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APPLICATION NUMBER:

207964Orig1s000

NON-CLINICAL REVIEW(S)

Memorandum to File
Pharmacology/Toxicology, Division of Nonprescription Drug Products

NDA: 207964	Sponsor: Medline Industries, Inc.
Drug: ReadyPrep CHG (Chlorhexidine Gluconate 2% Cloth)	Indication: Pre-Operative Skin Preparation

Subject: Addendum to Nonclinical Pharmacology/Toxicology Review

Background

This NDA was received on 20 October 2017 (SDN-16) as a resubmission following a Refuse-to-File action by DNDP. In the original resubmission package, the Sponsor had included a patent certification for the original NDA 017768 (Hibiclens, 4% topical solution, approved 1976) while at the same time stating affirmatively that they "…will not be relying on the FDA's findings of safety and/or effectiveness for any listed drugs." The application stated that the Sponsor would be relying, instead, solely on published literature to provide the nonclinical safety support for the drug product.

The Sponsor's citation and summary of what they considered to be the relevant published literature was subsequently reviewed by this reviewer[1] and found to be largely inadequate as a stand-alone basis of support:

> "From a nonclinical perspective, the data and information provided by the Sponsor from the published literature are not compliant with generally accepted regulatory standards and guidance and, for the most part, have little relevance for a new drug product with an acute-use indication that is applied by the topical dermal route of administration. The cited publications provide little, if anything, beyond brief summary information and do not afford FDA an opportunity for a full and independent evaluation of the original study data."

Following further internal discussion and communication with the Sponsor informing them of this inadequacy, the Sponsor now "…proposes to rely on the FDA's findings of nonclinical safety for Hibiclens®, a 4.0% w/v chlorhexidine gluconate (CHG) topical solution (NDA 017768; Mölnlycke Health Care US, LLC; Approval Date: 17 September 1976)" (SDN-37, received 28 September 2018).

Evaluation and Recommendations

Following internal evaluation of this information, it is concluded that the estimated dose and duration for the Hibiclens® product supports the proposed product with respect to anticipated exposures to the CHG active ingredient. It is also concluded that the Sponsor's previously submitted literature survey and summary are supportive but not pivotal to supporting the safety of CHG. The application remains approvable from a from a nonclinical perspective.

[1] NDA 207964: Pharmacology/Toxicology NDA Review and Evaluation, D. Charles Thompson, RPh, PhD, DABT, 29 June 2018.

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/s/

DONALD C THOMPSON
10/04/2018

JANE J SOHN
10/04/2018
I concur.

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

PHARMACOLOGY/TOXICOLOGY NDA REVIEW AND EVALUATION

Application number:	207964
Supporting document/s:	16
Applicant's letter date:	17 October 2017
CDER stamp date:	20 October 2017
Product:	ReadyPrep CHG (Chlorhexidine Gluconate 2% Cloth)
Indication:	Pre-Operative Skin Preparation
Applicant:	Medline Industries, Inc. One Medline Place Mundelein, IL 60060
Review Division:	Nonprescription Drug Products
Reviewer:	D. Charles Thompson, RPh, PhD, DABT
Team Leader:	Jane J. Sohn, PhD
Division Director:	Theresa Michele, MD
Project Manager:	Celia R. Peacock, MPH, RDN

Disclaimer

Except as specifically identified, all data and information discussed below and necessary for approval of 207964 are owned by Medline Industries, Inc. or are data for which Medline Industries, Inc. has obtained a written right of reference.
Any information or data necessary for approval of 207964 that Medline Industries, Inc. does not own or have a written right to reference constitutes one of the following: (1) published literature, or (2) a prior FDA finding of safety or effectiveness for a listed drug, as reflected in the drug's approved labeling. Any data or information described or referenced below from reviews or publicly available summaries of a previously approved application is for descriptive purposes only and is not relied upon for approval of 207964.

