# CENTER FOR DRUG EVALUATION AND RESEARCH

*APPLICATION NUMBER:*

**21-451**

## CHEMISTRY REVIEW(S)

# Memo to file

NDA 21451: Oraqix® (Lidocaine and prilocaine periodontal gel) 2.5%/2.5%, 1.7 g
CMC Review # 4
Ravi S. Harapanhalli, Ph.D.
Acting Chemistry Team Leader, HFD-170
December 17, 2003

CMC review # 3 from Mike Theodorakis, Ph.D., was filed into the DFS on December 10, 2003. This review and the secondary review by Ravi S. Harapanhalli, Ph.D. identified the following four minor CMC issues that needed to be addressed by Dentsply before the approval of this NDA. Consequently, Review # 3 recommended "approvable" pending satisfactory resolution of the identified issues. Dentsply submitted an amendment dated December 11, 2003 and responded satisfactorily to the four comments. These are reviewed here. The NDA is therefore recommended for "approval".

FDA Question 1:

Revise the stability commitment by replacing the phrase "and/or discuss the deviation..." with "and discuss the deviation....".

Dentsply response:

Revised stability protocol for post approval stability studies is provided with the recommended revisions.

Evaluation: Adequate

The revised post approval stability protocol is attached and it conforms to the recommended changes.

FDA Question 2:

Revise the stability protocol for post approval stability studies to include testing of microbial quality at 18 and 36 months.

Dentsply response:

Revised stability protocol for post approval stability studies is provided with the recommended revisions.

Evaluation: Adequate

The revised post approval stability protocol is attached and it conforms to the recommended changes.

FDA Question 3:

Revise the stability protocol with a provision for annual testing for the in vitro drug release.

Dentsply response:

Revised stability protocol for post approval stability studies is provided with the recommended revisions.

Evaluation: Adequate

The revised post approval stability protocol is attached and it conforms to the recommended changes.

FDA Question 4:

Revise the drug product specifications for the degradants as follows:

Replace "any single impurity: NMT [redacted] %" with "Individual unspecified drug-related degradation product: NMT [redacted] %"

Replace "Total impurities: NMT [redacted] %" with "Total (sum of all reportable degradation products > [redacted]%): NMT [redacted] %"

Dentsply response:

Revised specification sheet for the drug product is provided. However, the wordings are slightly different.

Evaluation: Adequate

The following wordings are described in the specifications.

Individual unspecified: NMT [redacted] %
Total (sum of all individual unspecified > [redacted]) NMT [redacted] %.

# 3 Page(s) Withheld

0 § 552(b)(4) Trade Secret / Confidential

_____ § 552(b)(4) Draft Labeling

_____ § 552(b)(5) Deliberative Process

*Withheld Track Number: Chemistry-* 1

---

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

---

/s/

---

Ravi Harapanhalli
12/17/03 06:19:29 PM
CHEMIST
AP.

# NDA 21-451

## Oraqix (lidocaine and prilocaine) Periodontal Gel, 2.5%/2.5%

Dentsply Pharmaceutical

Michael C. Theodorakis, Ph.D.

Division of New Drug Chemistry II
(HFD-820)

Division of Anesthetic, Critical Care
and
Addiction Drug Products
(HFD-170)

# Table of Contents

Chemistry Assessment Section

# Chemistry Review Data Sheet

1. NDA 21-451

2. REVIEW # 3

3. November 25, 2003

4. Michael C. Theodorakis, Ph.D.

5. PREVIOUS DOCUMENTS:

| Previous Documents | Document Date |
|---|---|
| Original | 22-JAN-2002 |

6. SUBMISSION(S) BEING REVIEWED:

| Submission(s) Reviewed | Document Date |
|---|---|
| | 6/19/03 |
| Amendments | 9/17/2003 |
| | 11/21/2003 |

7. NAME & ADDRESS OF APPLICANT:

| | |
|---|---|
| Name: | Dentsply Pharmaceutical |
| Address: | Concord Executive Center<br>3427 Concord Road<br>York, PA 17402 |
| Representative: | Lee A. Zagar<br>Director |
| Telephone: | 717-757-0200 |

8. **DRUG PRODUCT NAME/CODE/TYPE:**

a. Proprietary Name: Oraqix Periodontal Gel
b. Non-Proprietary Name lidocaine and prilocaine Periodontal Gel, 2.5%/2.5%,
c. Code Name/# :
d. Chem. Type/Submission Priority (ONDC only):
Chem. Type : 3
Submission Priority: S

9. **LEGAL BASIS FOR SUBMISSION:**

505(b)

10. **PHARMACOL. CATEGORY:**

Local dental anesthetic

11. **DOSAGE FORM:**

Gel

12. **STRENGTH/POTENCY:**

2.5% lidocaine and 2.5% prilocaine
1 g of gel contains 25 mg lidocaine and 25 mg prilocaine
Cartridge contains 1.7 g (1.8 mL) of gel

13. **ROUTE OF ADMINISTRATION:**

Periodontal

14. **Rx/OTC DISPENSED:** __X_Rx ___OTC

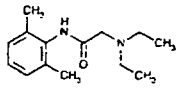
15. **SPOTS (SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM):**

