CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

207964Orig1s000

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW(S)

CLINICAL PHARMACOLOGY REVIEW

NDA(s): 207964/SDN-016 and SDN-033	Submission Date(s): 10/20/2017 and 6/13/2018 (major amendment)
Drug/Strengths	ReadyPrep CHG (Chlorhexidine Gluconate 2% cloth)
OCP Reviewer	Kunyi Wu, PharmD
OCP Team Leader	Seong H. Jang, PhD
OCP Division	DCP4
OND Division	DNDP
Applicant	Medline Industries Inc.
Dosage Regimen	Dry surgical sites (such as abdomen or arm) • Use one cloth to cleanse each 161 cm^2 area (approximately 5 x 5 inches) of skin to be prepared. Vigorously scrub skin back and forth for 3 minutes, completely wetting treatment area, then discard. Allow area to dry for one (1) minute. Do not rinse. Moist surgical sites (such as inguinal fold) • Use one cloth to cleanse each 65 cm^2 area (approximately 2 x 5 inches) of skin to be prepared. Vigorously scrub skin back and forth for 3 minutes, completely wetting treatment area, then discard. Allow area to dry for one (1) minute. Do not rinse.
Indication(s)	Pre-Surgical Skin Preparation

1. EXECUTIVE SUMMARY

Chlorhexidine has bacteriostatic and/or bactericidal activity, depending on its concentration, against gram-positive and gram-negative organisms, facultative anaerobes, aerobes, and yeast. Medline Industries, Inc., has submitted a 505(b)(2) application for ReadyPrep CHG (Chlorhexidine Gluconate 2% Cloth) used as a nonprescription (OTC) preoperative patient skin preparation. To support the approval of this 505(b)(2) application, the Applicant relies on information from Applicant-conducted studies and the published literature.

ReadyPrep CHG is composed of a 2% CHG solution (equivalent to 500 mg chlorhexidine gluconate per cloth) on single fiber, polyester cloth in the two-cloth per pack configuration. The application is a resubmission following an initial Refuse-to-File action, which was taken because of the (b) (4)

The clinical development program for the ReadyPrep CHG product includes:

- Three pivotal safety and efficacy studies to assess antimicrobial efficacy of a Medline 2% CHG cloth product, in comparison to placebo and active control (Study R13-052, Study R13- 053 and Study R15-029).

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- Three pilot safety and efficacy studies to assess antimicrobial efficacy of a Medline 2% CHG cloth product, in comparison to an active control (Study R13-042, Study R14-015, and Study R15-028)
- One pharmacokinetic (PK) study in adult subjects to assess the systemic exposure to chlorhexidine from ReadyPrep CHG (Study R17-023)
- One clinical study to evaluate the cumulative irritation and contact sensitizing potential of ReadyPrep CHG (Study R13-051)
- One clinical study to assess the skin coverage and administered dose from one ReadyPrep CHG cloth (Study R16-034)

(b) (4) were proposed in the draft label. In the Directions section, instructions were provided as "Use with care in premature infants or infants under 2 months of age. These products may cause irritation or chemical burns" (b) (4)

(b) (4)

2. RECOMMENDATIONS

The clinical pharmacology information provided by the Applicant in support of the 505 (b)(2) application is acceptable and supports the approval of ReadyPrep CHG pending the safety review and an agreement on the labeling.

[1] Lee, A., Harlan, R., Breaud, A.R., Speck, K., Perl, T.M., Clarke, W., and Milstone, A.M. (2011). Blood concentrations of chlorhexidine in hospitalized children undergoing daily chlorhexidine bathing. Infection control and hospital epidemiology 32, 395-397

[2] Aggett, P.J., Cooper, L.V., Ellis, S.H., and McAinsh, J. (1981). Percutaneous absorption of chlorhexidine in neonatal cord care. Arch. Dis. Child 56, 878-880.

[3] Chapman, A.K., Aucott, S.W., Gilmore, M.M., Advani, S., Clarke, W., and Milstone, A.M. (2013). Absorption and tolerability of aqueous chlorhexidine gluconate used for skin antisepsis prior to catheter insertion in preterm neonates. J.Perinatol. 33, 768-771.

[4] Cowen, J., Ellis, S.H., and McAinsh, J. (1979). Absorption of chlorhexidine from the intact skin of newborn infants. Arch. Dis. Child 54, 379-383.

