

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:
NDA 19-422 / S-032

ADMINISTRATIVE DOCUMENTS

EXCLUSIVITY SUMMARY for NDA # 19-422 SUPPL # 032
Trade Name Exidine Generic Name 2% chlorhexidine gluconate
solution Applicant Name Xttrium Laboratories, Inc.

HFD-560

Approval Date December 19, 2003

PART I: IS AN EXCLUSIVITY DETERMINATION NEEDED?

1. An exclusivity determination will be made for all original applications, but only for certain supplements. Complete Parts II and III of this Exclusivity Summary only if you answer "YES" to one or more of the following questions about the submission.

a) Is it an original NDA? YES/___/ NO / x /

b) Is it an effectiveness supplement? YES / x / NO / ___ /

If yes, what type (SE1, SE2, etc.)? SE-8

c) Did it require the review of clinical data other than to support a safety claim or change in labeling related to safety? (If it required review only of bioavailability or bioequivalence data, answer "NO.")

YES / x / NO / ___ /

If your answer is "no" because you believe the study is a bioavailability study and, therefore, not eligible for exclusivity, EXPLAIN why it is a bioavailability study, including your reasons for disagreeing with any arguments made by the applicant that the study was not simply a bioavailability study.

If it is a supplement requiring the review of clinical data but it is not an effectiveness supplement, describe the change or claim that is supported by the clinical data:

d) Did the applicant request exclusivity?

YES /___/ NO /x_/

If the answer to (d) is "yes," how many years of exclusivity did the applicant request?

e) Has pediatric exclusivity been granted for this Active Moiety?

YES /___/ NO /_x_/

IF YOU HAVE ANSWERED "NO" TO ALL OF THE ABOVE QUESTIONS, GO DIRECTLY TO THE SIGNATURE BLOCKS ON Page 9.

2. Has a product with the same active ingredient(s), dosage form, strength, route of administration, and dosing schedule previously been approved by FDA for the same use? (Rx to OTC Switches should be answered No - Please indicate as such).

YES /___/ NO /_x_/

If yes, NDA # _____ Drug Name

IF THE ANSWER TO QUESTION 2 IS "YES," GO DIRECTLY TO THE SIGNATURE BLOCKS ON Page 9.

3. Is this drug product or indication a DESI upgrade?

YES /___/ NO /_x_/

IF THE ANSWER TO QUESTION 3 IS "YES," GO DIRECTLY TO THE SIGNATURE BLOCKS ON Page 9 (even if a study was required for the upgrade).

PART II: FIVE-YEAR EXCLUSIVITY FOR NEW CHEMICAL ENTITIES

(Answer either #1 or #2, as appropriate)

1. Single active ingredient product.

Has FDA previously approved under section 505 of the Act any drug product containing the same active moiety as the drug under consideration? Answer "yes" if the active moiety (including other esterified forms, salts, complexes, chelates or clathrates) has been previously approved, but this particular form of the active moiety, e.g., this particular ester or salt (including salts with hydrogen or coordination bonding) or other non-covalent derivative (such as a complex, chelate, or clathrate) has not been approved. Answer "no" if the compound requires metabolic conversion (other than deesterification of an esterified form of the drug) to produce an already approved active moiety.

YES / x / NO / ___ /

If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).

NDA # 19-422

NDA #

NDA #

2. Combination product.

If the product contains more than one active moiety (as defined in Part II, #1), has FDA previously approved an application under section 505 containing any one of the active moieties in the drug product? If, for example, the combination contains one never-before-approved active moiety and one previously approved active moiety, answer "yes." (An active moiety that is marketed under an OTC monograph, but that was never approved under an NDA, is considered not previously approved.)

Not applicable.

YES / ___ / NO / ___ /

If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).

NDA #

NDA #

NDA #

IF THE ANSWER TO QUESTION 1 OR 2 UNDER PART II IS "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON Page 9. IF "YES," GO TO PART III.

PART III: THREE-YEAR EXCLUSIVITY FOR NDA'S AND SUPPLEMENTS

To qualify for three years of exclusivity, an application or supplement must contain "reports of new clinical investigations (other than bioavailability studies) essential to the approval of the application and conducted or sponsored by the applicant." This section should be completed only if the answer to PART II, Question 1 or 2, was "yes."

1. Does the application contain reports of clinical investigations? (The Agency interprets "clinical investigations" to mean investigations conducted on humans other than bioavailability studies.) If the application contains clinical investigations only by virtue of a right of reference to clinical investigations in another application, answer "yes," then skip to question 3(a). If the answer to 3(a) is "yes" for any investigation referred to in another application, do not complete remainder of summary for that investigation.

YES / x / NO / ___ /

IF "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON Page 9.

2. A clinical investigation is "essential to the approval" if the Agency could not have approved the application or supplement without relying on that investigation. Thus, the investigation is not essential to the approval if 1) no clinical investigation is necessary to support the supplement or application in light of previously approved applications (i.e., information other than clinical trials, such as

bioavailability data, would be sufficient to provide a basis for approval as an ANDA or 505(b)(2) application because of what is already known about a previously approved product), or 2) there are published reports of studies (other than those conducted or sponsored by the applicant) or other publicly available data that independently would have been sufficient to support approval of the application, without reference to the clinical investigation submitted in the application.

For the purposes of this section, studies comparing two products with the same ingredient(s) are considered to be bioavailability studies.

- (a) In light of previously approved applications, is a clinical investigation (either conducted by the applicant or available from some other source, including the published literature) necessary to support approval of the application or supplement?

YES / / NO / /

If "no," state the basis for your conclusion that a clinical trial is not necessary for approval **AND GO DIRECTLY TO SIGNATURE BLOCK ON Page 9:**

- (b) Did the applicant submit a list of published studies relevant to the safety and effectiveness of this drug product and a statement that the publicly available data would not independently support approval of the application?

YES / / NO / /

- (1) If the answer to 2(b) is "yes," do you personally know of any reason to disagree with the applicant's conclusion? If not applicable, answer NO.

YES / / NO / /

If yes, explain:

(2) If the answer to 2(b) is "no," are you aware of published studies not conducted or sponsored by the applicant or other publicly available data that could independently demonstrate the safety and effectiveness of this drug product?

YES /___/ NO /_x_/

If yes, explain:

(c) If the answers to (b)(1) and (b)(2) were both "no," identify the clinical investigations submitted in the application that are essential to the approval:

Investigation #1, Study # Report #010206-102

Investigation #2, Study #

Investigation #3, Study #

3. In addition to being essential, investigations must be "new" to support exclusivity. The agency interprets "new clinical investigation" to mean an investigation that 1) has not been relied on by the agency to demonstrate the effectiveness of a previously approved drug for any indication and 2) does not duplicate the results of another investigation that was relied on by the agency to demonstrate the effectiveness of a previously approved drug product, i.e., does not redemonstrate something the agency considers to have been demonstrated in an already approved application.

(a) For each investigation identified as "essential to the approval," has the investigation been relied on by the agency to demonstrate the effectiveness of a previously approved drug product? (If the investigation was relied on only to support the safety of a previously approved drug, answer "no.")

Investigation #1 Rpt #010206-102 YES /___/NO /_x_/

Investigation #2 YES /___/ NO /___/

Investigation #3 YES /___/ NO /___/

If you have answered "yes" for one or more investigations, identify each such investigation and the NDA in which each was relied upon:

NDA # _____ Study #
NDA # _____ Study #
NDA # _____ Study #

- (b) For each investigation identified as "essential to the approval," does the investigation duplicate the results of another investigation that was relied on by the agency to support the effectiveness of a previously approved drug product?

Investigation #1 Rpt #010206-102 YES /___/NO /_x_/

Investigation #2 YES /___/ NO /___/

Investigation #3 YES /___/ NO /___/

If you have answered "yes" for one or more investigations, identify the NDA in which a similar investigation was relied on:

NDA # _____ Study #

NDA # _____ Study #

NDA # _____ Study #

- (c) If the answers to 3(a) and 3(b) are no, identify each "new" investigation in the application or supplement that is essential to the approval (i.e., the investigations listed in #2(c), less any that are not "new"):

Investigation #__, Study # Rpt #010206-102

Investigation #__, Study #

Investigation #__, Study #

4. To be eligible for exclusivity, a new investigation that is essential to approval must also have been conducted or sponsored by the applicant. An investigation was "conducted or sponsored by" the applicant if, before or during the conduct of the investigation, 1) the applicant was the sponsor of the IND named in the form FDA 1571 filed with the Agency, or 2) the applicant (or its predecessor in interest) provided substantial support for the study. Ordinarily, substantial support will mean providing 50 percent or more of the cost of the study.

(a) For each investigation identified in response to question 3(c): if the investigation was carried out under an IND, was the applicant identified on the FDA 1571 as the sponsor?

Investigation #1 !
IND # _____ YES /___/ ! NO /___/ Explain:
!
!

Investigation #2 !
IND # _____ YES /___/ ! NO /___/ Explain:
!
!

(b) For each investigation not carried out under an IND or for which the applicant was not identified as the sponsor, did the applicant certify that it or the applicant's predecessor in interest provided substantial support for the study?

Investigation #1 !
YES /_x_/ Explain _____ ! NO /___/ Explain _____
Although the clinical study described in Report #010206-102 was not submitted to an IND, Xttrium Laboratories did sponsor this clinical study that was submitted to NDA 19-422, Supplement 032.
!

Investigation #2 !
YES /___/ Explain _____ ! NO /___/ Explain _____

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/s/

Charles Ganley
2/19/04 09:49:50 AM

MEMORANDUM OF TELECON

DATE: December 26, 2002

Time: 11:00-11:15AM

APPLICATION NUMBER: NDA 19-422/S-032, Dyna-Hex 2® (2% chlorhexidine gluconate)
Solution

BETWEEN:

Name: Dennis Gronek, Attorney at Law
Phone: (312) 655-1800
Representing: Xttrium Laboratories

AND

Name: Tia Frazier, Project Manager, HFD-560
Division of Over-the-Counter Drug Products, HFD-560

SUBJECT: FDA's request to include inactive ingredients in product labeling

Mr. Gronek telephoned to inform FDA that he intended to respond to FDA's December 19, 2002, request for information about Xttrium Laboratories' trade secret inactive ingredients, and assertion that these ingredients should not be included in the product's labeling. Mr. Gronek informed me that his client's response to the first deficiency listed in the December 19, 2002, approvable letter for this supplement would arrive by the second week of January, 2003. Mr. Gronek elaborated on the cosmetic properties of the final formulation that his client claimed made the formulation for this product a trade secret.

FDA requested that Mr. Gronek and Xttrium Laboratories send all responses to the December 19, 2002, approvable action directly to the New Drug Application file in the FDA Document Room. Mr. Gronek agreed to confer this request to Xttrium Laboratories.

The conversation ended cordially.

Tia Frazier
Regulatory Project Manager

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/s/

Tia Frazier
12/26/02 12:08:07 PM
CSO

December 18, 2002

Administrative memorandum

Drug Product: Exidine solution
Indication: pre-surgical hand-scrubbing
Applicant: Xttrium Laboratories, Inc.
Contact: Ram Chakroborty

Letter date: January 10, 2002
Receipt date: February 25, 2002
Filing date: April 26, 2002
Action date: December 25, 2002

RE: Explanation chemistry and pharmacology-toxicology reviews for
Supplemental New Drug Application (sNDA) 19-422, Supplement 32

FDA issued an approvable action for a sNDA submitted Xttrium Laboratories that provided for revised **Directions for Use** for the pre-surgical scrubbing indication. The purpose of this memorandum is to provide a rationale for the omission of the chemistry and pharmacology-toxicology reviews for this sNDA, as described below:

1. The application contained no change to the drug product, manufacturing process, or testing that would drive the need for a chemistry review of this sNDA.
2. The application provided for no new degradents, impurities, or inactive ingredients that would prompt the need for a pharmacology-toxicology review of this sNDA.

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/s/

Tia Frazier
12/19/02 01:53:06 PM
CSO

MEMORANDUM OF TELECON

DATE: August 5, 2002

APPLICATION NUMBER: NDA 19-422/S-032, Dyna-Hex 2® (2% chlorhexidine gluconate) Solution

BETWEEN:

Name: Dennis Gronek, Attorney at Law
Phone: (312) 655-1800
Representing: Xttrium Laboratories

AND

Name: Tia Frazier, Project Manager, HFD-560
Debbie Lumpkins, Team Leader, HFD-560
Gerald Rachanow, Regulatory Counsel, HFD-560
Division of Over-the-Counter Drug Products, HFD-560

SUBJECT: FDA request to include inactive ingredients in product labeling

We called Mr. Gronek in reference to the July 18, 2002, submission and referred to the firm's refusal to list the inactive ingredients contained in this 2% chlorhexidine gluconate solution.

Mr. Rachanow asked Mr. Gronek why all the reasons for not listing the inactive ingredients provided by Mr. Gronek during a July 8, 2002, conversation with Mr. Rachanow had not been included in the sponsor's July 18, 2002, submission to the agency.

At Mr. Rachanow's request, Mr. Gronek agreed to provide a written summary of the past FOI requests for disclosure of the sponsor's inactive ingredients, and FDA denials of these requests. Mr. Gronek reported that his correspondence would also reference the legislative history of the 1997 amendment to Section 502(e)(1)(A) of the Food, Drug, and Cosmetic Act, which he thought provided legal support for the sponsor's refusal to list all inactive ingredients.

Finally, Mr. Rachanow asked Mr. Gronek to note that there was no patent for this product, which would contain inactive ingredient information.

The conversation ended cordially.

Gerald Rachanow, Esq.
Regulatory Counsel

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/s/

Tia Frazier
8/30/02 01:32:06 PM
CSO

Gerald Rachanow
9/9/02 09:08:02 AM
DIRECTOR

MEMORANDUM OF TELECON

DATE: June 11, 2002

APPLICATION NUMBER: NDA 19-422/S-032, Exidine (2% chlorhexidine gluconate) Solution

BETWEEN:

Name:

Dr. Ram Chokraborty, Vice President

Leslie Foutch, Vice President of Regulatory Affairs

(773) 268-9790

Phone:

Representing: Xttrium Laboratories, Inc.

AND

Name:

Tia Frazier, Regulatory Project Manager, Division of Over-the-Counter
Drug Products, HFD-560

Dr. Daphne Lin, Team Leader, Division of Biometry III, HFD-725

Dr. Joel Jiang, Statistical Reviewer, Division of Biometry III, HFD-725

SUBJECT: Statistical issues

FDA requested each dataset be provided as a SAS transport file according to our agency's "Guidance for Industry: Providing Regulatory Submissions in Electronic Format - NDAs".

