PDI®
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Prevantics™

PATIENT PREOPERATIVE & PREINJECTION SKIN PREPARATION

Chlorhexidine Gluconate (3.15% w/v) and Isopropyl Alcohol (70% v/v)

CLINICAL COMPENDIUM

Table of Contents

All Studies contained within this clinical compendium were performed by a third-party, independent clinical laboratory approved by the US Food and Drug Administration.

Introduction

CHLORHEXIDINE GLUCONATE USAGE FOR SKIN ANTISEPSIS

Chlorhexidine Gluconate (CHG) was first introduced in the United States in the 1970s as a handwashing agent for healthcare workers. Since that time, aqueous CHG agents have been widely used as an effective antiseptic handwashing and surgical scrub. The use of CHG for antiseptic skin prepping was studied by Maki et al. in the early 1990s.[1] Dr. Maki compared the use of 2% aqueous CHG, 70% Alcohol, and 10% Povidone-Iodine (the most common iodophor) for skin prepping prior to surgical procedures. The results of this study showed that use of an aqueous 2% CHG substantially reduced the incidence of procedure-related infections. Another study by Mimoz et al. showed Chlorhexidine was more efficacious than Povidone-Iodine skin preparation in reducing contamination of blood cultures.[2] In 2000, the first Chlorhexidine Gluconate [CHG] and 70% Isopropyl Alcohol [IPA] skin antiseptic was approved by the Food and Drug Administration (FDA) in the United States. Since that time, antiseptic skin prepping agents that contain a combination of two antiseptics, CHG/IPA, are favored by clinicians.

Many evidence-based studies have been published showing that CHG/IPA skin antiseptics are effective in reducing bloodstream infections.

Summary of US Clinical Guidelines for Skin Antisepsis

ORGANIZATION AND GUIDELINE	SKIN ANTISEPSIS RECOMMENDATIONS
Centers for Disease Control and Prevention: Guidelines for the Prevention of Intravascular Catheter-Related Rnfections, 2011 **www.cdc.gov**	Prepare clean skin with a >0.5% chlorhexidine preparation with alcohol before central venous catheter and peripheral arterial catheter insertion and during dressing changes. If there is a contraindication to chlorhexidine, tincture of iodine, and iodophor, or 70% alcohol can be used as alternatives. **Category 1A** Prepare clean skin with an antiseptic (70% alcohol, tincture of iodine, and iodophor or chlorhexidine gluconate) before peripheral venous catheter insertion. **Category 1B**
Infusion Nurses Society (INS): Infusion Nursing Standards of Practice, 2011 **www.ins1.org**	Chlorhexidine solution is preferred for skin antisepsis. One percent to two percent tincture of iodine, iodophor, and 70% alcohol may also be used. Chlorhexidine is not recommended for infants under 2 months of age.
Society for Healthcare Epidemiology of America (SHEA): Strategies to Prevent Central-Line Associated Bloodstream Infections in Acute Care Hospitals **www.shea-online.org**	Use a chlorhexidine-based antiseptic for skin preparation in patients older than 2 months of age (A-I).43-46; Before catheter insertion, apply an alcoholic chlorhexidine solution containing a concentration of chlorhexidine gluconate greater than 0.5% to the insertion site.
The Join Commission: 2011 National Patient Safety Goals for Hospitals **www.jointcommission.org**	Use an antiseptic for skin preparation during central venous catheter insertion that is cited in scientific literature or endorsed by professional organizations.
Infectious Diseases Society of America (IDSA): Clinical Practice Guidelines for the Diagnosis and Management of Intravascular Catheter-Related Infection: 2009 Update by the Infectious Diseases Society of America **www.idsociety.org**	Skin preparation for obtaining percutaneously drawn blood samples should be performed carefully, with use of either alcohol or tincture of iodine or alcoholic chlorhexidine greater than 0.5% CHG, rather than povidone-iodine. Skin preparation with either alcohol, alcoholic chlorhexidine (>0.5%), or tincture of iodine (10%) leads to lower blood culture contaimination rates than does the use of povidone-iodine.
APIC Guide to the Elimination of Catheter-Related Bloodstream Infections, 2009 **www.apic.org**	Although a preparation containing a concentration of alcoholic chlorhexidine gluconate greater than 0.5% is preferred, tincture of iodine, and iodophor, or 70% alcohol can be used.
APIC Guide to the Elimination of Infections in Hemodialysis, 2010 **www.apic.org**	For patients older than 2 months, a skin preparation solution containing greater than 0.5% chlorhexidine gluconate and 70% isopropyl alcohol should be applied to the insertion site and allowed to dry before the skin is punctured.

The Food and Drug Administration (FDA) issued a labeling change to all manufacturers of skin antiseptics containing Chlorhexidine Gluconate (CHG) to revise the current product labeling regarding the use on infants under two months of age. The new labeling states "**use with care in premature infants or infants under 2 months of age**. These products may cause irritation or chemical burns." in the Directions for use section.

PREVANTICS™ SKIN ANTISEPTIC FEATURES

The unique formulation of Prevantics™ features a combination of two active ingredients which work synergistically together: 3.15% Chlorhexidine Gluconate (w/v) and 70% Isopropyl Alcohol (v/v). Together, these ingredients kill most pathogens including bacteria, fungi/yeast, and viruses. Prevantics™ (previously known as Chlorascrub) was approved by the FDA on June 3, 2005 as a topical antiseptic for the preparation of skin prior to surgery (Swabstick and Maxi Swabstick) or injection (Swab, Swabstick, and Maxi Swabstick)

User-friendly delivery systems.

