CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: NDA 20-774

CHEMISTRY REVIEW(S)

MAY 6 1998

DIVISION OF DERMATOLOGICAL AND DENTAL DRUG PRODUCTS
Review of Chemistry, Manufacturing, and Controls

NDA #: 20-774 **CHEM.REVIEW #:** 6 **REVIEW DATE:** 05-MAY-98

SUBMISSION/TYPE	DOCUMENT DATE	CDER DATE	ASSIGNED DATE
ORIGINAL	20-DEC-96	26-DEC-97	Approvable
NDA 20-774/BC	05-DEC-97	10-DEC-97	16-DEC-97
NDA 20-774/AC	15-DEC-97	17-DEC-97	22-DEC-97

NAME & ADDRESS OF APPLICANT:

Perio Products, Inc.
7 HaMarpeh Street
P.O. Box 23950
Har Hotzvim Industrial Zone
Jerusalem 91237, Israel
ATTN: Dr. Daniel P. Levy
Quality Assurance Manager
Tel: 011-972-2-532-2836
Fax: 011-972-2-581-2722

U.S. AGENT FOR PERIO PRODUCTS:
Oxford Research
International Corporation
1425 Broad Street
Clifton, New Jersey 07013-4221
ATTN: Dr. Robert J. McCormack
Tel: 201-777-2800

DRUG PRODUCT NAME

Proprietary:	PerioChip™
Nonproprietary/USAN:	chlorhexidine digluconate
Code Names/#'s:	CAS RN: 18472-51-0
Chemical Type/ Therapeutic Classes:	3S

PHARMACOLOGICAL CATEGORY/INDICATION: Antimicrobial/Periodontitis treatment

DOSAGE FORM:	A biodegradable gelatin matrix chip
STRENGTHS:	2.5 mgs./chip
ROUTE OF ADMINISTRATION:	Oral
DISPENSED:	X Rx __ OTC

CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOL.WT:

1,1'-hexamethylenebis[5-(p-chlorophenyl)biguanide]di-D-gluconate
Molecular Formula: $C_{34}H_{54}Cl_2N_{10}O_{14}$
Molecular Weight: 897.77
CAS No.: 18472-51-0

SUPPORTING DOCUMENTS:
Target Research Associates Letter, dated 5/4/98, from R.J. McCormack to R. Blay, entitled: "Response to the Supervisory Chemist's question regarding additional data for the agar plate release rate method."

CONSULTS: None

REMARKS / COMMENTS:
It was noted in CMC Review #5 that a statement in the Pharmacokinetics Section of PerioChip Labeling might become misconstrued. The statement questioned was the first sentence in that section which read,

Since the PerioChip drug product's current Regulatory Specification reads,
, it did not agree with the above statement. **Therefore this pharmacokinetic statement could be modified by the addition of the following sentence,**

CONCLUSIONS & RECOMMENDATIONS:
Minor modification of the labeling for the pharmacokinetic section of PerioChip is recommended to avoid possible confusion. The modification includes the addition of the single sentence highlighted above. The incluson of this sentence will allow for a more accurate description of the source of the release rate data.

/S/ 5/6/98
James D. Vidra, Ph.D.
Review Chemist

cc: Orig. NDA 20-774
HFD-540/Division File
HFD-540/ProjMngt/Blay
HFD-540/DentOff/Hyman
HFD-88 0/PK/Bashaw 5/6/98
HFD-540/Chm/Vidra
HFD-540/ChmSup/DeCamp 5/6/98
filename: N20774.6

5/6/98

APR 16 1998

DIVISION OF DERMATOLOGICAL AND DENTAL DRUG PRODUCTS
Review of Chemistry, Manufacturing, and Controls

NDA #: 20-774 **CHEM.REVIEW #:** 5 **REVIEW DATE:** 31-MAR-98

SUBMISSION/TYPE	DOCUMENT DATE	CDER DATE	ASSIGNED DATE
ORIGINAL	20-DEC-96	26-DEC-97	Review #1
NDA 20-774/BC	05-DEC-97	10-DEC-97	16-DEC-97
NDA 20-774/AC	15-DEC-97	17-DEC-97	22-DEC-97

NAME & ADDRESS OF APPLICANT:

Perio Products, Inc.
7 HaMarpeh Street
P.O. Box 23950
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Jerusalem 91237, Israel
ATTN: Dr. Daniel P. Levy
Quality Assurance Manager
Tel: 011-972-2-532-2836
Fax: 011-972-2-581-2722

U.S. AGENT FOR PERIO PRODUCTS:
Oxford Research
International Corporation
1425 Broad Street
Clifton, New Jersey 07013-4221
ATTN: Dr. Robert J. McCormack
Tel: 201-777-2800

DRUG PRODUCT NAME

Proprietary:	PerioChip™
Nonproprietary/USAN:	chlorhexidine digluconate
Code Names/#'s:	CAS RN: 18472-51-0
Chemical Type/ Therapeutic Classes:	3S

ANDA Suitability Petition/DESI/Patent Status: NOT APPLICABLE!
PHARMACOLOGICAL CATEGORY/INDICATION: Antimicrobial/Periodontitis
DOSAGE FORM: A biodegradable gelatin matrix chip
STRENGTHS: 2.5 mgs./chip
ROUTE OF ADMINISTRATION: Oral
DISPENSED: X Rx __ OTC

CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOL.WT:

1,1'-hexamethylenebis[5-(p-chlorophenyl)biguanide]di-D-gluconate
Molecular Formula: $C_{34}H_{54}Cl_2N_{10}O_{14}$

Molecular Weight: 897.77
CAS No.: 18472-51-0

SUPPORTING DOCUMENTS: None

CONSULTS: None

REMARKS / COMMENTS:
NDA 20-774 received an APPROVABLE rating on 11/25/97 due to two CMC deficiencies. The first deficiency was the sponsor's assay which was considered inaccurate by both sponsor and the FDA. The second deficiency was a deficient DMF for the synthesis of chlorhexidine gluconate, the sponsor's drug substance in PERIOCHIP. Chemistry Review #4 recommended approval for the modified Assay on 3/6/98 while this current Chemistry Review #5 documents within NDA 20-774 that DMF for chlorhexidine gluconate and manufactured by was found to be ADEQUATE. This recommendation of ADEQUATE is documented in Chemistry Review #2 for DMF With the issuance of the completed Informational Request Letter for DMF all requirements have been completed.

CONCLUSIONS & RECOMMENDATIONS:
The review of DMF was found ADEQUATE on 3/10/98 which successfully completes the two deficiencies for NDA 20-774. The second deficiency, pertaining to the corrected Assay, was RECOMMENDED FOR APPROVAL on 3/6/98. It is recommended the CMC APPROVABLE rating for NDA 20-774 be converted to an APPROVAL RECOMMENDATION at this time.