FDA requested that the firm amend the statistical information provided on January 11, 2002, received on February 25, 2002, by identifying each study participant with a unique identification number. FDA also requested that the sponsor provide a description of the variable codes used in the study. The sponsor agreed to these requests.

FDA inquired whether or not the number of subjects with the baseline bacterial counts in the dataset were the same as the number of subjects with the testing bacterial counts, as depicted in Tables III and IV. The sponsor agreed to re-examine these data sets, and report errors to the FDA.

FDA noted that 30 subjects dropped out of the study, bringing the total evaluable patients from 90 to 60. FDA asked the sponsor to clarify the timing of the drop-outs. The FDA specifically requested to know whether the drop-outs occurred before, or after, the study subjects were randomized.

Outcomes:

1. The firm agreed to provide the statistical data in SAS transport files within two weeks of the date of this teleconference.

The conversation ended cordially.

Tia Frazier
Project manager

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/s/

Tia Frazier
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CSO

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:
NDA 19-422 / S-032

CORRESPONDENCE



...INNOVATIONS IN
PRODUCTS AND SYSTEMS

ORIGINAL

December 1, 2003

Ms. Tia Frazier, Regulatory Project Manager
General Correspondence
Attention: Document Control Room
Food and Drug Administration
Division of OTC Products
Office of Drug Evaluation V
Center for Drug Evaluation and Research
9201 Corporate Boulevard
HFD - 560
Rockville, MD 20850

RECEIVED

DEC 03 2003

MEGA/CDER

SEB-032 (4)
SUPPL NEW CORRESP

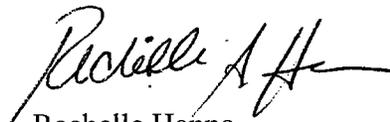
Dear Ms. Frazier,

Thank you for your e-mail dated November 28, 2003. The labels to be considered for supplement 032 come from the following submissions:

- 4- and 8-ounce labels from the submission dated October 31, 2003
- 16-, 30-, 32- and 128-ounce labels from the submission dated September 3, 2003.

Thank you for your attention to this matter. Please feel free to contact me at (773) 268-5800 or via e-mail at rhanna@xttrium.com if you have any questions or concerns regarding this matter.

Sincerely,

 12/1/03

Rachelle Hanna
Regulatory Affairs
Xttrium Laboratories, Inc.



...INNOVATIONS IN
PRODUCTS AND SYSTEMS

October 31, 2003

Ms. Tia Frazier
Food and Drug Administration
Division of OTC Drug Products
Office of Drug Evaluation V
Center for Drug Evaluation and Research
5600 Fishers Lane, HFD-560
Rockville, MD 20857

Dear Ms. Frazier,

Thank you for your most recent letter indicating the status of supplement 032 for NDA 19-422. This letter serves as a response to that communication. The FDA findings appear in bold print and Xttrium's answer appears in regular print.

We completed our review of this application, and it is approvable. Before the application may be approved, however, you must submit draft labeling revised as follows:

- 1. Add the phrase "Peel here for Drug Facts" to the outermost surface of the 4- and 8-ounce containers, rather than on page 2 of the leaflet. The statement is located on the wrong panel. Currently, the statement appears *inside* the folded label, but should be located on the principal display panel (PDP) so that it is visible to the reader looking at the bottle.**

The outermost surface of the label contains both the Principal Display Panel (PDP) and page 2. Therefore the phrase "Peel here for Drug Facts" has been included at the top of page 2. In addition, that phrase is outside of the Drug Facts box to ensure that it is not part of Drug Facts labeling. The consumer will thus be able to read the phrase "Peel here for Drug Facts" and view the remainder of the Drug Facts contents. There will be a tab from which to open the label in order to read all the pertinent information. Refer to Attachment 1: 4- and 8-ounce labels (unmarked copies). In addition, hand made mock up copies have been included so that the Agency can physically lift up the tab on the right side to view all the Drug Facts. Refer to Attachment 2 : 4- and 8-ounce mock ups.

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NAI
Danie Shelly
11/26/03

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S(18-032)(BZ)
NDA SUPPL AMENDMENT

In addition, all previous revisions as reflected in the most recently approved package insert must be included. To facilitate review of your submission, provide a highlighted or marked up copy that shows the changes.

Xttrium complies with this request. Refer to Attachment 3 – 4- and 8-ounce labels (highlighted copies).

When you respond to the above deficiencies, include a safety update as described at 21 CFR 314.50 (d)(5)(vi)(b). The safety update should include data from all non-clinical and clinical studies of the drug under consideration regardless of indication, dosage form, or dose level.

1. Describe in detail any significant changes or findings in the safety profile.

Since submission of a periodic safety update report on September 3, 2003, there has been only one adverse experience reported. On October 3, 2003, Xttrium was notified by _____ in Mexico that a 7 year old experienced “a small chemical abrasion, corneal burn or chemical conjunctivitis after a facial skin prep for removal of a lesion from the side of a child’s nose.” An investigation was conducted by Xttrium Quality Assurance. The field sample was not returned for analysis but Xttrium Quality Control chemists analyzed the retained samples. All results met finished product specifications. A 15 day report was sent to the FDA on October 9, 2003 as per CFR regulations.

2. When assembling the sections describing discontinuations due to adverse events, serious adverse events, and common adverse events, incorporate new safety data as follows:

- **Present new safety data from the studies for the proposed indication using the same format as the original NDA submission.**
- **Present tabulations of the new safety data combined with the original NDA data.**
- **Include tables that compare frequencies of adverse events in the original NDA with the retabulated frequencies described in the bullet above.**
- **For indications other than the proposed indication, provide separate tables for the frequencies of adverse events occurring in clinical trials.**

No new safety data has been received regarding clinical trials for the proposed indication so there is no new information to include for the first three bullets of question 2. No new clinical trials have been conducted for other indications. The researched literature contains only case studies as shown in the periodic safety update report included in the September 3, 2003 submission.

3. Present a retabulation of the reasons for premature study discontinuation by incorporating the drop-outs from the newly completed studies. Describe any new trends or patterns identified.

All clinical studies involving Xttrium Laboratories, Inc. have not had any drop-outs from studies.

4. Provide case report forms and narrative summaries for each patient who died during a clinical study or who did not complete a study because of an adverse event. In addition, provide narrative summaries for serious adverse events.

No such incidences have occurred during any studies conducted under the sponsorship of Xttrium Laboratories, Inc.

5. Describe any information that suggests a substantial change in the incidence of common, but less serious, adverse events between the new data and the original NDA data.

There have been no incidences in the literature indicating any substantial change in the incidence of common though less serious adverse events since the submission of the original NDA data.

6. Provide a summary of worldwide experience on the safety of this drug. Include an updated estimate of use for drug marketed in other countries.

Chlorhexidine gluconate has repeatedly been proven effective in reducing bacteria. Most hospitals use chlorhexidine gluconate as a surgical scrub, patient preoperative skin preparation, and/ or healthcare personnel handwash. Chlorhexidine gluconate has also proved to be effective as an oral rinse. Several recent articles have reinforced these claims. After the incidences of anthrax in ¹October and November of 2001, researchers sought to test the efficacy of chlorhexidine gluconate against the anthrax bacteria. A surrogate of the anthrax bacteria was used. Use of 2% chlorhexidine gluconate solution reduced spore contamination as compared to ethyl alcohol.² In addition, further investigation is also warranted after initial testing demonstrating that chlorhexidine is effective against agents causing fungal keratitis.³ Chlorhexidine gluconate has also been tested against agents that cause sexually transmitted disease. Further studies are still needed, but initial results show promising results.⁴ Chlorhexidine gluconate has also been studied after root canal. Concentrations of 2% and 0.2% have been used. According to researchers, "chlorhexidine gluconate resulted in the greatest percentage reduction of microbial flora."⁵ Chlorhexidine gluconate has also been shown to reduce incidences of infections related to catheters.⁶ In addition, the FDA has approved numerous NDAs and ANDAs with chlorhexidine gluconate as the active ingredient.

Review of recent literature has found that most adverse reactions to chlorhexidine gluconate have been relatively mild. When chlorhexidine gluconate was used as an oral rinse, adverse reactions were relatively mild in nature and short-lived⁷. There were also instances of adverse reactions when chlorhexidine gluconate was used as a healthcare personnel handwash as most Xttrium CHG products are. In these instances, chlorhexidine gluconate was shown to produce some dryness while being more effective than alcohol.⁸ Other instances of adverse reactions when using as a handwash occurred in health care workers who were older, theoretically because their skin is less pliable. In addition, in these cases, damage is long term and may not be treated easily.⁹ In one

instance, a patient developed acute urticaria after showering with chlorhexidine gluconate. However, after treatment with steroids, the problem was resolved in 6 hours.¹⁰ There were instances, however, of anaphylactic shock. These instances mostly occurred in Japan and Denmark where use of chlorhexidine gluconate in catheters is more prevalent.^{11 12 13 14 15 16}

Since the last amendment for supplement 32 for this NDA on February 10, 2003, there has been only one reported adverse reaction to this product. A surgical technician experienced redness from fingertips to elbows after using this product for a period of three weeks. A complaint was made to the distributor of the product. The distributor then forwarded the complaint to Xttrium Laboratories, Inc. The health care practitioner of the complainant (with prior permission from that complainant) released a statement that chlorhexidine was most likely not the cause of the reaction. All test results demonstrated that the product fell within finished product specifications. A 15-day report was filed with the FDA as per 21 CFR 314.80. In addition, according to Xttrium standard operating procedures, a full investigation was conducted.

1

²² Weber DJ, Sickbert-Bennett E, Gergen MF, and Rutala WA. Efficacy of Selected Hand Hygiene Agents Used to Remove *Bacillus atrophaeus* (a Surrgate of *Bacillus anthracis*) From Contaminated Hands. *JAMA*. 2003; 289: 1274-1277.

³ Rahman MR, Johnson GJ, Husain R, Howlader SA, and Minassian DC. Randomised trial of 0.2% chlorhexidine gluconate and 2.5% natamycin for fungal keratitis in Bangladesh. *British Journal of Ophthalmology*. 1998; 82: 919-925.

⁴ Lampe MF, Ballweber LM, and Stamm WE. Susceptibility of *Chlamydia trachomatis* to Chlorhexidine Gluconate Gel. *Antimicrobial Agents and Chemotherapy*. 1998; 42; 1726-1730.

⁵ Lekshmy DS and Kamath PM. Antimicrobial efficacy of 0,2 and 2 percent chlorhexidine and sodium hypochlorite as root-canal irrigants: an in-vivo study. *Endodontology*. 2001; 13(2); 57-62.

⁶ Chaiyakunapruk N, Veenstra DL, Lipsky BA et al. Chlorhexidine compared with povidone-iodine solution for vascular catheter-site care; a meta-analysis. *Annals of Internal Medicine*. 2002; 136; 792-801.

⁷ Soskolne WA, Proskin HM, Stabholz A. Probing depth changes following 2 years of periodontal maintenance therapy including adjunctive controlled release of chlorhexidine. *Journal of Periodontology*, 2003; 74; 420-427.

⁸ Kovach TL. Maintaining Intact Skin During Handwashing: The First Line of Defense Against the Chain of Septic Flow. www.infectioncontroltoday.com/articles/151feat1.html

⁹ Cimiotti JP, Marmur ES, Nesin M, Hamlin-Cook P, Larson EL. Adverse Reaction Associated With An Alcohol-Based Hand Antiseptic. *Journal of Infection Control*, 2003; 31; 43-48.

¹⁰ Beitia JM, Moreno A, Minguez G, DelaParte B, Rubio y M. De Barrio. Acute urticaria due to chlorhexidine. *Alergol Immunol Clin*. 2001; 16; 351-354.

¹¹ Chisolm DG, Calder I, Peterson D, and Powell M. Intranasal chlorhexidine resulting in anaphylactic circulatory arrest. *BMJ*. 1997; 315; 785.

¹² Garvey LH, Roed-Petersen J, and Husum, B. Is there a risk of sensitization and allergy to chlorhexidine in health care workers? *Acta Anaesthesiologica Scandinavica*. 2003. 47; 720.

¹³ Kesler, LG. FDA Alert: Hypersensitivity Reactions to Central Venous Catheters. *American Society of Anesthesiologists*. 1998; 62.

¹⁴ Powers, RJ. Skin Disinfection in the Neonate. Children's Hospital Oakland.

¹⁵ Barrett, SP. HIS: Chlorhexidine (Prof. Haxhe). www.his.org.uk/archive/msg03715.html.

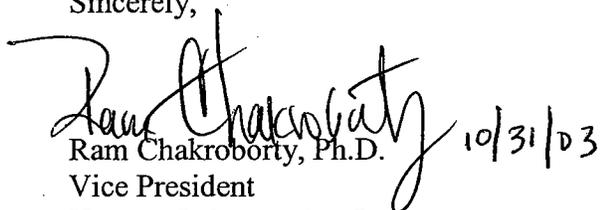
¹⁶ Wicki J, Deluze C, Cirafici L, Desmeules, J. Anaphylactic shock induced by intraurethral use of chlorhexidine. *Allergy*. 1999, 54, 765-770.

7. Provide English translations of current approved foreign labeling not previously submitted.

This does not apply to this response.

Thank you again for your continued attention to this matter. Please feel free to contact me at (773) 268-5800 or via e-mail at rchakroborty@xttrium.com if you have any questions or concerns regarding this matter.

Sincerely,


Ram Chakroborty, Ph.D.

Vice President

Xttrium Laboratories, Inc.