_____SPOTS product - Form Completed

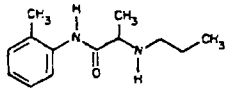
____x_____Not a SPOTS product

## 16. CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOLECULAR WEIGHT:

**Lidocaine** (lye' doe kane). **USP.** $C_{14}H_{22}N_2O$. 234.34. [Lignocaine is BAN.] (1) Acetamide, 2-(diethylamino)-*N*-(2,6-dimethylphenyl)-; (2) 2-(Diethylamino)-2',6'-acetoxylidide. *CAS-137-58-6.* INN; JAN. *Anesthetic (topical).* Lida-Mantle (Bayer†); Solarcaine Aloe Extra Burn Relief Cream (Schering-Plough HealthCare); Xylocaine (Astra); component of Cracked Heel Relief Cream (Schering-Plough HealthCare); component of Emla Cream (Astra); component of Lidaform-HC (Bayer†); component of Lidamantle-HC (Bayer†); component of Neosporin Plus (Glaxo Wellcome†)



**Prilocaine** [*1996*] (pril' oh kane). $C_{13}H_{20}N_2O$. 220.31. (1) Propanamide, *N*-(2-methylphenyl)-2-(propylamino)-; (2) 2-(Propylamino)-*o*-propionotoluidide. *CAS-721-50-6.* INN; BAN. *Anesthetic (local).* (Astra Pharmaceutical Production AB, Sweden); component of EMLA Cream (Astra)



17. RELATED/SUPPORTING DOCUMENTS:

A. DMFs:

| DMF # | TYPE | HOLDER | ITEM REFERENCED | CODE[1] | STATUS[2] | DATE REVIEW COMPLETED | COMMENTS |
|---|---|---|---|---|---|---|---|
| | III | | | 1 | Adequate | 10/10/02 | |
| | III | | | 1 | Adequate | 10/14/02 | |
| | IV | | | 7 | Adequate | Not reviewed | NF grade excipient |

[1] Action codes for DMF Table:
1 - DMF Reviewed.
Other codes indicate why the DMF was not reviewed, as follows:
2 -Type 1 DMF
3 - Reviewed previously and no revision since last review
4 - Sufficient information in application
5 - Authority to reference not granted
6 - DMF not available
7 - Other (explain under "Comments")

[2] Adequate, Inadequate, or N/A (There is enough data in the application, therefore the DMF did not need to be reviewed)

B. Other Documents:

| DOCUMENT | APPLICATION NUMBER | DESCRIPTION |
|---|---|---|
| NDA | 19-941; approved | EMLA (lidocaine 2.5%, prilocaine 2.5%) Cream |
| NDA | 20-962; approved | EMLA (lidocaine 2.5% prilocaine 2.5%) Cream Topical Adhesive System |
| | | |
| | | |
| | | |
| | | |
| | | |

18. STATUS:

| CONSULTS/CMC RELATED REVIEWS | RECOMMENDATION | DATE | REVIEWER |
|---|---|---|---|
| Biometrics | N/A | | |
| EES | acceptable | 10/15/03 | Janine D' Ambrogio |
| Pharm/Tox | o-toluidine levels, acceptable also poloxamer | 11/8/02<br>11/12/02 | Timothy J. McGovern |
| Biopharm | N/A | | |
| LNC | acceptable | 12/2/03 | Dan Boring concurred with the name |
| Methods Validation | In-process/On going | | |
| OPDRA | No objection, comments | 10/3/02 | Tia M. Harper-Velazquez |
| EA | N/A (categorical exclusion claim) | | |
| Microbiology | Does not need to be sterile | 11/8/02 | Paul S. Stinavage |

## The Chemistry Review for NDA 21-451

### The Executive Summary:

### I. Recommendations

#### A. Recommendation and Conclusion on Approvability:

From the Chemistry standpoint this Application is approvable. The comments listed in the draft letter must be conveyed to the Applicant. The Applicant has already been contacted for these comments (telcon 12/8/03).

There was a concern raised by the review team that the product could have been inadvertently injected because the cartridge looked very similar to dental drug products that have been designed to be administered as injections. The Applicant addressed this concern by placing a collar on the cartridge. This modification makes it impossible for the cartridge to fit into the

dental syringes. A special dispenser was developed for the modified cartridge.

B. Recommendation on Phase 4 (Post-Marketing) Commitments, Agreements, and/or Risk Management Steps, if Approvable:

No Phase IV commitments were made.

## II. Summary of Chemistry Assessments

### A. Description of the Drug Product(s) and Drug Substance(s)

The drug substances, lidocaine and prilocaine are the same active ingredients as those used in EMLA (lidocaine 2.5% and prilocaine 2.5%) Cream, which was approved under NDA 19-941 and NDA 20-962. Any information concerning the production and testing of lidocaine and prilocaine drug substances was incorporated into this NDA by reference to the approved NDA 19-941. The names and addresses of the suppliers and testers of these drug substances and the regulatory specifications for acceptance of lidocaine and prilocaine as well as the impurities were included in this review.

Oraqix (lidocaine 2.5% and prilocaine 2.5%) Gel has been developed for application into the periodontal pocket prior to scaling procedures. The formulation is similar to that of EMLA Cream. It contains the same active ingredients, that is, a eutectic mixture of lidocaine and prilocaine in a ratio of 1:1. This gel contains purified poloxamer 407 and 188 to give the formulation thermoreversible gelling properties.

### B. Description of How the Drug Product is Intended to be Used

The formulation will be applied to the periodontal pocket using a standard dental cartridge system equipped with a blunt applicator. Once applied, the body temperature will cause an increase in viscosity making the formulation stay in the pocket for the time necessary to induce local anesthesia.