Prevantics™ is the only FDA approved 3.15% w/v CHG/70% v/v IPA skin antiseptic and is available in four delivery systems: Swab, Swabstick, Compact Swabstick, and Maxi Swabstick. The Prevantics™ Swab is the only FDA approved CHG/IPA swab on the market. The Prevantics Swabstick and Maxi Swabstick are available in an easy to open peel apart package or tear open package. Each Prevantics™ applicator is pre-saturated with the right amount of solution for delivery to the site. No activation is necessary. After application, the area prepped can be visualized by the appearance of a clear sheen marking the area prepped. The Prevantics™ Swab contains 1.0 mL of solution, which provides a coverage area of 2.5" x 2.5" (6.25 sq. in.) The Prevantics™ Swabstick contains 1.6 mL of solution. This provides a coverage area of 4" x 4" (16 sq. in) for dry sites or 3" x 5" (15 sq. in.) for moist sites. The Maxi Swabstick contains 5.1 mL of solution. This provides a coverage for a 7" x 7" area (49 sq. in.) for dry sites or 3" x 7.5" (22.5 sq. in.) for moist sites. The foam tip applicators of the Swabstick and Maxi Swabstick design makes it easy to use and provides enough friction for adequate scrubbing to remove transient flora from the epidermis.

REFERENCES:

1. Maki DG et al. Prospective randomized trial of Povidone-Iodine, alcohol, and Chlorhexidine for prevention of infection associated with central venous and arterial catheters. *The Lancet* 1991; Vol. 338: 339-343.
2. Mimoz O, Karim A, et al. Chlorhexidine compared with Povidone-Iodine as skin preparation before blood culture. *Annals of Internal Medicine* 1999; Vol.131; No. 11; 834-837.

Properties and Comparison of Antiseptic Agents

PROPERTIES OF 3.15% CHLORHEXIDINE GLUCONATE AND 70% ISOPROPYL ALCOHOL

The 3.15% Chlorhexidine Gluconate (CHG) and 70% Isopropyl Alcohol (IPA) formulation of Prevantics™ provides a fast kill time after application, persistence, and broad spectrum skin antisepsis.

Clinical studies have demonstrated that 60 seconds after application Prevantics™ Swabstick and Maxi Swabstick achieve a greater than 3 $\log_{10}$ reduction, exceeding the FDA log reduction requirements for preoperative skin antiseptics. The Prevantics™ Swab achieves a greater than 2 $\log_{10}$ reduction 30 seconds after application, thus exceeding the FDA requirements for preinjection. A 2% CHG and 70% IPA skin antiseptic achieved FDA requirements for preoperative skin antiseptics 10 minutes after application. Unlike 2% CHG and 70% IPA, there is no difference in prepping time for dry sites and moist (wet) sites using Prevantics™.

Combined prepping and drying time with Prevantics'™ unique formulation provides fast microbial kill, thus greater log reduction.

The persistent properties of 3.15% Chlorhexidine Gluconate and 70% Isopropyl Alcohol prevented the re-growth of microorganisms after a single application.

The risk of skin irritation with Prevantics™ is minimal. Clinical studies have determined that 3.15% CHG and 70% IPA solution is no more irritating than 2% CHG and 70% IPA with irritation equivalent to that of normal saline under semi-occlusive dressing. Clinical studies with both 2% CHG and 70% IPA as well as 3.15% CHG and 70% IPA skin antiseptics show irritancy when used with an occlusive patch. An occlusive patch is a dressing that does not permit air and moisture vapor to permeate through the dressing material. Therefore use of a semi-occlusive, semi-permeable (transparent) dressing is recommended.[1]

REFERENCES:

[1] 3M™ Tegaderm Family of Transparent Dressings Product Profile.

COMPARISON OF ANTISEPTIC AGENTS

Prevantics™ is a broad spectrum antiseptic that kills pathogens including most bacteria, fungi/yeast, and viruses. The solution in a 1:10 dilution killed 99.9% of pathogenic microorganisms.

Table 1 below provides an overview of the properties and antimicrobial activity of several skin antiseptics that are utilized for patient prepping before surgery or other medical procedures.

TABLE 1:
Properties and Antimicrobial Activity of Antiseptic Agents[1,2]

				ANTIMICROBIAL ACTIVITY		
ANTISEPTIC	MODE OF ACTION	SPECTRUM OF ACTIVITY	SAFETY AND TOXICITY	KILL TIME	RESIDUAL, PERSISTENT ACTIVITY	INACTIVATION BY BLOOD OR BODY FLUIDS
Prevantics™ 3.15% CHG/ 70% IPA	Denatures proteins and disrupts cell membranes	GM+, GM–* bacteria, fungi, viruses	Minimal risk of skin irritation or sensitization Minimal absorption.	Rapid	Excellent	No
2% CHG/ 70% IPA	Denatures proteins and disrupts cell membranes	GM+, GM– bacteria, fungi, viruses	Minimal risk of skin irritation or sensitization. Minimal absorption.	Rapid	Excellent	No
70% Alcohol	Denatures proteins	GM+, GM– bacteria, fungi, viruses	Minimal risk of skin irritation or sensitization. Skin dryness	Rapid	None	No data
Chlorhexidine 2-4% Aqueous	Disrupts cell membranes	GM+, GM– bacteria, fungi, viruses	Minimal risk of skin irritation or sensitization. Minimal absorption.	Intermediate	Excellent	No
Iodine and Iodophors 10% PVP-I	Oxidizes cell membranes and cytoplasm	GM+, GM– bacteria, fungi, viruses	Moderate skin irritation or sensitization. Absorption with possible toxicity	Intermediate	Minimal	Moderate to Inactive

REFERENCES:

* GM + is gram positive bacteria, GM- is gram negative bacteria

1 Denton GW. Chlorhexidine. In: Block SS, ed. Disinfection, Sterilization, and Preservation; 5th ed. Philadelphia: Lippincott Williams & Wilkins; 2001:321-336.