/S/

James D. Vidra, Ph.D.
Review Chemist

cc: Orig. NDA 20-774
HFD-540/Division File
HFD-540/ProjMngt/Blay
HFD-540/DentOff/Hyman
HFD-540/Chm/Vidra
HFD-540/ChmSup/DeCamp WDH 4/16/98
filename: N20774.Rev5

APR 13 1998

DIVISION OF DERMATOLOGICAL AND DENTAL DRUG PRODUCTS
Review of Chemistry, Manufacturing, and Controls

NDA #: 20-774 **CHEM.REVIEW #:** 4. **REVIEW DATE:** 06-MAR-98

SUBMISSION/TYPE	DOCUMENT DATE	CDER DATE	ASSIGNED DATE
ORIGINAL	20-DEC-96	26-DEC-97	Review #1
NDA 20-774/BC	05-DEC-97	10-DEC-97	16-DEC-97
NDA 20-774/AC	15-DEC-97	17-DEC-97	22-DEC-97

NAME & ADDRESS OF APPLICANT:

Perio Products, Inc.
7 HaMarpeh Street
P.O. Box 23950
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Jerusalem 91237, Israel
ATTN: Dr. Daniel P. Levy
Quality Assurance Manager
Tel: 011-972-2-532-2836
Fax: 011-972-2-581-2722

U.S. AGENT FOR PERIO PRODUCTS:
Oxford Research
International Corporation
1425 Broad Street
Clifton, New Jersey 07013-4221
ATTN: Dr. Robert J. McCormack
Tel: 201-777-2800

DRUG PRODUCT NAME

Proprietary: PerioChip™
Nonproprietary/USAN: chlorhexidine digluconate

Code Names/#'s: CAS RN: 18472-51-0
Chemical Type/
Therapeutic Classes: 3S

ANDA Suitability Petition/DESI/Patent Status: NOT APPLICABLE!
PHARMACOLOGICAL CATEGORY/INDICATION: Antimicrobial/Periodontitis treatment

DOSAGE FORM: A biodegradable gelatin matrix chip

STRENGTHS: 2.5 mgs./chip
ROUTE OF ADMINISTRATION: Oral
DISPENSED: X Rx __ OTC

CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOL.WT:

1,1'-hexamethylenebis[5-(p-chlorophenyl)biguanide]di-D-gluconate
Molecular Formula: $C_{34}H_{54}Cl_2N_{10}O_{14}$

Molecular Weight: 897.77

CAS No.: 18472-51-0

SUPPORTING DOCUMENTS: None

CONSULTS: None

REMARKS / COMMENTS:

NDA 20-774 received an APPROVABLE rating on 11/25/97 because of two CMC areas of deficiencies, i.e. first, their assay was considered inaccurate by both sponsor and the FDA at the time of review, and secondly, DMF was deficient for the synthesis of chlorhexidine gluconate, the sponsor's drug substance. Chemistry Review #4 will address only the assay deficiency.

Sponsor's response to the assay deficiency was submitted as two minor chemistry amendments. An inaccurate assay was considered serious since is a known and recognized by the sponsor as an inaccurate analytical method.

The ORIGINAL ASSAY involved the following individual steps:

CONCERNS WITH ORIGINAL ASSAY:

This correction factor was later found to be erroneous.

The "NEW" [redacted] ASSAY Activities:
In updating their original [redacted] assay and validation procedures, the sponsor realized their new data actually supported their original assay. This possibility was confirmed by the following data/information:

Analytical Method :

In summary, the modifications used in Analytical Method should not affect previous Methods Validations which assayed only chlorhexidine gluconate content in both drug substance and drug product.

CONCLUSIONS & RECOMMENDATIONS:

A review of two Minor BC Amendments for a assay in NDA 20-774 has led to a RECOMMENDATION FOR APPROVAL. Adequate data and information have been submitted to reverse the earlier findings.

/S/

James D. Vidra, Ph.D.
Review Chemist

cc: Original NDA 20-774
HFD-540/Division File
HFD-540/Chm/Vidra
HFD-540/DO/Hyman
HFD-540/Pharm/See
HFD-540/Micro/Marsik
HFD-540/PrjMgt/Blay
HFD-540/ChmLdr/DeCamp WD 4/13/98
filename: 20774BC

4/13/98

APR 13 1998

DIVISION OF DERMATOLOGICAL AND DENTAL DRUG PRODUCTS
Review of Chemistry, Manufacturing, and Controls

NDA #: 20-774 **CHEM.REVIEW #**: 3 **REVIEW DATE**: 18-Feb-98

SUBMISSION/TYPE	DOCUMENT DATE	CDER DATE	ASSIGNED DATE
ORIGINAL	20-DEC-96	26-DEC-97	30-DEC-97
NDA 20-774 Methods Validation Results	05-Feb-98	NA	NA

NAME & ADDRESS OF APPLICANT:

Perio Products, Inc.
7 HaMarpeh Street
P.O. Box 23950
Har Hotzvim Industrial Zone
Jerusalem 91237, Israel
ATTN: Dr. Daniel P. Levy
Quality Assurance Manager
Tel: 011-972-2-532-2836
Fax: 011-972-2-581-2722

U.S. AGENT FOR PERIO PRODUCTS:
Oxford Research
Intenational Corporation
1425 Broad Street
Clifton, New Jersey 07013-4221
ATTN: Dr. Robert J. McCormack
Tel: 201-777-2800

DRUG PRODUCT NAME

Proprietary:	PerioChip™
Nonproprietary/USAN:	chlorhexidine digluconate
Code Names/#'s:	CAS RN: 18472-51-0
Chemical Type/ Therapeutic Classes:	3S

ANDA Suitability Petition/DESI/Patent Status: NOT APPLICABLE!
PHARMACOLOGICAL CATEGORY/INDICATION: Antimicrobial/Periodontitis treatment
DOSAGE FORM: A biodegradable gelatin matrix chip

STRENGTHS: 2.5 mgs./chip
ROUTE OF ADMINISTRATION: Oral
DISPENSED: X Rx ____ OTC

CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOL.WT:
1,1'-hexamethylenebis[5-(p-chlorophenyl)biguanide]di-D-gluconate

Molecular Formula: $C_{34}H_{54}Cl_2N_{10}O_{14}$

Molecular Weight: 897.77
CAS No.: 18472-51-0

SUPPORTING DOCUMENTS:
Original NDA 20-774

CONSULTS: Not Applicable.

SUPPORTING DOCUMENTS:
Original NDA 20-774

CONSULTS: Not Applicable.