10/31/03

ATTACHMENT 1

APPEARS THIS WAY
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Drug Facts (continued)

Directions

Healthcare personnel handwash: • wet hands with water
 • dispense about 5 ml of product into cupped hands and wash in a vigorous manner for 15 seconds • rinse and dry thoroughly

Preoperative skin preparation: • apply product to surgical site and swab for at least 2 minutes
 • use a sterile towel • repeat procedure for an additional 2 minutes and dry with a sterile towel

Skin wound and general skin cleansing: • thoroughly rinse the area to be cleaned with water • apply the minimum amount of product necessary to cover the skin or wound area and wash gently • rinse again thoroughly

Other information • store at 20-25°C (68-77°F)
 • avoid excessive heat above 40°C (104°F)

Inactive ingredients citric acid, cocamide DEA, hydroxyethylcellulose, isopropyl alcohol, lauramine oxide, purified water

Questions or comments? Call 1-773-268-5800 Monday through Friday 8:00 AM to 4:30 PM

Page 5

Peel here for Drug Facts ▶

Drug Facts

Active ingredient	Purposes
chlorhexidine gluconate 2% solution	surgical hand scrub healthcare personnel handwash patient preoperative skin preparation skin wound and general skin cleansing

Uses

- **surgical hand scrub:** significantly reduces the number of microorganisms on the hands and forearms prior to surgery or patient care
- **healthcare personnel handwash:** helps reduce bacteria that potentially can cause disease
- **patient preoperative skin preparation:** preparation of the patient's skin prior to surgery
- **skin wound and general skin cleansing**

Warnings
 For external use only ▶

Page 2

Leaflet Top

Page 3

Page 4

Leaflet Inside

Drug Facts (continued)

Do not use

- if you are allergic to chlorhexidine gluconate or any other ingredients
- in contact with meninges • in the genital area
- as a preoperative skin preparation of the head or face

When using this product

- keep out of eyes, ears, and mouth. May cause serious and permanent eye injury if placed or kept in the eye during surgical procedures or may cause deafness when instilled in the middle ear through perforated eardrums
- if solution should contact these areas, rinse out promptly and thoroughly with water
- wounds which involve more than the superficial layers of the skin should not be routinely treated
- repeated general skin cleansing of large body areas should not be done except when the underlying condition makes it necessary to reduce the bacterial population of the skin ▶

Drug Facts (continued)

Warnings

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

Surgical hand scrub • wet hands and forearms under running water for 30 seconds. Clean fingernails using a nailstick or similar cleaner. • scrub for 1.5 minutes with about 8 ml of product with or without a wet brush paying close attention to the nails, cuticles, and skin between the fingers • rinse thoroughly under running water for 30 seconds • wash for an additional 1.5 minutes with 8 ml of product and rinse under running water for 30 seconds • dry thoroughly ▶

NDC 17187-1021-1

DYNA-HEX 2°
 (Chlorhexidine Gluconate 2% Solution)
 Antiseptic

Contains: 2% Chlorhexidine Gluconate
 Manufactured By: Xtium Laboratories, Inc.
 415 West Pershing Road
 Chicago, IL 60609

FOR EXTERNAL USE ONLY

Net Contents: 4 fl oz (118 ml)

Lot Number:
 Exp. Date:

Laminated Flap

Base

Drug Facts (continued)

Other information

- store at 20-25°C (68-77°F)
- avoid excessive heat above 40°C (104°F)

Active ingredients citric acid, cocamide DEA, xythylcellulose, isopropyl alcohol, lauramine oxide, and water

Questions or comments? Call 1-773-268-5800 Monday through Friday 8:00 AM to 4:30 PM

Page 5

Peel here for **Drug Facts** ▶

Drug Facts

Active ingredient	Purposes
chlorhexidine gluconate 2% solution	surgical hand scrub healthcare personnel handwash patient preoperative skin preparation skin wound and general skin cleansing

Uses

- **surgical hand scrub:** significantly reduces the number of microorganisms on the hands and forearms prior to surgery or patient care
- **healthcare personnel handwash:** helps reduce bacteria that potentially can cause disease
- **patient preoperative skin preparation:** preparation of the patient's skin prior to surgery
- **skin wound and general skin cleansing**

Warnings

For external use only

Do not use

- if you are allergic to chlorhexidine gluconate or any other ingredients
- in contact with meninges
- in the genital area
- as a preoperative skin preparation of the head or face

Page 2

Leaflet Top

Page 3

Page 4

<p>Drug Facts (continued)</p> <p>When using this product</p> <ul style="list-style-type: none"> • Keep out of eyes, ears, and mouth. May cause serious and permanent eye injury if placed or kept in the eye during surgical procedures or may cause deafness when instilled in the middle ear through perforated eardrums • if solution should contact these areas, rinse out promptly and thoroughly with water • wounds which involve more than the superficial layers of the skin should not be routinely treated • repeated general skin cleansing of large body areas should not be done except when the underlying condition makes it necessary <p>to reduce the bacterial population of the skin</p> <p>Stop use and ask a doctor if irritation, sensitization or allergic reaction occurs. These may be signs of a serious condition.</p> <p>Keep out of reach of children. If swallowed, get medical help or contact a Poison Control Center right away.</p> <p>Directions</p> <p>Surgical hand scrub:</p> <ul style="list-style-type: none"> • wet hands and forearms under running water for 30 seconds. Clean fingernails using a nailstick or similar cleaner. 	<p>Drug Facts (continued)</p> <p>Directions</p> <ul style="list-style-type: none"> • scrub for 1.5 minutes with about 8 ml of product with or without a wet brush paying close attention to the nails, cuticles, and skin between the fingers • rinse thoroughly under running water for 30 seconds • wash for an additional 1.5 minutes with 8 ml of product and rinse under running water for 30 seconds • dry thoroughly <p>Healthcare personnel handwash:</p> <ul style="list-style-type: none"> • wet hands with water • dispense about 5 ml of product into cupped hands and wash in a vigorous manner for 15 seconds • rinse and dry thoroughly <p>Patient preoperative skin preparation:</p> <ul style="list-style-type: none"> • apply product liberally to surgical site and swab for at least 2 minutes • dry with a sterile towel • repeat procedure for an additional 2 minutes and dry with a sterile towel <p>Skin wound and general skin cleansing:</p> <ul style="list-style-type: none"> • thoroughly rinse the area to be cleaned with water • apply the minimum amount of product necessary to cover the skin or wound area and wash gently • rinse again thoroughly
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Leaflet Inside

Base

NDC 17187-1021-2

DYNA-HEX2®
(Chlorhexidine Gluconate 2% Solution)
Antiseptic

Contains: 2% Chlorhexidine Gluconate
Manufactured By: Xttrium Laboratories, Inc.
415 West Pershing Road
Chicago, IL 60609

FOR EXTERNAL USE ONLY

Net Contents: 8 fl oz (237 ml)

Lot Number:
Exp. Date:

Chlorhexidine Gluconate

ATTACHMENT 2

APPEARS THIS WAY
ON ORIGINAL

NDC 17187-1021-1

DYNA-HEX 2[®]
(Chlorhexidine Gluconate 2% Solution)
Antiseptic

Contains: 2% Chlorhexidine Gluconate
Manufactured By: Xtrium Laboratories, Inc.
415 West Pershing Road
Chicago, IL 60609

FOR EXTERNAL USE ONLY

Net Contents: 4 fl oz (118 ml)

Lot Number:
Exp. Date:

Peel here for **Drug Facts** ▶

Drug Facts	
Active ingredient	Purposes
chlorhexidine gluconate 2% solution	surgical hand scrub healthcare personnel handwash patient preoperative skin preparation skin wound and general skin cleansing
Uses	
<ul style="list-style-type: none"> • surgical hand scrub: significantly reduces the number of microorganisms on the hands and forearms prior to surgery or patient care • healthcare personnel handwash: helps reduce bacteria that potentially can cause disease • patient preoperative skin preparation: preparation of the patient's skin prior to surgery • skin wound and general skin cleansing 	
Warnings	
For external use only ▶	

NDC 17187-1021-2

DYNA-HEX 2[®]
(Chlorhexidine Gluconate 2% Solution)
Antiseptic

Contains: 2% Chlorhexidine Gluconate
Manufactured By: Xtrium Laboratories, Inc.
415 West Pershing Road
Chicago, IL 60609

FOR EXTERNAL USE ONLY

Net Contents: 8 fl oz (237 ml)

Lot Number:
Exp. Date:

Peel here for **Drug Facts** ▶

Drug Facts	
Active ingredient	Purposes
chlorhexidine gluconate 2% solution	surgical hand scrub healthcare personnel handwash patient preoperative skin preparation skin wound and general skin cleansing
Uses	
<ul style="list-style-type: none"> • surgical hand scrub: significantly reduces the number of microorganisms on the hands and forearms prior to surgery or patient care • healthcare personnel handwash: helps reduce bacteria that potentially can cause disease • patient preoperative skin preparation: preparation of the patient's skin prior to surgery • skin wound and general skin cleansing 	
Warnings	
For external use only	
Do not use	
<ul style="list-style-type: none"> • if you are allergic to chlorhexidine gluconate or any other ingredients • in contact with meninges • in the genital area • as a preoperative skin preparation of the head or face ▶ 	

ATTACHMENT 3

Peel here for Drug Facts ▶					
<p>Drug Facts (continued)</p> <p>Directions</p> <p>Healthcare personnel handwash:</p> <ul style="list-style-type: none"> wet hands with water dispense about 5 ml of product into cupped hands and wash in a vigorous manner for 15 seconds rinse and dry thoroughly <p>Preoperative skin preparation:</p> <ul style="list-style-type: none"> apply product to surgical site and swab for at least 2 minutes with a sterile towel repeat procedure for an additional 2 sites and dry with a sterile towel <p>Skin wound and general skin cleansing:</p> <ul style="list-style-type: none"> thoroughly rinse the area to be cleaned with water apply the minimum amount of product necessary to cover the skin or wound area and wash gently rinse again thoroughly <p>Other information</p> <ul style="list-style-type: none"> store at 20-25°C (68-77°F) avoid excessive heat above 40°C (104°F) <p>Inactive ingredients: citric acid, cocamide DEA, hydroxyethylcellulose, isopropyl alcohol, lauramine oxide, purified water</p> <p>Questions or comments? Call 1-773-268-5800 Monday through Friday 8:00 AM to 4:30 PM</p>	<p>Drug Facts</p> <table border="1"> <thead> <tr> <th>Active ingredient</th> <th>Purposes</th> </tr> </thead> <tbody> <tr> <td>chlorhexidine gluconate 2% solution</td> <td>surgical hand scrub healthcare personnel handwash patient preoperative skin preparation skin wound and general skin cleansing</td> </tr> </tbody> </table> <p>Uses</p> <ul style="list-style-type: none"> surgical hand scrub: significantly reduces the number of microorganisms on the hands and forearms prior to surgery or patient care healthcare personnel handwash: helps reduce bacteria that potentially can cause disease patient preoperative skin preparation: preparation of the patient's skin prior to surgery skin wound and general skin cleansing <p>Warnings</p> <p>For external use only ▶</p>	Active ingredient	Purposes	chlorhexidine gluconate 2% solution	surgical hand scrub healthcare personnel handwash patient preoperative skin preparation skin wound and general skin cleansing
Active ingredient	Purposes				
chlorhexidine gluconate 2% solution	surgical hand scrub healthcare personnel handwash patient preoperative skin preparation skin wound and general skin cleansing				

Leaflet Top

Page 3

Page 4

Page 5

Page 2

Leaflet Inside

<p>Drug Facts (continued)</p> <p>Do not use</p> <ul style="list-style-type: none"> if you are allergic to chlorhexidine gluconate or any other ingredients in contact with meninges in the genital area as a preoperative skin preparation of the head or face <p>When using this product</p> <ul style="list-style-type: none"> keep out of eyes, ears, and mouth. May cause serious and permanent eye injury if placed or kept in the eye during surgical procedures or may cause deafness when instilled in the middle ear through perforated eardrums if solution should contact these areas, rinse out promptly and thoroughly with water wounds which involve more than the superficial layers of the skin should not be routinely treated repeated general skin cleansing of large body areas should not be done except when the underlying condition makes it necessary to reduce the bacterial population of the skin ▶ 	<p>Drug Facts (continued)</p> <p>Warnings</p> <p>Stop use and ask a doctor if irritation, sensitization or allergic reaction occurs. These may be signs of a serious condition.</p> <p>Keep out of reach of children. If swallowed, get medical help or contact a Poison Control Center right away.</p> <p>Directions</p> <p>Surgical hand scrub</p> <ul style="list-style-type: none"> wet hands and forearms under running water for 30 seconds. Clean fingernails using a nailstick or similar cleaner. scrub for 1.5 minutes with about 8 ml of product with or without a wet brush paying close attention to the nails, cuticles, and skin between the fingers rinse thoroughly under running water for 30 seconds wash for an additional 1.5 minutes with 8 ml of product and rinse under running water for 30 seconds dry thoroughly ▶
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Base

NDC 17187-1021-1	
DYNA-HEX 2° (Chlorhexidine Gluconate 2% Solution) <i>Antiseptic</i>	
Contains:	2% Chlorhexidine Gluconate
Manufactured By:	Xitrium Laboratories, Inc. 415 West Pershing Road Chicago, IL 60609
FOR EXTERNAL USE ONLY	
Net Contents:	4 fl oz (118 ml)
Lot Number:	
Exp. Date:	

Laminated Flap

<p>Drug Facts (continued)</p> <p>Other information</p> <ul style="list-style-type: none"> • store at 20-25°C (68-77°F) • avoid excessive heat above 40°C (104°F) <p>Active ingredients citric acid, cocamide DEA, hydroxyethylcellulose, isopropyl alcohol, lauramine oxide, purified water</p> <p>Questions or comments? Call 1-773-268-5800 Monday through Friday 8:00 AM to 4:30 PM</p>	<p style="text-align: right;">Peel here for Drug Facts ▶</p> <p>Drug Facts</p> <p>Active ingredient chlorhexidine gluconate 2% solution</p> <p>Purposes surgical hand scrub healthcare personnel handwash patient preoperative skin preparation skin wound and general skin cleansing</p> <p>Uses</p> <ul style="list-style-type: none"> • surgical hand scrub: significantly reduces the number of microorganisms on the hands and forearms prior to surgery or patient care • healthcare personnel handwash: helps reduce bacteria that potentially can cause disease • patient preoperative skin preparation: preparation of the patient's skin prior to surgery • skin wound and general skin cleansing <p>Warnings</p> <p>For external use only</p> <p>Do not use</p> <ul style="list-style-type: none"> • if you are allergic to chlorhexidine gluconate or any other ingredients • in contact with meninges • in the genital area • as a preoperative skin preparation of the head or face
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Page 5

Page 2

Leaflet Top

Page 3

Page 4

<p>Drug Facts (continued)</p> <p>When using this product</p> <ul style="list-style-type: none"> • keep out of eyes, ears, and mouth. May cause serious and permanent eye injury if placed or kept in the eye during surgical procedures or may cause deafness when instilled in the middle ear through perforated eardrums • if solution should contact these areas, rinse out promptly and thoroughly with water • wounds which involve more than the superficial layers of the skin should not be routinely treated • repeated general skin cleansing of large body areas should not be done except when the underlying condition makes it necessary <p>to reduce the bacterial population of the skin</p> <p>Stop use and ask a doctor if irritation, sensitization or allergic reaction occurs. These may be signs of a serious condition.</p> <p>Keep out of reach of children. If swallowed, get medical help or contact a Poison Control Center right away.</p> <p>Directions</p> <p>Surgical hand scrub:</p> <ul style="list-style-type: none"> • wet hands and forearms under running water for 30 seconds. • Clean fingernails using a nailstick or similar cleaner. 	<p>Drug Facts (continued)</p> <p>Directions</p> <ul style="list-style-type: none"> • scrub for 1.5 minutes with about 8 ml of product with or without a wet brush paying close attention to the nails, cuticles, and skin between the fingers • rinse thoroughly under running water for 30 seconds • wash for an additional 1.5 minutes with 8 ml of product and rinse under running water for 30 seconds • dry thoroughly <p>Healthcare personnel handwash:</p> <ul style="list-style-type: none"> • wet hands with water • dispense about 5 ml of product into cupped hands and wash in a vigorous manner for 15 seconds • rinse and dry thoroughly <p>Patient preoperative skin preparation:</p> <ul style="list-style-type: none"> • apply product liberally to surgical site and swab for at least 2 minutes • dry with a sterile towel • repeat procedure for an additional 2 minutes and dry with a sterile towel <p>Skin wound and general skin cleansing:</p> <ul style="list-style-type: none"> • thoroughly rinse the area to be cleaned with water • apply the minimum amount of product necessary to cover the skin or wound area and wash gently • rinse again thoroughly
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Leaflet Inside

Base

NDC 17187-1021-2

DYNA-HEX 2[®]
(Chlorhexidine Gluconate 2% Solution)
Antiseptic

Contains: 2% Chlorhexidine Gluconate
 Manufactured By: Xitrium Laboratories, Inc.
 415 West Pershing Road
 Chicago, IL 60609

FOR EXTERNAL USE ONLY

Net Contents: 8 fl oz (237 ml)

Lot Number:
Exp. Date:

Laminated Flap



NDA 19-422/S-032

Xttrium Laboratories
Attention: Ram Chakroborty, Ph.D.
Vice President
415 West Pershing Road
Chicago, IL 60609-2731

Dear Dr. Chakroborty:

We acknowledge receipt on August 27, 2003, of your August 22, 2003, resubmission to your supplemental new drug application for Dyna-Hex 2 (2% chlorhexidine gluconate) solution.

