CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

21-451

ADMINISTRATIVE and CORRESPONDENCE DOCUMENTS

13. Patent Information

Patent Information as per Title 21 CFR § 314.53 (c)(1) is summarised below. In addition a declaration statement is provided in accordance with Title 21 CFR § 314.53(c)(2) for the two patents.

US Patent No.	Date of Patent Expiry	Type of Patent	Patent Owner	Authorised representative to Receive Notice of Patent Certification
4,529,601	16 July 2002	Drug Product Method of Use	Astra Läkemedel Aktiebolag	AstraZeneca LP 1800 Concord Pike Wilmington, DE 19850
6,031,007	1 April 2017	Drug Product Method of Use	Dentsply Anesthetics S.à.r.l.	Dentsply Anesthetics S.à.r.l., c/o DENTSPLY International 570 W. College Ave. York, PA 17405 Attn: JB Bieber, Esq. Patent Cousel

DECLARATION

The undersigned declares that U.S. Patent Numbers 4,529,601 and 6,031,007 cover the formulation, composition and/or method of use of Lidocaine, prilocaine (lidocaine 2.5% and prilocaine 2.5%) Periodontal Gel. This product is the subject of this application for which approval is being sought.

James B. Bieber, Esq.
DENTSPLY International
Patent Counsel

14. Patent Certification

NOT APPLICABLE

This application is not a 505(b)(2) application; therefore, the Patent Certification as described under 21 U.S.C 355(b)(2) or (j)(2)(A) and 21 CFR 314.50(i) is not required.

EXCLUSIVITY SUMMARY for NDA # 21-451 SUPPL #
Trade Name Oraqix (lidocaine and prilocaine periodontal gel) 2.5%/2.5% Generic Name lidocaine and prilocaine periodontal gel 2.5%/2.5%
Applicant Name Dentsply Pharmaceutical HFD- 170
Approval Date December 19, 2003

PART I: IS AN EXCLUSIVITY DETERMINATION NEEDED?

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

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

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

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

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

      YES /X/ NO /___/

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

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

d) Did the applicant request exclusivity?

YES /__/ NO /X/

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

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

YES /___/ NO /X/

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

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

YES /___/ NO /X/

If yes, NDA # _____ Drug Name

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

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

YES /___/ NO /X/

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

PART II: FIVE-YEAR EXCLUSIVITY FOR NEW CHEMICAL ENTITIES
(Answer either #1 or #2, as appropriate)

1. Single active ingredient product.

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

YES /X/ NO /___/

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

NDA # 20-575(Lidocaine)

NDA # 20-612 Lidoderm)

NDA # 14-127(Xylocaine)
+ others to numerous to list (see Orange Book)

2. Combination product.

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

YES /X/ NO /___/

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

NDA # 19-941 (Emla Cream)

NDA # 20-962 (Emla Disc)

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

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

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

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

YES /X/ NO /___/

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

2. A clinical investigation is "essential to the approval" if the Agency could not have approved the application or supplement without relying on that investigation. Thus, the investigation is not essential to the approval if 1) no clinical investigation is necessary to support the supplement or application in light of previously approved applications (i.e., information other than clinical trials, such as bioavailability data, would be sufficient to provide a basis for approval as an ANDA or 505(b)(2) application because of

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

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

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

YES /X/ NO /___/

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

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

YES /___/ NO /X/

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

YES /___/ NO /X/

If yes, explain:

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

YES /___/ NO /X/

If yes, explain:

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

Investigation #1, Study # B1

Investigation #2, Study # B2

Investigation #3, Study # B3

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

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

Investigation #1 YES /___/ NO /X/

Investigation #2 YES /___/ NO /X/

Investigation #3 YES /___/ NO /X/

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

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

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

Investigation #1 YES /___/ NO / X /

Investigation #2 YES /___/ NO / X /

Investigation #3 YES /___/ NO / X /

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

NDA # _____ Study #

NDA # _____ Study #

NDA # _____ Study #

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

Investigation # 1, Study # B1

Investigation # 2, Study # B2

Investigation # 3, Study # B3

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

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

Investigation #1

IND # 52, 677 YES /___/ ! NO /X/ Explain: IND was held by AstraZeneca, which sold all rights for this product and all of their dental products to the current sponsor of this NDA, Densply Pharmaceuticals. AstraZeneca continues to work with the current sponsor on the development of this product.