REMARKS/COMMENTS:

Two Method Validation packages were submitted to the Philadelphia and San Juan District Laboratories on 10-Oct-97 for an impartial assessment of the methods validation conducted in NDA 20-774. The Philadelphia Laboratory results were completed on 05-Feb-98 and found suitable for control and regulatory purposes

However, in addition to this Method Validation review, there exists two outstanding deficiencies that are currently being addressed, e.g. the review of a questionable assay (submitted as NDA 20-774/BC, dated 05-Dec-97, and a second BC document, dated 15-Dec-97) and a deficient DMF Therefore approval of this Method Validation does not approve those two outstanding deficiencies.

CONCLUSIONS & RECOMMENDATIONS:
The Philadelphia District Laboratory's Method Validation for NDA 20-774, PerioChip (chlorhexidine gluconate), 2.5 mg., is RECOMMENDED FOR APPROVAL since the evaluation of the methods validation package was found suitable for the regulatory control of this product. However, as stated previously, this approval does not pertain to the two outstanding deficiencies currently under review.

/S/ 2/18/98
James D. Vidra, Ph.D.
Review Chemist

cc: Orig. ~~IND~~ NDA #20-774
HFD-540/Division File
HFD-540/ProjMgr/Blay
HFD-540/DO/Hyman
HFD-540/Chm/Vidra
HFD-540/ChmSup/DeCamp
filename: n20774.mv1

4/15/98
4/15/98

HFD-540 Blair

FEB 9 1998

DIVISION OF DERMATOLOGICAL AND DENTAL DRUG PRODUCTS
Review of Chemistry, Manufacturing, and Controls

NDA #: 20-774 **CHEM.REVIEW #:** 2 **REVIEW DATE:** 09-Jan-98

SUBMISSION/TYPE	DOCUMENT DATE	CDER DATE	ASSIGNED DATE
ORIGINAL	20-DEC-96	26-DEC-97	30-DEC-97
NDA 20-774/BZ	14-Oct-97	15-Oct-97	20-Oct-97
NDA 20-774/BL	29-Jul-97	31-Jul-97	04-Aug-97
NDA 20-774/BC	05-Sep-97	08-Sep-97	11-Sep-97
NDA 20-774/BC	18-Sep-97	19-Sep-97	24-Sep-97
Desk Copy	14-Oct-97	-	-
IND 35,524	03-APR-96	04-APR-96	-
NDA 20-774/BF	10-Dec-97	12-Dec-97	01-Jan-98

NAME & ADDRESS OF APPLICANT:

Perio Products, Inc.
7 HaMarpeh Street
P.O. Box 23952
Har Hotzvim Industrial Zone
Jerusalem 91235, Israel
ATTN: Dr. Daniel P. Levy
Quality Assurance Manager
Tel: 011-972-2-532-2836
Fax: 011-972-2-551-2722

U.S. AGENT FOR PERIO PRODUCTS:
Oxford Research
Intenational Corporation
1425 Broad Street
Clifton, New Jersey 07013-4221
ATTN: Dr. Robert J. McCormack
Tel: 201-777-2300

DRUG PRODUCT NAME

Proprietary:	PerioChip™
Nonproprietary/USAN:	chlorhexidine digluconate
Code Names/#'s:	CAS RN: 18472-51-0
Chemical Type/ Therapeutic Classes:	3S

ANDA Suitability Petition/DESI/Patent Status: NOT APPLICABLE!
PHARMACOLOGICAL CATEGORY/INDICATION: Antimicrobial/Periodontitis treatment
DOSAGE FORM: A biodegradable gelatin matrix chip

STRENGTHS: 2.5 mgs./chip
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CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOL.WT:
1,1'-hexamethylenebis[5-(p-chlorophenyl)biguanide]di-D-gluconate

Molecular Formula: $C_{34}H_{54}Cl_2N_{10}O_{14}$

Molecular Weight: 897.77
CAS No.: 18472-51-0

SUPPORTING DOCUMENTS:
Original NDA 20-774
NDA 20-774/BC, dated 12/10/97
NDA 20-774/BC, dated 12/17/97

CONSULTS: Not Applicable.

REMARKS/COMMENTS:

The final printed labeling for the PerioProduct's PerioChip outer carton and foil cover has been reviewed for its CMC content.

However, in addition to this CMC labeling review, there continues to be two outstanding deficiencies that are currently being addressed, i.e. the review of a questionable analytical procedure and a deficient DMF, in NDA 20-774/BC, dated 12/10/97, and NDA 20-774/BC, dated 12/17/97. Therefore approval of this labeling does not approve these two outstanding deficiencies.

CONCLUSIONS & RECOMMENDATIONS:
Submission NDA 20-774/BF, which pertains to the final printed labeling for PerioChip, is recommended for APPROVABLE. However, as stated previously, this approval does not pertain to the two outstanding deficiencies currently being reviewed.

/S/
2/6/98
James D. Vidra, Ph.D.
Review Chemist

cc: Orig. ~~IND~~ NDA # 20-774
HFD-540/Division File
HFD-540/ProjMan/Blay
HFD-540/DentOff/Hyman
HFD-540/Chem/Vidra
HFD-540/TeamLdr/DeCamp 2/9/98

filename: N20774.BF

2/20/98

BLN 540

NOV 11 1997

DIVISION OF DERMATOLOGICAL AND DENTAL DRUG PRODUCTS
Review of Chemistry, Manufacturing, and Controls

NDA #: 20-774 CHEM.REVIEW #: 1 REVIEW DATE: 08-AUG-97

SUBMISSION/TYPE	DOCUMENT DATE	CDER DATE	ASSIGNED DATE
ORIGINAL	20-DEC-96	26-DEC-97	30-DEC-97
NDA 20-774/BZ	14-Oct-97	15-Oct-97	20-Oct-97
NDA 20-774/BL	29-Jul-97	31-Jul-97	04-Aug-97
NDA 20-774/BC	05-Sep-97	08-Sep-97	11-Sep-97
NDA 20-774/BC	18-Sep-97	19-Sep-97	24-Sep-97
Desk Copy	14-Oct-97	-	-
IND 35,524	03-APR-96	04-APR-96	-

NAME & ADDRESS OF APPLICANT:

Perio Products, Inc.
7 HaMarpeh Street
P.O. Box 23950
Har Hotzvim Industrial Zone
Jerusalem 91237, Israel
ATTN: Dr. Daniel P. Levy
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Tel: 011-972-2-532-2836
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U.S. AGENT FOR PERIO PRODUCTS:
Oxford Research
Intenational Corporation
1425 Broad Street
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ATTN: Dr. Robert J. McCormack
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DRUG PRODUCT NAME

