

**CENTER FOR DRUG EVALUATION AND  
RESEARCH**

*APPLICATION NUMBER:*

**73695**

**CHEMISTRY REVIEW(S)**

ANDA or AADA Numbers: ~~73-695~~

FIRM: Colgate Palmolive Co.

DOSAGE FORM: Chlorhexidine Gluconate Oral Rinse STRENGTH: 0.12%

CGMP STATEMENT/EER UPDATE STATEMENT: EER sent 10/15/93 and 10/27/93 to HFD-320 is outstanding.

BIO STUDY: Bio waiver granted on 7/7/93.

METHODS VALIDATION - (DESCRIPTION OF DOSAGE FORM SAME AS FIRM)

Methods validated by the Cincinnati District Laboratory. The chemist described the product as a "clear light blue free flowing liquid with a mint like odor." All data within limits and is satisfactory.

STABILITY - ARE THE CONTAINERS USED IN STUDY IDENTICAL TO THOSE IN CONTAINER SECTION - Yes - 16 oz. Pet bottles with CRC cap.

Three months accelerated data at 40°C/75% RH were satisfactory. Four batches were tested to 9 months and several batches to 24 months at ambient conditions. All data were satisfactory. A cycle study (4°C, 25°C and 40°C) was carried out successfully.

LABELING: FPL satisfactory, see review dated 12/13/93.

STERILIZATION VALIDATION (IF APPLICABLE): N/A

SIZE OF BIO BATCH - (FIRM'S SOURCE OF NDS O.K.) N/A

SIZE OF STABILITY BATCHES - (IF DIFFERENT FROM BIO BATCH WERE THEY MANUFACTURED BY THE SAME PROCESS?)

Several Gallon batches.

PROPOSED PRODUCTION BATCHES - MANUFACTURING PROCESS THE SAME AS BIO/STABILITY? Yes

Gal batches.

Stephen Sherken  
(on annual leave)

Date

/S/

12/16/93  
HFD-625

1. CHEMIST'S REVIEW NO. 1
2. ANDA: 73-695
3. NAME AND ADDRESS OF APPLICANT:  
  
Colgate-Palmolive Company  
909 River Road  
Piscataway, NJ 08854-5596
4. LEGAL BASIS for ANDA SUBMISSION:  
  
Information in vol. 1.2, page 224, states that Robert L. Stone, Managing Patent Counsel of Colgate-Palmolive Company, certifies on behalf of applicant, Colgate-Palmolive Co., any patent that claims 1:6-di-4'-chlorophenyldiguanidohexane (also known as 1,6-di-p-chlorophenylbiguanidohexane and as chlorhexidine), for which the application to which this Certification is attached, has expired.
5. SUPPLEMENT(s): None
6. PROPRIETARY NAME: PerioGard® Oral Rinse
7. NONPROPRIETARY NAME: Chlorhexidine gluconate 0.12%
8. SUPPLEMENT(s) PROVIDE(s) FOR: N/A
9. AMENDMENTS AND OTHER DATES: None
10. PHARMACOLOGICAL CATEGORY: Antimicrobial
11. Rx or OTC: Rx

CONCLUSIONS AND RECOMMENDATIONS: NOT APPROVABLE

REVIEWER:

Daniel S. James, Ph.D.

/S/  
4/16/92

DATE COMPLETED:

3/12/92

Endorsed by P. Schwartz, Ph.D.

4/9/92

/S/, 4/16/92

12. RELATED IND/NDA/DMF(s):

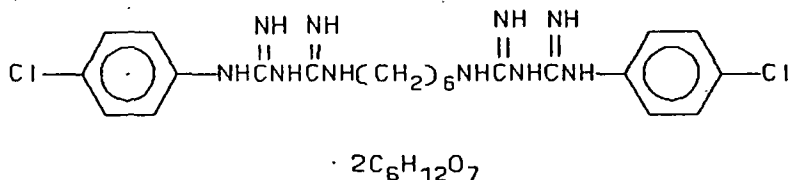
NDA 19-028: Proctor & Gamble, Ohio  
DMF  
DMF  
DMF  
DMF  
DMF

Proctor & Gamble - Innovative Drug, Peridex® Oral Rinse

13. DOSAGE FORM: Liquid (Oral Rinse) 14. POTENCY: 0.12% w/w

15. CHEMICAL NAME AND STRUCTURE:

N,N'-Bis(4-chlorophenyl)-3,12-diimino-2,4,11,13-tetraza-  
tetradecanediimidamide di-D-gluconate.