The dental cartridge system is composed of a ——— glass cartridge (1.8 mL) with a rubber plunger ——————————— and a

"combi cap" made of aluminum and rubber

A plastic collar has been attached to the cartridge so that the dental cartridge cannot fit into the various dental syringes available in the market. This for the purpose of avoiding accidental injection of the contents of the cartridge. The dental cartridge has been designed to fit into a specially designed dispenser.

The dental applicator is sterile and disposable (single use) and it is made of stainless steel

The applicator has a cap and case made of . The cap and case are sealed.

The dental applicator will only be sold as an integral part of the Oraqix package. It is very similar in design to dental needles. The only difference is that the dental applicator has a blunt tip as opposed to the sharp tip of the dental needle. The Applicant maintained that the difference between the dental applicator and the common dental needle was insignificant. Since dental syringes are considered as Class I Medical Devices that are exempt from 510(k) submission (see 21 CFR 872.4730), the dental applicator should also be considered as Class I Medical Device.

The dental dispenser will not be supplied with the drug product. None of the componets of the dental dispenser are coming in direct contact with the gel.

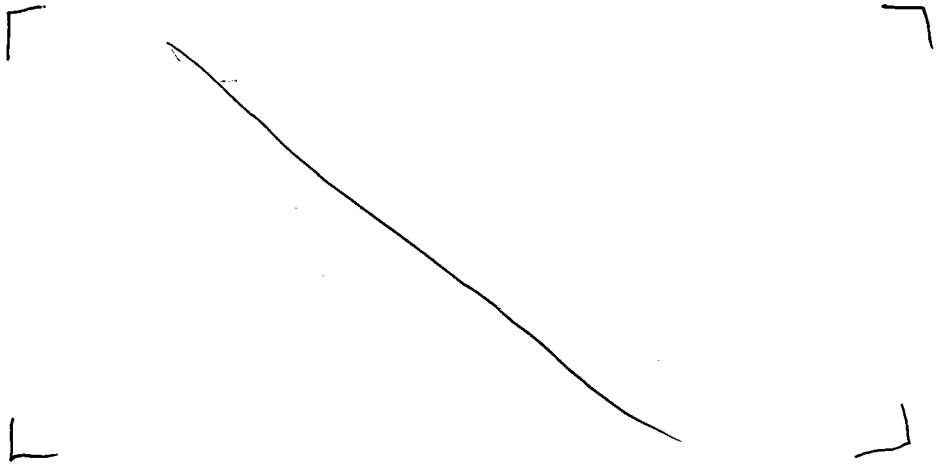
CDRH reviewed the device componet of Oraqix and determined that the components were safe and effective for their intended use (see Consult review by Robert S. Betz of CDRH dated 11/19/03).

The maximum daily dose (MDD) is 212.5 mg of lidocaine and 212.5 mg of prilocaine.

**C. Basis for Approvability or Not-Approval Recommendation**

All CMC aspects have been adequately addressed and supported by data. The Applicant provided a narrative description and flow diagrams describing the manufacturing process for Oraqix Dental Gel. Also it

included executed batch records for solution preparation and filling of one of the full scale batches used in the primary stability program for the drug, and blank master batch records that detail the intended commercial process up through filling of the product.



The Applicant provided 36 month stability data on three commercial lots stored at 25°C/60% RH, 36 months at 30°C/50% RH, and — months at 40°C/75% RH. In addition, stability data on pilot scale lots for up to — months as well as results of temperature cycle and photo stability testing were included in this submission.

The 36-month data at 25°C/60% RH and — month data at 30°C/50% RH, and — months at 40°C/75% RH showed that the product was stable and all values were well within specifications. The — month data from a pilot scale batch were also well within specifications. Additional tests showed that the product was stable under UV light and during transportation.

Statistical analysis of the 36 months data showed that the drug product will be stable for 36 months when stored at 25°C/60%RH and — months at 30°C/50%RH. Based on these data, the Applicant requested a shelf life of 36 months when stored between 5°C and 30°C with the only restriction is that the drug product should not be frozen. The Applicant's request should be granted.

The Compliance has found all facilities involved in the manufacturing of this drug product to be acceptable.

Microbiology consult review indicated that this product does not need to be sterile.

The Applicant requested a categorical exclusion pursuant to 21 CFR 25.31(b). This was based on the Applicant's certification that the estimated concentration of the substance at the point of entry into the aquatic environment will be below 1 part per billion (ppb), calculated according to FDA's Guidance for Industry, Environmental Assessment of Human Drug and Biologics Applications, July 1998.

## III. Administrative

### A. Reviewer's Signature

### B. Endorsement Block

Review Chemist/MCTheodorakis/
Acting Team Leader/RSHarapanhalli/
CSO/KCompton/

### C. CC Block

19 Page(s) Withheld

0 § 552(b)(4) Trade Secret / Confidential

_____ § 552(b)(4) Draft Labeling

_____ § 552(b)(5) Deliberative Process

*Withheld Track Number: Chemistry-* 2

---

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

---

/s/

---

Michael Theodorakis
12/10/03 09:50:07 AM
CHEMIST

Ravi Harapanhalli
12/10/03 10:17:00 AM
CHEMIST

AE pending resolution of four CMC issues conveyed to the sponsor on 12/8/03. Sponsor should provide revised specification sheet for the DP and revised stability protocol in an amendment to the NDA.