2. Larson E. Guideline for use of topical antimicrobial agents. *Am J Infect Control*. 1988;16(6):253-266.

Prevantics™ Studies

IN VITRO STUDIES

Prevantics™ meets the requirements of the FDA's Tentative Final Monograph for Healthcare Antiseptic Drug Products. The following in vitro studies were performed to assess the antimicrobial activity of Prevantics™.

Time Kill Study

A time kill study was conducted to evaluate the efficacy of Prevantics™ against the following strains of bacteria:

MICROORGANISM	CLASSIFICATION	ATCC#
Staphylococcus aureus	Gram positive	6538
Staphylococcus aureus	Gram positive	29213
Staphylococcus epidermidis	Gram positive	12228
Micrococcus luteus	Gram positive	7468
Enterococcus faecalis	Gram positive	29212
Escherichia coli	Gram negative	11229
Escherichia coli	Gram negative	25922
Pseudomonas aeruginosa	Gram negative	15442
Pseudomonas aeruginosa	Gram negative	27853
Serratia marcescens	Gram negative	14756

At a 1:10 dilution, Prevantics™ reduced the bacterial count by more than 99.9% in less than 3 minutes. The majority of the strains were killed immediately upon exposure to Prevantics™.[1]

Minimum Inhibitory Concentration (MIC) Study

A MIC study was conducted to assess the in vitro efficacy of Prevantics™ against 1104 microorganisms. 1083 (98.1%) of the 1104 organisms tested were inhibited by ≤50 µg/mL of Prevantics™ solution. A concentration of 50 µg/mL represents a 1:630 dilution of the 3.15% (w/v) topical solution. Therefore, Prevantics™ was effective against all the microorganisms listed in Table 2, including antibiotic resistant strains. Results are presented in Table 2.

REFERENCES:

1. Data on file, PDI, Orangeburg, New York.

TABLE 2: List of Organisms Tested Susceptible to Prevantics™

SPECIES	NUMBER OF STRAINS	MINIMUM (µG/ML)	MAXIMUM (µG/ML)	MIC50* (µG/ML)	MIC90* (µG/ML)
All Aerobic Strains Combined	896	0.20	200	16	64
All Gram-Negative Aerobic Strains Combined	448	0.78	200	32	64
All Gram-Positive Aerobic Strains Combined	448	0.20	100	8	16
A. ANITRATUS	17	6.25	50	16	32
A. BAUMANNII	28	6.25	50	32	64
A. LWOFFII	4	6.25	25	N.A.	N.A.
B. CEPACIA	21	12.50	200	64	128
E. AEROGENES	26	25	50	32	64
E. CLOACAE	26	0.78	50	32	64
E. COLI	51	0.78	13	4	4
E. COLI ESBL+	6	1.56	25	N.A.	N.A.
E. FAECALIS, VANCO RESISTANT	23	6.25	25	16	32
E. FAECALIS, VANCO SENSITIVE	31	3.13	25	16	16
E. FAECIUM, VANCO RESISTANT	26	3.13	13	8	8
E. FAECIUM, VANCO SENSITIVE	26	0.78	13	8	16
E. HIRAE	1	6.25	6	N.A.	N.A.
H. INFLUENZAE B-LACTAMASE NEGATIVE	28	6.25	25	16	32
H. INFLUENZAE B-LACTAMASE POSITIVE	28	6.25	50	16	32
K. OXYTOCA	11	12.50	50	32	64
K. OXYTOCA-ESBL+	5	6.25	50	N.A.	N.A.
K. PNEUMONIAE	16	6.25	50	32	64
K. PNEUMONIAE-ESBL+	5	6.25	25	N.A.	N.A.
M. LUTEUS	3	0.78	2	N.A.	N.A.
P. AERUGINOSA	36	6.25	50	32	32
P. AERUGINOSA, Cipro-R	15	25	50	32	64
P. MIRABILIS	36	6.25	100	32	64
P. VULGARIS	16	12.50	50	32	64
S. AGALACTIAE	53	1.56	13	8	8
S. AUREUS, METHICILLIN RESISTANT	53	0.78	6	4	8
S. AUREUS, METHICILLIN SUSCEPTIBLE	53	0.78	6	4	4
S. EPIDERMIDIS, METHICILLIN RESISTANT	13	1.56	6	4	8
S. EPIDERMIDIS, METHICILLIN SUSCEPTIBLE	16	1.56	6	4	4
S. HAEMOLYTICUS, METHICILLIN RESISTANT	21	0.78	6	4	8
S. HAEMOLYTICUS, METHICILLIN SENSITIVE	7	0.78	3	N.A.	N.A.
S. HOMINIS	5	0.78	2	N.A.	N.A.
S. MALTOPHILIA	21	0.78	100	64	64
S. MARCESCENS	51	3.13	100	64	64
S. PNEUMONIAE PEN INTERMEDIATE	17	12.50	100	32	128
S. PNEUMONIAE PEN RESISTANT	17	12.50	100	64	64
S. PNEUMONIAE PEN SENSITIVE	22	1.56	50	16	64
S. PYOGENES	51	0.20	6	4	8
S. SAPROPHYTICUS	11	0.20	2	1	1
Anaerobic Species					
All Anaerobic Strains Combined	99	0.78	200	16	32
B. FRAGILIS	55	6.25	200	16	32
B. THETAIOTAOMICRON	19	6.25	200	16	>35
BACTEROIDES SPP.	13	6.25	100	16	32
P. BIVIA	11	0.78	13	8	8
E. LENTUM	1	25	25	N.A.	N.A.
Yeast Species					
All Yeast Strains Combined	109	3.13	50	16	32
C. ALBICANS	57	3.13	25	32	32
C. KRUSEI	17	6.25	50	16	32
C. PARAPSILOSIS	19	6.25	50	16	64
C. TROPICALIS	16	6.25	13	16	16
Total Number of Strains	**1104**				

