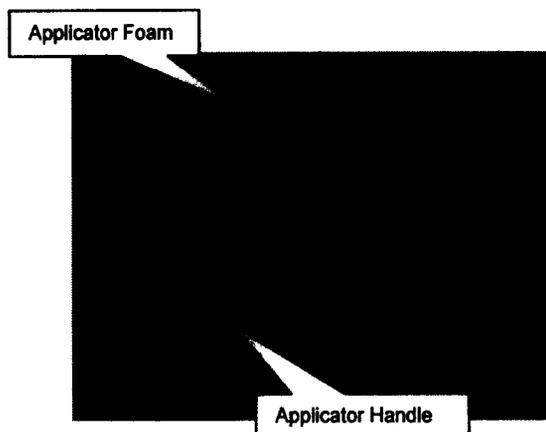


Image #2 – Photo of proposed product (left) and RLD (right)

The proposed change from an applicator requiring the user to saturate the foam sponge prior to use to presaturated sponges requires minimal changes to the product labeling; only in regard to preparing the applicator for use. The following table outlines the current RLD product Directions for Use of the 3 mL dosage form (see Attachment 2) and the proposed change:

Directions for Use	
3 mL Chloraprep®	3 mL Proposed Drug Product
<ul style="list-style-type: none"> ■ Pinch the wings on the applicator to break the ampule and release the antiseptic. Do not touch the sponge. Wet the sponge by repeatedly pressing and releasing the sponge against the treatment area until liquid is visible on the skin. 	<ul style="list-style-type: none"> ■ Open package at tear notch. <p><i>Change: Statement revised as it does not apply to presaturated sponges.</i></p>

All other text on the labeling remains identical and no other changes are proposed; **the drug product formulation would be identical to the RLD in regard to both the active and inactive ingredients.**

The following table summarizes the physical and chemical similarities and differences between the 3 mL RLD and the proposed product.

	RLD	Proposed Product
Active Ingredients	Chlorhexidine Gluconate (CHG) Isopropyl Alcohol (IPA)	Chlorhexidine Gluconate (CHG) Isopropyl Alcohol (IPA)
Inactive Ingredients	Purified water	Purified water
Strength	2% CHG (w/v) 70% IPA (v/v)	2% CHG (w/v) 70% IPA (v/v)
Dosage Form	Liquid	Liquid
Route of Administration	Topical	Topical
Volume	3 mL (approx.)	3 mL (approx.)
Applicator Foam	100 PPI white polyurethane foam sponge	100 PPI white polyurethane foam sponge
Applicator handle length	4.5" (approx)	4" (approx)
Packaging / drug contact surface	Inert glass	Inert plastics in a foil based laminate.
# Applicator devices / product	One	One

The petitioner notes that the proposed presaturated sponge as outlined above is safer to use than the RLD. The RLD product solution is contained within a glass ampule that must be broken by the user prior to administration. Resulting injury from glass shards on similar products have been reported via MedWatch reports to the Agency (see Attachment 3). The proposed product does not contain any glass components and is safer from this perspective. Similarly, because the proposed product contains no glass, breakage during shipment or handling, especially at low temperatures, is not a concern.

Copies of labels of the reference-listed drug product upon which this petition is based and draft labels for the proposed product are included as Attachment 2 and Attachment 4, respectively.

Therefore, the petitioner requests that the Commissioner find the requested change in dosage form equivalent to the RLD because the change does not raise issues of safety or effectiveness. The Agency should approve this petition to allow submission of an ANDA for the proposed dosage form.

C. Environmental Impact

The petitioner claims a categorical exclusion under 21 CFR 25.31.

D. Economic Impact

The petitioner believes that an economic impact assessment is not applicable for this petition, but agrees to provide such an analysis if requested by the Commissioner.

E. Certification

The undersigned certifies that to the best knowledge and belief of the undersigned, this petition includes all information and views on which the petition relies, and that it includes representative data and information known to the petitioner, which are unfavorable to the petition.

Apicare, Inc.
June 8, 2005
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Division of Dockets Management
Food and Drug Administration

Respectfully submitted,



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Attachments: 1. Copy of Electronic Orange Book (<http://www.fda.gov/cder/ob/default.htm>) of the RLD under NDA 20-832
2. Copy of RLD label (including Directions for Use) upon which this petition is based
3. References to glass causing injury in devices similar to the RLD
4. Copies of labels of the proposed product

cc: Mr. Gary Buehler (OGD)

ATTACHMENT 1

Copy of Electronic Orange Book
(<http://www.fda.gov/cder/ob/default.htm>)
of the RLD under NDA 20-832