# NDA 21-451

## Oraqix (lidocaine 2.5% and prilocaine 2.5%) Dental Gel

**Dentsply Pharmaceutical**

**Michael C. Theodorakis, Ph.D.**

**Division of New Drug Chemistry II**
**(HFD-820)**

**Division of Anesthetic, Critical Care**
**and**
**Addiction Drug Products**
**(HFD-170)**

# Table of Contents

# Chemistry Review Data Sheet

1. NDA 21-451

2. REVIEW # **2**

3. November 15, 2002

4. **Michael C. Theodorakis, Ph.D.**

5. **PREVIOUS DOCUMENTS:**

| Previous Documents | Document Date |
|---|---|
| Original | 22-JAN-2002 |
| Amendment BC | 14-MAR-2002 |
| Amendment BC | 27-JUN-2002 |
| Amendment BC | 16-AUG-2002 |
| Amendment BC | 20-SEP-2002 |

6. **SUBMISSION(S) BEING REVIEWED:**

| Submission(s) Reviewed | Document Date |
|---|---|
| Amendment BC | 13-NOV-2002 |

7. **NAME & ADDRESS OF APPLICANT:**

Name: Dentsply Pharmaceutical

Address: Concord Executive Center
3427 Concord Road
York, PA 17402

Representative: Lee A. Zagar
Director

Telephone: 717-757-0200

8. DRUG PRODUCT NAME/CODE/TYPE:

a) Proprietary Name: Oraqix Periodontal Gel
b) Non-Proprietary Name lidocaine 2.5% and prilocaine 2.5% gel
c) Code Name/# :
d) Chem. Type/Submission Priority (ONDC only):

- Chem. Type : 3
- Submission Priority: S

9. LEGAL BASIS FOR SUBMISSION:

505(b)

10. PHARMACOL. CATEGORY:

Local dental anesthetic

11. DOSAGE FORM:

Gel

12. STRENGTH/POTENCY:

2.5% lidocaine and 2.5% prilocaine
1 g of gel contains 25 mg lidocaine and 25 mg prilocaine

13. ROUTE OF ADMINISTRATION:

Oral

14. Rx/OTC DISPENSED: __X_Rx ___OTC

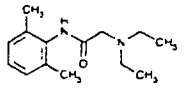
15. SPOTS (SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM):

_____SPOTS product - Form Completed

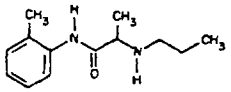
____x_____Not a SPOTS product

16. CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOLECULAR WEIGHT:

**Lidocaine** (lye' doe kane). **USP.** $C_{14}H_{22}N_2O$. 234.34. [Lignocaine is BAN.] (1) Acetamide, 2-(diethylamino)-*N*-(2,6-dimethylphenyl)-; (2) 2-(Diethylamino)-2',6'-acetoxylidide. *CAS-137-58-6.* INN; JAN. *Anesthetic (topical).* Lida-Mantle (Bayer†); Solarcaine Aloe Extra Burn Relief Cream (Schering-Plough HealthCare); Xylocaine (Astra); component of Cracked Heel Relief Cream (Schering-Plough HealthCare); component of Emla Cream (Astra); component of Lidaform-HC (Bayer†); component of Lidamantle-HC (Bayer†); component of Neosporin Plus (Glaxo Wellcome†)



**Prilocaine** [*1996*] (pril' oh kane). $C_{13}H_{20}N_2O$. 220.31. (1) Propanamide, *N*-(2-methylphenyl)-2-(propylamino)-; (2) 2-(Propylamino)-*o*-propionotoluidide. *CAS-721-50-6.* INN; BAN. *Anesthetic (local).* (Astra Pharmaceutical Production AB, Sweden); component of EMLA Cream (Astra)



17. RELATED/SUPPORTING DOCUMENTS:

**A. DMFs:**

| DMF # | TYPE | HOLDER | ITEM REFERENCED | CODE[1] | STATUS[2] | DATE REVIEW COMPLETED | COMMENTS |
|---|---|---|---|---|---|---|---|
| | III | | | 1 | Adequate | 10/10/02 | |
| | III | | | 1 | Adequate | 10/14/02 | |
| | IV | | | 7 | Adequate | Not reviewed | NF grade excipient |

[1]Action codes for DMF Table:
1 - DMF Reviewed.
Other codes indicate why the DMF was not reviewed, as follows:
2 -Type 1 DMF
3 - Reviewed previously and no revision since last review
4 - Sufficient information in application
5 - Authority to reference not granted
6 - DMF not available
7 - Other (explain under "Comments")

[2]Adequate, Inadequate, or N/A (There is enough data in the application, therefore the DMF did not need to be reviewed)

**B. Other Documents:**

| DOCUMENT | APPLICATION NUMBER | DESCRIPTION |
|---|---|---|
| NDA | 19-941; approved | EMLA (lidocaine 2.5%, prilocaine 2.5%) Cream |
| NDA | 20-962; approved | EMLA (lidocaine 2.5% prilocaine 2.5%) Cream Topical Adhesive System |
| | | |
| | | |
| | | |
| | | |
| | | |