*Actual MICs were rounded up to nearest 2 $\log^{10}$ dilution for calculating MIC50 and MIC90.

RESISTANCE DEVELOPMENT

The Prevantics™ MIC study shows that 98.1% of the 1104 organisms tested[1] were inhibited by ≤50 µg/mL of Prevantics™ solution. The tested pathogens included several antibiotic resistant strains.[1] The concentration of Chlorhexidine in Prevantics™ is 31,500 µg/mL, thereby far exceeding the 50 µg/mL concentration.

Acquired resistance to Chlorhexidine is rare and has only been found when dilute aqueous solutions have been used for disinfection.[2] When used undiluted and as directed, Prevantics™ with its 3.15% (w/v) CHG and 70% (v/v) IPA concentrations is expected to be highly effective against most pathogens, including antibiotic-resistant microorganisms.

Literature reports indicate that there is no evidence of increased resistance development after prolonged and extensive use of Chlorhexidine in clinical use concentrations.[3]

REFERENCES:

1. Data on file, PDI, Orangeburg, New York.
2. Maki DG et al. Prospective randomized trial of Povidone-Iodine, alcohol, and Chlorhexidine for prevention of infection associated with central venous and arterial catheters. *Lancet*. 1991;338:339-343.
3. Denton GW. Chlorhexidine. In: Block SS, ed. Disinfection, Sterilization, and Preservation; 5th ed. Philadelphia: Lippincott Williams & Wilkins; 2001:321-336.

SUMMARY OF CLINICAL STUDY RESULTS

Prevantics™ Swabs reduce the microbial count on the forearm by greater than 2 $\log_{10}$ 30 seconds post application. The greater than 2 $\log_{10}$ reduction is maintained for at least 24 hours.

Prevantics™ Swabsticks and Maxi Swabsticks reduce the microbial count on the abdomen by greater than 2 $\log_{10}$ 30 seconds post application. After 24 hours the microbial count reduction increased to greater than 3 $\log_{10}$. These results confirm the rapid-acting, effective, and persistent antimicrobial activity of Prevantics™ on a dry site.

Prevantics™ Swabsticks and Maxi Swabsticks reduce the microbial count on the inguinal region by greater than 3 $\log_{10}$ 1 minute post application. The greater than 3 $\log_{10}$ reduction is maintained for at least 24 hours. These results confirm the rapid-acting, effective, and persistent antimicrobial activity of Prevantics™ on a wet site (inguinal region).

Prevantics™ Swabsticks and Maxi Swabsticks when applied to the forearm, abdomen, and inguinal region are the only skin antiseptic delivery systems available with proven antimicrobial persistence of up to 7 days with a single application.

IN VIVO EFFICACY STUDIES

Efficacy and Safety Study: Comparison to IPA and 4% CHG

A study was conducted to evaluate and compare the immediate and persistent antimicrobial activity of Prevantics™ 3.15% (w/v) Chlorhexidine Gluconate with 70% (v/v) Isopropyl Alcohol, 70% (v/v) Isopropyl Alcohol (active vehicle), and Hibiclens® (4% Chlorhexidine Gluconate, reference product) when used as an antimicrobial skin preparation prior to surgery or injection.[1] In addition, this randomized, parallel-group study evaluated and compared the safety of the products.

METHODS

Healthy subjects of mixed age, gender, and race between 18 and 70 years of age and with no evidence of dermatoses, inflammation, or injury to the treatment areas were enrolled in the study. The skin preparations were tested on the forearm, on the abdomen, and in the inguinal region. A minimum of 81 volunteers for the inguinal and 60 volunteers for the forearm and abdominal portions were employed, using bilateral applications. Bacterial counts of the subjects in the various treatment groups did not differ significantly at baseline.

Prevantics™ Swabsticks and Maxi Swabsticks were tested on the abdomen and in the inguinal region to evaluate their efficacy for preoperative patient skin prepping. The abdominal and inguinal sites were prepped for 2 minutes, allowed to air dry for 1.5 minutes, and then evaluated at 30 seconds, 10 minutes, 6 hours, and 24 hours after skin prepping.

