





# CardinalHealth

1500 Waukegan road  
McGaw Park, IL 60085  
847-473-1500

11/18/04

Mr. Gary Buehler  
Food and Drug Administration  
Office of Generic Drugs  
Document Mail Center (HFD-600)  
7500 Standish Place  
Rockville, MD 20855

Dear Mr. Buehler:

Cardinal Health is submitting this Suitability Petition to the FDA requesting permission to file an ANDA for a preoperative prep containing a chlorhexidine gluconate (CHG) / isopropol alcohol (IPA) solution with tint. More specifically, the intent of this petition is to address the change in applicator volume from 10.5 ml to 26 ml.

**A. Action Requested:**

As indicated above, Cardinal Health proposes to file an ANDA based upon the reference listed drug (RLD) ChloroPrep® One-Step chlorhexidine gluconate 2% (w/v) and isopropyl alcohol 70% (v/v) antiseptic patient preoperative skin preparation (10.5 mL) (hereinafter referred to as ChloroPrep) manufactured by Medi-Flex, Inc., (NDA 20-832) and the recent ANDA submission by Cardinal Health for a similar product (ANDA 77-271). The marketing exclusivity of the reference listed drug expired July 14, 2003. The specific intent of this petition is to request approval for a change in applicator volume from 10.5 ml to 26 ml.

**B. Statement of Grounds:**

The active ingredients in the proposed Cardinal Health drug product, CHG and IPA, are the same as those of the reference listed drug approved in NDA No. 20-832. The dosage form and strength of the proposed product are also the same as those of the reference listed drug approved in NDA No. 20-832. The inactive ingredients in Cardinal Health's Prevail-CHG and ChloroPrep are presented in the following table.

| Inactive Ingredients in Prevail-CHG and ChloroPrep                           |                         |
|--|-------------------------|
| Prevail-CHG  | ChloroPrep <sup>a</sup> |
| Purified Water, USP  | Purified Water, USP     |
| FD&C Red No. 40  |                         |
| <sup>a</sup> Inactive ingredients listed on ChloroPrep labeling are provided |                         |

There is considerable commercial experience with one-step preoperative prep products containing alcohol. As summarized in the following table, the widespread use of Povidone Iodine-plus-alcohol based products, such as 3M's Dura-Prep (26 ml) and Cardinal Health's Prevail (59 ml) and Prevail-FX (40 ml) represent an estimated 70% of the entire preoperative prepping market.

2004P-0528

CPI

| <b>Currently Marketed Patient Preoperative Prepping Solutions Containing Alcohol</b> |   |  |
|--|---|--|
| <b>DuraPrep<sup>®</sup>, 26 ml</b>   | <b>Iodophor and IPA (0.7% Available Iodine and 74% IPA w/w)</b>   | <b>6,000,000 units est. sold annually.</b> |
| <b>Cardinal Large Applicators (Prevail<sup>®</sup>, 59 ml; Prevail-FX, 40 ml)</b>    | <b>Povidone Iodine USP and Alcohol (Prevail: 0.5% Available Iodine and 62% v/v Ethanol) (Prevail-Fx: .83% Available Iodine and 72.5% IPA w/w)</b> | <b>1,000,000 units est. sold annually.</b> |
| <b>ChloraPrep<sup>®</sup>, 10.5 ml</b>   | <b>Chlorhexidine Gluconate and IPA (2% CHG w/v and 70% IPA v/v)</b>   | <b>1,500,000 units est. sold annually.</b> |

It is speculated that the reason for the relatively high use of products containing more than 10.5 ml of solution is that a majority of surgical procedures require larger volumes of solution to prep the area of concern. The surface area of a typical human body is approximately 2800 square inches, (referencing Cornell University website <http://www-users.med.cornell.edu/~spon/picu/calc/bsacalc.htm>). The 10.5 ml applicator covers an area of about 8.4 square inches. It is evident that preparing a patient for typical procedures such as laparoscopies would normally require more than a single applicator. Through clinical observation and discussion with practitioners, it has been determined that a full-body prep commonly uses 80 ml of antimicrobial solution in the preparation of skin for surgery. Eight (8) separate containers of the 10.5 ml RLD would have to be opened in this case, significantly increasing the time for prepping as well as negatively impacting the cost of the procedure. Using Cardinal Health products as a case study, the packaging and sterilization costs are approximately half of the total product cost. In addition, it would take practitioners extra time and effort to obtain and open the units without improving patient or clinician safety. The proposed Cardinal Health product has been developed in consideration of cost and convenience.