18. STATUS:

| CONSULTS/CMC RELATED REVIEWS | RECOMMENDATION | DATE | REVIEWER |
|---|---|---|---|
| Biometrics | N/A | | |
| EES | acceptable | 11/15/02 | Janine D' Ambrogio |
| Pharm/Tox | o-toluidine levels, acceptable also poloxamer | 11/8/02<br>11/12/02 | Timothy J. McGovern |
| Biopharm | N/A | | |
| LNC | N/A | | |
| Methods Validation | In-process | | |
| OPDRA | No objection, comments | 10/3/02 | Tia M. Harper-Velazquez |
| EA | N/A | | |
| Microbiology | Does not need to be sterile | 11/8/02 | Paul S. Stinavage |

The Chemistry Review for NDA 21-397

The Executive Summary:

I. Recommendations

## II. Summary of Chemistry Assessments

### A. Description of the Drug Product(s) and Drug Substance(s)

The drug substances, lidocaine and prilocaine are the same active ingredients as those used in EMLA (lidocaine 2.5% and prilocaine 2.5%) Cream, which was approved under NDA 19-941 and NDA 20-962. Any information concerning the production and testing of lidocaine and prilocaine drug substances was incorporated into this NDA by reference to the approved NDA 19-941. The names and addresses of the suppliers and testers of these drug substances and the regulatory specifications for acceptance of lidocaine and prilocaine as well as the impurities were included in this review.

Oraqix (lidocaine 2.5% and prilocaine 2.5%) Gel has been developed for application into the periodontal pocket prior to scaling procedures. The formulation is similar to that of EMLA Cream. It contains the same active ingredients, that is, a eutectic mixture of lidocaine and prilocaine in a ratio of 1:1. This gel contains purified poloxamer 407 and 188 to give the formulation thermoreversible gelling properties.

### B. Description of How the Drug Product is Intended to be Used

The formulation will be applied to the periodontal pocket using a standard dental cartridge system equipped with a blunt applicator. Once applied, the body temperature will cause an increase in viscosity making the formulation stay in the pocket for the time necessary to induce local anesthesia.

The dental cartridge system is composed of a ' glass cartridge (1.8 mL) with a rubber plunger and a "combi cap" made of aluminum and rubber ). The dental applicator for single use is made of stainless steel . The applicator has a cap and case made of . The cap and case are sealed.

The dental applicator will only be sold as an integral part of the Oraqix package. It is very similar in design to dental needles. The only difference is that the dental applicator has a blunt tip as opposed to the sharp tip of the dental needle. The Applicant maintained that the difference between the dental applicator and the common dental needle was insignificant. Since dental syringes are considered as Class I Medical Devices that are exempt from 510(k) submission (see 21 CFR 872.4730), the dental applicator should also be considered as Class I Medical Device.

The dental cartridge syringe will not be supplied with the drug product. It is not part of this Application. Dental cartridge syringes are considered Class II medical devices (see 21 CFR 872.6770) and are commonly available in all dental offices. The dental cartridge syringe does not come in direct contact with the gel.

The maximum daily dose (MDD) is 212.5 mg of lidocaine and 212.5 mg of prilocaine.

**C. Basis for Approvability or Not-Approval Recommendation**

All CMC aspects have been adequately addressed and supported by data. The Applicant provided a narrative description and flow diagrams describing the manufacturing process for Oraqix Dental Gel. Also it included executed batch records for solution preparation and filling of one of the full scale batches used in the primary stability program for the drug, and blank master batch records that detail the intended commercial process up through filling of the product.

The Applicant provided — month stability data on three commercial lots stored at 25°C/60% RH and 30°C/50% RH, and ~ months at 40°C/75% RH. In addition, stability data on pilot scale lots for up to ~ months as well as results of temperature cycle and photo stability testing were included in this submission.

The ~ month data at 25°C/60% RH and 30°C/50% RH, and ~ months at 40°C/75% RH showed that the product was stable and all values were well within specifications. The— month data from a pilot scale batch were also well within specifications. Additional tests showed that the product was stable under UV light and during transportation.

Statistical analysis of the — months data showed that the drug product will be stable for — months when stored at 25°C/60%RH or at 30°C/50%RH. Based on these data, the Applicant requested a shelf-life of —months when stored between 5°C and 30°C with the only restriction is that the drug product should not be frozen.

The Compliance has found all facilities involved in the manufacturing of this drug product to be acceptable.

Microbiology consult review indicated that this product does not need to be sterile.

The Applicant requested a categorical exclusion pursuant to 21 CFR 25.31(b). This was based on the Applicant's certification that the estimated concentration of the substance at the point of entry into the aquatic environment will be below 1 part per billion (ppb), calculated according to FDA's Guidance for Industry, Environmental Assessment of Human Drug and Biologics Applications, July 1998.