Prevantics™ Swabs were tested on the forearm to evaluate their efficacy for patient skin preparation prior to injection. The forearm sites were prepped for 15 seconds, allowed to air dry for 30 seconds and then evaluated at 30 seconds and 24 hours post application.

The CHG reference product was applied twice for 2 minutes followed by drying with a sterile towel for all three treatment sites (manufacturer's recommendation). Application of the active vehicle (IPA) was performed identically to that of the Prevantics™ products.

The *FDA Tentative Final Monograph for Health-Care Antiseptic Drug Products: Proposed Rule* published in the *Federal Register* of June 17, 1994 requires a:

- 2 $\log_{10}$ reduction in CFU/cm2 of skin on the abdomen and
- 3 $\log_{10}$ reduction in CFU/cm2 of skin on inguinal sites

ten (10) minutes after drug application to approve a material as a preoperative skin preparation antiseptic. In addition, the colony forming units (CFUs) from both sites must remain below the baseline CFU count for 6 hours.

The monograph also requires a 1 $\log_{10}$ reduction in CFU/cm^2 of skin on a dry site (forearm or abdomen) thirty (30) seconds after application to approve an antiseptic for preinjection skin preparation.

RESULTS

Prevantics™ Swabs produced a 2.70 log_{10} reduction on the forearm 30 seconds after application, therefore exceeding the monograph requirement of 1 log_{10} reduction for preinjection skin preparation. At 24 hours post application the log_{10} reduction was still 2.55 log_{10}, confirming the persistent activity of Prevantics™ Swabs.

Prevantics™ Swabsticks and Maxi Swabsticks achieved the following microbial count reductions from average baseline on the abdomen:

- 2.79 log_{10} reduction at 30 seconds post application
- 2.86 log_{10} reduction at 10 minutes post application
- 2.83 log_{10} reduction at 6 hours post application
- 3.09 log_{10} reduction at 24 hours post application

Prevantics™ Swabsticks and Maxi Swabsticks exceeded the FDA requirements of a 1 log_{10} reduction at 30 seconds for preinjection skin preparation and of a 2 log_{10} reduction at 10 minutes for preoperative skin preparation on the abdomen. Prevantics™ reached a >2 log_{10} reduction on the abdomen 30 seconds post application. After 24 hours microbial counts had further decreased to a >3 log_{10} reduction, attesting to the persistent activity of Prevantics™.

On the inguinal region, Prevantics™ Swabsticks and Maxi Swabsticks were the only products tested that achieved a >3 log_{10} reduction at 10 minutes, 6 hours, and 24 hours post prepping, therefore exceeding the FDA criteria. A post application wait time of 30 seconds resulted in a 2.92 log_{10} reduction that was just below the 3 log_{10} requirement for patient preoperative skin preparation.

Prevantics™ was more efficacious than Isopropyl Alcohol alone. At 24 hours after initial prepping, a significant difference in microbial count was detected in the inguinal and abdominal test sites ($p \leq 0.05$).

Prevantics™ reduced microbial populations at a significantly lower level than did IPA. On the IPA-prepped sites, the populations were beginning to recover to baseline levels at 24 hours after prepping, while Prevantics™ continued to maintain a greater than 3 log_{10} reduction.

No adverse events were reported during the study.

A graphic representation of the study results can be seen in the charts below:

FIGURE 1

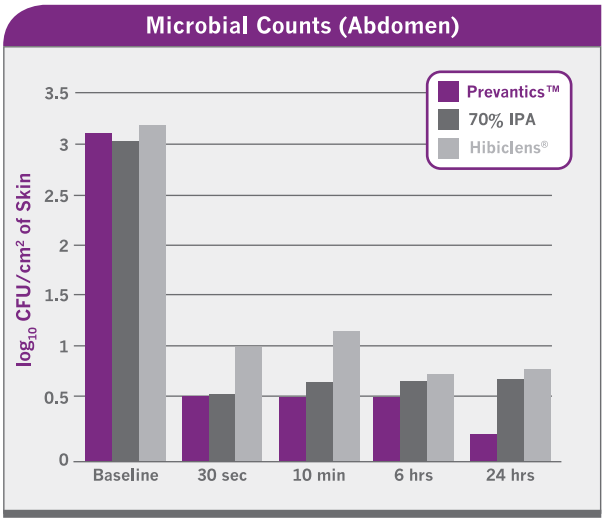
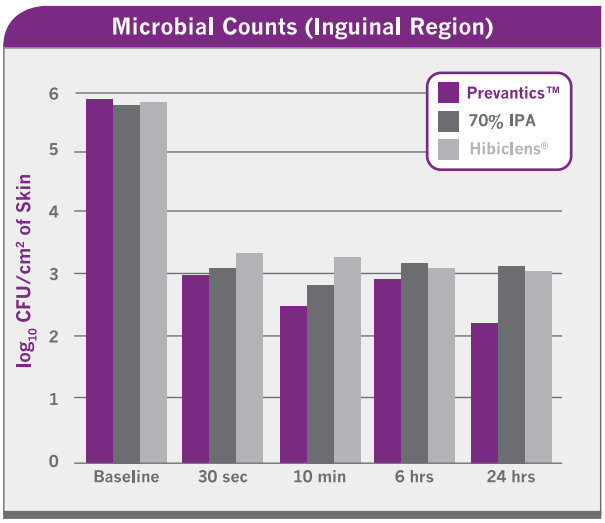


FIGURE 2



CONCLUSION

Prevantics™ was found to be safe and effective as a patient skin antimicrobial preparation for use prior to surgery and injection. Prevantics™ exceeds the FDA requirements in terms of wait time for full efficacy, microbial count reduction, and duration of antimicrobial activity. A microbial count reduction of 3.5 $\log_{10}$ on the inguinal site after 24 hours verifies the product's excellent persistent activity. The >2 $\log_{10}$ reduction on the abdomen and forearm 30 seconds after application attests to the fast and effective antimicrobial activity of Prevantics™.