<u>020111</u>	No	CHLORHEXIDINE GLUCONATE	SOLUTION; TOPICAL	0.75%	DYNA-HEX	XTTRIUM
<u>019422</u>	Yes	CHLORHEXIDINE GLUCONATE	SOLUTION; TOPICAL	2%	EXIDINE	XTTRIUM
<u>019125</u>	No	CHLORHEXIDINE GLUCONATE	SOLUTION; TOPICAL	4%	EXIDINE	XTTRIUM
<u>072525</u>	No	CHLORHEXIDINE GLUCONATE	SPONGE; TOPICAL	4%	CHLORHEXIDINE GLUCONATE	DESERET
<u>019822</u>	No	CHLORHEXIDINE GLUCONATE	SPONGE; TOPICAL	4%	BIOSCRUB	GRIFFEN
<u>072295</u>	No	CHLORHEXIDINE GLUCONATE	SPONGE; TOPICAL	4%	MICRODERM	J AND J
<u>019490</u>	No	CHLORHEXIDINE GLUCONATE	SPONGE; TOPICAL	4%	CHLORHEXIDINE GLUCONATE	KENDALL IL
<u>019793</u>	No	CHLORHEXIDINE GLUCONATE	SPONGE; TOPICAL	4%	PHARMASEAL SCRUB CARE	PHARMASEAL
<u>018423</u>	Yes	CHLORHEXIDINE GLUCONATE	SPONGE; TOPICAL	4%	HIBICLENS	REGENT
<u>020832</u>	Yes	CHLORHEXIDINE GLUCONATE; ISOPROPYL ALCOHOL	SPONGE; TOPICAL	2%;70%	CHLORAPREP ONE-STEP FREPP	MEDI FLEX INC
<u>020832</u>	Yes	CHLORHEXIDINE GLUCONATE; ISOPROPYL ALCOHOL	SPONGE; TOPICAL	2%;70%	CHLORAPREP WITH TINT	MEDI FLEX INC

Search results from the "OB_OTC" table for query on "020832."

Active Ingredient: CHLORHEXIDINE GLUCONATE; ISOPROPYL ALCOHOL
Dosage Form;Route: SPONGE; TOPICAL
Proprietary Name: CHLORAPREP ONE-STEP FREPP
Applicant: MEDI FLEX INC
Strength: 2%;70%
Application Number: 020832
Product Number: 001
Approval Date: Jul 14, 2000
Reference Listed Drug: Yes
RX/OTC/DISCN: OTC
Patent and Exclusivity Info for this product: [View](#)

Active Ingredient: CHLORHEXIDINE GLUCONATE; ISOPROPYL ALCOHOL
Dosage Form;Route: SPONGE; TOPICAL
Proprietary Name: CHLORAPREP WITH TINT
Applicant: MEDI FLEX INC
Strength: 2%;70%
Application Number: 020832
Product Number: 002
Approval Date: May 3, 2005
Reference Listed Drug: Yes
RX/OTC/DISCN: OTC
Patent and Exclusivity Info for this product: [View](#)

[Return to Electronic Orange Book Home Page](#)

FDA/Center for Drug Evaluation and Research
Office of Generic Drugs

Patent and Exclusivity Search Results from query on Appl No 020832 Product 001 in the OB_OTC list.

Patent Data

Appl No	Prod No	Patent No	Patent Expiration	Drug Substance Claim	Drug Product Claim	Patent Use Code
<u>020832</u>		5538353				
<u>020832</u>		5690958				
<u>020832</u>		5752363				
<u>020832</u>		5772346				
<u>020832</u>		6536975				
<u>020832</u>		D386849				
<u>020832</u>		D396911				

Exclusivity Data

There is no unexpired exclusivity for this product.

Additional information:

1. Patents are published upon receipt by the Orange Book Staff and may not reflect the official receipt date as described in 21 CFR 314.53(d)(5).
2. Patents submitted on FDA Form 3542 and listed after August 18, 2003 will have one to three patent codes indicating specific patent claims as submitted by the sponsor and are detailed in the above table.
3. Patents listed prior to August 18, 2003 are flagged with method of use claims only as applicable and submitted by the sponsor. These patents may not be flagged with respect to other claims which may apply.
4. *PED and PED represent pediatric exclusivity. Patents with pediatric exclusivity granted after August 18, 2003 will be indicated with *PED as was done prior to August 18, 2003. Patents with *PED added after August 18, 2003 will not contain any information relative to the patent itself other than the *PED extension. Information related specifically to the patent will be conveyed on the original patent only.

Patent and Exclusivity Search Results from query on Appl No 020832 Product 002 in the OB_OTC list.