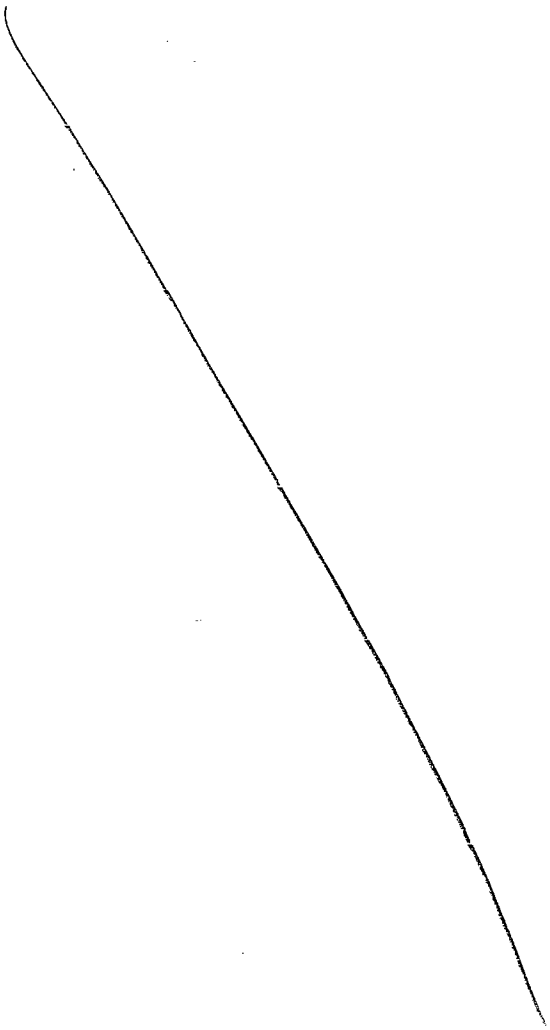
## III. Administrative

### A. Reviewer's Signature

### B. Endorsement Block

Review Chemist/MCTheodorakis/September 7, 2002
Team Leader/DLKoble/
CSO/KCompton/

### C. CC Block



17 Page(s) Withheld

0 § 552(b)(4) Trade Secret / Confidential

_____ § 552(b)(4) Draft Labeling

_____ § 552(b)(5) Deliberative Process

*Withheld Track Number: Chemistry* 3

# NDA 21-451

## Oraqix (lidocaine 2.5% and prilocaine 2.5%) Dental Gel

Dentsply Pharmaceutical

Michael C. Theodorakis, Ph.D.

Division of New Drug Chemistry II
(HFD-820)

Division of Anesthetic, Drug Addiction
and
Critical Care Drug Products
(HFD-170)

# Table of Contents

# Chemistry Review Data Sheet

1. NDA 21-451

2. REVIEW # 1

3. September 26, 2002

4. **Michael C. Theodorakis, Ph.D.**

5. **PREVIOUS DOCUMENTS:**

| Previous Documents | Document Date |
|---|---|
| N/A Original application | |

6. **SUBMISSION(S) BEING REVIEWED:**

| Submission(s) Reviewed | Document Date |
|---|---|
| Original | 22-JAN-2002 |
| Amendment BC | 14-MAR-2002 |
| Amendment BC | 27-JUN-2002 |
| Amendment BC | 16-AUG-2002 |
| Amendment BC | 20-SEP-2002 |

7. **NAME & ADDRESS OF APPLICANT:**

Name: Dentsply Pharmaceutical

Address: Concord Executive Center
3427 Concord Road
York, PA 17402

Representative: Lee A. Zagar
Director

Telephone: 717-757-0200

8. DRUG PRODUCT NAME/CODE/TYPE:

a) Proprietary Name: Oraqix Dental Gel
b) Non-Proprietary Name lidocaine 2.5% and prilocaine 2.5% gel
c) Code Name/# :
d) Chem. Type/Submission Priority (ONDC only):
- Chem. Type : 3
- Submission Priority: S

9. LEGAL BASIS FOR SUBMISSION:
505(b)

10. PHARMACOL. CATEGORY:
Local dental anesthetic

11. DOSAGE FORM:
Gel

12. STRENGTH/POTENCY:
2.5% lidocaine and 2.5% prilocaine
1 g of gel contains 25 mg lidocaine and 25 mg prilocaine

13. ROUTE OF ADMINISTRATION:
Oral

14. Rx/OTC DISPENSED: __X_Rx ___OTC

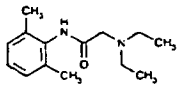
15. SPOTS (SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM):

_____SPOTS product - Form Completed

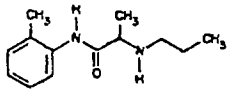
____x_____Not a SPOTS product

## 16. CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOLECULAR WEIGHT:

**Lidocaine** (lye' doe kane). USP. $C_{14}H_{22}N_2O$. 234.34. [Lignocaine is BAN.] (1) Acetamide, 2-(diethylamino)-*N*-(2,6-dimethylphenyl)-; (2) 2-(Diethylamino)-2',6'-acetoxylidide. *CAS-137-58-6*. INN; JAN. *Anesthetic (topical)*. Lida-Mantle (Bayer†); Solarcaine Aloe Extra Burn Relief Cream (Schering-Plough HealthCare); Xylocaine (Astra); component of Cracked Heel Relief Cream (Schering-Plough HealthCare); component of Emla Cream (Astra); component of Lidaform-HC (Bayer†); component of Lidamantle-HC (Bayer†); component of Neosporin Plus (Glaxo Wellcome†)



**Prilocaine** [*1996*] (pril' oh kane). $C_{13}H_{20}N_2O$. 220.31. (1) Propanamide, *N*-(2-methylphenyl)-2-(propylamino)-; (2) 2-(Propylamino)-*o*-propionotoluidide. *CAS-721-50-6*. INN; BAN. *Anesthetic (local)*. (Astra Pharmaceutical Production AB, Sweden); component of EMLA Cream (Astra)



17. RELATED/SUPPORTING DOCUMENTS:

A. DMFs:

| DMF # | TYPE | HOLDER | ITEM REFERENCED | CODE[1] | STATUS[2] | DATE REVIEW COMPLETED | COMMENTS |
|---|---|---|---|---|---|---|---|
| [redacted] | III | [redacted] | Cartridge tubular glass 1.8 mL | 1 | Adequate | 10/10/02 | |
| | III | | Rubber FM 258 grey | 1 | Adequate | 10/14/02 | |
| | IV | | Poloxamers NF | 7 | Adequate | Not reviewed | NF grade excipient |