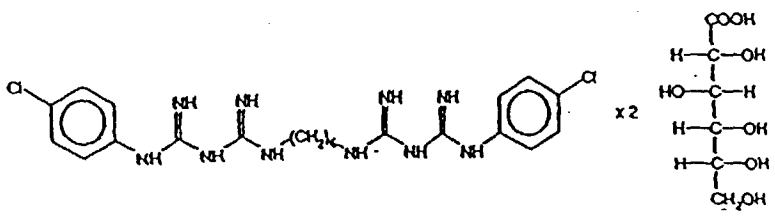
Proprietary: PerioChip™
Nonproprietary/USAN: chlorhexidine digluconate
Code Names/#'s: CAS RN: 18472-51-0
Chemical Type/
Therapeutic Classes: 3S

ANDA Suitability Petition/DESI/Patent Status: NOT APPLICABLE!
PHARMACOLOGICAL CATEGORY/INDICATION: Antimicrobial/Periodontitis treatment
DOSAGE FORM: A biodegradable gelatin matrix chip

STRENGTHS: 2.5 mgs./chip
ROUTE OF ADMINISTRATION: Oral
DISPENSED: X Rx ____ OTC

CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOL.WT:
1,1'-hexamethylenebis[5-(p-chlorophenyl)biguanide]di-D-gluconate

Molecular Formula: $C_{34}H_{54}Cl_2N_{10}O_{14}$



Molecular Weight: 897.77

CAS No.: 18472-51-0

SUPPORTING DOCUMENTS:
DMF
DMF
DMF
DMF
DMF
DMF

CONSULTS:
(1) Nomenclature & Labeling Committee - Trademark Reviewed on 3/4/97 (APPENDIX #1).
(2) Microbiology Consult for the Review of Microbiological Data in the Primary Stability Results (APPENDIX #2).
(3) Establishment Evaluation Request (APPENDIX #3).
(4) Categorical Exclusion of the Environmental Assessment for PerioChip (APPENDIX #4).

REMARKS/COMMENTS:
NDA 20-774 has a 3-S classification for a new drug dosage form, PerioChip, (Chlorhexidine Gluconate Solution, 20%), 2.5 mg/chip. This thin rectangular non-sterile chip is used for the treatment of adult periodontitis. Each 7.4 mg PerioChip contains 2.5 mg chlorhexidine gluconate. This 4.8mm x 3.8mm chip is orange-brown in color, rigid, with the rectangular film rounded on one end for easy insertion. PerioChip is packaged in a blister pack unit containing an aluminum laminate base foil shaped into blisters and covered with a flat aluminum laminate cover foil. The blister pack base holds ten chips in ten separate cavities. The drug substance to be used in the commercialized drug product is manufactured by while the drug substance used in Phase III Pivotal Clinical Trials was manufactured by PerioChip is manufactured by PerioProducts, Ltd., Jerusalem, Israel.

Synthesis of the chlorhexidine gluconate antimicrobial begins with the drug intermediate, chlorhexidine base, which was referred to in another DMF. Thus two DMFs were reviewed for both the

This drug product has the following DEFICIENCIES or INFORMATIONAL REQUESTS:
1. In the Regulatory Specifications & Methods Section, (Vol.1.3, p.308), the complex Analytical Method is considered an inaccurate analytical procedure by PerioProducts which results in a questionable amount of assayed, i.e by as much as a . An alternate analytical procedure should be pursued since is a known

2. DMF DMF, was considered deficient. An FDA Letter dated October 24, 1997 was sent to requesting additional information on eight separate areas.
3. In Vitro Release Rate Specifications provides for specifications for only the first 15 hours. The labeling insert indicates an initial biphasic release within 24 hours followed by an almost linear release

rate for 7-10 days (Vol.1.4, p.253). Please provide release rate specifications for Explain why two in vitro assays exist, i.e.

4. conducted in an agar plate indicated a % of drug was released. The lack of % drug release could suggest that the highly reactive/substantive chlorhexidine gluconate might be reacting with and saturating the agar in the immediate location of the disk to prevent further drug release. An type of release rate assay may be more appropriate.

5. Although Resins are generally tested in accordance with USP Protocol and meet USP Class VI Certification, there was no specific indication that was one of the approved resins. Please provide this information.

6. Confirm that the sampling plan, described in the Regulatory Specifications Section, is conducted on a "per shift" basis or a "per batch" basis.

7. Identify the peaks in Figure 1, Vol.1.3, p.274, depicting the

8. The Molecular Formula is incorrect and should read:

9. The Investigational Drug Product Formulations lacked specific chlorhexidine gluconate (CHG) lot numbers used in the Phase III Clinicals. Provide for the relationship between CHG Batch No.s and PerioChip Lot No.s.

10. A number of labeling changes were made to the CMC portion of the label. All CMC comments will be communicated with all other discipline comments.

PerioProducts, Inc. requested a 24 month expiry date and is recommended for a 24 month expiry date using the bulk drug. The 24 month secondary stability data using the bulk drug also supports the data. A further extension of the expiry date can be obtained as additional positive stablity data is received.

CONCLUSIONS & RECOMMENDATIONS:
This original NDA is recommended as APPROVABLE. A listing of both Deficiencies/Informational Requests are provided in the Remarks Section.

/S/

James D. Vidra, Ph.D.
Review Chemist

cc: Orig. IND#
HFD-540/Division File
HFD-540/ProjMan/Blay
HFD-520/Micro/Marsik
HFD-540/Pharm/See
HFD-540/DentOff/Hyman
HFD-540/Chem/Vidra
HFD-540/TeamLdr/DeCamp
HFD-830/Chen
filename: N20774

WS 11/4/97
JV 11/11/97

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: NDA 20-774

PHARMACOLOGY REVIEW(S)

NDA 20-774

Review and Evaluation of Pharmacology and Toxicology Data Division of Dermatologic and Dental Drug Products (HFD-540)

JUL 11 1997

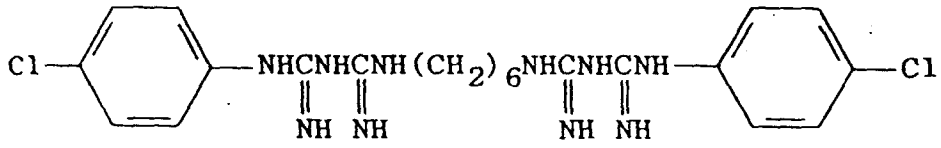
Norman A. See, Ph.D., R.Ph.
Draft Completed: 6/18/97

Original Summary
Submission Date: 12/20/96
Center Receipt Date: 12/20/96

Sponsor: Perio Products, Ltd.