Individual Study and Literature Review

STUDY NO. R17-023

STUDY TITLE:
Single Dose Pharmacokinetic Study to Assess the Systemic Exposure of Chlorhexidine from Readyprep® CHG (2% Chlorhexidine Gluconate Cloth)

STUDY DESIGN:
The study was a single center, randomized, single dose, laboratory-blinded, 3-period, 3- sequence, crossover design in healthy male and female adult subjects. A total of 12 subjects were enrolled. The three treatment groups are listed below and study sequence is in Table 1.

Treatment-1: Abdominal application of ReadyPrep® CHG
Treatment-2: Groin application of ReadyPrep® CHG
Treatment-3: Control treatment with no application

Table 1. Study Sequences

	Period 1	Period 2	Period 3
Sequence 1 (n=4)	Treatment-1	Treatment-2	Treatment-3
Sequence 2 (n=4)	Treatment-2	Treatment-3	Treatment-1
Sequence 3 (n=4)	Treatment-3	Treatment-1	Treatment-2

A single topical application of ReadyPrep CHG was done on either the abdomen (Treatment-1) or the groin (Treatment-2) according to the randomization scheme. Treatment-3 consisted of a control treatment where the same procedures as Treatment-1 and -2 were performed, but without the topical application of ReadyPrep CHG. The drug was applied to a clean, dry, non-irritated, normal skin area. The topical application of ReadyPrep® CHG consisted of a 3-minute vigorous rub followed by a 1 minute dry time at the application site. The application sites were the abdomen (surface area of approximately 5x5 inches) and groin (surface area of approximately 2x5 inches).

Blood samples for PK measurements were collected at -10.00, -2.00 and -0.50 hours prior to treatment application and at 1.00, 2.00, 3.00, 4.00, 5.00, 6.00, 8.00, 12.00, and 24.00 hours following treatment application.

Bioanalytical Analysis: The bioanalytical analysis was conducted by (b) (4)

SUMMARY OF RESULTS:
Bioanalytical Validation (Report CLN-W7-210): The following section details the bioanalytical method validation for the analysis of chlorhexidine in human plasma samples.

Information Requested	**Data**
Bioanalytical method validation report location	Analytical Validation Report CLN-W7-210

Reference ID: 4333732

Analyte	Chlorhexidine
Internal standard (IS)	Chlorhexidine-D8
Method description	Reverse-phase HPLC with MS/MS detection
Limit of quantitation	200 pg/mL
Average recovery of drug (%)	92.9-102.3%
Average recovery of IS (%)	95.8%
Standard curve concentrations (units/mL)	200 pg/mL to 7500 pg/mL
QC concentrations (units/mL)	200 pg/mL, 600 pg/mL, 3750 pg/mL and 5625 pg/mL.
Bench-top stability (hrs)	Confirmed up to 24.1 hours for Chlorhexidine in LC-MS MeOH at 100.00 µg/mL at 22 C nominal. % deviation: 1.7%. Confirmed up to 24.1 hours for Chlorhexidine in LC-MS MeOH at 20.00 ng/mL at 22 C nominal. % deviation: -4.0%. Confirmed up to 24.1 hours for Chlorhexidine-D8 in LC-MS MeOH at 100.00 µg/mL at 22 C nominal. % deviation: 6.9%.
Long term Stock stability (days)	Confirmed up to 31 days for Chlorhexidine in LC-MS MeOH at 100.00 µg/mL at 4 C nominal % deviation: 0.1%. Confirmed up to 29 days for Chlorhexidine in LCMS MeOH at 20.00 ng/mL at 4 C nominal % deviation: 8.3%. Confirmed up to 31 days for Chlorhexidine-D8 in LC-MS MeOH at 100.00 µg/mL at 4 C nominal % deviation: -0.7%.
Freeze-thaw stability (cycles)	4 cycles. Accuracy (% nominal): 95.6% for Low Stability QC and 98.0% for High Stability QC.
Long-term storage stability (days)	Confirmed up to 36 days at -20 C nominal Accuracy (% nominal): 104.8% for Low Stability QC and 107.3% for High Stability QC. Confirmed up to 19 days at -80 C nominal Accuracy (% nominal): 98.1% for Low Stability QC and 103.8% for High Stability QC
Selectivity	No significant interference observed in the 12 blank

Pharmacokinetic Results: The concentrations of all PK samples were blow limit of quantitation.