[1]Action codes for DMF Table:
1 - DMF Reviewed.
Other codes indicate why the DMF was not reviewed, as follows:
2 -Type 1 DMF
3 - Reviewed previously and no revision since last review
4 - Sufficient information in application
5 - Authority to reference not granted
6 - DMF not available
7 - Other (explain under "Comments")

[2]Adequate, Inadequate, or N/A (There is enough data in the application, therefore the DMF did not need to be reviewed)

B. Other Documents:

| DOCUMENT | APPLICATION NUMBER | DESCRIPTION |
|---|---|---|
| NDA | 19-941; approved | EMLA (lidocaine 2.5%, prilocaine 2.5%) Cream |
| NDA | 20-962; approved | EMLA (lidocaine 2.5% prilocaine 2.5%) Cream Topical Adhesive System |
| | | |
| | | |
| | | |
| | | |
| | | |

18. STATUS:

| CONSULTS/CMC RELATED REVIEWS | RECOMMENDATION | DATE | REVIEWER |
|---|---|---|---|
| Biometrics | | | |
| EES | pending | | |
| Pharm/Tox | o-toluidine levels | | |
| Biopharm | | | |
| LNC | | | |
| Methods Validation | In-process | | |
| OPDRA | | | |
| EA | | | |
| Microbiology | Microbial quality/sterility | | |

**The Chemistry Review for NDA 21-397**

**The Executive Summary:**

**I. Recommendations**

**A. Recommendation and Conclusion on Approvability:**

This Application is approvable from the chemistry standpoint. The deficiencies listed in the draft letter must be conveyed to the Applicant.

**B. Recommendation on Phase 4 (Post-Marketing) Commitments, Agreements, and/or Risk Management Steps, if Approvable:**

No Phase IV commitments were made.

**II. Summary of Chemistry Assessments**

**A. Description of the Drug Product(s) and Drug Substance(s)**

The drug substances, lidocaine and prilocaine are the same active ingredients as those used in EMLA (lidocaine 2.5% and prilocaine 2.5%) Cream, which was approved under NDA 19-941 and NDA 20-962. Any information concerning the production and testing of lidocaine and prilocaine drug substances was incorporated into this

NDA by reference to the approved NDA 19-941. The names and addresses of the suppliers and testers of these drug substances and the regulatory specifications for acceptance of lidocaine and prilocaine as well as the impurities were included in this review.

Oraqix (lidocaine 2.5% and prilocaine 2.5%) Gel has been developed for application into the periodontal pocket prior to scaling procedures. The formulation is similar to that of EMLA Cream. It contains the same active ingredients, that is, a eutectic mixture of lidocaine and prilocaine in a ratio of 1:1. This gel contains purified poloxamer 407 and 188 to give the formulation thermoreversible gelling properties.

**B. Description of How the Drug Product is Intended to be Used**

The formulation will be applied to the periodontal pocket using a standard dental cartridge system equipped with a blunt applicator. Once applied, the body temperature will cause an increase in viscosity making the formulation stay in the pocket for the time necessary to induce local anesthesia.

The dental cartridge system is composed of a ——— glass cartridge (1.8 mL) with a rubber plunger ——————————— and a "combi cap" made of aluminum and rubber ——————————. The dental applicator for single use is made of stainless steel ——————————— ——. The applicator has a cap and case made of ——————. The cap and case are sealed.

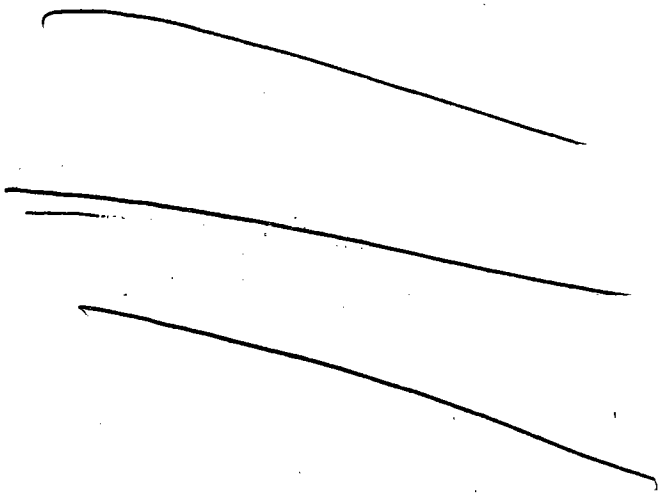
The dental applicator will only be sold as an integral part of the Oraqix package. It is very similar in design to dental needles. The only difference is that the dental applicator has a blunt tip as opposed to the sharp tip of the dental needle. The Applicant maintained that the difference between the dental applicator and the common dental needle was insignificant. Since dental syringes are considered as Class I Medical Devices that are exempt from 510(k) submission (see 21 CFR 872.4730), the dental applicator should also be considered as Class I Medical Device.

The dental cartridge syringe will not be supplied with the drug product. It is not part of this Application. Dental cartridge syringes are considered Class II medical devices (see 21 CFR 872.6770) and are commonly available in all dental offices. The dental cartridge syringe does not come in direct contact with the gel.