Maxi Swabstick Efficacy Study: Comparison to IPA and 4% CHG

A study was conducted to evaluate and compare the immediate and persistent antimicrobial activity of Prevantics™ Maxi Swabsticks (3.15% Chlorhexidine Gluconate (w/v) and 70% Isopropyl Alcohol), Maxi Swabsticks Vehicle (70% (v/v) Isopropyl Alcohol), and Hibiclens® (4% (w/v) Chlorhexidine Gluconate, reference product) and to evaluate and compare the safety of all three test articles.[1]

METHODS

Healthy subjects of mixed age, gender, and race between 18 and 64 years of age and with no evidence of dermatoses, inflammation or injury to the treatment areas were enrolled in the study. Bacterial counts of the subjects in the various treatment groups did not differ significantly at baseline. All skin preparations were tested in the inguinal region. The subjects were randomized and 41 inguinal areas were treated and analyzed with each test preparation. Prevantics™ Maxi Swabstick (3.15% (w/v) CHG with 70% (v/v) IPA) was applied topically for 2 minutes over a 3 x 7.5 square-inch area on the inguinal region and allowed to air dry for 1.5 minutes.

A Maxi Swabstick vehicle saturated with 5.1 mL of the 70% (v/v) IPA was applied topically for 2 minutes over a 3 x 7.5 square-inch area on the inguinal region and allowed to air dry for 1.5 minutes. The CHG reference product was applied topically for 2 minutes over a 3 x 7.5 square-inch area on the inguinal region and dried with a sterile towel and applied for another 2 minutes and dried with another sterile towel (per manufacturer's recommendation).

RESULTS

For a Healthcare Antiseptic to be approved by the FDA for the indication of preoperative skin preparation, it must achieve a 3 $\log_{10}$ reduction in microbial count (CFU)/cm^2 in the inguinal region within 10 minutes of initial drug application. In addition, the microbial count must remain below the baseline CFU count for 6 hours.

Prevantics™ Maxi Swabsticks demonstrated significantly better antimicrobial activity than Maxi Swabsticks Vehicle (IPA) and the CHG reference product after antiseptic application at ten (10) minutes, six (6) hours, and twenty-four (24) hours ($p \leq 0.05$).

Treatment with Prevantics™ Maxi Swabsticks resulted in a 3.77 $\log_{10}$ reduction at 10 minutes, increasing to a reduction in microbial count of 4.24 $\log_{10}$ after 24 hours. The Maxi Swabsticks Vehicle (IPA) achieved the 3 $\log_{10}$ reduction at 10 minutes; however, the microbial load started rising and the product was not able to maintain the 3 $\log_{10}$ reduction after 6 or 24 hours.

REFERENCES:

1. Data on file, PDI, Orangeburg, New York.

Only Prevantics™ Maxi Swabsticks and Maxi Swabsticks Vehicle (IPA) achieved the required 3 $\log_{10}$ reduction at 10 minutes. For all products, the microbial counts remained below baseline at 6 hours.

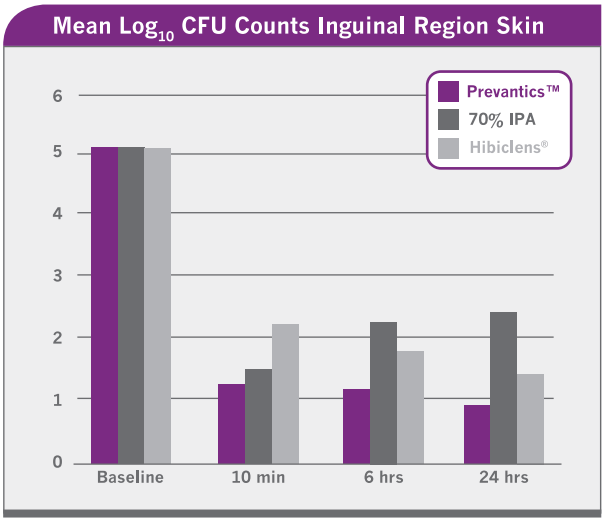
TABLE 3:
Summary of the $\log_{10}$ Reductions Achieved on the Inguinal Region Sites

		MEAN $\log_{10}$ REDUCTIONS FROM BASELINE		
PRODUCT	N	10 MINUTES	6 HOURS	24 HOURS
Prevantics™ Maxi Swabsticks	41	3.77	4.01	4.24
Maxi Swabsticks Vehicle (IPA)	41	3.48	2.78	2.57
CHG Reference Product	41	2.89	3.34	3.68

CONCLUSION

Prevantics™ Maxi Swabsticks exceeded the FDA criteria in the inguinal region for patient preoperative skin preparation. Prevantics™ Maxi Swabsticks demonstrated significantly greater antimicrobial activity than 70% (v/v) IPA; Maxi Swabsticks and the CHG reference product after antiseptic application at 10 minutes, 6 hours, and 24 hours. Microbial counts decreased over the 24-hour period, confirming the persistent activity of Prevantics™.