Investigation #2

IND # 52, 677 YES /___/ ! NO /X/ Explain: See explanation above.

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

Investigation #1

YES /X/ Explain See explanation above ! NO /___/ Explain

Investigation #2

YES /X/ Explain See explanation above ! NO /___/ Explain _____

(c) Notwithstanding an answer of "yes" to (a) or (b), are there other reasons to believe that the applicant should not be credited with having "conducted or sponsored" the study? (Purchased studies may not be used as the basis for exclusivity. However, if all rights to the drug are purchased (not just studies on the drug), the applicant may be considered to have

sponsored or conducted the studies sponsored or conducted by its predecessor in interest.)

YES /___/ NO /X/

If yes, explain: _____

_____

_____

Kimberly Compton, Project Mgr., and Parinda Jani, CPMS
Signature of Preparers

12-19-03
Date

Bob Rappaport, M.D.,
Signature of Division Director

12-22-03
Date

cc:
Archival NDA
HFD- /Division File
HFD- /RPM
HFD-093/Mary Ann Holovac
HFD-104/PEDS/T.Crescenzi

Form OGD-011347
Revised 8/7/95; edited 8/8/95; revised 8/25/98, edited 3/6/00

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/s/

Bob Rappaport

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16. Debarment Certification

As required by Section 306(k)(1) of the Generic Drug Enforcement Act [21 U.S.C. 335a(k)(1)], we hereby certify that, in connection with this application, DENTSPLY Pharmaceutical did not and will not use in any capacity the services of any person debarred under subsection 306(a) or (b) of the Act.

Lee A. Zagar
Director, Quality & Regulatory Affairs
DENTSPLY Pharmaceutical

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 21-451

Dentsply Pharmaceutical
3427 Concord Road
York, PA 17402

Attention: Ronald R. Zentz, R.Ph., D.D.S.
Director of Clinical Affairs

Dear Dr. Zentz:

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Oraqix (lidocaine 2.5% and prilocaine 2.5%) Periodontal Gel.

We also refer to your March 31, 2003, submission containing your request for comment on planned documentation you propose to submit with respect to the device aspect of your applicator and collar.

We have reviewed the referenced material and have the following comments.

1. Your submission indicates that the blunt tipped applicator (irrigation needle) will not be supplied sterile. The standard of care for periodontal treatment is to introduce only sterile instruments into the periodontium to prevent a transfer of infectious materials into the subepithelial tissues of the pocket. The standard of care in Dentistry requires that all periodontal surgical instruments are to be sterilized before use.

   Needles for injection are single patient use devices, and are supplied sterile. The same standards should apply to blunt application/irrigation needles. The Center for Devices and Radiologic Health (CDRH) recommends that the blunt tipped needle should be supplied sterile.

2. The following comment pertains to the collar design of the proposed cartridge.

   The collar on each individual cartridge of Periodontal Gel is intended as the primary mechanism to prevent inadvertent placement of the cartridge into a standard dental syringe, the goal being to eliminate the possibility of accidental intravascular injection. The collar in its present form can be removed without much difficulty. In a practice environment where assistants assemble and lay out instruments for oral surgery the potential for placement of the cartridge into a standard syringe with a sharp needle by inexperienced staff without the dentist's knowledge seems possible. To prevent this occurrence, the collar should be

fashioned onto the cartridge so that it cannot be removed without tools and considerable physical effort. Marking the collar with a warning not to tamper with it is also recommended to discourage attempts at modifying the product.

If you have any questions, call Kimberly Compton, Regulatory Project Manager, at (301) 827-7432.