Cardinal is aware that there is concern with OR fires associated with prepping solutions containing a high percentage of alcohol. This concern, as well as customer safety, was taken into consideration during the design of the Cardinal applicator. With many products on the market, notably DuraPrep and ChloraPrep, the container holding the fluid is a glass ampoule, which is broken during applicator activation. Once broken, there is no means of controlling fluid flow through the sponge of the applicator and onto the surgical site. With the Cardinal Health applicator system, the container for the fluid is an HDPE bottle. Once the foil seal on the neck of the bottle is punctured, fluid can be expelled through the neck of the bottle by squeezing or, conversely, fluid flow will be slowed significantly by merely holding the bottle without squeezing. This applicator is the same as that of Cardinal's currently sold prep products, i.e., Prevail and Prevail-Fx.

The proposed prep contains 70% isopropyl alcohol, which provides fast and broad-spectrum antimicrobial kill. Additionally, this alcohol allows for quick dry time (2-3 minutes). Combined with CHG, this system yields an extremely fast-acting, persistent preoperative skin preparation.

Based on investigations, published figures, and searches of the U.S. Food and Drug Administration's (FDA) medical device reporting databases, ECRI estimates that 100 surgical fires per year occur in the United States each year (Risk Management Reporter, Oct 2003). In conversations with Mark E. Bruley (ECRI Vice President, Accident and Forensic Investigation), roughly 5-15% of these surgical fires are attributed to alcohol-based preps.

It has been well established that for a fire to occur, an ignition source, fuel and oxidizer must be present. Alcohol and alcohol-based preps are flammable until all liquid has evaporated (Health Devices, November 2003). Once dry, the solution is no longer flammable. It is important to note that the OR fires are easily prevented through education and training of proper application methods and dry times.

In conjunction with the concern of excess fluid being applied to the area being prepped, there is also a concern that hospital linens or drapes will become saturated and will not be removed or replaced prior to coming in contact with an ignition source. The proposed product label clearly warns of the concerns with use of a flammable solution. It also provides instructions on removal of soaked materials and advises users to allow for sufficient drying of solutions prior to surgery. Please refer to correspondence between the 3M Corporation and the FDA, docket Management Branch (HFA-305), dated June 15, 1995 Docket No. 75N-183H, where a detailed review of cause and corrective action, notably awareness and training of the professional OR staff.

In conclusion, Cardinal Health's proposed prep product has been developed to address cost, convenience and the safety concerns of the OR staff. It is our opinion that the proposed Cardinal product with a change in packaging size to 26 ml as compared to the 10.5 ml packaging size of the RLD is suitable to be filed as an ANDA.

**C. Environmental Impact Statement:**

By providing a single applicator containing 26 mls of solution, the end user is cutting in half the amount of waste generated during patient preoperative prepping with use of the RLD.

**D. Economic Impact Statement:**

Not required at this time.

**E. Certification:**

The undersigned certified 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 that are unfavorable to the petition.



Michael L. Groesbeck

Vice President, Quality Operations, Infection  
Infection Prevention, Cardinal Health

1500 Waukegan Rd., Bldg. WM  
McGaw Park, IL 60085  
(847) 785-3267

Attachments:

Label copy for Prevail-CHG2: Bottle, Pouch, Case Label  
Label copy for ChloroPrep® Bottle, Pouch, Dispenser

TO OPEN PEEL HERE

Cat. 4VAIL-CHG2

NDC 63517-015-26

Prevail CHG

One Step Topical Preoperative Prep Solution and Applicator

Contains Chlorhexidine Gluconate 2% (w/v) and Isopropyl Alcohol 70% (v/v)

Each bottle contains 26 mL

Single application provides fast-acting, broad-spectrum, persistent antimicrobial activity.