We consider this a complete, class 1 response to our August 11, 2003, action letter. Therefore, the primary user fee goal date is October 27, 2003, and the secondary user fee goal date is February 27, 2004.

If you have any question, call Tia Frazier, Regulatory Project Manager, at (301) 827-2271.

Sincerely,

{See appended electronic signature page}

David Hilfiker
Supervisor, Project Management Staff
Division of Over-the-Counter Drug Products
Office of Drug Evaluation V
Center for Drug Evaluation and Research

This is a representation of an electronic record that was signed electronically and
this page is the manifestation of the electronic signature.

/s/

David Hilfiker
10/7/03 02:16:40 PM

ORIGINAL



...INNOVATIONS IN
PRODUCTS AND SYSTEMS

618-032(B2)
NDA SUPPL AMENDMENT

September 3, 2003

Ms. Tia Frazier, Regulatory Project Manager
General Correspondence
Attention: Document Control Room
Food and Drug Administration
Division of OTC Products
Office of Drug Evaluation V
Center for Drug Evaluation and Research
9201 Corporate Boulevard
HFD - 560
Rockville, MD 20850

RECEIVED
SEP 08 2003
MEGA/CDER

Dear Ms. Frazier,

Thank you for the action letter sent on August 11, 2003. In this response, Xttrium Laboratories, Inc. addresses the issues contained in the action letter and demonstrates the correction of all deficiencies in NDA 19-422/S-032. This letter also serves as an amendment to the paper and electronic correspondence sent from Xttrium on August 22, 2003.

Following this letter is the FDA form 356h. A table of contents is included so that all sections of this submission are clearly marked. ***The revised labels have been included as attachments. Please note that each attachment contains 3 pages: an unmarked copy, a call-out copy to indicate font sizes, and a highlighted copy to indicate revisions.*** The included response indicates which attachments to refer to for the appropriate revision. A safety profile has also been included as requested.

Please feel free to contact me at (773) 268-5800 if you have any questions or concerns regarding this matter.

Sincerely,

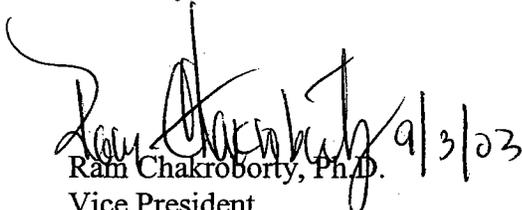

Ram Chakroborty, Ph.D.
Vice President
Xttrium Laboratories, Inc.

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Response of Xttrium Laboratories, Inc. to Action Letter Dated August 11, 2003

In the spirit of cooperation and compliance, Xttrium Laboratories, Inc. has addressed all deficiencies from the action letter dated August 11, 2003. A full copy of the letter can be found in Section 10 of this submission. The concerns that the FDA addresses appear in bold and Xttrium's response appears in regular type.

(4) THE VALUE OF THE INFORMATION ABOUT THE IDENTITY OF THE CLAIMED TRADE SECRET INGREDIENT TO THE PETITIONER AND TO ITS COMPETITORS

You state that ~~—~~% of your business is the manufacture and sale of your chlorhexidine gluconate products and that you produce over ~~—~~ of all such products used in the United States. You add that not only are these products safe and effective, but also gentle to the skin, and that your formulations are widely accepted by health care personnel. You attribute these factors as primary reasons for your success in marketing those products. You contend that disclosure of the inactive ingredients in your products would provide your competitors with confidential information that would allow them to bypass the lengthy and costly research and development process in creating competitive chlorhexidine gluconate products, which you describe as a complex undertaking. You describe a number of these complexities involving inorganic anions, surfactants, alcohol, and pH of the final product to develop a stable and non-irritating product. You conclude that disclosure of the inactive ingredients in your products would have a significant impact on your business.

We note your comments that your product is “gentle to the skin” and “widely accepted by health care personnel.” You attribute these factors as primary reasons for your success in marketing these products and use this argument to support the value to you of nondisclosure of the inactive ingredients in these products.

We also note your correspondence to FDA dated October 8, 2002 and April 9, 2003 stating that, as of those dates, there have been no reports of any adverse effects received at your company regarding 2% chlorhexidine gluconate (NDA 19-422). As you are aware, during the recent FDA inspection of your company, our inspectors found several adverse reaction reports for the chlorhexidine gluconate products marketed under this NDA that were not reported to FDA: complaints [your numbers] 000214 (skin rashes in 4 people) and 990602-A (severe skin reactions in 3 hospital staff members). Our inspectors also found a number of adverse reaction reports for your chlorhexidine gluconate products marketed under other NDAs that were not reported to FDA. These reports cast considerable doubt on the value of the identity of the ingredients you wish to shield. If such ingredients do not in fact mitigate irritation, then the marketing success of the product cannot be attributed to its supposed gentleness to the skin.

Further, the _____ obtained in our inspection _____ and are therefore not adequate to serve as an adverse reaction reporting system. Our inspection also revealed that your company did not have standard operating procedures in place for collecting, evaluating, processing, and submitting adverse event reports to FDA [in violation of 21 CFR 314.80]. It is impossible to determine how many adverse reactions to your product have actually occurred because of your noncompliant system for collecting and evaluating adverse event reports. Without such a system in place, there is no procedure to collect and save all adverse event reports and, therefore, the existence of only a limited number of reports fails to demonstrate the value of your inactive ingredients in alleviating irritation, as you contend.

Xttrium Laboratories, Inc. has noted the observations of the FDA investigators regarding adverse experience reporting during their inspection from May 12, 2003 – June 23, 2003. These observations have been addressed in the reply to the FDA district office in Chicago. Pursuant to this action letter, Xttrium Laboratories, Inc. has revised the labeling for this supplement and is in the process of revising all labeling for all CHG products so that the inactive ingredients are listed according to 21 CFR 201.66.

(6) THE EASE OR DIFFICULTY WITH WHICH THE IDENTITY OF THE INGREDIENT COULD BE PROPERLY ACQUIRED OR DUPLICATED BY OTHERS

You state that you do not believe that it is possible to duplicate formulas without undergoing the same extensive procedures and processes that you undertook to develop your formulas. You contend this would take many years of research and development at great expense to anyone seeking to duplicate your formulas. You conclude by stating that you have undertaken extreme measures to maintain the secrecy of your formulas and it is not possible to acquire them without undertaking extensive research and development procedures.

We have reviewed your product formulation for Exidine (NDA 19-422) and the product formulation for a competing product (NDA 19-258). Both products contain chlorhexidine gluconate. We note that these two products have a number of common active ingredients. See chart below.

Exidine (NDA 19-422)	Cidastat (NDA 19-258)
_____ (hydroxyethylcellulose)	Hydroxyethylcellulose
_____ (lauramine oxide)	Lauramine oxide
_____ (cocamide DEA)	Cocamide DEA
Isopropyl alcohol	Isopropyl alcohol

There is a slight difference in the remaining inactive ingredients present in the products. Your Exidine product contains citric acid, while the Cidastat product contains several other ingredients. The presence of alcohol is listed in each product's labeling. While we cannot disclose the percentage of the inactive ingredients in each product, it appears that others can accomplish qualitative duplication of the Exidine formulation.

Both products were approved at about the same time. Your NDA was approved on December 17, 1985 and the Cidastat NDA was approved on July 22, 1986. Further, the NDA for Cidastat was submitted in April 1984 before the NDA for Exidine was submitted in January 1985. Based on the time that product testing necessarily would have been conducted under an IND, the time that the NDA for each product was submitted, and the requirements with respect to formulation that must be satisfied before an NDA can be filed, at least one other company was able to develop a similar product formulation even before your product was approved for marketing. This could indicate that the inactive ingredients used in both products were easily obtained and logical inactive ingredients to use in these types of product formulation. It might also indicate that it was not necessary to wait until your product was approved for marketing to conduct "reverse engineering" to determine the inactive ingredients present in your product formulations.

We have also looked at the formulation of other approved chlorhexidine gluconate products. Several contain _____ or N,N-diethyl lauramine oxide. Again, this appears to indicate that these ingredients are common inactive ingredients to use in these types of product formulations.

Xttrium Laboratories, Inc. is not contesting your statements regarding this factor at this time. As indicated, Xttrium has revised the draft labeling for this supplement to include the inactive ingredients. These ingredients are also being added to the labels of all other Xttrium CHG products as well.

In addition, you must submit draft labeling revised as follows. Refer to the attached prototype Principle Display Panels (PDPs) for more information.

- 1. Place the established drug name (chlorhexidine gluconate 2% solution) in direct conjunction with the trade name, followed by the pharmacological category (antiseptic).**

Xttrium Laboratories, Inc. has complied with this requirement. The established drug name has been placed in direct conjunction with the trade name and is followed by the pharmacological category for each label. Refer to Attachments 1-6 – Draft labeling, for verification.

- 2. Revise the 16- and 30- ounce and 1-gallon container labels to retain the standard order and required flow of *Drug Facts* information onto multiple panels, as required by 21 CFR 201.66(d)(5). Relocate Net Contents, Lot**

Number and Expiration Date information so as not to interrupt the flow and order of the *Drug Facts* panels.

Xttrium Laboratories, Inc. has complied with this requirement. The Net Contents, Lot Number, and Expiration Date have been relocated so as not to interrupt the flow and order of the *Drug Facts* panels. Refer to Attachments 3, 4, and 6 for verification.

- 3. Revise the PDPs for the 30- and 32-ounce container sizes so that the net contents information is listed only once, and is contained in the lower 30% of the PDP. Refer to 21 CFR 201.62(e) for clarification.**

Xttrium Laboratories, Inc. has complied with this requirement. The net contents information is listed only once and in the lower 30% of the PDP for the 30 and 32-ounce container sizes. Refer to Attachments 4 and 5 for verification.

- 4. Revise the Drug Facts labeling for all container sizes to incorporate barlines that surround information by a box or similar enclosure, as required by CFR 201.66(d)(8).**

Xttrium Laboratories, Inc. has complied with this requirement. All Drug Facts labeling for all container sizes incorporates barlines that surround information by a box. Refer to Attachments 1-6 for verification.

- 5. Revise the 4- and 8-ounce container labels so that their outermost labeling surfaces contain the title, headings, subheadings and information set forth in paragraphs (c)(1) through (c)(8) in 21 CFR 201.66. Adding the phrase "Peel here for Drug Facts" to the outermost surface of your 4 and 8 ounce container labeling would satisfy this requirement. Refer to 21 CFR 201.66(c) for further information.**

Xttrium Laboratories, Inc. has complied with this requirement. The phrase "Peel here for Drug Facts" has been added to the 4 and 8 ounce labels. Refer to Attachments 1 and 2 for verification.

- 6. Revise the laminate panels for the 4- and 8-ounce containers to include the statement "*Drug Facts (continued)*" directly above the header Directions on the next adjacent panel.**

Xttrium Laboratories, Inc. has complied with this requirement. The statement "*Drug Facts (continued)*" has been placed directly above the Directions header on the 4 and 8-ounce labels. Refer to Attachments 1 and 2 for verification.

- 7. Revise the labeling for the 16-, 30-, 32-ounce, and 1-gallon container sizes so that the bulleted statements under *Directions* are vertically aligned, to ensure visual separation and adequate white space between discrete chunks of**

information. Bulleted statements can be only wrapped when using the modified format. See 21 CFR 201.66(d)(10).

Xttrium Laboratories, Inc. has complied with this requirement. All bullets are vertically aligned in the 16, 30, 32-ounce, and 1 gallon sizes. Refer to Attachments 3, 4, 5, and 6 for verification.

- 8. Remove _____ from the 8-ounce container labels currently located after *Active ingredient*; at the end of the bulleted statement patient preoperative skin preparation, under Uses; after Do not use; and, at the end of the first bulleted statement under When using this product.**

Xttrium Laboratories, Inc. has complied with this requirement. The _____ have been removed from the 8-ounce label. Refer to Attachment 2 for verification.

In addition, we encourage the following revisions to your proposed labeling. The following revisions are not required for approval.

- 9. Under *Questions or comments?*, for the 16-ounce container size, revise your labeling to include a telephone number for consumer inquiries. Specify the days of the week and the hours of operation when a person is available to respond to questions.**

Xttrium Laboratories, Inc. has complied with this requirement. The telephone number as well as appropriate hours have been included in the 16-ounce label. Refer to Attachment 3 for verification.

- 10. Revise the labeling for the 4- and 8-ounce containers so that the *Drug Facts* contents fit within the two panels inside the leaflet. Thus, place the first panel (page 2) directly behind the PDP, and the second panel (page 3) flush against the container so that it is immediately visible. The exposed *Drug Facts* panel should include the *Directions, Other information, Inactive ingredient, and Questions?* sections.**

As indicated in a previous e-mail, it is not possible to fulfill this requirement due to the requirement of not going below 6 point type.