Sincerely,

{See appended electronic signature page}

Bob Rappaport, M.D.
Acting Director
Division of Anesthetic, Critical Care, and
Addiction Drug Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

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/s/

Bob Rappaport

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DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 21-451

Dentsply Pharmaceutical
3427 Concord Road
York, PA 17402

Attention: Ronald R. Zentz, R.Ph., D.D.S.
Director of Clinical Affairs

Dear Dr. Zentz:

Please refer to the meeting between representatives of your firm and FDA on March 19, 2003. The purpose of the meeting was to discuss your proposed response to the Agency's approvable letter of November 20, 2002 for your Oraqix (lidocaine 2.5% and prilocaine 2.5%) Periodontal Gel.

The official minutes of that meeting are enclosed. You are responsible for notifying us of any significant differences in understanding regarding the meeting outcomes.

If you have any questions, call me at 301-827-7432.

Sincerely,

{See appended electronic signature page}

Kimberly Compton
Regulatory Project Manager
Division of Anesthetic, Critical Care, and
Addiction Drug Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

Enclosure

INDUSTRY MEETING MINUTES

Meeting Date: March 19, 2003

Location: Parklawn Building, Conference Room 12B-02

Sponsor: Dentsply Pharmaceutical

NDA: 21-451

Drug Name: Oraqix (lidocaine 2.5% and prilocaine 2.5%) Periodontal Gel

Type of Meeting: End-of-Review Meeting

Meeting Chair: Nancy Chang, M.D.
Division of Anesthetics, Critical Care and Addiction Drug Products

Minutes Recorder: Kimberly Compton, Regulatory Project Manager

Industry	Title
Dentsply Pharmaceutical Representatives	
Carol Bjorkheden, Ph.D.	Toxicologist, AstraZeneca
Birgitta Flensburg	Regulatory Affairs Manager
Bruce Manning	Consultant and Regulatory Correspondent
Ingrid Otterbom	Clinical Development Leader
Karenlee Voltz	Director, Regulatory Affairs and Quality Assurance
Ron Zentz, R.Ph., D.D.S.	Director, Clinical Affairs
FDA	**Title**
Bob Rappaport, M.D.	Acting Division Director
Nancy Chang, M.D.	Anesthesia Team Leader
Lester Schultheis, M.D.	Medical Officer
Michael Theodorakis, Ph.D.	Chemistry Reviewer
Dale Koble, Ph.D.	Chemistry Team Leader
Tim McGovern, Ph.D.	Supervisory Pharmacologist
David Lee, Ph.D.	Biopharmaceutical Reviewer
Fred Hyman, D.D.S., M.P.H.	Dental Officer
Tom Permutt, Ph.D.	Statistical Team Leader
Milton Fan, Ph.D.	Statistical Reviewer
Mark Kramer	Director, Office of Combination Products
Patricia Y. Love, M.D.	Acting Associate Director, Office of Combination Products
Kim Compton	Regulatory Project Manager

Meeting Objective: The purpose of the meeting was to discuss the sponsor's plan for resubmission of NDA 21-451.

General Discussion:
The sponsor's questions are listed in *Italics* with the FDA responses presented at the meeting following. Pertinent discussion that took place at the meeting regarding a specific question will follow the question and FDA response.

The sponsor opened the meeting with a brief, regulatory history of the product and presented diagrams of the newly proposed collar and delivery device designed to prevent accidental injection of the periodontal gel. The sponsor informed the Division that they had submitted a Request for Designation (RFD) to the Office of Combination Products. The sponsor stated that they hoped to get an idea from the Agency if the proposed delivery system is evaluable due to restrictive costs of continuing development of such a system. The sponsor noted that the collar was designed only to prevent accidental injection of the gel by preventing the gel from being mistaken for an injectable anesthetic, not to make it impossible to make the cartridge fit into a standard dental injector. A prototype applicator device and cartridge were demonstrated and passed around the table. Dr. Chang noted that the collar was relatively easy to remove from the cartridge. The sponsor stated that the final materials would be much harder plastic and therefore more difficult to remove.