Sterile  
For Single External Use Only

**Prevail-CHG™** 

Contains  
One (1) 26 mL Applicator (urethane sponge)  
Contents in unopened, undamaged package are sterile



| Drug Facts  |  |
|---|--|
| <b>Active Ingredient</b><br>Chlorhexidine gluconate 2% (w/v)<br>Isopropyl alcohol 70% (v/v)   | <b>Purpose</b><br>Antiseptic<br>Antibiotic |
| <b>Use:</b> for preparation of the patient skin prior to surgery  |  |
| <b>Warnings</b><br><ul style="list-style-type: none"> <li>Do not use on patients less than 2 months of age because of the potential for excessive skin irritation and increased drug absorption.</li> <li>Do not use on patients with known allergies to chlorhexidine gluconate or isopropyl alcohol.</li> <li>Do not use on patients with open wounds or on a general skin cleanser.</li> <li>When using this product keep out of eyes, nose, and mouth. May cause serious or permanent injury if permitted to enter and remain. If contact occurs, rinse with cold water right away and contact a physician.</li> <li>Stop use and ask a doctor if irritation, sensitization, or allergic reaction occurs. There may be signs of a serious condition.</li> <li>Keep out of reach of children. If swallowed, get medical help or contact a Poison Control Center right away.</li> </ul>   |  |
| <b>Directions</b><br><ul style="list-style-type: none"> <li>Wash hands, wearing gloves.</li> <li>Remove applicator from pouch.</li> <li>Hold bottle and neck of the applicator cap.</li> <li>Use bottle as dispenser of solution and push applicator down onto bottle until a snap is heard.</li> <li>Insert bottle and applicator in dispenser solution.</li> <li>Do not use applicator until the treatment area is completely dry.</li> <li>Use repeated back-and-forth strokes of the sponge for approximately 30 seconds.</li> <li>Completely wet the treatment area with antiseptic.</li> <li>Allow the area to air dry for approximately 30 seconds. Do not blot or wipe away.</li> <li>Do not use applicator until the treatment area is completely dry.</li> <li>Use repeated back-and-forth strokes of the sponge for approximately 2 minutes.</li> <li>Completely wet the treatment area with antiseptic.</li> <li>Allow the area to air dry for approximately one (1) minute. Do not blot or wipe away.</li> <li>Use minimum treatment area for one applicator is approximately 736 cm<sup>2</sup> (17 in x 17 in).</li> <li>Cleanse the applicator after a single use.</li> </ul> |  |
| <b>Other Information</b> Store between 20-25°C (68-77°F) in cool, dry place and exposure heat above 40°C (above 104°F)  |  |
| <b>Inactive Ingredients</b> See PCAC (Part No. 43) and product water: USP   |  |
| <b>Questions?</b> 800-622-6222 (Monday to Friday 9 AM - 5 PM)   |  |

Cardinal Health  
McGaw Park, IL 60085 USA  
30-XXXX



(01) 0 0380470 17878 0



NK080411  
Medivac-Prep-Thermal B.U.  
McGaw Park, IL  
M. Kraemer  
9/30/04  
30-XXXX

|                           |                     |
|---------------------------|---------------------|
| Proofed by: _____         | Date: _____         |
| Dimensions checked: _____ | Copy checked: _____ |

Cat 4VAIL-CHG2 N 63517-015-26

Prevail-CHG  
One Step Topical  
Preoperative Prep  
Solution and Applicator

Contains Chlorhexidine Gluconate  
2% (w/v) and Isopropyl Alcohol  
70% (v/v)

For Single External Use Only

Warning: Solution is flammable  
until dry.

Contains 26 mL  
Cardinal Health  
McGaw Park, IL 60085 USA  
37-XXXXX



Cardinal Health

MK090413  
Medivac-Prep-Thermal B.U.  
McGaw Park, IL  
M. Kraemer  
9/30/04  
37-XXXXX

Proofed by: \_\_\_\_\_ Date: \_\_\_\_\_

Dimensions checked: \_\_\_\_\_ Copy checked: \_\_\_\_\_

Cat. **4VAIL-CHG2**

NDC  
63517-015-26

Qty. **20**

**Prevail-CHG™**  
**One Step Topical Preoperative Prep**  
**Solution and Applicator**

Contains Chlorhexidine Gluconate 2% (w/v) and  
Isopropyl Alcohol 70% (v/v)

Sterile

Lot No.