Drug: Chlorhexidine gluconate

Structure:



Formulation: A sustained-release gelatin wafer (the "PerioChip") that is intended for placement within a periodontal pocket:

Component	Percent (w/w)	Amount/Dosage Unit (mg)
Chlorhexidine gluconate		
Gelatin, N.F.		
Purified Water, U.S.P.		
Glycerin, U.S.P.		
Totals	%	mg

Note: Each unit contains approximately 0.1mg of free glutaraldehyde as a residual impurity. Glutaraldehyde is used as a cross-linking agent during manufacture of the units.

Proposed Indication: Periodontal disease

Related Drugs/INDs/NDAs: IND

Maximum Recommended Dosage: One unit per periodontal pocket; the

sponsor estimates that four units would be placed within the oral cavity during a typical treatment episode. However, a patient with severe disease might receive many units (up to one for each remaining tooth). For the purposes of this summary, I will assume that 20 units per treatment episode would represent a realistic worst-case scenario. Therefore, the estimated maximum dosage of chlorhexidine per treatment episode is 50mg. The estimated maximum exposure to free glutaraldehyde is 2mg per treatment episode.

Table of Contents: **Page**

1. Pharmacology. Chlorhexidine is a broad spectrum antimicrobial agent. The mechanism by which chlorhexidine exerts antimicrobial effects is not well defined, but may include damage to the bacterial cell wall through action as a surfactant. Various species of bacteria are thought to be involved in the pathogenesis of periodontal disease, and it is hypothesized that the therapeutic effects of the PerioChip are mediated through effects on the oral flora.

2. ADME, Pharmacokinetics. PerioChip units are intended to provide sustained release of chlorhexidine within a periodontal pocket, resulting in maintenance of the chlorhexidine concentration of the gingival crevicular fluid (GCF) above the minimum inhibitory concentration (MIC) for suspected pathogens. The submission states that placement of a PerioChip unit results in high initial levels of chlorhexidine in the GCF (C_{max} of 1100 to 2000µg/ml, T_{max} 1 to 2 hours), followed by a gradual decline in the concentration, such that the concentration of chlorhexidine in the GCF is maintained above the MIC of "99% of subgingival bacteria" (125µg/ml) for 7 to 10 days. Chlorhexidine was not detected in plasma or urine samples obtained during clinical studies, and chlorhexidine is known to be very poorly absorbed from the GI tract (essentially not at all). A cursory review of a clinical PK study is included below because the level of clinical exposure to the drug substance, or lack of exposure, is germane to the safety evaluation of the drug product. Please see the Biopharmaceutics summary of this submission for critical review of the clinical pharmacokinetic data.

Cursory Review of Submitted Clinical PK Data:

2.1 An *in vivo* study of the chlorhexidine release profile of the PerioChip in the gingival crevicular fluid, plasma, and urine, study No. 95-000A, principle investigator Prof. W.A. Soskolne (Dept. of Periodontology, Hebrew University, Jerusalem, Israel).

This study enrolled 7 male and 12 female human subjects that had adult periodontitis; inclusion criteria included the presence of at least four teeth with periodontal pockets of 5 to 8mm depth which bled upon probing. This population was considered to be representative of the U.S. population of periodontal patients. On day one of the study, baseline samples of gingival crevicular fluid (GCF), blood, and urine were obtained, and four PerioChip units were placed in periodontal pockets (2.5mg chlorhexidine gluconate/unit for 10mg total). Samples of GCF were obtained at 0, 2, 4, 24, 48, 72, 96, 120, 168, 192, and 216 hours after placement. Samples of blood and urine were collected 24, 48, and 96 hours, and 24 and 96 hours following placement, respectively. The limit of quantitation for the analytical method that was used was ng/ml ppb).

Results.

Concentration in GCF. The concentration of chlorhexidine in the GCF peaked within two hours after placement of the PerioChip units, remained fairly constant through 72 hours post-placement,

and tapered over the remainder of the observation period:

Time post-insertion (hours)	Mean Conc. of Chlorhex. in GCF (µg/ml±SD)
0	0
2	2007±1791
4	1444±783
24	1527±651
48	1714±877
72	1902±1073
96	1292±759
120	329±239
168	169±297
192	128±122
216	57±57

Concentration in plasma. Chlorhexidine was not detected in any plasma sample.

Concentration in urine. Chlorhexidine was not detected in any urine sample.

Discussion of data. These data suggest that little or no chlorhexidine is systemically absorbed following placement of PerioChip units within periodontal pockets. These data are not representative of a "worst case" scenario, since only four chips were placed in this study, and it is conceivable that some patients may receive more than four chips (theoretically, 20 or more at one time). However, this study was designed to enroll a population that was considered to be representative of periodontitis patients in the U.S., and these data suggest that substantial systemic exposure to chlorhexidine is unlikely to result from use of the PerioChip. It should be noted that no data were submitted that concerned metabolites of chlorhexidine (which may not have been detected by the analytical technique that was used), and that blood and urine samples were not obtained until 24 hours after dosing, meaning that the C_{max} may have been missed.

3. Toxicology.

3.1 Acute Toxicity. No single-dose (acute) toxicology studies were submitted. Published LD_{50} values for chlorhexidine gluconate are as follows:

Species	Route	LD_{50}
Rat	PO	2000mg/kg
Rat	SC	3320mg/kg
Rat	IV	24mg/kg
Mouse	PO	1260mg/kg
Mouse	SC	1140mg/kg
Mouse	IV	13mg/kg

3.2 Multiple Dose Toxicity.

3.2.1 A 30-day oral toxicity study in the rat with perio chip powder via gastric intubation, study No. 88-3373, in-life 3/89-4/89, report dated 11/21/89, conducted by , in compliance with U.S. Good Laboratory Practice regulations (21 CFR 58).

This study was performed to provide information concerning the effects of ingestion of PerioChip units or their components. PerioChip powder (lot No. ATR-58 31; January, 1989) was studied; PerioChip powder has the same composition as PerioChip units, and contains approximately % chlorhexidine gluconate by weight. Placebo powder that contained no chlorhexidine gluconate was also studied. The test materials were suspended in PEG 400 and administered by gavage to groups of 12 CD (SD) rats of each sex in dosages of 0 (vehicle control), 7.5, 37.5, and 125mg/kg/day ("active" PerioChip powder) and 85mg/kg/day (placebo powder) for 30 consecutive days. The volume administered, and amount of PEG per dose, are not indicated. The mean weights of the male and female rats used were 216 and 155 grams, respectively, meaning that the approximate daily exposures to chlorhexidine gluconate of the male and female animals in the treatment groups were as follows:

Group	Amt. chlorhexidine/day
Low dose males	1.6mg
Low dose females	1.2mg
Mid dose males	8.1mg
Mid dose females	5.8mg
High dose males	27.0mg
High dose females	19.0mg

The dosages used in this study, expressed in terms of chlorhexidine content and averaged for males and females, are compared to the sponsor's estimated "typical" dose (4 units/treatment, or 10mg chlorhexidine gluconate) and to the assumed maximum clinical dosage (20 units/treatment, or 50mg of chlorhexidine gluconate) below:

Rat dose (mg/day)	Multiple of "Typical" human dose (mg/day)	Multiple of "Worst Case" human dose (mg/day)
1.4	0.14	0.028
7.0	0.7	0.14
23	2.3	0.46

Notes: 1) Clinical treatment with PerioChip units would not be repeated for at least three months, whereas animals in this study received the material for 30 consecutive days, providing an additional margin of safety; 2) I believe it is inappropriate to

express oral dosages of chlorhexidine in terms of unit body weight (mg/kg), since the compound is not well absorbed or distributed throughout the body; 3) The above estimations of "dose-multiples" assume that all the chlorhexidine would be released prior to defecation.