Patent Data

Appl No	Prod No	Patent No	Patent Expiration	Drug Substance Claim	Drug Product Claim	Patent Use Code
<u>020832</u>		5538353				
<u>020832</u>		5690958				
<u>020832</u>		6536975				
<u>020832</u>		6729786				

Exclusivity Data

Appl No	Prod No	Exclusivity Code	Exclusivity Expiration
<u>020832</u>	002	<u>NP</u>	MAY 03,2008

Additional information:

1. Patents are published upon receipt by the Orange Book Staff and may not reflect the official receipt date as described in 21 CFR 314.53(d)(5).
2. Patents submitted on FDA Form 3542 and listed after August 18, 2003 will have one to three patent codes indicating specific patent claims as submitted by the sponsor and are detailed in the above table.
3. Patents listed prior to August 18, 2003 are flagged with method of use claims only as applicable and submitted by the sponsor. These patents may not be flagged with respect to other claims which may apply.
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[View a list of all patent use codes](#)

ATTACHMENT 2

Copy of RLD label (including Directions for Use)
upon which this petition is based

NDC # 054885-400-01

DIN # 02160757

ChloroPrep®

Chlorhexidine Gluconate 2% w/v and Iodopropyl Alcohol 70% w/v
Povidone Iodine Antiseptic Preparation • 1.0% w/v Antiseptic
Sterile, Single-Use, Disposable Antiseptic Preparation
Net Content: 100 mL (3.38 FL OZ)

Drug Facts	
Active Ingredients	Purpose(s)
Chlorhexidine gluconate 2% w/v	Antiseptic
Iodopropyl alcohol 70% w/v	Antiseptic
Uses for the preparation of the patient's skin prior to surgery	
Warnings ■ Flammable, keep away from fire or flame. ■ Do not use with electrolytic procedures ■ For external use only	
Do not use	
■ in children less than 2 months of age because of the potential for excessive skin irritation and increased drug absorption	
■ on patients with known allergies to chlorhexidine gluconate or iodopropyl alcohol	
■ for further procedure or in contact with the mucosae	
■ on open skin wounds or on a surgical skin closure	
Without seeking medical attention keep out of eyes, ears, and mouth. May cause irritation or permanent injury if permitted to enter and remain. If contact occurs, flush with cold water for 15 minutes and contact a physician.	
Stop use and seek medical attention if irritation, redness, or allergic reaction occurs. There may be signs of a serious condition.	
Keep out of reach of children. If swallowed, get medical help or contact a Poison Control Center right away.	
Directions	
■ pinch the wings on the applicator to break the seal and release the antiseptic. Do not touch the sponge. Wet the sponge by repeatedly pressing and releasing the sponge against the treatment area until liquid is visible on the skin.	
■ dry surgical sites (such as abdomen or arm): Use repeated back-and-forth strokes of the sponge for approximately 30 seconds. Completely wet the treatment area with antiseptic. Allow the area to air dry for approximately 30 seconds. Do not blot or wipe away.	
■ moist surgical sites (such as the inguinal fold): Use repeated back-and-forth strokes of the sponge for approximately 30 seconds. Completely wet the treatment area with antiseptic. Allow the area to air dry for approximately one (1) minute. Do not blot or wipe away.	
■ maximum treatment area for one applicator is approximately 130 cm ² (approx. 4 x 8 in.). Discard the applicator after a single use.	
Other Information ■ store between 20-30 °C (68-77 °F) ■ avoid freezing and excessive heat above 40 °C (104 °F)	
Inactive Ingredients ■ USP purified water	
Questions? Call 1-800-828-6222 (9 a.m.-5 p.m. EST) Med-Plus Hospital Products, Inc., Cleveland Park, KS 66210	

Single Use
Applicator is STERILE if package is intact
Catalog No. 280400

ATTACHMENT 3

References to glass causing injury
in devices similar to the RLD

From the MAUDE database at the FDA's website:

Adverse Event Report
MEDI-FLEX SEPP 10% POVIDONE IODINE APPLICATOR

Catalog Number 26-02-86

Event Description

When ampule was broken, a sliver of glass penetrated the outer plastic sleeve and cut the employee's hand while blood cultures were being done. There did not appear to be any blood-to-blood contact.

Brand Name SEPP 10% POVIDONE IODINE APPLICATOR

Type of Device APPLICATOR

Manufacturer (Section D) MEDI-FLEX
overland park KS 66210

Device Event Key 28651

MDR Report Key 27734

Event Key 25929

Report Number 27734

Device Sequence Number 1

Product Code EFQ

Report Source Voluntary

Report Date 11/01/1995

1 Device Was Involved in the Event

1 Patient Was Involved in the Event

Date FDA Received 11/01/1995

Is This An Adverse Event Report? Yes

Is This A Product Problem Report? No

Device Operator Health Professional

Device EXPIRATION Date 05/01/1998

Device Catalogue Number 26-02-86

Device LOT Number 503032

Was Device Available For Evaluation? Yes

Patient Outcome Other

See

http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfMAUDE/Detail.CFM?MDRFOI_ID=27734

From the MAUDE database at the FDA's website:

Adverse Event Report
MEDI-FLEX HOSP PRODUCTS IODINE SEPP APPLICATOR

Catalog Number 260286

Event Description

Gauze applicator tip fell off. Pt's skin was prepped with alcohol. Bleeding and small pinhole-like marks noted over intended insertion area. Small piece of glass on skin noted.