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1 Executive Summary

1.1 Introduction

Medline Industries, Inc., has submitted a 505(b)(2) application proposing their ReadyPrep CHG (Chlorhexidine Gluconate 2% Cloth) for use as a nonprescription (OTC) preoperative patient skin preparation. The application is a resubmission following an initial Refuse-to-File action, which was taken because of (b) (4) The Sponsor states they are relying on published literature for nonclinical safety support of CHG. Topical CHG solutions have been available for OTC use since 1976 (NDA 017768).

1.2 Brief Discussion of Nonclinical Findings

No original nonclinical data were submitted in support of the current application. Rather, the Sponsor has submitted and summarized available published literature to support the nonclinical safety of CHG for the proposed indication. These published data are lacking by current regulatory standards. However, in the context of the existing substantial prior history of safe clinical use of CHG in the marketplace, these published nonclinical data are considered sufficient and adequate to support approvability of the application from a nonclinical perspective.

1.3 Recommendations

1.3.1 Approvability: Yes

1.3.2 Additional Nonclinical Recommendations: None

1.3.3 Labeling: Acceptable

2 Drug Information

2.1 Drug

CAS Registry Number: 18472-51-0

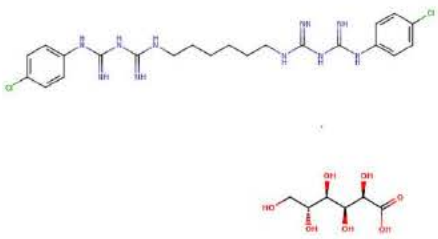
Generic Name: Chlorhexidine gluconate (CHG)

Code Name: N/A

Chemical Name: 2,4,11,13-Tetraazatetradecanediimidamide, N,N''-bis(4-chlorophenyl)-3,12-diimino-, di-D-gluconate

Molecular Formula/Molecular Weight: $C_{22}H_{30}Cl_2N_{10}•2C_6H_{12}O_7$/897.76

Structure:



Pharmacologic Class: Topical antiseptic

2.2 Relevant INDs, NDAs, BLAs and DMFs

IND 107899; DMF (b) (4)

2.3 Drug Formulation

The proposed drug product is comprised of a polyester cloth saturated with 2% Chlorhexidine Gluconate Topical Solution USP (CHG), the formulation of which is summarized in the Sponsor's table below (b) (4) The product is intended for patient pre-operative skin preparation to reduce microorganisms on patients' skin. The product is packaged in a single-use, unit dose presentation consisting of two cloths sealed in a (b) (4) pouch, which provides the equivalent of 500 mg of chlorhexidine gluconate per cloth. The product is presented nonsterile.

Table 2: Composition of 2% Chlorhexidine Gluconate Solution

Component	Quality Standard	Function	Amount (% w/w)
Purified Water	USP	(b) (4)	(b) (4)
Chlorhexidine Gluconate Solution	(b) (4) USP	Drug Substance	
Glycerin	USP	(b) (4)	
Propylene Glycol	USP		
(b) (4) Dimethicone NF Emulsion	(b) (4)		
Isopropyl Alcohol	USP		
(b) (4) Benzalkonium Chloride Solution	NF		

2.4 Comments on Novel Excipients

The proposed drug product formulation as summarized above contains no novel excipients. All proposed excipients are listed in the IID as having previously been used in approved drug products of a comparable dosage form, route of administration, and use concentration. The formulation as proposed does not raise nonclinical safety concerns.

2.5 Comments on Impurities/Degradants of Concern

The Sponsor proposes a finished product specification of NMT (b) (4) ppm (b) (4) for (b) (4) (b) (4) This specification is consistent with (equal or less than) levels that DNDP has previously approved for OTC CHG topical products and is acceptable from a nonclinical perspective (b) (4) No other impurities/degradants of concern were identified by the CMC team.

2.6 Proposed Clinical Population and Dosing Regimen

The drug product is proposed for use as a non-sterile (product and packaging), pre-operative patient skin preparation to reduce bacteria that can potentially cause skin infection. Proposed labeling includes the precautionary statement, "Use with care in premature infants or infants under 2 months of age. These products may cause irritation or chemical burns."