FIGURE 3



No adverse events were reported during the course of the study.

Efficacy Study: Evaluation of Post Application Wait Time

The FDA Tentative Final Monograph for Healthcare Antiseptic Drug Products: Proposed Rule published in the *Federal Register* of June 17, 1994, requires a 3 $\log_{10}$ reduction in microbial count on inguinal region sites ten (10) minutes after drug application to approve an antiseptic solution with the indication of preoperative skin antisepsis. In addition, the colony forming units (CFUs) must remain below the baseline CFU count for 6 hours.

In the clinical setting it is often not desired or even possible to wait the additional 10 minutes to assure that the product reaches the required 3 $\log_{10}$ reduction. Therefore, this study was designed and conducted to determine the minimum wait time after application of Prevantics™ Maxi Swabsticks until the 3 $\log_{10}$ reduction is achieved on the inguinal region.[1]

METHODS

Healthy subjects of mixed age, gender, and race between 18 and 64 years of age and with no evidence of dermatoses, inflammation or injury to the treatment areas were enrolled in the study.

Prevantics™ Maxi Swabstick (5.1 mL of 3.15% (w/v) CHG and 70% (v/v) IPA) was applied topically for two minutes over a 3 x 7.5 square-inch area on the inguinal region using the following technique. The Prevantics™ Maxi Swabstick, a flat two-sided device with a foam tip, was removed from the package with sterile gloves. One of the flat sides of the foam tip of Prevantics™ Maxi Swabstick was placed in the center of the 3 x 7.5 square-inch prep area. The skin was held taut and prepped vigorously in a rapid back-and-forth technique for one minute. The Swabstick was turned over and the unused side of the foam tip was used to prep the same area. The skin was held taut and prepped vigorously in a back-and-forth technique for one minute. The area was again air dried for 1.5 minutes prior to beginning the contact time.

The inguinal sites were randomly sampled after the following post application wait times: thirty (30) seconds, one (1) minute, three (3) minutes, and ten (10) minutes.The technicians responsible for plating and data collection were blinded as to the post application sample time assignment.

REFERENCES:

1. Data on file, PDI, Orangeburg, New York.

RESULTS

Prevantics™ Maxi Swabsticks significantly reduced the microbial count (CFU) in the inguinal region at all time points.

Prevantics™ achieved a >3 $\log_{10}$ reduction after a wait time of one minute post application. The mean $\log_{10}$ reductions in CFU/cm2 of inguinal region skin are listed in Table 4 below.

TABLE 4:
Microbial Count Reductions a Various Time Intervals After Prevantics™ Application in the Inguinal Region

	WAIT TIME POST APPLICATION					
	30 SEC.	1 MIN.	3 MIN.	5 MIN.	10 MIN. (LEFT) A	10 MIN. (RIGHT) B
Mean $\log_{10}$ Reduction	2.85	3.22	3.18	3.10	3.08	3.24

A – left inguinal site; B – right inguinal site

CONCLUSION

Prevantics™ reduces the microbial count on the inguinal region by more than 3 $\log_{10}$ one minute after application, thus exceeding the ten (10) minute FDA required wait time in the inguinal region for approval as a patient preoperative skin preparation drug product.

REFERENCES:

1. Data on file, PDI, Orangeburg, New York.

Prevantics™ 7-Day Persistence Data

Prevantics™ products combine the immediate antimicrobial activity of 70% (v/v) Isopropyl Alcohol with the persistent properties of 3.15% (w/v) Chlorhexidine Gluconate. This formulation results in a broad-spectrum skin antiseptic that is both fast acting and demonstrates a persistent log reduction. Prevantics™ kills transient and resident skin microorganisms rapidly and then prevents the recolonization of microorganisms post application for up to seven days.

A clinical study was performed to effectively evaluate the persistent properties of Prevantics™ Swabsticks and Maxi Swabsticks. The treatment sites were covered with a semi-permeable, semi-occlusive dressing for the duration of the study to simulate actual clinical practice. The results are listed in Table 5 below:

TABLE 5:
Mean log_{10} Reductions After Skin Preparation with Prevantics™ Products

	MEAN LOG_{10} REDUCTIONS FROM BASELINE			
TREATMENT SITE	30 SEC.	10 MINUTES	48 HOURS	7 DAYS
Abdomen	N/A	2.01 (N=24)	N/A	1.76 (N=23)
Inguinal Region	N/A	3.29 (N=38)	3.07 (N=35)	1.51 (N=28)
Forearm	1.80 (N=33)	N/A	N/A	1.70 (N=28)

CONCLUSION

The study results confirm the long-lasting antimicrobial activity of Prevantics™ products. A single application of the Prevantics™ Swabstick or Maxi Swabstick is sufficient enough to produce a persistent log reduction for up to 7 days.

SKIN SENSITIZATION AND IRRITATION STUDIES

Sensitization Safety Study: Evaluation of a Repeated Insult Patch Test

A study was conducted with 210 volunteers to evaluate Prevantics™ for induction of contact sensitization.[1]

METHODS

Each subject received applications of both Prevantics™ (3.15% (w/v) Chlorhexidine Gluconate in 70% (v/v) Isopropyl Alcohol) and saline solution (0.9% Sodium Chloride). Saline served as the negative control. Prevantics™ was tested under semi-occlusive and saline under occlusive conditions.