Exp.



**Warning:** Solution is  
flammable until dry.



Store at 20–25°C (68–77°F). Avoid freezing and  
excessive heat above 40°C (above 104°F).



Each Bottle Contains 26 mL

U.S. components assembled in Mexico

**Cardinal Health**  
McGaw Park, IL 60085 USA  
37-XXXXX



(01) 5 0380470 17978 5



**MK090412**  
Medivac-Prep-Thermal B.U.  
McGaw Park, IL  
M. Kraemer  
9/30/04  
37-XXXXX

|                           |                     |
|---------------------------|---------------------|
| Proofed by: _____         | Date: _____         |
| Dimensions checked: _____ | Copy checked: _____ |



Cat. No. 260700 NDC #054365-400-04 DIN#02160757

## ChlorPrep® One-Step

Chlorhexidine Gluconate 2% w/v and Isopropyl Alcohol 70% v/v  
Patient Preoperative Skin Preparation • 10.5mL Applicator

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

| <b>Drug Facts</b>  |                |
|--|----------------|
| <b>Active Ingredients</b>  | <b>Purpose</b> |
| Chlorhexidine gluconate 2% w/v   | Antiseptic     |
| Isopropyl alcohol 70% v/v  | Antiseptic     |
| <b>Use</b> for the preparation of the patient's skin prior to surgery  |                |
| <b>Warnings</b>  |                |
| For external use only  |                |
| Flammable. Keep away from fire or flame. Do not use with electrocautery procedures.  |                |
| <b>Do not use</b>  |                |
| <ul style="list-style-type: none"> <li>■ in children less than 2 months of age because of the potential for excessive skin irritation and increased drug absorption.</li> <li>■ on patients with known allergies to chlorhexidine gluconate or isopropyl alcohol</li> <li>■ for lumbar puncture or in contact with the meninges</li> <li>■ on open skin wounds or as a general skin cleanser</li> </ul>  |                |
| When using this product: keep out of eyes, ears, and mouth. May cause serious or permanent injury if permitted to enter and remain. If contact occurs, rinse with cold water right away and contact a physician.   |                |
| Stop use and ask a doctor if irritation, sensitization, or allergic reaction occurs. These 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.   |                |
| <b>Directions</b>  |                |
| <ul style="list-style-type: none"> <li>■ pinch the wings on the applicator to break the ampule and release the antiseptic. Do not touch the sponge.</li> <li>■ Wet the sponge by repeatedly pressing and releasing the sponge against the treatment area until liquid is visible on the skin.</li> <li>■ 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.</li> <li>■ non-let surgical sites (such as the inguinal fold): Use repeated back-and-forth strokes of the sponge for approximately 2 minutes. Completely wet the treatment area with antiseptic. Allow the area to air dry for approximately one (1) minute. Do not blot or wipe away.</li> <li>■ maximal treatment area for one applicator is approximately 457 cm<sup>2</sup> (approximately 8.4 x 8.4 inches). Discard the applicator after a single use.</li> </ul> |                |
| <b>Other information</b>   |                |
| <ul style="list-style-type: none"> <li>■ store between 20-25°C (68-77°F)</li> <li>■ avoid freezing and excessive heat above 40°C (104°F)</li> </ul>  |                |
| <b>Inactive ingredients</b> ■ USP purified water   |                |
| <b>Questions?</b> Call 1-800-323-0202 (8 a.m.-5 p.m. CST)  |                |

Single Use  
Applicator is **sterile** if package is intact

Lot No:

Exp. Date:



**ChlorPrep® 10.5-ml Applicator**  
**2% (w/v) Chlorhexidine Gluconate**  
**and 70% (v/v) Isopropyl Alcohol**  
**Lot No. 405060      Exp. Date 04/06**  
**Medi-Plaz, Inc. Leawood, KS 66211**