Directions for use include the following:

- "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. After package has been opened discard any unused cloths."
- "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. After package has been opened discard any unused cloths."

2.7 Regulatory Background

The current submission constitutes an original 505(b)(2) NDA, which is resubmitted following an initial Refuse-to-File action (RTF Letter, 8 April 2016). The primary deficiency that was the basis for the RTF action was inclusion (b) (4) The current submission provides patent certification for the original NDA 017768 (Hibiclens, 4% topical solution, approved 1976); however, the Sponsor indicates in the introduction that they "…will not be relying on the FDA's findings of safety and/or effectiveness for any listed drugs." Rather, they indicate they are relying on published literature for nonclinical

safety support (see **Appendix 1**). Complete copies of cited references were included in the submission.

3 Studies Submitted

No original nonclinical studies were included with the submission.

3.1 Studies Reviewed

N/A

3.3 Previous Reviews Referenced

- IND 107899: Pharmacology/Toxicology IND Review and Evaluation, R.T. Dorsam, PhD, 6 February 2014.
- NDA 207964: Refusal to File Letter, T.M. Michele, MD, 8 April 2016.
- NDA 207964: Meeting Minutes, T.M. Michele, MD, 21 June 2016.

11 Integrated Summary and Safety Evaluation

The current 505(b)(2) NDA 207964 has been submitted by Medline Industries, Inc., in support of market registration of ReadyPrep CHG (2% chlorhexidine gluconate cloth) for the OTC indication of preoperative patient skin preparation. The current submission constitutes a resubmission of the application following an initial Refuse-To-File action taken in 2016, (b) (4)

Topical CHG solutions have been available for OTC use since 1976 (NDA 017768). However, the Sponsor states they are relying on published literature for nonclinical safety support of the proposed drug product and its indicated use. There are no novel excipients included in the formulation and the proposed excipients and excipient use levels are covered by prior marketplace experience with respect to dosage form, route of administration, and use level. All proposed drug product impurity specifications are acceptable and raise no safety concerns from a nonclinical perspective.

The Sponsor has included in the submission electronic copies of numerous published literature references as nonclinical safety support for the application, which they have summarized in their Toxicology Written Summary (Section 2.6.6) (see **Appendix 1** for a tabular listing of these references). However, the relevance and robustness of the cited literature are less than optimal (cf., Guidance for Industry: M3(R2) Nonclinical Safety Studies for the Conduct of Human Clinical Trials and Marketing Authorization for Pharmaceuticals, ICH, 2010).

Specifically, the Sponsor acknowledges that “the majority of published studies of acute chlorhexidine toxicity evaluate application conditions or routes of administration that do not directly apply to the ReadyPrep CHG product” and that “no published studies

examining the acute toxicity of topically administered CHG were identified." In addition, in most instances, the publications provide only summary descriptions of the studies and not "full reports of investigations" as required by regulation. Available repeated-dose toxicity data are summarized in the table below, with the caveat that not all test articles were the gluconate salt of chlorhexidine and, again, in only one of the studies was the test article administered via the relevant topical dermal route of exposure.

Selected Published Studies on Repeat-Dose Toxicity of Chlorhexidine*

Species	Application Site or Route	Concentration	Duration	Study
Monkey (neonatal)	Topical (bathing)	8%	90 days	Gongwer, 1980
Rat	Oral (drinking water)	≤40 mg/kg	2 years	Case, 1977
Cat	Middle ear	0.05% or 2%	QOD x 3	Igarashi, 1988
Dog	External ear canals	0.2%	BID x 21 days	Merchant, 1992
Rat	Middle ear	0.1%	5 days	Perez, 2000
Rabbit	Nasal mucosa	0.03 – 0.2%	BID x 5 days	Cankaya, 2003
Rat	Lower abdominal cavity via infusion pump	5%-14%	28 days	Komatsu, 2008
Rat	intraperitoneal	0.1%	3x per wk, 3 weeks	Kushiyama, 2011
Rat	intraperitoneal	0.1%	28 days	Ucar, 2010