CONCLUSION: Chlorhexidine was not detectable in any blood samples following any of the three treatments in adult subjects. These results demonstrate that there is no to negligible systemic exposure to chlorhexidine in adults from a single usage of ReadyPrep CHG as instructed by the draft label.

LITERATURE REVIEW

The review of literature listed in Table 2 indicated that chlorhexidine can be absorbed even after a single topical application of chlorhexidine products in pediatric patients from birth to < 18 years. The formulations of chlorhexidine used in these studies were different from ReadyPrep CHG (Table 2). We defer the safety and efficacy of ReadyPrep CHG to the Clinical review team.

Table 2. Dosing Regimen and Treatment Duration of CHG Products in Pediatric Populations from the Published Literature

Reference	Age	Subject number	Dosing regimen	Treatment duration
Chapman et al[3]., 2013	Preterm neonates (< 32 weeks)	20	Skin wiped with 2% CHG cloth prior to placement of PICC line	Single dose
Cowen et al[4]., 1979	0-3 months; term and preterm infants	34	Full body baths in 4% CHG solution	Single dose; or up to 32 days
Lee et al[1]., 2011	3 months to < 18 years	12	Daily baths with 2% CHG cloths	Up to 30 days

- In the study conducted by Alison K. Chapman et al[3]., enrolled infants had their skin cleansed prior to placement of a peripherally inserted central catheter (PICC)with a 2% aqueous CHG-impregnated cloth (Sage Products Inc., Cary, IL, USA). Each cloth contains 500 mg CHG. A CHG cloth was folded into quarters and one quarter was used to cleanse the infant's extremity to limit the total dose exposure. The extremity was cleaned with the CHG cloth using an up and down motion. The skin site was then allowed to dry for one minute prior to PICC insertion attempt. The CHG was not wiped or washed off of the skin prior to PICC insertion attempt. Blood samples were collected 1–2 hours and 6–12 hours after CHG exposure. Residual blood samples collected for other purposes up to > 72 hours, if available, were also used for CHG serum concentration measurement. Serum CHG concentrations were determined using liquid chromatography-tandem mass spectrometry (LC-MS/MS). The limit of quantitation is 12.5 ng/mL for Group 1 (first 11 infants). Based on concentrations detected in Group 1 infants, the assay was recalibrated to have a better sensitivity with respect to limit of quantification. Consequently, the limit of quantitation is 1.06 ng/mL for Group 2 (second 9 infants). In Group 1, 5 of 30 samples (4 of 11 subjects) had detectable chlorhexidine and concentrations ranged from 16 to 274 ng/mL. In Group 2, 13 of 34 samples (6 of 9 subjects) had detectable chlorhexidine and concentrations ranged from 1.6 to 54.4 ng/ml.
- In the study conducted by Jennifer Cowen et al[4], blood samples were collected by heel prick (n = 10) or from venous blood (n = 24) from 34 newborn preterm infants that were bathed (full body) in 4% CHG solution (Hibiscrub). The serum chlorhexidine concentration was measured by LC. For the heel prick group, chlorhexidine was detected at 1 h (n = 10) and 4 h (n = 8) after first bath, ranging from 31 to 1021 ng/mL. Of the 24 infants that gave venous blood, 5 had positive samples, ranging from 4 to 460 ng/mL.

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- In the study conducted by Andrew Lee et al.[1], blood samples were collected from 12 pediatric subjects (7 males, 5 females; patients aged 3 months to 17 years) that underwent daily baths (median 9 days, range 1-30 days) with 2% CHG cloths. Blood chlorhexidine concentrations were measured using LC-MS/MS. Of the 27 post-exposure samples, 4 (15%) had CHG concentrations above the LOD (4.5 ng/mL). Of those 4 samples, 3 were below the LOQ (17 ng/mL) and one was at 57 ng/mL. The 4 positive samples came from 4 different patients with varying exposures (4 – 22 days of baths; blood samples drawn 8 to 24 hrs after bath) to CHG. No subject had more than 1 positive sample and no evidence of accumulation was found. The patients with positive samples were aged 9 months, 2 years, 5 years, and 10 years.

Conclusion:

- The clinical relevance of chlorhexidine systemic absorption in pediatric patients is unknown.
- There appears to be no chlorhexidine systemic exposure related adverse events in the studies conducted in pediatric patients.

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/s/

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10/12/2018

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10/12/2018