The products were applied ten (10) times during a twenty-three (23) day period (induction period), followed by a rest period, and then were applied again at day thirty-six (36), thirty-eight (38), and forty (40) (challenge period).

RESULTS

Under the semi-occlusive conditions of this study and under simulated clinical conditions, Prevantics™ did not induce any sensitization. In addition, irritation elicited by Prevantics™ (under semi-occlusive conditions) was slightly less than that of saline (which is isotonic and non-irritating to intact skin) under occlusive conditions.

CONCLUSION

Prevantics™ does not elicit evidence of sensitization when used under semi-occlusive conditions (clinical use conditions).

Primary Irritation Study in Humans to Evaluate CHG/IPA Combination products (Three 24-Hour Applications)

This study represents a three application (3 doses over 8 days) primary irritation evaluation[2]. In this study, 15 subjects tested the irritation potential of dressings under occlusive and semi-occlusive conditions in presence of Iodine or Chlorhexidine Gluconate/Isopropyl Alcohol (CHG/IPA) combinations. This Primary Irritation study method is a modification of the method described by J. H. Draize et al., "Methods for the Study of Irritation and Toxicity of Substances Applied to the Skin and Mucous Membranes," in 1944.

METHODS

Fully occlusive dressing conditions consisted of a non-woven cotton pad covered by and held securely to the skin on all sides with an occlusive waterproof hypoallergenic tape. The semi-occluded conditions involved the use of the same fabric pad, not covered by tape, and held securely to the skin with hypoallergenic breathable surgical tape applied to the four sides.

REFERENCES:

1. Data on file, PDI, Orangeburg, New York.
2. Data on file, PDI, Orangeburg, New York.

Patches were applied for 24 hours. Patches were then removed, test sites wiped with sterile water, and scored repeat application at 48 hours and 72 hours for the last evaluation.

A numeric score was assigned based upon the average cumulation of scores for degree of erythema, fissuring, and blistering assigned by an investigator experienced in conducting this type of evaluation.

Experimental formulations were 1.5%, 2.0%, 2.5% CHG tincture, Prevantics™, 10% iodine, 0.1% Sodium lauryl sulfate (known irritant), and normal 0.9% saline (non irritant).

RESULTS

TABLE 6:
Irritation Score Chart per Solution

SOLUTION	FULLY OCCLUDED IRRITATION SCORE	SEMI-OCCLUDED IRRITATION SCORE
1.5% CHG -70% IPA	1.000	0.000
2.0% CHG -70% IPA	0.822	0.000
2.5% CHG -70% IPA	1.022	0.000
3.15% CHG-70% IPA (Prevantics™)	0.778	0.000
Betadine® 10%	1.000	0.111
Sodium Lauryl sulfate 0.1% (Positive Control – Irritant)	0.778	*NT*
Saline (Negative Control – Non-irritant)	0.089	*NT*

NT: Not tested

CONCLUSION

Under fully occluded conditions, applications of 1.5%, 2.0%, 2.5% CHG tinctures and Prevantics™ induced similar levels of irritation, ranging from 0.778 to 1.022, overall. These values were similar or slightly greater than the overall irritation induced by the positive control and similar or slightly lower than irritation induced by the competitor's marketed Iodine product, Betadine®.

No visible irritation was induced by Chlorhexidine under semi-occlusive (simulated clinical) conditions with 1.5%, 2.0%, 2.5% CHG tinctures, or Prevantics™ with demonstrated irritation equivalent to normal saline, which is isotonic to the skin.

REFERENCES:

1. Hill Top Research, MB, Canada, Study HTR #01-108751-76

Safety Profile of Prevantics™

Prevantics™ clinical studies have demonstrated that there is only minimal risk of skin irritation under clinical use conditions (semi-occlusive).[1] To prevent irritation and to ensure efficacy, it is important to:

- Let the treatment area dry completely before applying a semi-occlusive dressing such as Tegaderm™ or OpSite®
- Use transparent, or other semi-occlusive, semi-permeable or gauze dressings (semi-permeable dressings are considered similar to a plain gauze dressing or a highly permeable dressing)

Prevantics™ can be used with care in premature or infants under 2 months of age. These products may cause irritation or chemical burns.

Like other products containing Chlorhexidine Gluconate, Prevantics™ should not be used in the following situations:

- Under occlusive dressings because this can cause irritation.
- For lumbar puncture or in contact with the meninges.[1]
- On patients with known allergies to Chlorhexidine Gluconate or Isopropyl Alcohol.[2] Chlorhexidine has an extremely low potential for sensitization reactions. Isolated cases of generalized allergic reactions have been reported in the literature.[2]
- On open wounds or as a general cleanser.

Prevantics™ is for external use only. Keep it out of eyes, ears, mouth, and mucous membranes, where it may cause serious or permanent injury if permitted to enter and remain. If such contact occurs, rinse immediately with cold water and contact Poison Control.

Like other alcohol-containing topical antiseptics, Prevantics™ is a flammable solution and should be kept away from fire and flames. This product should not be used with electrocautery procedures.[2]

For external use only.[2]

Keep out of reach of children. If swallowed seek medical help or contact Poison Control Center right away.[2]

REFERENCES:

1. Data on file, PDI, Orangeburg, New York.
2. Denton GW. Chlorhexidine. In: Block SS, ed. Disinfection, Sterilization, and Preservation; 5th ed. Philadelphia: Lippincott Williams & Wilkins; 2001:321-336.

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Released: [TBD] 2012