*Test articles were not CHG in all cases

Submitted summaries of genotoxicity data are suggestive of a low potential for genotoxicity potential, but these data also are limited and not in keeping with generally accepted regulatory standards (cf., Guidance for Industry: S2(R1) Genotoxicity Testing and Data Interpretation for Pharmaceuticals Intended for Human Use, ICH, 2012). The Sponsor also provides a summary of safety data (in vitro, animal, and human) on chlorhexidine (various salts, including acetate and hydrochloride) from the National Toxicology Program (NTP, 2015) that addresses genotoxicity as well as other toxicological endpoints. However, none of these reports afford FDA an opportunity for a full and independent evaluation of the original raw data.

Overall, the Sponsor concludes from their review of the literature as follows:

> "CHG has been administered safely for more than 40 years at a variety of concentrations in topical antiseptics, antimicrobial hand washes, oral care rinses, and cleansing solutions for pre-operative skin preparation. Based on information available in the published literature, CHG applied topically to intact skin has little to no toxic effect. Some nonclinical studies indicate that mild irritation at the site of application may occur in a small number of cases. The lack of absorption of chlorhexidine through intact skin limits systemic exposure, and therefore limits the potential for systemic toxicity from the ReadyPrep CHG product."
>
> "The toxic effects of chlorhexidine from other routes of administration were also reviewed, and no notable safety signals were identified. As the CHG absorption from topical application (as in ReadyPrep CHG) is lower than that of other routes of administration, the findings of nonclinical safety from these studies support the safety of the ReadyPrep CHG product."

From a nonclinical perspective, the data and information provided by the Sponsor from the published literature are not compliant with generally accepted regulatory standards and guidance and, for the most part, have little relevance for a new drug product with an acute-use indication that is applied by the topical dermal route of administration. The cited publications provide little, if anything, beyond brief summary information and do not afford FDA an opportunity for a full and independent evaluation of the original study data.

Nevertheless, when viewed in light of the long history of previous human experience with CHG as an OTC topical antiseptic, the totality of the data and information described above is generally supportive of and consistent with previous Agency findings of safety for CHG drug products for the proposed indication. The application is considered approvable from a nonclinical perspective.

12 Appendix/Attachments

Appendix 1

Table 2 Nonclinical Toxicity Information to Rely on for Approval of ReadyPrep CHG

Section	Source of Information
Single-dose toxicity	(Giannelli, 2008) (Babich, 1995) (Hidalgo, 2001) (Case, 1977) (NTP, 2016) (Chow, 1977) (Green, 1980) (MacRae, 1984) (Olson, 1984) (Henschen, 1984) (Aursnes, 1978) (Orito, 2006) (Severyns, 1991)
Repeat-dose toxicity	(Gongwer, 1980) (Igarashi, 1988) (Perez, 2000) (Merchant, 1992) (Kushiyama, 2011) (Ucar, 2010) (Komatsu, 2008) (Case, 1977) (Cankaya, 2003)
Genotoxicity	(Ribeiro, 2005) (Ribeiro, 2004) (NTPC, 2015)
Carcinogenicity	(Case, 1977)
Reproductive and Developmental Toxicity	(Case, 1977) (NTPC, 2015)
Local Tolerance	(Yucca, 2006) (Sadakane, 2015) (Gongwer, 1980) (Lambrechts, 2004) (Gibson, 1997) (Coolman, 1998)
Other Toxicity and Excipient Safety	(Saatman, 1986) (Bassetti, 1980) (Toxnet, Bzk, 2015)

Section	Source of Information
	(RTECS, 2016) (Revelle, 1993) (Chhabra, 1990) (Toxnet, PCA, 2015) (USP, 2014)

2.6.6.10. References

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/s/

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06/29/2018

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I concur.