Dr. Chang noted that the Division would take into consideration the possibility that the collar might be removed intentionally by untrained individuals, such as by technical assistants who might remove the collar to make the cartridge fit into the standard dental injectors while stocking carts. Dr. Theodorakis proposed that the sponsor inscribe on the collar "Do Not Remove." The sponsor noted that there might be a way to inscribe "Do Not Remove" or other similar language on the collar.

Response/Question #1 a.

The applicant proposes to perform this study as a Phase IV commitment. Does the Agency agree with this proposal?

FDA Response

The proposed in vitro chromosome aberration assay should be submitted with the formal response to the Approvable letter.

Adequate justification should be provided to support proposed Phase 4 submission (report by December 2003).

Discussion of Question 1a.
Dr. McGovern stated that the assay outlined is fairly standard, so the Division would expect to see them submitted with the application. The sponsor stated it would take them approximately four months to perform and completely prepare the reports for these assays. Dr. McGovern stated there was a possibility the Division could accept these reports during the review cycle (no later than 3 months in), but the sponsor would be required to propose timelines for the study report submission, with appropriate justification, prior to resubmitting the NDA. The Division

will review the proposals and determine if they are acceptable. Dr. Rappaport emphasized that this was the limit the Division was willing to go to on this issue. The Division has been more than flexible on this point, since the sponsor has been aware of the deficiency for some time now.

Response/Question #1 b.

The amended report will be included in our NDA Amendment responding to the November 20, 2002 Approvable letter. Does the Agency agree that this will be sufficient to respond to this request?

FDA Response

The proposal to amend the in vivo mouse micronucleus report with pilot study data and clinical observations from the main study to support dose selection is acceptable. The information will be reviewed to determine the adequacy of the study.

Response/Question #2 a.

Does the Agency agree that inclusion of this report in our NDA Amendment will be an adequate response to this request?

FDA Response

Inclusion of the referenced fertility and general reproductive performance study in rats with lidocaine (Document No. T1593) is acceptable. The information will be reviewed to determine the adequacy of the study. Please provide information concerning the previous submission of this data (IND or NDA#, date of submission).

Response/Question #2 b (i).

Does the Agency agree that inclusion of this report in our NDA Amendment will be an adequate response to this request?

FDA Response

Inclusion of the referenced embryo-fetal development study in rabbits with lidocaine (Document No. T1442) is acceptable. The information will be reviewed to determine the adequacy of the study. Please provide information concerning the previous submission of this data (IND or NDA#, date of submission).

Response/Question #2 b (ii).

Does the Agency agree that inclusion of this report in our NDA Amendment will be an adequate response to this request?

FDA Response

Inclusion of the referenced embryo-fetal development study in rabbits with prilocaine (Document No. ET177) is acceptable. The information will be reviewed to determine the adequacy of the study. Please provide information concerning the previous submission of this data (IND or NDA#, date of submission).

Response/Question #2 c (i).

Does the Agency agree that inclusion of this report in our NDA Amendment will be an adequate response to this request?

FDA Response

Inclusion of the referenced pre- and post-natal development studies in rats with lidocaine (Document No. T1756 and T1781) is acceptable. The information will be reviewed to determine the adequacy of the studies. Please provide information concerning the previous submission of this data (IND or NDA#, date of submission).

Response/Question #2 c (ii).

Does the Agency agree that inclusion of this report in our NDA Amendment will be an adequate response to this request?