Mol. Form.:  $C_{22}H_{30}Cl_2N_{10} \cdot 2C_6H_{12}O_7$   
Mol. Wt.: 897.77  
(Mol. Wt. of  $C_{22}H_{30}Cl_2N_{10}$ : 505.46)

16. RECORDS AND REPORTS: None

17. COMMENTS:

This application is deficient and not approved for the following summarized reasons:

1. Specific responsibilities of the applicant and contract manufacturer need clarification.
2. Not sufficient analytical data submitted for raw materials.

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Chem Review #1

1. CHEMIST'S REVIEW NO. 2

2. ANDA: 73-695

3. NAME AND ADDRESS OF APPLICANT:

Colgate-Palmolive Company  
909 River Road  
Piscataway, NJ 08854-5596

4. LEGAL BASIS for ANDA SUBMISSION: **Satisfactory.**

See Review No. 1

5. SUPPLEMENT(s): None

6. PROPRIETARY NAME: PerioGard® Oral Rinse

7. NONPROPRIETARY NAME: Chlorhexidine Gluconate, 0.12%

8. SUPPLEMENT(s) PROVIDE(s) FOR: N/A

9. AMENDMENTS AND OTHER DATES:

Firm: Facsimile communication - 11/2/92 (Vol. 1.1)

Agency: Telecon with Colgate - 11/2/92 (Vol. 1.1)

Amendment: 10/13/92 *ADD 1/2/92*

10. PHARMACOLOGICAL CATEGORY: *Antimicrobial*

11. Rx or OTC: Rx

12. RELATED IND/NDA/DMF(s):

NDA 19-028: Proctor & Gamble, Ohio

DMF (LOA, no date; vol. 1.1, page 67)

Proctor & Gamble - Innovative Drug, Peridex® Oral Rinse

CONCLUSIONS AND RECOMMENDATIONS: **NOT APPROVABLE**

REVIEWER:

DATE COMPLETED:

Daniel S. James, Ph.D.

12/3/92

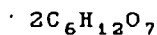
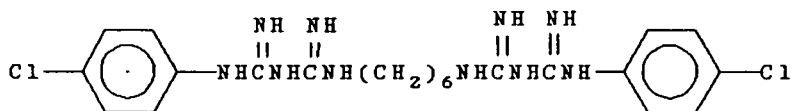
Endorsed by P. Schwartz, Ph.D.

1/4/93

13. DOSAGE FORM: Liquid (Oral Rinse) 14. POTENCY: 0.12% w/w

15. CHEMICAL NAME AND STRUCTURE:

*N,N''*-Bis(4-chlorophenyl)-3,12-diimino-2,4,11,13-tetraaza-tetradecanediimidamide di-D-gluconate.



Mol. Form.:  $\text{C}_{22}\text{H}_{30}\text{Cl}_2\text{N}_{10} \cdot 2\text{C}_6\text{H}_{12}\text{O}_7$

Mol. Wt.: 897.77

(Mol. Wt. of  $\text{C}_{22}\text{H}_{30}\text{Cl}_2\text{N}_{10}$ : 505.46)

16. RECORDS AND REPORTS: None

17. COMMENTS:

This application remains deficient and is not approved for the following summarized reasons:

1. Not sufficient analytical data submitted for raw materials.
2. Description and size of equipment must be provided.
3. Clarification is needed for container component materials.
4. Laboratory control area needs additional information: executed batch records for pilot-scale production batches, batch product filling reconciliation data, analytical and methods validation data.
5. Confirmation to withdraw long-term stability studies as basis for expiration date is needed.
6. Stability report forms require additional information.