- 11. Left justify *Active ingredient* information and right justify the corresponding *Purposes* information so that it runs continuously, one on line for the 4- and 8-ounce container labels.**

Xttrium Laboratories, Inc. has complied with this requirement. The *Active ingredient* phrase has been left justified and the *Purposes* phrase has been right justified so they fit on the same line for the 4 and 8-ounce labels. Refer to Attachments 1 and 2 for verification.

12. Under *Active ingredient*, place the phrase “chlorhexidine gluconate 2% solution” on two separate lines, so that the phrase “chlorhexidine gluconate” lies on the first line, and “2% solution” lies on the second line followed by a succession of dots for the 4- and 8-ounce container labels.

Xttrium Laboratories, Inc. has complied with this requirement. The phrase “chlorhexidine gluconate 2% solution” has been broken up into two lines. Refer to Attachments 1 and 2 for verification.

13. Remove the term “—————” that follows the Warnings and Directions headers for the 4- and 8- ounce container labels, to reduce redundancy and confusion with required “Drug Facts (continued)” headers.

Xttrium Laboratories, Inc. has complied with this requirement. The term “—————” has been removed from Warnings and Directions. Refer to Attachments 1 and 2 for verification.

When you respond to the above deficiencies, include a safety update as described at 21 CFR 314.50(d)(5)(vi)(b). The safety update should include data from all non-clinical and clinical studies of the drug under consideration regardless of indication, dosage form, or dose level.

A safety profile has been submitted for every amendment to this supplement. Numerous NDAs including chlorhexidine gluconate have been approved and have periodic safety data on file. In the safety update for this amendment, Xttrium has included data from a literature search as well as an experience reported directly to Xttrium Laboratories, Inc. Refer to Section 8 – Periodic Safety Update Report.

**APPEARS THIS WAY
ON ORIGINAL**

4 ounce labels
9/3/03 submission

3 page(s) of draft
labeling has been
removed from this
portion of the review.

*Source labels
from 9/3/03 submission*

3 page(s) of draft
labeling has been
removed from this
portion of the review.

NDC 17187-1021-3

DYNA-HEX 2[®]
(Chlorhexidine Gluconate 2% Solution)
Antiseptic

Contains: 2% Chlorhexidine Gluconate
Manufactured By: Xtrium Laboratories, Inc. Chicago, IL 60609
FOR EXTERNAL USE ONLY
Net Contents: 16 fl oz (1 pt) (473 ml)

Lot Number:
Exp. Date:

Drug Facts

Active ingredient

chlorhexidine gluconate 2% solution.

Purposes

.....surgical hand scrub
healthcare personnel handwash
patient preoperative skin preparation
skin wound and general skin cleansing

Uses

- surgical hand scrub; significantly reduces the number of microorganisms on the hands and forearms prior to surgery or patient care
- healthcare personnel handwash; helps reduce bacteria that potentially can cause disease
- patient preoperative skin preparation; preparation of the patient's skin prior to surgery
- skin wound and general skin cleansing

Warnings

For external use only

- Do not use • if you are allergic to chlorhexidine gluconate or any other ingredients
- in contact with meninges • in the genital area • as a preoperative skin preparation of the head or face

When using this product

- keep out of eyes, ears, and mouth. May cause serious and permanent eye injury if placed or kept in the eye during surgical procedures or may cause deafness when instilled in the middle ear through perforated eardrums

Drug Facts (continued)

- if solution should contact these areas, rinse out promptly and thoroughly with water
 - wounds which involve more than the superficial layers of the skin should not be routinely treated
 - repeated general skin cleansing of large body areas should not be done except when the underlying condition makes it necessary to reduce the bacterial population of the skin
- 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

- Surgical hand scrub:** • wet hands and forearms under running water for 30 seconds. Clean fingernails using a nailstick or similar cleaner.
- scrub for 1.5 minutes with about 8 ml of product with or without a wet brush paying close attention to the nails, cuticles, and skin between the fingers
 - rinse thoroughly under running water for 30 seconds
 - wash for an additional 1.5 minutes with 8 ml of product and rinse under running water for 30 seconds
 - dry thoroughly

Healthcare personnel handwash:

- wet hands with water
 - dispense about 5 ml of product into cupped hands and wash in a vigorous manner for 15 seconds
 - rinse and dry thoroughly
- Patient preoperative skin preparation:** • apply product liberally to surgical site and swab for at least 2 minutes

- dry with a sterile towel
 - repeat procedure for an additional 2 minutes and dry with a sterile towel
- Skin wound and general skin cleansing:** • thoroughly rinse the area to be cleaned with water
- apply the minimum amount of product necessary to cover the skin or wound area and wash gently
 - rinse again thoroughly

Other information

• store at 20-25°C (68-77°F) • avoid excessive heat above 40°C (104°F)

Inactive ingredients

citric acid, cocamide DEA, hydroxyethylcellulose, isopropyl alcohol, lauramine oxide, purified water

Questions or comments?

Call 1-773-268-5800 Monday through Friday 8:00 AM to 4:30 PM

NDC 17187-1021-3

DYNA-HEX 2^o
(Chlorhexidine Gluconate 2% Solution)
Antiseptic

Contains: 2% Chlorhexidine Gluconate
Manufactured By: Xenium Laboratories, Inc., Chicago, IL 60609

Lot Number: **FOR EXTERNAL USE ONLY**
Exp. Date: Net Contents: 16 fl oz (1 pt) (473 ml)

Drug Facts

Active ingredient
chlorhexidine gluconate 2% solution

Uses

- surgical hand scrub: significantly reduces the number of microorganisms on the hands and forearms prior to surgery or patient care
- healthcare personnel handwash: helps reduce bacteria that potentially can cause disease
- patient preoperative skin preparation: preparation of the patient's skin prior to surgery
- skin wound and general skin cleansing

Warnings

- Do not use if you are allergic to chlorhexidine gluconate or any other ingredients
- in contact with meninges
- as a preoperative skin preparation of the head or face
- when using this product
- keep out of eyes, ears, and mouth. May cause serious and permanent eye injury if placed or kept in the eye during surgical procedures or may cause deafness when instilled in the middle ear through perforated eardrums

Drug Facts (continued)

- if solution should contact these areas, rinse out promptly and thoroughly with water
 - wounds which involve more than the superficial layers of the skin should not be routinely treated
 - repeated general skin cleansing of large body areas should not be done except when the underlying condition makes it necessary to reduce the bacterial population of the skin
- Stop use and ask a doctor if irritation, sensitization or allergic reaction occurs. These may be signs of a serious condition.**

Directions

Surgical hand scrub: • wet hands and forearms under running water for 30 seconds. Clean fingernails using a nailstick or similar cleaner.

scrub for 1.5 minutes with about 8 ml of product with or without a wet brush paying close attention to the nails, cuticles, and skin between the fingers

rinse thoroughly under running water for 30 seconds

wash for an additional 1.5 minutes with 8 ml of product and rinse under running water for 30 seconds

dry thoroughly

Healthcare personnel handwash:

- wet hands with water
 - dispense about 5 ml of product into cupped hands and wash in a vigorous manner for 15 seconds
 - rinse and dry thoroughly
- Patient preoperative skin preparation:** • apply product liberally to surgical site and swab for at least 2 minutes

dry with a sterile towel • repeat procedure for an additional 2 minutes and dry with a sterile towel

Skin wound and general skin cleansing: • thoroughly rinse the area to be cleaned with water

- apply the minimum amount of product necessary to cover the skin or wound area and wash gently
- rinse again thoroughly

Other information

- store at 20-25°C (68-77°F)
- avoid excessive heat above 40°C (104°F)

Inactive ingredients citric acid, cocamide DEA, hydroxyethylcellulose, isopropyl alcohol, lauramine oxide, purified water

Questions or comments? Call 1-773-268-5800 Monday through Friday 8:00 AM to 4:30 PM

NDC 17187-1021-3

DYNA-HEX 2°

(Chlorhexidine Gluconate 2% Solution)
Antiseptic

Contains:
2% Chlorhexidine Gluconate
Manufactured By:
Xcrinum Laboratories, Inc. Chicago, IL 60609

FOR EXTERNAL USE ONLY

Net Contents: 16 fl oz (1 pt) (473 ml)

Lot Number:
Exp. Date:

Drug Facts

Active Ingredient

chlorhexidine gluconate 2% solution

Purposes

..... surgical hand scrub
healthcare personnel handwash
patient preoperative skin preparation
skin wound and general skin cleansing

Uses

- surgical hand scrub: significantly reduces the number of microorganisms on the hands and forearms prior to surgery or patient care
- healthcare personnel handwash: helps reduce bacteria that potentially can cause disease
- patient preoperative skin preparation: preparation of the patient's skin prior to surgery
- skin wound and general skin cleansing

Warnings

For external use only
Do not use
• if you are allergic to chlorhexidine gluconate or any other ingredients
• in contact with menses
• in the genital area
• as a preoperative skin preparation of the head or face

When using this product

- keep out of eyes, ears, and mouth. May cause serious and permanent eye injury if placed or kept in the eye during surgical procedures or may cause deafness when instilled in the middle ear through perforated eardrums

Drug Facts (continued)

- if solution should contact these areas, rinse out promptly and thoroughly with water
- wounds which involve more than the superficial layers of the skin should not be routinely treated
- repeated general skin cleansing of large body areas should not be done except when the underlying condition makes it necessary to reduce the bacterial population of the skin
- 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

- Surgical hand scrub:**
- wet hands and forearms under running water for 30 seconds. Clean fingernails using a nailstick or similar cleaner.
 - scrub for 1.5 minutes with about 8 ml of product with or without a wet brush paying close attention to the nails, cuticles, and skin between the fingers
 - rinse thoroughly under running water for 30 seconds
 - wash for an additional 1.5 minutes with 8 ml of product and rinse under running water for 30 seconds
 - dry thoroughly

Healthcare personnel handwash:

- wet hands with water
- dispense about 5 ml of product into cupped hands and wash in a vigorous manner for 15 seconds
- rinse and dry thoroughly

Patient preoperative skin preparation:

- apply product liberally to surgical site and swab for at least 2 minutes
 - dry with a sterile towel
 - repeat procedure for an additional 2 minutes and dry with a sterile towel
- Skin wound and general skin cleansing:**
- thoroughly rinse the area to be cleaned with water
 - apply the minimum amount of product necessary to cover the skin or wound area and wash gently
 - rinse again thoroughly

Other information

• store at 20-25°C (68-77°F) • avoid excessive heat above 40°C (104°F)
oxides, Purified water

Inactive Ingredients citric acid, cocamide DEA, hydroxyethylcellulose, isopropyl alcohol, leauramine

Questions or comments? Call 1-773-268-5800 Monday through Friday 8:00 AM to 4:30 PM

NDC 0116-4242-30

DYNA-HEX 2[®]

(Chlorhexidine Gluconate 2% Solution)
Antiseptic

Contains:
Manufactured By:

2% Chlorhexidine Gluconate
Xtrium Laboratories, Inc.
415 West Pershing Road
Chicago, IL 60609
Tel: 773-268-5800

FOR EXTERNAL USE ONLY

Lot Number:
Exp. Date:

Net Contents: 30 fl oz (887 ml)

Drug Facts

Active ingredient

chlorhexidine gluconate 2% solution

Purposes

surgical hand scrub
healthcare personnel handwash
patient preoperative skin preparation
skin wound and general skin cleansing

Uses

- surgical hand scrub: significantly reduces the number of microorganisms on the hands and forearms prior to surgery or patient care
- healthcare personnel handwash: helps reduce bacteria that potentially can cause disease
- patient preoperative skin preparation: preparation of the patient's skin prior to surgery
- skin wound and general skin cleansing

Drug Facts (continued)

Warnings

For external use only

- Do not use • if you are allergic to chlorhexidine gluconate or any other ingredients • in contact with meninges • in the genital area
• as a preoperative skin preparation of the head or face

When using this product

- keep out of eyes, ears, and mouth. May cause serious and permanent eye injury if placed or kept in the eye during surgical procedures or may cause deafness when instilled in the middle ear through perforated eardrums
 - if solution should contact these areas, rinse out promptly and thoroughly with water
 - wounds which involve more than the superficial layers of the skin should not be routinely treated
 - repeated general skin cleansing of large body areas should not be done except when underlying condition makes it necessary to reduce the bacterial population of the skin
- 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

- Surgical hand scrub:** • wet hands and forearms under running water for 30 seconds. Clean fingernails using a nailstick or similar cleaner.
• scrub for 1.5 minutes with about 8 ml of product with or without a wet brush paying close attention to the nails, cuticles, and skin between the fingers
• rinse thoroughly under running water for 30 seconds
• wash for an additional 1.5 minutes with 8 ml of product and rinse under running water for 30 seconds
• rinse and dry thoroughly
- Healthcare personnel handwash:** • wet hands with water
• dispense about 5 ml of product into cupped hands and wash in a vigorous manner for 15 seconds
• dry thoroughly
- Patient preoperative skin preparation:** • apply product liberally to surgical site and swab for at least 2 minutes
• dry with a sterile towel
• repeat procedure for an additional 2 minutes and dry with a sterile towel
- Skin wound and general skin cleansing:** • thoroughly rinse the area to be cleaned with water
• apply the minimum amount of product necessary to cover the skin or wound area and wash gently
• rinse again thoroughly

Other information • store at 20-25°C (68-77°F) • avoid excessive heat above 40°C (104°F)

Inactive ingredients citric acid, cocamide DEA, hydroxyethylcellulose, isopropyl alcohol, lauramine oxide, purified water

Questions or comments? Call 1-773-268-5800 Monday through Friday 8:00 AM to 4:30 PM

NDC 0116-4242-30

DYNA-HEX 2[®]

(Chlorhexidine Gluconate 2% Solution)
Antiseptic

Contains:
Manufactured By:

2% Chlorhexidine Gluconate
Xttrium Laboratories, Inc.
415 West Pershing Road
Chicago, IL 60609
Tel: 773-268-5800

FOR EXTERNAL USE ONLY

Lot Number:
Exp. Date:

Net Contents: 30 fl oz (887 ml)

Drug Facts

Active ingredient

chlorhexidine gluconate 2% solution

Purposes

surgical hand scrub
healthcare personnel handwash
patient preoperative skin preparation
skin wound and general skin cleansing

Uses

- **surgical hand scrub:** significantly reduces the number of microorganisms on the hands and forearms prior to surgery or patient care
- **healthcare personnel handwash:** helps reduce bacteria that potentially can cause disease
- **patient preoperative skin preparation:** preparation of the patient's skin prior to surgery
- **skin wound and general skin cleansing**

Drug Facts (continued)

Warnings

For external use only

- Do not use**
- if you are allergic to chlorhexidine gluconate or any other ingredients
 - in contact with meninges
 - in the genital area
 - as a preoperative skin preparation of the head or face