FDA Response

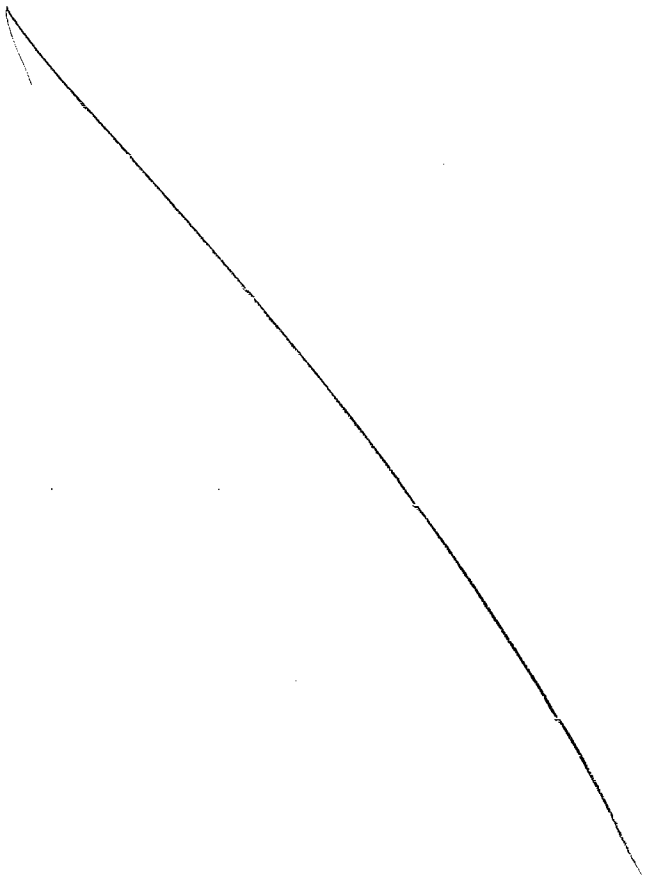
Inclusion of the referenced pre- and post-natal development study in rats with prilocaine (and also lidocaine) is acceptable. The information will be reviewed to determine the adequacy of the study. Please provide information concerning the previous submission of this data (IND or NDA#, date of submission).

Response/Question #4

Does the Agency agree that inclusion of these measures in our NDA Amendment will adequately address concerns about the accidental injection of Oraqix?

FDA Response

The proposed modifications to the cartridge, dispenser and the blunt tipped applicator appear to be reasonably adequate to address the Agency's concerns regarding accidental injection of Oraqix. However, a final determination will be made after actual samples are reviewed. There may also be a need for formal review by CDRH (see following).



Response/Question #5

Does the Agency agree with the suggested revisions in the package insert?

Discussion of labeling issues

Dr. Rappaport referred to the sponsor's fax of March 18, 2003 (questions from the fax are listed at end of this document), requesting clarification of the outlined labeling issues. Regarding points # 1-6, he stated that the Division preferred to discuss those types of issues after they had had a chance to review the resubmission. He noted the points were quite specific, and that labeling changes are part of the review. He requested that the sponsor include any annotations/justifications for changes in their response.

Regarding item #7, Dr. Theodorakis stated that this issue was discussed by the sponsor in their original submission (page # 47), where the sponsor states that the product show sensitivity to

temperature. Dr. Theodorakis stated that the sponsor should provide data to indicate why the product would remain acceptable to use if it had been frozen. The sponsor stated that they did not suggest freezing the product was acceptable, but noted this was mainly a transportation issue. Dr. Koble stated that the Agency did not want to allow the dental providers to decide if the product was acceptable based on visual inspection. The information the Division had suggested the product was not amenable to freezing. The sponsor stated they would address this issue in their support of the proposed labeling changes. Dr. Koble stated that if the Division had information on the performance of the product after it had been frozen, such changes in the labeling might be acceptable and that this issue could be discussed with the sponsor further after they provided justification for such a change in the label.

Dr. Rappaport assured the sponsor that the Division would allow a reasonable amount of time to negotiate labeling during the review cycle.

Closing Discussion

Mr. Kramer inquired about how the sponsor would proceed regarding their RFD. The sponsor agreed to withdraw the RFD since the device would be reviewed within the context of the NDA rather than requiring separate device clearance. CDER agreed to take the lead on the review of this drug product/syringe combination, consulting with CDRH as appropriate.

The sponsor stated they were not sure of a timeframe for resubmission yet as it would be important for them to first know what information on the device would need to be included in the package (see Action Items below).