The parameters that were monitored included mortality, clinical observations, body weight, food consumption, water consumption, ophthalmology, hematology, blood chemistry, gross pathology, organ weights, and histopathology of the control and high-dose animals. Toxicokinetic analysis was apparently not performed.

Results:

Mortalities. Four high-dose males and two-high-dose females died prematurely (one male died during week 1, the remaining deaths occurred during weeks 2 and 3). No other unscheduled deaths occurred. The report attributed at least some of the deaths to gavage error. However, it must be assumed that the deaths were directly related to treatment, since only high-dose animals were affected. It is possible that the high-dose animals struggled more than the other animals (perhaps due to bad taste of the test material), and that this lead to gavage errors.

Clinical signs. Some of the animals that were later found dead exhibited emaciation, lethargy, dyspnea, ano-genital staining, and reduced food and water consumption. It is unclear if these signs were directly due to the test material or were secondary to damage induced by gavage-error. No other remarkable observations were made.

Ophthalmology. No remarkable observations.

Body weight. Slightly reduced in high-dose males (circa 4%) at termination; it is unclear if this was toxicologically significant. No other remarkable effects.

Food consumption. No remarkable observations.

Hematology. No remarkable observations.

Blood chemistry. No remarkable observations.

Gross necropsy. No remarkable observations.

Organ weights. No remarkable observations.

Histopathology. An increased incidence of liver vacuolization was observed in high-dose females, as was an increased incidence of thymic hemorrhage in high-dose males.

Conclusion. Toxicity was observed only at the highest dose

studied. Since histopathology was not performed on low or mid-dose animals, it cannot be stated that a NOAEL was observed in this study. However, given that this study involved 30 consecutive daily administrations of the test material, whereas clinical use would only involve one administration (at least for several months), these data tend to support the safety of the test material.

3.3 Specialty Toxicology studies.

3.3.1 Hamster cheek pouch irritation assay, study No. MB 89-9480, in-life 5/89-8/89, report dated 6/5/90, conducted by in compliance with U.S. Good Laboratory Practice regulations (21 CFR 58).

This study was performed to provide information concerning the potential of PerioChip units to induce irritation within the oral cavity. Four groups of male Golden Syrian hamsters were used, each group containing 24 animals. Female hamsters were not studied. Treatment groups consisted of animals that were implanted with a PerioChip (group 1), a placebo unit (group 2), a PVC chip (group 3, positive controls), and sham operated animals (group 4). Implantation (on day 0) consisted of anesthetization, eversion of a cheek pouch, placement of 5-0 ethicon suture in a circular (purse string) fashion, placement of the assigned material within the suture-circle (except the group 4 animals, which were sutured in an identical manner but received no test article), and drawing the suture sufficiently tight to retain the material. On day 7, the implanted materials were removed from 8 animals from each of the four treatment groups; four of these animals per group were sacrificed and processed for histopathologic examination and the remaining four animals per group were grossly examined for erythema and edema at the implantation site and allowed to recover for 14 days with gross observations weekly. On day 14, the remaining 16 animals per group had the implanted materials removed. Half of these animals were immediately sacrificed and processed and the remaining animals were examined for erythema and edema and allowed to recover for up to 14 days. Histopathology was limited to the tongue, sublingual salivary glands, left check pouch, and the hard and soft palate.

Results.

Erythema and edema.

1. Animals with implantation removed on day 7:

A. Group 1 (PerioChip): Both erythema and edema rated moderate on day 7, slight on day 14, no reaction on day 21.

B. Group 2 (placebo chip): Both erythema and edema rated slight to moderate on day 7, none to slight on day 14, no reaction on day 21.

C. Group 3 (positive controls): Both erythema and edema ranged from slight to severe on day 7, none to slight on day 14, no reaction on day 21.

D. Group 4 (sham operated): Both erythema and edema ranged from none to severe on day 7, none to slight on day 14, no reaction on day 21.

2. Animals with implantation removed on day 14:

A. Group 1 (PerioChip): Erythema ranged from none to moderate on day 14, no reaction on day 21. Edema slight to moderate on day 14, no reaction on day 21. Note: One animal had an abscess and exhibited severe erythema and edema on day 14; this was probably

an aberration caused by infection of the site that was sutured that was unrelated to the PerioChip.
B. Group 2 (placebo chip): Erythema slight in most animals on day 14, no reaction on day 21 or 28. Edema slight to moderate on day 14, no reaction on day 21 or 28.
C. Group 3 (positive controls): Erythema slight in most animals on day 14, no reaction on day 21 or 28. Edema moderate on day 14, no reaction on day 21 or 28.
D. Group 4 (sham operated): Both erythema and edema ranged from none to slight on day 14, no reaction on day 21.

Histopathology. On day 7, the mucosa and submucosa exhibited edema, granulomatous inflammation, and hemorrhage in all groups, ranging from none to marked. Necrosis of the mucosa was observed only in the positive control group. Overall, animals that received PerioChip units did not exhibit more severe signs of local reaction than did the sham operated animals, suggesting that the PerioChip was not irritating. Similar data were obtained from animals in which the implantation was removed on day 14. The reactions that were observed reversed within 7 to 14 days. No remarkable observations of the tongue, hard or soft palate, or salivary glands were made.

Conclusions. PerioChip units were not excessively irritating under the conditions of this study.

3.3.2 Cytotoxicity assays on Perio Chip powder and perio Chip matrix, study No. 96/1141, in-life 5/89, original report dated 7/10/89, amended report dated 11/6/96 (report amended to include certificates of analysis for the test materials), conducted by in compliance with OECD Good Laboratory Practice regulations.