When using this product

- keep out of eyes, ears, and mouth. May cause serious and permanent eye injury if placed or kept in the eye during surgical procedures or may cause deafness when instilled in the middle ear through perforated eardrums
- if solution should contact these areas, rinse out promptly and thoroughly with water
- wounds which involve more than the superficial layers of the skin should not be routinely treated
- repeated general skin cleansing of large body areas should not be done except when underlying condition makes it necessary to reduce the bacterial population of the skin

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

- Surgical hand scrub:**
- wet hands and forearms under running water for 30 seconds. Clean fingernails using a nailstick or similar cleaner.
 - scrub for 1.5 minutes with about 8 ml of product with or without a wet brush paying close attention to the nails, cuticles, and skin between the fingers
 - rinse thoroughly under running water for 30 seconds
 - wash for an additional 1.5 minutes with 8 ml of product and rinse under running water for 30 seconds
 - rinse and dry thoroughly
- Healthcare personnel handwash:**
- wet hands with water
 - dispense about 5 ml of product into cupped hands and wash in a vigorous manner for 15 seconds
 - dry thoroughly
- Patient preoperative skin preparation:**
- apply product liberally to surgical site and swab for at least 2 minutes
 - dry with a sterile towel
 - repeat procedure for an additional 2 minutes and dry with a sterile towel
- Skin wound and general skin cleansing:**
- thoroughly rinse the area to be cleaned with water
 - apply the minimum amount of product necessary to cover the skin or wound area and wash gently
 - rinse again thoroughly

Other information

- store at 20-25°C (68-77°F)
- avoid excessive heat above 40°C (104°F)

Inactive ingredients citric acid, cocamide DEA, hydroxyethylcellulose, isopropyl alcohol, lauramine oxide, purified water

Questions or comments? Call 1-773-268-5800 Monday through Friday 8:00 AM to 4:30 PM

NDC 0116-4242-30

DYNA-HEX 2[®]

(Chlorhexidine Gluconate 2% Solution)
Antiseptic

Contains: 2% Chlorhexidine Gluconate
Manufactured By: Xtrem Laboratories, Inc.
415 West Pershing Road
Chicago, IL 60609
Tel: 773-268-5800

FOR EXTERNAL USE ONLY

Lot Number:
Exp. Date:

Net Contents: 30 fl oz (887 ml)

Drug Facts	Purposes
Active ingredient chlorhexidine gluconate 2% solution	surgical hand scrub healthcare personnel handwash patient preoperative skin preparation skin wound and general skin cleansing
Uses	
<ul style="list-style-type: none"> surgical hand scrub: significantly reduces the number of microorganisms on the hands and forearms prior to surgery or patient care healthcare personnel handwash: helps reduce bacteria that potentially can cause disease patient preoperative skin preparation: preparation of the patient's skin prior to surgery skin wound and general skin cleansing 	

Drug Facts (continued)
Warnings
For external use only
Do not use
<ul style="list-style-type: none"> if you are allergic to chlorhexidine gluconate or any other ingredients in contact with meninges in the genital area as a preoperative skin preparation of the head or face
When using this product
<ul style="list-style-type: none"> keep out of eyes, ears, and mouth. May cause serious and permanent eye injury if placed or kept in the eye during surgical procedures or may cause deafness when instilled in the middle ear through perforated eardrums if solution should contact these areas, rinse out promptly and thoroughly with water wounds which involve more than the superficial layers of the skin should not be routinely treated repeated general skin cleansing of large body areas should not be done except when underlying condition makes it necessary to reduce the bacterial population of the skin
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
Surgical hand scrub:
<ul style="list-style-type: none"> wet hands and forearms under running water for 30 seconds. Clean fingernails using a nailstick or similar cleaner. scrub for 1.5 minutes with about 8 ml of product with or without a wet brush paying close attention to the nails, cuticles, and skin between the fingers rinse thoroughly under running water for 30 seconds wash for an additional 1.5 minutes with 8 ml of product and rinse under running water for 30 seconds rinse and dry thoroughly
Healthcare personnel handwash:
<ul style="list-style-type: none"> wet hands with water dispense about 5 ml of product into cupped hands and wash in a vigorous manner for 15 seconds dry thoroughly
Patient preoperative skin preparation:
<ul style="list-style-type: none"> apply product liberally to surgical site and swab for at least 2 minutes dry with a sterile towel repeat procedure for an additional 2 minutes and dry with a sterile towel
Skin wound and general skin cleansing:
<ul style="list-style-type: none"> thoroughly rinse the area to be cleaned with water apply the minimum amount of product necessary to cover the skin or wound area and wash gently rinse again thoroughly
Other information
<ul style="list-style-type: none"> store at 20-25°C (68-77°F) avoid excessive heat above 40°C (104°F)
Inactive ingredients
citric acid, cocamide DEA, hydroxyethylcellulose, isopropyl alcohol, lauramine oxide, purified water
Questions or comments? Call 1-773-268-5800 Monday through Friday 8:00 AM to 4:30 PM

NDC 17187-1021-4

DYNA-HEX 2[®]

(Chlorhexidine Gluconate 2% Solution)
Antiseptic

Contains: 2% Chlorhexidine Gluconate
Manufactured By: Xtrium Laboratories, Inc.
415 West Pershing Road
Chicago, IL 60609
Tel: 773-268-5800

FOR EXTERNAL USE ONLY

Lot Number: Net Contents: 32 fl oz (1 qt) (946 ml)
Exp. Date:

Drug Facts
Active Ingredient
chlorhexidine gluconate 2% solution surgical hand scrub
healthcare personnel handwash
patient preoperative skin preparation
skin wound and general skin cleansing

Drug Facts (continued)

Uses

- surgical hand scrub: significantly reduces the number of microorganisms on the hands and forearms prior to surgery or patient care
- healthcare personnel handwash: helps reduce bacteria that potentially can cause disease
- patient preoperative skin preparation: preparation of the patient's skin prior to surgery
- skin wound and general skin cleansing

Warnings

For external use only

- Do not use • if you are allergic to chlorhexidine gluconate or any other ingredients • in contact with meninges • in the genital area
- as a preoperative skin preparation of the head or face

When using this product

- keep out of eyes, ears, and mouth. May cause serious and permanent eye injury if placed or kept in the eye during surgical procedures or may cause deafness when instilled in the middle ear through perforated eardrums
- if solution should contact these areas, rinse out promptly and thoroughly with water
- wounds which involve more than the superficial layers of the skin should not be routinely treated
- repeated general skin cleansing of large body areas should not be done except when underlying condition makes it necessary to reduce the bacterial population of the skin

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

- **Surgical hand scrub:** • wet hands and forearms under running water for 30 seconds. Clean fingernails using a nailstick or similar cleaner.
- scrub for 1.5 minutes with about 8 ml of product with or without a wet brush paying close attention to the nails, cuticles, and skin between the fingers
- rinse thoroughly under running water for 30 seconds

- wash for an additional 1.5 minutes with 8 ml of product and rinse under running water for 30 seconds
- rinse and dry thoroughly

- **Healthcare personnel handwash:** • wet hands with water
- dispense about 5 ml of product into cupped hands and wash in a vigorous manner for 15 seconds

- dry thoroughly

Patient preoperative skin preparation: • apply product liberally to surgical site and swab for at least 2 minutes

- dry with a sterile towel
- repeat procedure for an additional 2 minutes and dry with a sterile towel

Skin wound and general skin cleansing: • thoroughly rinse the area to be cleaned with water

- apply the minimum amount of product necessary to cover the skin or wound area and wash gently
- rinse again thoroughly

Other information • store at 20-25°C (68-77°F) • avoid excessive heat above 40°C (104°F)

Inactive ingredients citric acid, cocamide DEA, hydroxyethylcellulose, isopropyl alcohol, lauramine oxide, purified water

Questions or comments? Call 1-773-268-5800 Monday through Friday 8:00 AM to 4:30 PM

NDC 17187-1021-4

DYNA-HEX 2[®]

(Chlorhexidine Gluconate 2% Solution)

Antiseptic

Contains: 2% Chlorhexidine Gluconate

Manufactured By: Xtrium Laboratories, Inc.

415 West Pershing Road

Chicago, IL 60609

Tel: 773-268-5800

FOR EXTERNAL USE ONLY

Lot Number: Net Contents: 32 fl oz (1 qt) (946 ml)

Exp. Date:

Drug Facts

Active Ingredient chlorhexidine gluconate 2% solution

Purposes healthcare personnel hand scrub patient preoperative skin preparation skin wound and general skin cleansing

Read Back Panel, Top - Avoid Respirator Use

Drug Facts (continued)

Uses

- surgical hand scrub: significantly reduces the number of microorganisms on the hands and forearms prior to surgery or patient care
- healthcare personnel handwash: helps reduce bacteria that potentially can cause disease
- patient preoperative skin preparation: preparation of the patient's skin prior to surgery
- skin wound and general skin cleansing

Warnings

For external use only

- Do not use if you are allergic to chlorhexidine gluconate or any other ingredients
- as a preoperative skin preparation of the head or face
- in contact with meninges
- in the genital area

When using this product

- keep out of eyes, ears, and mouth. May cause serious and permanent eye injury if placed or kept in the eye during surgical procedures or may cause deafness when instilled in the middle ear through perforated eardrums
 - if solution should contact these areas, rinse out promptly and thoroughly with water
 - wounds which involve more than the superficial layers of the skin should not be routinely treated
 - repeated general skin cleansing of large body areas should not be done except when underlying condition makes it necessary to reduce the bacterial population of the skin
- 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

- Surgical hand scrub:**
 - wet hands and forearms under running water for 30 seconds. Clean fingernails using a nailstick or similar cleaner.
 - scrub for 1.5 minutes with about 8 ml of product with or without a wet brush paying close attention to the nails, cuticles, and skin between the fingers
 - rinse thoroughly under running water for 30 seconds
- Healthcare personnel handwash:**
 - wash for an additional 1.5 minutes with 8 ml of product and rinse under running water for 30 seconds
 - rinse and dry thoroughly
- Healthcare personnel handwash:**
 - wet hands with water
 - dispense about 5 ml of product into cupped hands and wash in a vigorous manner for 15 seconds
 - dry thoroughly

Patient preoperative skin preparation: apply product liberally to surgical site and swab for at least 2 minutes

- dry with a sterile towel
- repeat procedure for an additional 2 minutes and dry with a sterile towel

Skin wound and general skin cleansing: thoroughly rinse the area to be cleaned with water

- apply the minimum amount of product necessary to cover the skin or wound area and wash gently
- rinse again thoroughly

Other Information store at 20-25°C (68-77°F) • avoid excessive heat above 40°C (104°F)

Inactive Ingredients citric acid, cocamide DEA, hydroxyethylcellulose, isopropyl alcohol, lauramine oxide, purified water

Questions or comments? Call 1-773-268-5800 Monday through Friday 8:00 AM to 4:30 PM

Read Back Panel, Top

Chlorhexidine Gluconate 2% Solution

Antiseptic

Read Back Panel, Top

Contains: 2% Chlorhexidine Gluconate

Manufactured By: Xtrium Laboratories, Inc.

415 West Pershing Road

Chicago, IL 60609

Tel: 773-268-5800

FOR EXTERNAL USE ONLY

Lot Number: Net Contents: 32 fl oz (1 qt) (946 ml)

Exp. Date:

Drug Facts

Active Ingredient chlorhexidine gluconate 2% solution

Purposes healthcare personnel hand scrub patient preoperative skin preparation skin wound and general skin cleansing

NDC 17187-1021-4

DYNA-HEX2[®]

(Chlorhexidine Gluconate 2% Solution)
Antiseptic

Contains:
2% Chlorhexidine Gluconate
Manufactured By:
Xtrium Laboratories, Inc.
415 West Pershing Road
Chicago, IL 60609
Tel: 773-268-5800

FOR EXTERNAL USE ONLY

Lot Number:
Exp. Date:
Net Contents: 32 fl oz (1 qt) (946 ml)

Drug Facts
Active ingredient
chlorhexidine gluconate 2% solution.....
Purposes
healthcare personnel hand scrub
patient preoperative skin preparation
skin wound and general skin cleansing

Drug Facts (continued)

Uses

- surgical hand scrub: significantly reduces the number of microorganisms on the hands and forearms prior to surgery or patient care
- healthcare personnel handwash: helps reduce bacteria that potentially can cause disease
- patient preoperative skin preparation: preparation of the patient's skin prior to surgery
- skin wound and general skin cleansing

Warnings

For external use only

- Do not use
- as a preoperative skin preparation of the head or face
- if you are allergic to chlorhexidine gluconate or any other ingredients
- in contact with meninges
- in the genital area

When using this product

- keep out of eyes, ears, and mouth. May cause serious and permanent eye injury if placed or kept in the eye during surgical procedures or may cause deafness when instilled in the middle ear through perforated eardrums
 - if solution should contact these areas, rinse out promptly and thoroughly with water
 - wounds which involve more than the superficial layers of the skin should not be routinely treated
 - repeated general skin cleansing of large body areas should not be done except when underlying condition makes it necessary to reduce the bacterial population of the skin
- 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

- Surgical hand scrub:**
 - wet hands and forearms under running water for 30 seconds. Clean fingernails using a nailstick or similar cleaner.
 - scrub for 1.5 minutes with about 8 ml of product with or without a wet brush paying close attention to the nails, cuticles, and skin between the fingers
 - rinse thoroughly under running water for 30 seconds
 - wash for an additional 1.5 minutes with 8 ml of product and rinse under running water for 30 seconds
 - rinse and dry thoroughly
- Healthcare personnel handwash:**
 - wet hands with water
 - dispense about 5 ml of product into cupped hands and wash in a vigorous manner for 15 seconds
 - dry thoroughly

Patient preoperative skin preparation: • apply product liberally to surgical site and swab for at least 2 minutes

• dry with a sterile towel

• repeat procedure for an additional 2 minutes and dry with a sterile towel

Skin wound and general skin cleansing: • thoroughly rinse the area to be cleaned with water

• apply the minimum amount of product necessary to cover the skin or wound area and wash gently

• rinse again thoroughly

Other information • store at 20-25°C (68-77°F) • avoid excessive heat above 40°C (104°F)

Inactive ingredients citric acid, cocamide DEA, hydroxyethylcellulose, isopropyl alcohol, lauramine oxide, purified water

Questions or comments? Call 1-773-268-5800 Monday through Friday 8:00 AM to 4:30 PM

NDC 17187-1021-5

DYNA-HEX 2^o

(Chlorhexidine Gluconate 2% Solution)
Antiseptic

Contains: 2% Chlorhexidine Gluconate
Manufactured By: Xcrium Laboratories, Inc. Chicago, IL 60609