Action Items:

- The Agency will prepare the official minutes of the meeting and provide the sponsor with a copy.

- The Division will schedule and meet with CDRH to discuss what information on the device would need to be included in the resubmission. The Division will convey this information to the sponsor.

- The sponsor will send the Division one device now and one prototype device in approximately 1-2 weeks when another is available.

Post Meeting Note:

On March 31, 2003, the sponsor submitted a proposal for device related information to be included in their response. This package was consulted to CDRH to determine if the proposal is appropriate and what additional information might be required. Once the results are returned from CDRH, the Division will convey them to the sponsor.

Minutes prepared by: Kim Compton
Minutes concurred by Chair: Nancy Chang, M.D.

Transcript of Sponsor's fax dated March 18, 2003

Here are the concepts for the package insert we would like to discuss tomorrow:

1. In the Pharmacokinetics section of the insert, we have inserted information on bioavailability (20-40% after the 8.5 gram dose) to supplement the information on AUC suggested by the Division. This concept carries over to the carcinogenicity section in calculation of o-toluidine exposure.

2. In the Dosage and Administration section, we believe it is appropriate to allow reapplication up to tire maximum allowed dose. The limitation to a single re-application in the pivotal efficacy studies (B1, B2 and B3) was to permit clarity in interpretation of data, and was not intended as a limitation for clinical use. The pharmacokinetic study (A3) and the patient preference study (B4) allowed reapplication up to 8.5 and 6.8 grams respectively.

3. Since FDA suggested adding the VRS data (a secondary objective) to the Clinical Studies section, we suggest adding the other secondary efficacy variable, Need for Rescue Anesthesia (Number of Interruptions due to Pain).

4. In the Adverse Reactions section, we have removed AEs in ≤ 1 patient in the placebo and lidocaine injection groups as the Division has done this in the Oraqix group.

5. Also in the Adverse Reactions section, we have addressed application site disorders by low level terms as the product has its effects locally, allowing clinicians to relate these events to normal post treatment reactions.

6. In the, Nursing Mothers section we suggest the text be modified to be more consistent with the risks, considering the low systemic exposure in the mother and the infrequent use of Oraqix.

7. Could the Division explain the rational for requiring disposal of all cartridges that are known to have been frozen? Freeze thaw studies suggest to us that this is not necessary.

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/s/

Kimberly Compton
4/15/03 06:58:41 PM

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 21-451

Dentsply Pharmaceutical
3427 Concord Road
York, PA 17402

Attention: Ronald R. Zentz, R.Ph., D.D.S.
Director of Clinical Affairs

Dear Dr. Zentz:

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Oraqix (lidocaine 2.5% and prilocaine 2.5%) Periodontal Gel.

We also refer to your December 20, 2002, submission containing your proposal to prevent inadvertent injection of the Drug Product.

We have reviewed the referenced material and have the following comment.

> The proposed modifications to the applicator and cartridge containing dental gel appear to be an appropriate approach to prevention of inadvertent injection of Oraqix periodontal Gel. However, samples of the entire injector system, including Oraqix cartridges, needles in the entire range of applicable sizes, and injectors must be submitted, along with a justification of the safety of the entire design in order for us to complete our review and determine the adequacy of they system.
>
> We recognize that the injection system may be conceptual at this stage and that you may not have a functional prototype dispenser, however, a fully functional system must be submitted and reviewed before this approach may be approved.

If you have any questions, call Kimberly Compton, Regulatory Project Manager, at (301) 827-7432.

Sincerely,

{See appended electronic signature page}

Bob Rappaport, M.D.
Acting Director
Division of Anesthetic, Critical Care, and
Addiction Drug Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

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/s/

Celia Winchell
1/31/03 04:37:49 PM
for Bob A. Rappaport, M.D., Acting Division Director

From: Runner, Mary S.
Sent: Friday, November 08, 2002 9:59 AM
To: Compton, Kimberly
Subject: RE: need for possible device consult on a pending NDA

After reviewing the documentation for your NDA the needle that is described is a standard type dental needle. These needles are exempt from CDRH premarket notification procedures. I therefore do not think that our review would be needed.