This study was performed to provide information concerning the potential of PerioChip units to induce local tissue damage. Perio Chip powder (the material used to manufacture Perio Chip units) and Perio Chip matrix (The "vehicle" in PerioChips) were suspended in DMSO and applied to cultured Chinese hamster lung (V79) cells, with and without prior incubation with S-9 mix. Cyclophosphamide and chlorhexidine gluconate were utilized as positive controls. Percentage cell survival (relative to vehicle controls) was calculated for all assays, and the LC_{50} (concentration at which 50% of the cells were killed) was calculated.

Results. PerioChip powder was cytotoxic under the conditions of the study, but partially detoxified by S-9; LC_{50} values of 17µg/ml and 57µg/ml were obtained without and with S-9, respectively. PerioChip matrix was considerably less toxic; LC_{50} values of 300µg/ml and 600-1000µg/ml were obtained without and with S-9, respectively. Chlorhexidine was highly toxic; LC_{50}

values of 1.5µg/ml and 12.2µg/ml were obtained without and with S-9, respectively.

Conclusions. These data confirm that the chlorhexidine released from PerioChips is capable of causing destruction of cells in the vicinity of a chip. However, this was predicable prior to conduct of this study, and these data contribute little to development of the safety profile of the PerioChip.

3.4 Reproductive Toxicology.

3.4.1 A segment II teratology study of hibitane in rats, Study No. 76-1495C, conducted by in-life phase 7/76, conducted prior to enactment of the Good Laboratory Practices regulations.

This study was conducted to assess the teratogenic potential of chlorhexidine gluconate (Hibitane) on pregnant rats during the period of organogenesis. Female Long-Evans rats were paired with a male until mating was confirmed by the presence of either sperm or a copulatory plug in the vagina. The day of confirmation was designated as day 0 of gestation. The study design involved 6 groups of 20 pregnant females each, including two vehicle (water) control groups and treatment groups that received chlorhexidine gluconate at levels of 0.113, 2.167, 6.855, or 68.541mg/kg/day. The animals were treated by gavage on days 6 through 15 of gestation. The daily dose was divided into two equal portions which were administered at least four hours apart. All surviving females were sacrificed and cesarean sectioned on day 20 of gestation; 2/3 of the fetuses were examined for visceral and skeletal abnormalities, and 1/3 were serially sectioned and examined for soft tissue malformations.

Results.

A. F0 females.

Mortality and clinical signs: No unscheduled deaths. Excessive salivation was observed in some high-dose animals.

Mean body weight and weight change: No remarkable observations.

Gross pathology of F0 females: No remarkable findings were observed during gross necropsy of the F0 rats.

Observations made following cesarean section: No remarkable observations were made following cesarian section, including no significant differences in the mean numbers of live fetuses, post-implantation loss, or the numbers of dams with multiple resorptions.

B. Fetal observations:

Mean Fetal Length and Weight: No remarkable observations.

Fetal external evaluations: No remarkable observations were made in regard to external variations or malformations of F1 animals.

Fetal soft tissue evaluations: No remarkable variations or malformations of the viscera were noted.

Fetal skeletal evaluations: No remarkable observations.

Conclusions: Under the conditions of this study, chlorhexidine gluconate was not maternally toxic or teratogenic in rats. This

is not surprising, since the compound is very poorly absorbed from the GI tract.

3.5 Genetic Toxicology.

3.5.1 PerioChip: Mouse micronucleus test, study No. 96/0986, in-life 7/96, conducted by
in compliance with OECD Good Laboratory Practice regulations.

PerioChip powder (suspended in 1% methylcellulose solution) was assessed for effect on the incidence of micronucleated polychromatic erythrocytes in CD-1 mice. The animals each received a single PO dose of either PerioChip powder (310, 620, or 1240mg/kg; equivalent to 105, 210, and 419mg/kg chlorhexidine gluconate, respectively), 1% methylcellulose solution (negative control), or 12mg/kg mytomycin C (positive control). Fifteen mice per gender were tested at each dose of PerioChip powder. Bone marrow smears were obtained from negative control and "PerioChip powder" animals (5/sex/time point) at 24, 48, and 72 hours post-dosing; positive controls (5/sex) were sacrificed at 24 hours only. The smears were processed and examined for the number of micronucleated cells per 1000 polychromatic cells examined; the ratios of polychromatic to normochromatic erythrocytes were recorded.

Results. No statistically significant differences were observed between the test substance and the negative control. A significant increase in the occurrence of micronucleated cells relative to the number of polychromatic erythrocytes was observed in smears from positive control animals. No mortalities or adverse clinical signs were observed.

Conclusions. These data provide no evidence that PerioChip powder (which includes 33% chlorhexidine gluconate and about 1.4% free glutaraldehyde) is clastogenic.

3.5.2 In vitro microbiological mutagenesis studies of four Colgate Palmolive compounds, study No. RPA 00024, report dated 8/77, conducted by
prior to enactment of Good Laboratory Practice regulations.

S. typhimurium strains TA 98, TA 100, TA 1535, TA 1537, and TA 1538 were plated with chlorhexidine gluconate; the amount of test material per plate ranged from µg (excessive cytotoxicity was observed at higher concentrations). Assays were conducted with and without metabolic activation (S9 produced from Aroclor-induced rat liver). Appropriate positive control compounds were used.

Results. No significant increase in the reverse mutation rate was observed at any concentration of test material, in either the presence or absence of S9. Appropriate responses were induced by the positive control substances.

Conclusions. This study provided no evidence that the test material was mutagenic.

3.5.3 Evaluation of clastogenic potential of chlorhexidine digluconate using Chinese hamster ovary cells, study No. 85/21/11, in-life 5/85, conducted by in compliance with Good Laboratory Practice regulations.

Chlorhexidine gluconate was assayed for the ability to induce chromosomal aberrations in cultured CHO-WBL cells, both in the presence and in the absence of metabolic activation (S9). The cells were exposed to chlorhexidine gluconate in concentrations ranging up to 100µg/ml according to standard procedures. Water was used as a negative control; cyclophosphamide was used as a positive control in experiments with S9, and triethylene melamine was used as a positive control in experiments without S9. All cultures were treated with colchicine prior to harvest. Prepared slides were examined for chromosomal aberrations.

Results. Exposure to chlorhexidine gluconate did not remarkably increase the frequency of occurrence of chromosomal aberrations, either with or without metabolic activation. The positive control compounds did significantly increase the incidence of chromosomal aberrations.

Conclusions. This study provided no evidence that chlorhexidine gluconate is clastogenic.

3.6 Carcinogenicity. The subject of NDA 20-774 has not been assessed for potential as a carcinogen. However, the drug product would not be used on a chronic basis, making such assessment unnecessary.