The maximum daily dose (MDD) is 212.5 mg of lidocaine and 212.5 mg of prilocaine.

C. **Basis for Approvability or Not-Approval Recommendation**

All CMC aspects have been adequately addressed and supported by data. The Applicant provided a narrative description and flow diagrams describing the manufacturing process for Oraqix Dental Gel. Also it included executed batch records for solution preparation and filling of one of the full scale batches used in the primary stability program for the drug, and blank master batch records that detail the intended commercial process up through filling of the product.



The Applicant provided month stability data on three commercial lots stored at 25°C/60% RH and 30°C/50% RH, and months at 40°C/75% RH. In addition, stability data on pilot scale lots for up to ~ months as well as results of temperature cycle and photo stability testing were included in this submission.

The ~ month data at 25°C/60% RH and 30°C/50% RH, and ~ months at 40°C/75% RH showed that the product was stable and all values were well within specifications. The ~ month data from a pilot scale batch were also well within specifications. Additional tests showed that the product was stable under UV light and during transportation.

Statistical analysis of the ~ months data showed that the drug product will be stable for ~ months when stored at 25°C/60%RH or at 30°C/50%RH. Based on these data, the Applicant requested a shelf-life of ~ months when stored between 5°C and 30°C with the only restriction is that the drug product should not be frozen.

The Applicant requested a categorical exclusion pursuant to 21 CFR 25.31(b). This was based on the Applicant's certification that the estimated concentration of the substance at the point of entry into the aquatic environment will be below 1 part per billion (ppb), calculated according to FDA's Guidance for Industry, Environmental Assessment of Human Drug and Biologics Applications, July 1998.

## III. Administrative

### A. Reviewer's Signature

### B. Endorsement Block

Review Chemist/MCTheodorakis/September 7, 2002
Team Leader/DLKoble/
CSO/KCompton/

### C. CC Block

87 Page(s) Withheld

6 § 552(b)(4) Trade Secret / Confidential

_____ § 552(b)(4) Draft Labeling

_____ § 552(b)(5) Deliberative Process

*Withheld Track Number: Chemistry-* 4

---

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

---

/s/

---

Michael Theodorakis
11/8/02 03:48:46 PM
CHEMIST

Dale Koble
11/8/02 04:03:16 PM
CHEMIST

Last Milestone: OC RECOMMENDATION

Milestone Date: 15-OCT-03

Decision : ACCEPTABLE

Reason : DISTRICT RECOMMENDATION

Profile : CTL OAI Status: NONE

Last Milestone: OC RECOMMENDATION

Milestone Date: 15-OCT-03

Decision : ACCEPTABLE

Reason : DISTRICT RECOMMENDATION

---

Establishment : CFN : 9612470 FEI : 3002806410

ASTRA ZENECA LIQUID PRODUCTION SWEDEN

KARLSKOGA PLANT, BJORKBORN

KARLSKOGA S-691 27, , SW

DMF No: AADA:

Responsibilities: FINISHED DOSAGE MANUFACTURER

Profile : OIN OAI Status: NONE

Last Milestone: OC RECOMMENDATION

Milestone Date: 15-OCT-03

Decision : ACCEPTABLE

Reason : DISTRICT RECOMMENDATION

---

ESTABLISHMENT EVALUATION REQUEST

SUMMARY REPORT

Application : NDA 21451/000
Org Code : 170
Priority : 4S

Sponsor: DENTSPLY PHARM
3427 CONCORD RD
YORK, PA 17402

Stamp Date : 22-JAN-2002
PDUFA Date : 20-DEC-2003
Action Goal :
District Goal: 21-OCT-2003

Brand Name : ORAQIX
Estab. Name:
Generic Name: LIDOCAINE 2.5% / PRILOCAINE 2.5%
Dosage Form: (GEL)
Strength : 2.5%, 2.5%

| | | | |
|---|---|---|---|
| FDA Contacts: | K. COMPTON | Project Manager (HFD-170) | 301-827-7410 |
| | M. THEODORAKIS | Review Chemist (HFD-170) | 301-827-7425 |
| | ID = 108283 | Team Leader | |

---

Overall Recommendation: ACCEPTABLE on 15-OCT-2003by J. D AMBROGIO(HFD-322) 301-827-9049

ACCEPTABLE on 24-DEC-2002by J. D AMBROGIO(HFD-322) 301-827-9049

ACCEPTABLE on 15-NOV-2002by S. ADAMS (HFD-322) 301-827-9051

---

Establishment : CFN : 9612840 FEI : 3002806411
ASTRA PHARMACEUTICAL PRODUCTION AB
SODERTALJE, , SW

DMF No: AADA:

Responsibilities: DRUG SUBSTANCE MANUFACTURER
FINISHED DOSAGE STABILITY TESTER

ESTABLISHMENT EVALUATION REQUEST

SUMMARY REPORT

Establishment : CFN : [redacted] FEI : [redacted]

[redacted]

[redacted]

DMF No: AADA:

Responsibilities: DRUG SUBSTANCE MANUFACTURER

Profile : CSS OAI Status: NONE

Last Milestone: OC RECOMMENDATION

Milestone Date: 15-OCT-03

Decision : ACCEPTABLE

Reason : DISTRICT RECOMMENDATION

---

---

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

---

/s/

---

Michael Theodorakis
11/19/02 02:28:22 PM
CHEMIST

Dale Koble
11/19/02 02:37:41 PM
CHEMIST