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Chem Review # 2



1. CHEMISTRY REVIEW NO. 3
2. ANDA # 73-695
3. NAME AND ADDRESS OF APPLICANT  
Colgate-Palmolive Co.  
Piscataway, NJ 08854-5596
4. LEGAL BASIS FOR SUBMISSIONS  
Remains satisfactory
5. SUPPLEMENT(s)  
N/A
6. PROPRIETARY NAME  
PerioGard® Oral Rinse
7. NONPROPRIETARY NAME  
Chlorhexidine Gluconate, 0.12%  
Oral Rinse
8. SUPPLEMENT(s) PROVIDE(s) FOR:  
N/A
9. AMENDMENTS AND OTHER DATES  
Bio Protocols, 11/13/92, 12/4/92, Reformulation Intention  
1/20/93, Deficiency letter #2, 1/12/93, Amend 5/17/93; ONC  
8/11/93
10. PHARMACOLOGICAL CATEGORY  
Antimicrobial
11. Rx or OTC  
Rx
12. RELATED IND/NDA/DMF(s)  
DMF
13. DOSAGE FORM  
Light blue liquid with alcoholic  
and peppermint taste
14. POTENCY  
0.12%
15. CHEMICAL NAME AND STRUCTURE  
See review #2.
16. RECORDS AND REPORTS  
N/A

17. COMMENTS

Firm changed container/closure system with new manufacturers of the 16 oz. plastic bottle and the cap. They then manufactured a full scale production batch of        liters, packaged the solution in the new container closure system and provided 3 month stability data at 40°C. Data is satisfactory. Will use        for testing of the active and all inactive ingredients.        remains the contract facility for manufacturing and testing of the finished product. DMF        remains satisfactory.

18. CONCLUSIONS AND RECOMMENDATIONS

Not-approvable - Minor amendment.

19. REVIEWER:

*/S/*

DATE COMPLETED:

*10/16/93*

Stephen Sherken /

cc: ANDA 73-695  
DUP Jacket  
Division File

Endorsements:

HFD-634/SSherken/10/21/93

HFD-634/MSmela/10/25/93

*S. Sherken 10/27/93*  
*M. Smela 10/27/93*

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Chem Review #3

1. CHEMISTRY REVIEW NO. 4

2. ANDA # 73-695

3. NAME AND ADDRESS OF APPLICANT

Colgate-Palmolive Co.  
Piscataway, NJ 08854-5596

4. LEGAL BASIS FOR ADA SUBMISSIONS

Remains satisfactory

5. SUPPLEMENT(S)

N/A

6. PROPRIETARY NAME

PerioGard® Oral Rinse

7. NONPROPRIETARY NAME

Chlorhexidine Gluconate, 0.12%  
Oral Rinse

8. SUPPLEMENT(S) PROVIDE(S) FOR:

N/A

9. AMENDMENTS AND OTHER DATES

Amendment 3/24/92, Bio amend 7/20/92 and 10/12/92,  
Bio Protocols, 11/13/92, 12/4/92, Reformulation Intention  
1/20/93, Deficiency letter #2, 1/12/93, Amend 5/17/93; ONC  
8/11/93; TC 8/19/93; Def Letter #3, 11/3/93; TC 11/11/93;  
\*Amend (minor) 11/22/93.

10. PHARMACOLOGICAL CATEGORY

Antimicrobial

11. Rx or OTC

Rx

12. RELATED IND/NDA/DMF(S)

DMF

13. DOSAGE FORM

Light blue liquid with alcoholic  
and peppermint taste 0.12%

14. POTENCY

15. CHEMICAL NAME AND STRUCTURE

See review #2.

16. RECORDS AND REPORTS

N/A

17. COMMENTS

All chemistry, labeling and bio problems have been adequately addressed by the applicant. EER still outstanding.

18. CONCLUSIONS AND RECOMMENDATIONS

Approve ANDA pending satisfactory EER.

19. REVIEWER: DATE COMPLETED:

Stephen Sherken

cc: ANDA 73-695 <sup>↑</sup> *Extended Annual Leave*  
DUP Jacket  
Division File

Endorsements:

HFD-625/SSherken/11/30/93  
HFD-625/MSmela/12/01/93  
F/T by cls/12/14/93

*ISI* 12/23/93  
12/16/93

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*Chem Review #4*