3.7 Impurities.

3.7.1 Glutaraldehyde. Each unit contains approximately mg of free glutaraldehyde as a residual impurity. According to the submission, typical use of the product would result in placement of approximately four units within the oral cavity (mg of glutaraldehyde). Theoretically, up to 32 units (one for each tooth) might be placed within an oral cavity during a single treatment episode, resulting in exposure to up to mg of glutaraldehyde (probably on a single occasion, although additional treatments might be administered at intervals of several months). To place this in perspective, the American Conference of Government and Industrial Hygienists (ACGIH) has recommended that the concentration of glutaraldehyde in air in a workplace not exceed mg/m^3; this level of exposure hours per day, days per week, for a lifetime is considered by the ACGIH to be without appreciable risk. Utilizing the standard assumption that approximately 7m^3 of air is inhaled during a typical hour work day, this would result in inhalation of approximately mg of glutaraldehyde per day. This level of exposure is considered by most European countries (and Australia) to present an acceptable level of risk, although the USA (OSHA) currently has no official acceptable exposure level for glutaraldehyde. In this context, it is apparent that occasional exposure to between mg of glutaraldehyde should present an acceptable level of risk, especially in consideration of the potential benefit to be derived from use of the product.

3.7.2 p-Chloroaniline. The amount of p-chloroaniline would be controlled at µg per PerioChip. Assuming (in the worst case) a level of µg per PerioChip, typical use of the product (placement of 4 units) would result in a single exposure to µg of p-chloroaniline. If 32 units were placed (worst case), the patient would be exposed to µg of p-chloroaniline on a single occasion. To place this in perspective, Peridex, which contains % chlorhexidine gluconate, has a specification for a maximum of ppm p-chloroaniline in the drug product. The recommended dosage of Peridex is ml per day (to be repeated indefinitely). A single day's dose of Peridex could therefore contain up to µg of p-chloroaniline. Exposure to p-chloroaniline as a result of use of PerioChip units should be considered to be acceptably safe.

Summary:

Pharmacology: Chlorhexidine is a broad spectrum antimicrobial agent. The mechanism by which chlorhexidine exerts antimicrobial effects is not well defined, but may include damage to the bacterial cell wall through action as a surfactant. Various species of bacteria are thought to be involved in the pathogenesis of periodontal disease, and it is hypothesized that the therapeutic effects of the PerioChip are mediated through effects on the oral flora.

Animal pharmacokinetics: PerioChip units are intended to provide sustained release of chlorhexidine within a periodontal pocket, resulting in maintenance of the chlorhexidine concentration of the gingival crevicular fluid (GCF) above the minimum inhibitory concentration (MIC) for suspected pathogens. The submission states that placement of a PerioChip unit results in high initial levels of chlorhexidine in the GCF (C_{max} of 1100 to 2000µg/ml, T_{max} 1 to 2 hours), followed by a gradual decline in the concentration, such that the concentration of chlorhexidine in the GCF is maintained above the MIC of "99% of subgingival bacteria" (125µg/ml) for 7 to 10 days. Chlorhexidine was not detected in plasma or urine samples obtained during clinical studies, and chlorhexidine is known to be very poorly absorbed from the GI tract.

Acute toxicology: No single-dose (acute) toxicology studies were submitted. Published LD_{50} values for chlorhexidine gluconate are as follows:

Species	Route	LD_{50}
Rat	PO	2000mg/kg
Rat	SC	3320mg/kg
Rat	IV	24mg/kg
Mouse	PO	1260mg/kg
Mouse	SC	1140mg/kg
Mouse	IV	13mg/kg

Multiple-dose toxicology: Data from a 30-day toxicity study in which rats received PerioChip powder by gavage are difficult to interpret, but suggested that toxicity may have been observed in the high-dose group. Observed signs of toxicity included mortality, emaciation, lethargy, dyspnea, ano-genital staining, reduced food and water consumption, and increased incidences of liver vacuolization in high-dose females and thymic hemorrhage in high-dose males. The study report suggested that the gross effects may have been secondary to gavage errors. Since histopathology was not performed on low or mid-dose animals, it cannot be stated that a NOAEL was observed in this study. However, given that this study involved 30 consecutive daily

administrations of the test material, whereas clinical use would only involve one administration (at least for months at a time), these data tend to support the safety of the test material.

Potential to cause local irritation: When held against the mucosa of a hamster cheek pouch for 7 or 14 days, PerioChip units did not appear to be excessively irritating, producing only minor reactions that were reversible within 7 days.

Reproductive toxicology:

Fertility/reproductive success. PerioChip units are not proposed for chronic use; NDA 20-774 does not require support from fertility data.

Teratology/fetal toxicity. Chlorhexidine gluconate was not maternally toxic or teratogenic in rats. The compound has not been tested for teratogenic effects in a non-rodent species in connection with NDA 20-774 (it was tested in rabbits and the results were negative, but those data do not belong to the sponsor). However, chlorhexidine gluconate has extremely low bioavailability in both a wide range of animal species and in humans (<1% of an oral dose is absorbed), and in my opinion, in view of: 1) the extremely low exposure to chlorhexidine that is proposed in NDA 20-774; and 2) the history of safe use of chlorhexidine products worldwide for over 20 years, additional teratology data are not necessary to support NDA 20-774.

Peri/post-natal assessment. PerioChip units are not proposed for chronic use; NDA 20-774 does not require support from peri/post-natal data.

Genetic Toxicology: No evidence that chlorhexidine gluconate has potential to cause genetic toxicity was obtained in a battery of mutagenicity studies, including (*in vitro*) an Ames test, a chromosome aberration assay in CHO cells, and (*in vivo*) a micronucleus assay conducted in mice.

Carcinogenicity: Chlorhexidine gluconate has not been assessed for potential as a carcinogen in connection with NDA 20-774. However, such assessment is unnecessary, since this NDA is for a drug product that is not labeled for chronic use.

Labeling: The following modifications of the draft labeling of NDA 20-774 are recommended:

1. Please change this section to read:

2. Please change this section to read:

Evaluation: Please see page 20 of this document for a summary of the pharmacology and toxicology of the drug substance and product.

In addition, chlorhexidine gluconate has been used clinically at much higher levels of exposure than proposed in this NDA without serious adverse consequences. In view of the database accumulated during over 20 years of human use of chlorhexidine gluconate, the existing nonclinical data are adequate to support the safety of NDA 20-774.

Recommendations: NDA 20-774 is approvable in regard to pharmacologic and toxicologic concerns. Recommended changes in the product label are indicated above.

/S/ 6/18/97

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Reviewing Pharmacologist

cc:
NDA 20-774
HFD-540 Div. File
HFD-540/TL/JACOBS
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HFD-540/MO/HYMAN
HFD-540/CHEM/VIDRA
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