Part No: 6-824248  
Rev. Date: 2/17/03



**ChloroPrep® One-Step**  
**10.5-mL Applicators • 25 qty.**

Store at room temperature 20-25 °C (68-77 °F)  
Avoid freezing and excessive heat above 40 °C (104 °F)

Cat. No. 260700 ND

**Chloro**

**Chlorhexidine Gluc**  
**Antiseptic Patient**

**ChloroPrep® One**  
**persistent anti**  
**number of micr**

**10.5-mL Applicator**  
**Single Use**

**Applicator is sterile**

**Contents: 1 Each Spor**  
**Quantity: 1 Box, 25 Ea**

**Store at room temper**  
**Avoid freezing and ex**

Part No: 6-824248  
Rev. Date: 2/17/03

**MEDI-FLEX**

**Chloraprep® One-Step**  
Applicators • 25 qty.

temperature 20-25 °C (68-77 °F)  
and excessive heat above 40 °C (104 °F)

Cat. No. 260700 NDC #054365-400-0

**Chloraprep**

**Chlorhexidine Gluconate 2% (w/v)**  
**Antiseptic Patient Preoperative S**

**Chloraprep® One-Step is a fo**  
**persistent antiseptic that s**  
**number of microorganisms c**

**10.5-mL Applicator**

**Single Use**

**Applicator is sterile if package is intact**

**Contents: 1 Each Sponge, Latex Free**  
**Quantity: 1 Box, 25 Each/Box**

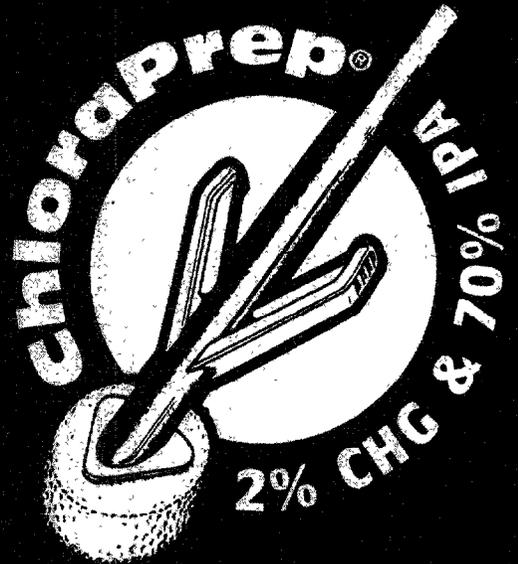
**Store at room temperature 20-25 °C (68-77 °F)**  
**Avoid freezing and excessive heat above 40 °C (104 °F)**

00-04 DIN#02160757

# ep<sup>®</sup> One-Step

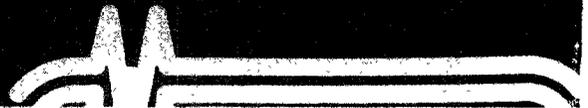
w/v) and Isopropyl Alcohol 70% (v/v)  
ive Skin Preparation

a fast-acting, broad spectrum,  
at significantly reduces the  
ms on intact skin.



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**ChloroPrep® One-Step**  
10.5-mL Applicators • 25 qty.

Store at room temperature 20-25 °C (68-77 °F)  
Avoid freezing and excessive heat above 40 °C (104 °F)



\*+H9852607002B\*

Lot No: **405060** Exp. Date: **04-06**

spectrum  
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step  
(A/A) %0Z 10

**Chloro**  
Chlorhexidine  
Patient Prep

**Drug Facts**

**Active ingredients**  
Chlorhexidine gluconate 2% w/v  
Isopropyl alcohol 70% v/v

**Use**  
for the preparation of the pr

**Warnings**  
For external use only  
**Flammable: Keep away!**

**Do not use**  
in children less than 2 mo  
on patients with known alle  
for lumbar puncture or in c  
on open skin wounds or ar

**When using this product**  
keep out of eyes, ears, an  
**Stop use and ask a doc**  
irritation, sensitization, or  
**Keep out of reach of ch**