FOR EXTERNAL USE ONLY

Net Contents: 128 fl oz (1 gal) (3.785 l)

Lot Number:
Exp. Date:

Drug Facts

Active ingredient

chlorhexidine gluconate 2% solution..... surgical hand scrub
healthcare personnel handwash
patient preoperative skin preparation
skin wound and general skin cleansing

Uses

- surgical hand scrub: significantly reduces the number of microorganisms on the hands and forearms prior to surgery or patient care
- healthcare personnel handwash: helps reduce bacteria that potentially can cause disease
- patient preoperative skin preparation: preparation of the patient's skin prior to surgery
- skin wound and general skin cleansing

Warnings

For external use only

- Do not use
 - if you are allergic to chlorhexidine gluconate or any other ingredients
 - in contact with meninges
 - in the genital area
 - as a preoperative skin preparation of the head or face

When using this product

- keep out of eyes, ears, and mouth. May cause serious and permanent eye injury if placed or kept in the eye during surgical procedures or may cause deafness when instilled in the middle ear through perforated eardrums

Drug Facts (continued)

- if solution should contact these areas, rinse out promptly and thoroughly with water
 - wounds which involve more than the superficial layers of the skin should not be routinely treated
 - repeated general skin cleansing of large body areas should not be done except when the underlying condition makes it necessary to reduce the bacterial population of the skin
- 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

- Surgical hand scrub:**
- wet hands and forearms under running water for 30 seconds. Clean fingernails using a nailstick or similar cleaner.
 - scrub for 1.5 minutes with about 8 ml of product with or without a wet brush paying close attention to the nails, cuticles, and skin between the fingers
 - rinse thoroughly under running water for 30 seconds
 - wash for an additional 1.5 minutes with 8 ml of product and rinse under running water for 30 seconds
 - dry thoroughly

- Healthcare personnel handwash:**
- wet hands with water
 - dispense about 5 ml of product into cupped hands and wash in a vigorous manner for 15 seconds
 - rinse and dry thoroughly

- Patient preoperative skin preparation:**
- apply product liberally to surgical site and swab for at least 2 minutes
 - dry with a sterile towel

- Skin wound and general skin cleansing:**
- thoroughly rinse the area to be cleaned with water
 - apply the minimum amount of product necessary to cover the skin or wound area and wash gently
 - rinse again thoroughly

Other information

- store at 20-25°C (68-77°F)
- avoid excessive heat above 40°C (104°F)

Inactive ingredients citric acid, cocamide DEA, hydroxyethylcellulose, isopropyl alcohol, lauramine oxide, purified water

Questions or comments? Call 1-773-268-5600 Monday through Friday 8:00 AM to 4:30 PM

NDC 17187-1021-5

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Warnings
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Do not use if you are allergic to chlorhexidine gluconate or any other ingredients
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• as a preoperative skin preparation of the head or face

When using this product
• keep out of eyes, ears, and mouth. May cause serious and permanent eye injury if placed or kept in the eye during surgical procedures or may cause deafness when instilled in the middle ear through perforated eardrums

Drug Facts (continued)

• if solution should contact these areas, rinse out promptly and thoroughly with water
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chlorhexidine gluconate 2% solution.

Purposes

healthcare personnel handwash
patient preoperative skin preparation
skin wound and general skin cleansing

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Questions or comments? Call 1-773-268-5600 Monday through Friday 8:00 AM to 4:30 PM

Periodic Safety Update Report for NDA 19-422

Chlorhexidine gluconate has repeatedly been proven effective in reducing bacteria. Most hospitals use chlorhexidine gluconate as a surgical scrub, patient preoperative skin preparation, and/ or healthcare personnel handwash. Chlorhexidine gluconate has also proved to be effective as an oral rinse. Several recent articles have reinforced these claims. After the incidences of anthrax in October and November of 2001, researchers sought to test the efficacy of chlorhexidine gluconate against the anthrax bacteria. A surrogate of the anthrax bacteria was used. Use of 2% chlorhexidine gluconate solution reduced spore contamination as compared to ethyl alcohol.¹ In addition, further investigation is also warranted after initial testing demonstrating that chlorhexidine is effective against agents causing fungal keratitis.² Chlorhexidine gluconate has also been tested against agents that cause sexually transmitted disease. Further studies are still needed, but initial results show promising results.³ Chlorhexidine gluconate has also been studied after root canal. Concentrations of 2% and 0.2% have been used. According to researchers, "chlorhexidine gluconate resulted in the greatest percentage reduction of microbial flora."⁴ Chlorhexidine gluconate has also been shown to reduce incidences of infections related to catheters.⁵ In addition, the FDA has approved numerous NDAs and ANDAs with chlorhexidine gluconate as the active ingredient.

Review of recent literature has found that most adverse reactions to chlorhexidine gluconate have been relatively mild. When chlorhexidine gluconate was used as an oral rinse, adverse reactions were relatively mild in nature and short-lived⁶. There were also instances of adverse reactions when chlorhexidine gluconate was used as a healthcare personnel handwash as most Xttrium CHG products are. In these instances, chlorhexidine gluconate was shown to produce some dryness while being more effective than alcohol.⁷ Other instances of adverse reactions when using as a handwash occurred in health care workers who were older, theoretically because their skin is less pliable. In addition, in these cases, damage is long term and may not be treated easily.⁸ In one instance, a patient developed acute urticaria after showering with chlorhexidine gluconate. However, after treatment with steroids, the problem was resolved in 6 hours.⁹ There were instances, however, of anaphylactic shock. These instances mostly occurred in Japan and Denmark where use of chlorhexidine gluconate in catheters is more prevalent.^{10 11 12 13 14 15}

Since the last amendment for supplement 32 for this NDA on February 10, 2003, there has been only one reported adverse reaction to this product. A surgical technician experienced redness from fingertips to elbows after using this product for a period of three weeks. A complaint was made to the distributor of the product. The distributor then forwarded the complaint to Xttrium Laboratories, Inc. The health care practitioner of the complainant (with prior permission from that complainant) released a statement that chlorhexidine was most likely not the cause of the reaction. All test results demonstrated that the product fell within finished product specifications. A 15-day report was filed with the FDA as per 21 CFR 314.80. In addition, according to Xttrium standard operating procedures, a full investigation was conducted. A copy of the 15-day report is found as Attachment 7.

-
- ¹¹ Weber DJ, Sickbert-Bennett E, Gergen MF, and Rutala WA. Efficacy of Selected Hand Hygiene Agents Used to Remove *Bacillus atrophaeus* (a Surrigate of *Bacillus anthracis*) From Contaminated Hands. *JAMA*. 2003; 289: 1274-1277.
- ² Rahman MR, Johnson GJ, Husain R, Howlader SA, and Minassian DC. Randomised trial of 0.2% chlorhexidine gluconate and 2.5% natamycin for fungal keratitis in Bangladesh. *British Journal of Ophthalmology*. 1998; 82: 919-925.
- ³ Lampe MF, Ballweber LM, and Stamm WE. Susceptibility of *Chlamydia trachomatis* to Chlorhexidine Gluconate Gel. *Antimicrobial Agents and Chemotherapy*. 1998; 42; 1726-1730.
- ⁴ Lekshmy DS and Kamath PM. Antimicrobial efficacy of 0,2 and 2 percent chlorhexidine and sodium hypochlorite as root-canal irrigants: an in-vivo study. *Endodontology*. 2001; 13(2); 57-62.
- ⁵ Chaiyakunapruk N, Veenstra DL, Lipsky BA et al. Chlorhexidine compared with povidone-iodine solution for vascular catheter-site care; a meta-analysis. *Annals of Internal Medicine*. 2002; 136; 792-801.
- ⁶ Soskolne WA, Proskin HM, Stabholz A. Probing depth changes following 2 years of periodontal maintenance therapy including adjunctive controlled release of chlorhexidine. *Journal of Periodontology*, 2003; 74; 420-427.
- ⁷ Kovach TL. Maintaining Intact Skin During Handwashing: The First Line of Defense Against the Chain of Septic Flow. www.infectioncontroltoday.com/articles/151feat1.html
- ⁸ Cimiotti JP, Marmur ES, Nesin M, Hamlin-Cook P, Larson EL. Adverse Reaction Associated With An Alcohol-Based Hand Antiseptic. *Journal of Infection Control*, 2003; 31; 43-48.
- ⁹ Beitia JM, Moreno A, Minguez G, DelaParte B, Rubio y M. De Barrio. Acute urticaria due to chlorhexidine. *Alergol Immunol Clin*. 2001; 16; 351-354.
- ¹⁰ Chisolm DG, Calder I, Peterson D, and Powell M. Intranasal chlorhexidine resulting in anaphylactic circulatory arrest. *BMJ*. 1997; 315; 785.
- ¹¹ Garvey LH, Roed-Petersen J, and Husum, B. Is there a risk of sensitization and allergy to chlorhexidine in health care workers? *Acta Anaesthesiologica Scandinavica*. 2003. 47; 720.
- ¹² Kesler, LG. FDA Alert: Hypersensitivity Reactions to Central Venous Catheters. *American Society of Anesthesiologists*. 1998; 62.
- ¹³ Powers, RJ. Skin Disinfection in the Neonate. Children's Hospital Oakland.
- ¹⁴ Barrett, SP. HIS: Chlorhexidine (Prof. Haxhe). www.his.org.uk/archive/msg03715.html.
- ¹⁵ Wicki J, Deluze C, Cirafici L, Desmeules, J. Anaphylactic shock induced by intraurethral use of chlorhexidine. *Allergy*. 1999, 54, 765-770.

APPEARS THIS WAY
ON ORIGINAL



...INNOVATIONS IN
PRODUCTS AND SYSTEMS

August 18, 2003

Central Document Room
12229 Wilkins Ave.
Rockville, MD 20852

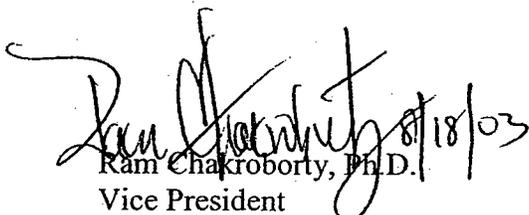
To whom it may concern,

Enclosed is a MedWatch FDA Form 3500A. This report is compiled and completed as per 21 CFR 314.80.

There was one report of redness resulting from use of 2% Chlorhexidine Gluconate NDA 19-422. The lot number in question is 210-1022-70. The report was received at Xttrium Laboratories, Inc. on August 13, 2003. The retained samples have been analyzed. All chemical testing results demonstrated that the product fell within finished product specifications. In addition, testing by the complainant's health care practitioners has concluded that she is not allergic to chlorhexidine. A statement to this effect has been attached.

A copy of this report will be included in the Periodic Adverse Experience Submission to be submitted after December 17, 2003. Please feel free to contact me at (773) 268-5800 or via e-mail at rchakroborty@xttrium.com if you have any questions or concerns regarding this matter.

Sincerely,


Ram Chakroborty, Ph.D.
Vice President
Xttrium Laboratories, Inc.

MEDWATCH

• FDA Safety Information and
• Diverse Event Reporting Program

For use by user-facilities,
distributors and manufacturers for
MANDATORY reporting

Page 1 of 2

Mir report #
UF/Diet report #
FDA Use Only

A. Patient information

1. Patient Identifier _____	2. Age at time of event: or _____ Date of birth: _____	3. Sex <input checked="" type="checkbox"/> female <input type="checkbox"/> male	4. Weight N/A lbs or _____ kgs
--------------------------------	--	---	---

B. Adverse event or product problem

1. Adverse event and/or Product problem (e.g., defects/malfunctions)

2. Outcomes attributed to adverse event (check all that apply)

<input type="checkbox"/> death (mo/day/yr)	<input type="checkbox"/> disability
<input type="checkbox"/> life-threatening	<input type="checkbox"/> congenital anomaly
<input type="checkbox"/> hospitalization - initial or prolonged	<input type="checkbox"/> required intervention to prevent permanent impairment/damage
	<input checked="" type="checkbox"/> other: <u>REDNESS</u>

3. Date of event (mo/day/yr) <u>12/2002</u>	4. Date of this report (mo/day/yr) <u>08/18/03</u>
--	---

5. Describe event or problem:
A HOSPITAL EMPLOYEE EXPERIENCED REDNESS FROM FINGER TIPS TO ELBOWS OVER A PERIOD OF TWO TO THREE WEEKS. WHEN THIS WAS REPORTED TO HER EMPLOYEE SUPERVISOR IN MID JANUARY SHE WAS SENT FOR PATCH TESTING. THE PATCH TESTING SHOWED A REACTION TO THE FOAM SCRUB. PATCH TESTING TO CHLORHEXIDINE WAS NEGATIVE. THIS COMPLAINT WAS RECEIVED BY XTRILUM LABORATORIES, INC. ON 8/13/2003.

6. Relevant tests/laboratory data, including dates
RETAINED SAMPLES WERE ANALYZED ON 8/15/2003. ALL TESTING RESULTS DEMONSTRATED THE PRODUCT FALLS WITHIN FINISHED PRODUCT SPECIFICATIONS.

7. Other relevant history, including preexisting medical conditions (e.g., allergies, race, pregnancy, smoking and alcohol use, hepatic/renal dysfunction, etc.)
PATCH TESTING SHOWED A REACTION TO THIS SCRUB AS WELL AS OTHER SCRUB SOAPS.