Brand Name IODINE SEPP APPLICATOR
Manufacturer (Section D) MEDI-FLEX HOSP PRODUCTS
overland park KS 66210 2103

Device Event Key 11321

MDR Report Key 11321

Event Key 7379

Report Number 11321

Device Sequence Number 1

Product Code KXF

Report Source Voluntary

Report Date 09/01/1993

1 Device Was Involved in the Event

1 Patient Was Involved in the Event

Date FDA Received 02/01/1994

Is This An Adverse Event Report? No

Device Operator Health Professional

Device Catalogue Number 260286

Device LOT Number 305-002

Was Device Available For Evaluation? No Answer Provided

See http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfMAUDE/Detail.CFM?MDRFOI_ID=11321

ATTACHMENT 4

Copy of Proposed Product label

APLICARE LABEL COPY

FG Part Number: S-1040	RM Part Number: TBD	Description: PreVent _{AC} Swabsticks
Rev. # 0605	Created By: Gita Roess	Date: 06/08/05
Print Colors: ■ PMS 7455 Blue ■ Black		Background Color: White

Draft

NDC 52380-0040-6 Reorder No. S-1040

Isopropyl Alcohol

PreVent_{AC}TM
Chlorhexidine Gluconate

◀ Tear Here Hold Upright Tear Here ▶

Chlorhexidine Gluconate 2% w/v and Isopropyl Alcohol 70% w/v

Patient Preoperative Skin Preparation = 3.0 mL Application

WARNING: FLAMMABLE. KEEP AWAY FROM FIRE OR FLAME.
DO NOT USE WITH ELECTROCAUTERY PROCEDURES.

Single Use • Latex Free

Drug Facts

Active Ingredients	Purpose
Chlorhexidine gluconate 2% w/v	Antiseptic
Isopropyl alcohol 70% w/v	Antiseptic

Use for the preparation of the patient's skin prior to surgery

Warnings

- Flammable**
- Keep away from fire or flame
 - Do not use with electrocautery devices
- Do not use**
- in children less than 2 months of age because of the potential for excessive skin irritation and increased drug absorption
 - on patients with known allergies to chlorhexidine gluconate or isopropyl alcohol
 - for lumbar puncture or in contact with the meninges
 - on open skin wounds or as a general skin cleanser

When using this product keep out of the eyes, ears, and mouth. May cause serious or permanent injury if swallowed or inhaled and inhaled. If contact occurs, rinse with cold water right away and contact a physician.

APPLICARE
BRANFORD, CT 06405
Made in U.S.A.
0605
NDC 52380-0040-6

Questions? Call 1-800-796-2228 (9:30 a.m. - 5 p.m. EST)

Inactive ingredients = USP purified water

Other information

- Store between 20-25°C (68-77°F)
- Most freezing and maximum heat above 40°C (104°F)

Directions

- Open package at one end
- Apply swabstick to skin (such as abdomen or arm). Use repeated back-and-forth strokes of the swabstick. Do not touch swabstick to the patient's skin.
- Allow the area to dry for approximately 30 seconds. Completely wet the treatment area with antiseptic back-and-forth strokes of the swabstick for approximately 30 seconds. Do not touch swabstick to the patient's skin.
- Repeat back-and-forth strokes of the swabstick for approximately 2 minutes. Completely wet the treatment area with antiseptic. Allow the area to dry for approximately 30 seconds. Do not touch swabstick to the patient's skin.
- Repeat back-and-forth strokes of the swabstick for approximately 2 minutes. Completely wet the treatment area with antiseptic. Allow the area to dry for approximately 30 seconds. Do not touch swabstick to the patient's skin.
- Repeat back-and-forth strokes of the swabstick for approximately 2 minutes. Completely wet the treatment area with antiseptic. Allow the area to dry for approximately 30 seconds. Do not touch swabstick to the patient's skin.

Warnings

Keep out of reach of children. If swallowed, get medical help or contact a Poison Control Center right away.

For external use only.

Drug use may cause a doctor to perform, anesthesia, or change reaction course. There may be signs of a severe reaction.

Drug Facts (continued)