**Directions**  
pinch the wings on the ap  
Wet the sponge by repea  
**dry surgical sites (su**  
Completely wet the treatm  
**moist surgical sites**  
Completely wet the treatm  
maximal treatment area f

**Other information**  
store between 20-25 °C

**Inactive ingredie**

**Questions? Call 1-8**



is a fast-acting, broad spectrum,  
that significantly reduces the

ative Skin Preparation  
(W/V) and Isopropyl Alcohol 70% (W/V)

**ep One-Step**®

5-400-04 DIN#02160757

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6 12  
||



**One-Step**  
ators • 25 qty.

re 20-25 °C (68-77 °F)  
heat above 40 °C (104 °F)



7002B\*

04 05

Date:

# ChloroPrep® One-Step

Chlorhexidine Gluconate 2% w/v and Isopropyl Alcohol 70% w/v Patient Preoperative Skin Preparation • 10.5-mL

## Drug Facts

**Active ingredients**  
Chlorhexidine gluconate 2% w/v  
Isopropyl alcohol 70% w/v

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

**Warnings**  
For external use only  
**Flammable: Keep away from fire or flame.** Do not use with electrocautery procedures

**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 eyes, ears, and mouth. May cause serious or permanent injury if permitted to enter and remain. If contact occurs,

**Stop use and ask a doctor if**  
■ irritation, sensitization, or allergic reaction occurs. These 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 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.  
■ **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.  
■ **moist surgical sites** (such as the inguinal fold): Use repeated back-and-forth strokes of the sponge for approximately 2 minutes. Completely wet the treatment area with antiseptic. Allow the area to air dry for approximately one (1) minute. Do not blot or wipe.  
■ maximal treatment area for one applicator is approximately 457 cm<sup>2</sup> (approximately 8 4 x 8 4 inches). Discard the applicator after use.

**Other information**  
■ store between 20-25 °C (68-77 °F) ■ avoid freezing and excessive heat above 40 °C (104 °F)

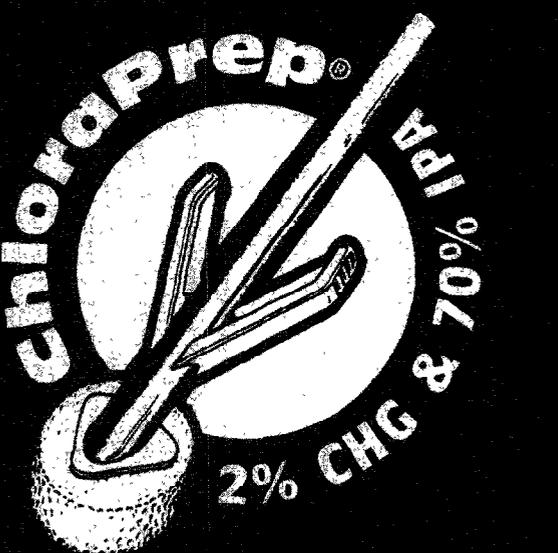
**Inactive ingredients** ■ USP purified water

**Questions?** Call 1-800-823-8903 (8 a.m.-5 p.m. CST)

Chloraprep® One-Step is a fast, persistent antiseptic that significantly reduces the number of microorganisms on the skin. Chloraprep Antiseptic Patient Preoperative Skin Preparation Solution contains Chlorhexidine Gluconate 2% (w/v) and Isopropyl Alcohol 70% (v/v).

# Chloraprep

CAT. NO. 260700 NDC #054365-400-04



## One-Step

and Isopropyl Alcohol 70% v/v  
 with 2% Chlorhexidine Gluconate  
 • 10.5-mL Applicator

**Purpose**  
 Antiseptic  
 Antiseptic

Increased drug absorption.

For use on skin. If contact occurs, rinse with cold water right away and contact a physician.

Center right away.

Wipe the sponge until liquid is visible on the skin. Hold the sponge for approximately 30 seconds. Do not blot or wipe away the sponge for approximately 2 minutes. Do not use for more than one (1) minute. Do not blot or wipe away (1/2 inch). Discard the applicator after a single use.