C. Suspect medication(s)

1. Name (give labeled strength & mfr/tablet, if known) #1 <u>BALLARD FOAM CARE SURSICAL HAND SCRUB 2%</u> #2 _____		3. Therapy dates (if unknown, give duration) from/to (or best estimate) #1 <u>MID-DECEMBER 2002 - JAN 03</u> #2 _____	
2. Dose, frequency & route used #1 <u>TOPICAL</u> #2 _____		4. Diagnosis for use (indication) #1 <u>SURSICAL HAND SCRUB</u> #2 _____	
6. Lot # (if known) #1 <u>210-1022-70</u> #2 _____		7. Exp. date (if known) #1 <u>03/05</u> #2 _____	
9. NDC # - for product problems only (if known) #1 _____ #2 _____		5. Event abated after use stopped or dose reduced #1 <input checked="" type="checkbox"/> yes <input type="checkbox"/> no <input type="checkbox"/> doesn't apply #2 <input type="checkbox"/> yes <input type="checkbox"/> no <input type="checkbox"/> doesn't apply	
10. Concomitant medical products and therapy dates (exclude treatment of event)		8. Event reappeared after reintroduction #1 <input type="checkbox"/> yes <input type="checkbox"/> no <input checked="" type="checkbox"/> doesn't apply #2 <input type="checkbox"/> yes <input type="checkbox"/> no <input type="checkbox"/> doesn't apply	

D. Suspect medical device

1. Brand name		4. Operator of device <input type="checkbox"/> health professional <input type="checkbox"/> lay user/patient <input type="checkbox"/> other: _____	
2. Type of device		5. Expiration date (mo/day/yr)	
3. Manufacturer name & address		7. If implanted, give date (mo/day/yr)	
6. model #		8. If explanted, give date (mo/day/yr)	
catalog #		9. Device available for evaluation? (Do not send to FDA) <input type="checkbox"/> yes <input type="checkbox"/> no <input type="checkbox"/> returned to manufacturer on _____ (mo/day/yr)	
serial #		10. Concomitant medical products and therapy dates (exclude treatment of event)	
lot #			
other #			

E. Initial reporter

1. Name & address _____	phone # _____
----------------------------	------------------

2. Health professional? <input type="checkbox"/> yes <input checked="" type="checkbox"/> no	3. Occupation <u>PROD/OCCUP. SAFETY</u>	4. Initial reporter also sent report to FDA <input type="checkbox"/> yes <input checked="" type="checkbox"/> no <input type="checkbox"/> unk
--	--	---

PLEASE TYPE IN BLACK INK



Submission of a report does not constitute an admission that medical personnel, user facility, distributor, manufacturer or product caused or contributed to the event.

Medication and Device Experience Report

(continued)

Refer to guidelines for specific instructions

Submission of a report does not constitute an admission that medical personnel, user facility, distributor, manufacturer or product caused or contributed to the event.

For use by user facility/distributor - devices only			
1. Check one <input type="checkbox"/> user facility <input type="checkbox"/> distributor		2. UF/Dist report number	
3. User facility or distributor name/address			
4. Contact person		5. Phone Number	
6. Date user facility or distributor became aware of event (mo/day/yr)		7. Type of report <input type="checkbox"/> Initial <input type="checkbox"/> follow-up # _____	8. Date of this report (mo/day/yr)
9. Approximate age of device	10. Event problem codes (refer to coding manual)		
	patient code	_____ - _____ - _____	
	device code	_____ - _____ - _____	
11. Report sent to FDA? <input type="checkbox"/> yes _____ (mo/day/yr) <input type="checkbox"/> no		12. Location where event occurred <input type="checkbox"/> hospital <input type="checkbox"/> outpatient diagnostic facility <input type="checkbox"/> home <input type="checkbox"/> ambulatory surgical facility <input type="checkbox"/> nursing home <input type="checkbox"/> outpatient treatment facility <input type="checkbox"/> other: _____ specify	
13. Report sent to manufacturer? <input type="checkbox"/> yes _____ (mo/day/yr) <input type="checkbox"/> no			
14. Manufacturer name/address			

G. All manufacturers	
1. Contact office - name/address (& mailing site for devices) RAM CHAKROBORTY, PhD XTRIM LABORATORIES, INC. 415 W. PERSHING ROAD CHICAGO, IL 60609	2. Phone number
4. Date received by manufacturer (mo/day/yr) 08/13/2003	3. Report source (check all that apply) <input type="checkbox"/> foreign <input type="checkbox"/> study <input type="checkbox"/> literature <input type="checkbox"/> consumer <input type="checkbox"/> health professional <input type="checkbox"/> user facility <input type="checkbox"/> company representative <input type="checkbox"/> distributor <input type="checkbox"/> other: _____
6. If IND, protocol #	5. (A)NDA # 19-422 IND # _____ PLA # _____ pre-1938 <input type="checkbox"/> yes OTC product <input type="checkbox"/> yes
7. Type of report (check all that apply) <input type="checkbox"/> 5-day <input checked="" type="checkbox"/> 15-day <input type="checkbox"/> 10-day <input type="checkbox"/> periodic <input type="checkbox"/> Initial <input type="checkbox"/> follow-up # _____	8. Adverse event term(s) REDNESS
9. Mfr. report number 710102270	

H. Device manufacturers only	
1. Type of reportable event <input type="checkbox"/> death <input type="checkbox"/> serious injury <input type="checkbox"/> malfunction (see guidelines) <input type="checkbox"/> other: _____	2. If follow-up, what type? <input type="checkbox"/> correction <input type="checkbox"/> additional information <input type="checkbox"/> response to FDA request <input type="checkbox"/> device evaluation
3. Device evaluated by mfr? <input type="checkbox"/> not returned to mfr. <input type="checkbox"/> yes <input type="checkbox"/> evaluation summary attached <input type="checkbox"/> no (attach page to explain why not) or provide code: _____	4. Device manufacture date (mo/yr)
5. Labeled for single use? <input type="checkbox"/> yes <input type="checkbox"/> no	
6. Evaluation codes (refer to coding manual)	
method	_____ - _____ - _____ - _____
results	_____ - _____ - _____ - _____
conclusions	_____ - _____ - _____ - _____
7. If remedial action initiated, check type <input type="checkbox"/> recall <input type="checkbox"/> notification <input type="checkbox"/> repair <input type="checkbox"/> inspection <input type="checkbox"/> replace <input type="checkbox"/> patient monitoring <input type="checkbox"/> relabeling <input type="checkbox"/> modification/adjustment <input type="checkbox"/> other: _____	8. Usage of device <input type="checkbox"/> Initial use of device <input type="checkbox"/> reuse <input type="checkbox"/> unknown
9. If action reported to FDA under 21 USC 360(i), list correction/removal reporting number:	

10. <input type="checkbox"/> Additional manufacturer narrative	and/or	11. <input type="checkbox"/> Corrected data
--	--------	---

The public reporting burden for this collection of information has been estimated to average one hour per response, including the time for reviewing instructions, searching existing data sources, gathering and maintaining the data needed, and completing and reviewing the collection of information. Send comments regarding this burden estimate or any other aspect of this collection of information, including suggestions for reducing this burden to:

DHHS Reports Clearance Office
Paperwork Reduction Project (0910-0291)
Hubert H. Humphrey Building, Room 531-H
200 Independence Avenue, S.W.
Washington, D.C. 20201

"An agency may not conduct or sponsor, and a person is not required to respond to, a collection of information unless it displays a currently valid OMB control number."

Please DO NOT RETURN this form to this address.

Medicine

Health System

8-18-03

This is a statement which you requested regarding ms. _____ 404
She had patch testing by Dr. _____
_____ Clinic, _____

He indicated that she was not allergic to Foam Care or Technicare so she could not be allergic to Chlorhexadene.

R.N. C.N.P.

From firm's September 3, 2003
submission

“Attachment 10, FDA Action Letter”

14 pages removed as duplicates

See 8/11/03 Approvable Letter
located in earlier section “Approvable
Letter(s)”



NDA 19-422\S-032

INFORMATION REQUEST LETTER

Xttrium Laboratories
Attention: Ram Chakroborty, Ph.D.
Vice President
415 West Pershing Road
Chicago, Illinois 60609-2731

Dear Dr. Chakroborty:

Please refer to your January 10, 2002 supplemental new drug application submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Exidine (2% chlorhexidine gluconate) solution.

We also refer to your submissions dated June 20, July 2 and 18, 2002, and August 12, 15, and 30, 2002.

We have completed a cursory review of the final study report (#010206-102) for the Microbiology section of your submission, and have the following information requests. The information requested is necessary in order for us to completely evaluate your submission. When you respond to this information request, include only the data and information requested, and refrain from providing your own interpretation of the consequences of your study design and conduct.

1. Section 12.11.7 states for the test product that "Subjects performed a final rinse under running tap water maintained at $40^{\circ} \pm 2^{\circ}C$ such that each hand and forearm was rinsed for thirty (30) seconds (for a total rinse time of one (1) minute)." In Section 12.11.19, it states for the control product, "Subjects performed a final rinse under running tap water such that each hand and forearm was rinsed for one (1) minute (for a total rinse time of two (2) minutes)." This difference introduces a bias in favor of the test product. Please explain why this difference in rinsing regimen was implemented.
2. Provide additional explanation for three of the "Protocol and/or SOP deviation recording forms" you submitted, as outlined below:
 - a. In the first form it states that 3 stacks of baseline plates had to be incubated for 113 hours as opposed to the protocol-specified 72 hours.

- i) Please explain why it was necessary to incubate the 3 stacks for 113 hours, as opposed to 72 hours.
 - ii) Submit data collected during any follow-up investigations that were made to explain the observation, if you conducted these.
 - iii) Clarify whether the plates represented the test or control product.
 - iv) What subjects were these samples taken from?
 - v) Was this data used in the final analysis?
- b. The second form states that some samples were taken at times prior to 3 and 6 hours post-scrub, and at times that exceeded 3 and 6 hours post scrub.
- (i) Please identify the subjects in which this occurred, and specify whether the noted sample times represent test and/or control drug product.
 - (ii) Provide the *actual times* that sampling occurred, and clarify whether or not the data was used in the analysis?
- c. In the third form, it is stated that there were three occurrences where washes occurred prior to the protocol defined one hour time. Please identify the subject in which this occurred, the time frames actually used in the study, and whether they represent the test or control product.

We may have additional questions regarding your neutralization validation experiments and/or the clinical simulations study once we complete an in-depth review of your submission.

If you have any questions, call Tia Frazier, Project manager, at 301-827-2271.

Sincerely yours,

{See appended electronic signature page}

David Hilfiker
Supervisor, Project Management Staff
Division of Over-the-Counter Drug Products
Office of Drug Evaluation V
Center for Drug Evaluation and Research

This is a representation of an electronic record that was signed electronically and
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/s/

David Hilfiker
9/24/02 11:13:07 AM



NDA 19-422\S-032

INFORMATION REQUEST LETTER

Xttrium Laboratories, Inc.
Attention: Ram Chakraborty, Ph.D.
Vice President
415 West Pershing Road
Chicago, IL 60609-2731

Dear Dr. Chakraborty:

Please refer to your January 10, 2002 supplemental new drug application submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Exidine (2% chlorhexidine gluconate solution).

We also refer to your submission dated July 18, 2002, and to a teleconference between Mr. Creevy and Tia Frazier on June 5, 2002, in which an update of all adverse event reports and other information related to the product's safety was requested.

We are reviewing the clinical section of your submission, and find the reports of clinical experience related to safety that are required under 21 CFR 314.50(d)(5)(vi)(b) to be missing. We request a prompt written response in order to continue our evaluation of your supplemental NDA.

We remind you that the requirements for a safety update, as described at 21 CFR 314.50(d)(5)(vi)(b), include data from all non-clinical and clinical studies of the drug under consideration regardless of indication, dosage form, or dose level.

1. Describe in detail any significant changes or findings in the safety profile.
2. When assembling the sections describing discontinuations due to adverse events, serious adverse events, and common adverse events, incorporate new safety data as follows:
 - Present any new safety data from the studies for the proposed indication using the same format as the original supplemental NDA submission.
 - Present tabulations of the new safety data combined with the original NDA data.
 - Include tables that compare frequencies of adverse events in the original NDA with the retabulated frequencies described above.
 - For indications other than the proposed indication, provide separate tables for the frequencies of adverse events occurring in clinical trials.

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3. Present a retabulation of the reasons for premature study discontinuation by incorporating the drop-outs from the newly completed studies. Describe any new trends or patterns identified.
4. Provide case report forms and narrative summaries for each patient who died during a clinical study or who did not complete a study because of an adverse event. In addition, provide narrative summaries for serious adverse events.
5. Describe any information that suggests a substantial change in the incidence of common, but less serious, adverse events between the new data and the original NDA data.
6. Provide a summary of worldwide experience on the safety of this drug. Include an updated estimate of use for drug marketed in other countries.
7. Provide English translations of current approved foreign labeling not previously submitted.

If you have further questions, call Tia Frazier, Project Manager, at 301-827-2271.

Sincerely yours,

{See appended electronic signature page}

David Hilfiker, M.S.
Supervisor, Project Management Staff
Division of Over-the-Counter Drug Products
Office of Drug Evaluation V
Center for Drug Evaluation and Research

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/s/

David Hilfiker
8/30/02 01:06:16 PM



NDA 19-422\S-032

INFORMATION REQUEST LETTER

Xttrium Laboratories
Attention: Kevin Creevy
President, Xttrium Laboratories
415 West Pershing Road
Chicago, IL 60609

Dear Mr: Creevy:

Please refer to your January 10, 2002, supplemental new drug application submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Exidine (2% chlorhexidine gluconate solution).

We are reviewing your submission, and have the following information request. Submit a more precise representation of the to-be-marketed labeling, so that we have an understanding of how the label will be read and understood by consumers at the time of purchase. Also submit annotated specifications for the font size for headings, text, bullets, and bar/hairlines, in accordance with 21 CFR 201.66(d). More detailed labeling comments will be provided when these items are received.

In terms of the timing of your response to this information request, we remind you that we intend (as stipulated under 21 CFR 314.71 and 314.100) to review and act on this supplemental application, with or without an amendment, on or before August 25, 2002.

If you have any questions, please call Tia Frazier, Regulatory Project Manager, at (301) 827-2271.

Sincerely yours,

{See appended electronic signature page}

David Hilfiker, M.S.
Supervisor, Project Management Staff
Division of Over-the-Counter Drug Products
Office of Drug Evaluation V
Center for Drug Evaluation and Research

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/s/

David Hilfiker
6/20/02 08:35:56 AM

CENTER FOR DRUG EVALUATION AND RESEARCH
FOOD AND DRUG ADMINISTRATION

FACSIMILE TRANSMISSION RECORD

DATE: October 22, 2003
FROM: Tia Frazier, R.N., M.S.
Division of OTC Drug Products, HFD-560
PHONE: 301-827-2271 FAX: 301-827-2315
TO: Ram Chakroborty, Ph.D.

FAX #: 773-268-9790 No. of pages (including cover) 2

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Message: Please refer to the labeling submitted on September 3, 2003, for 2% Chlorhexidine Gluconate Solution.

According to our telephone conversation on October 21, 2003, you agreed to make the following labeling revision in order for this supplement to be approved:

1. Add the phrase "Peel here for *Drug Facts*>" to the outermost surface of their 4- and 8-ounce containers. It appears that the statement was placed on the wrong panel and should not be part of *Drug Facts*. As currently placed the statement appears inside the folded label.
2. Remove the hairline after the header *Directions* on the last page of label for the 4-ounce container and on page 4 of the 8-ounce container label.

If you have any questions, please contact Tia Frazier, Regulatory Project Manager, at 301-827-2271.

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/s/

Tia Frazier

10/27/03 11:36:13 AM

CSO

Sent on 10-22-03, noted not to be in DFS
on 10-27-03. Assume computer problems, and DFS'd second
time.