Susan

Susan Runner, DDS, MA
Branch Chief Dental Devices
Food and Drug Administration
9200 Corporate Blvd
Rockville, MD 20850
301-827-5283 x 117
msr@cdrh.fda.gov

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/s/

Kimberly Compton
11/22/02 02:18:38 PM
CSO

9 Page(s) Withheld

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

9 § 552(b)(4) Draft Labeling

_____ § 552(b)(5) Deliberative Process

MEMORANDUM

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

Memo of Clinical Issues - Communicated to Sponsor by fax

DATE: November 8, 2002

TO: Dentsply, c/o Bruce Manning, NEBR (508-393-3780)

THROUGH : Parinda Jani, CPMS, HFD-170
Lex Schultheis, M.D., Medical Officer, HFD-170
Nancy Chang, M.D., Anesthesia Team Leader, HFD-170
Bob Rappaport, M.D., Acting Division Director, HFD-170

FROM: Kim Compton (Comptonk@cder.fda.gov, fax # 301-443-7068, phone 301-827-7432)

RE: NDA 21-451, Oraqix (lidocaine 2.5% and prilocaine 2.5%) Periodontal Gel

In a teleconference with the sponsor's representative on today, two clinical issues were outlined for the sponsor that would require their additional follow-up. We are providing these issues in writing for clarity. These issues follow in this memo and were communicated to the sponsor by fax on November 8, 2002.

1. What is the systemic bioavailability of o-toluidine when applied to oral mucosa? Is this known?

2. What is known about the expected % of metabolism of prilocaine to the o-toluidine metabolite?

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/s/

Kimberly Compton
11/8/02 06:05:49 PM
CSO

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 21-451

DISCIPLINE REVIEW LETTER

Dentsply Pharmaceutical
3427 Concord Road
York, PA 17402

Attention: Lee A. Zagar
Director, Quality and Regulatory Affairs

Dear Mr. Zagar:

Please refer to your January 22, 2002, new drug application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Oraqix (Lidocaine 2.5% and prilocaine 2.5%) Periodontal gel.

We also refer to your submissions dated March 14, June 27, August 16, and September 20, 2002.

Our review of the Chemistry, Manufacturing and controls section of your submission is complete, and we have identified the following deficiencies:

1. Provide information about the [redacted] r used in the manufacturing process.

2. Include in the regulatory specifications for acceptance of the drug product a specification for monitoring the release of the active ingredients from the gel matrix.

3. Add a lower limit to the specification for [redacted]
The current specification of [redacted] is not adequate.

4. Tighten the specification limits for 2,4 xylidine and o-toluidine.

5. Provide updated 24-month data (including for in-vitro release) for the three commercial size lots placed on stability (primary stability studies). Also, provide statistical analysis of the stability attributes (e.g., assay, individual degradation products and in-vitro release. Or provide justification why this is not necessary.

6. The release of the active ingredients from the gel matrix should be included as a parameter to be monitored in the post-approval stability protocol.

7. Provide information about the stability of the drug product between 15°C and 25°C. The following parameters should be monitored: assay, degradation products, temperature of gelation, and in-vitro release. Or, justify why this is not appropriate.

8. Clarify with appropriate documentation if the product placed on stability at 25°C was liquid or gel.

9. Provide data and information to justify proposed revised specifications for the drug product (see above).

10. Provide appropriate information about the secondary container for the drug product.

11. The description section of the package insert should include the pKa values for lidocaine and prilocaine.

12. In the HOW SUPPLIED Section of the package insert, the storage temperature should be modified to be consistent in the manner suggested in the Draft Guidance for Industry: Stability Testing of Drug Substances and Drug Products, June 1998 (http://www.fda.gov/cder/guidance/index.htm).

13. Regarding the labels for the primary container(cartridge), secondary container (blister foil) and carton, the establish name "lidocaine 2.5% and prilocaine 2.5%" should be revised to read as follows: "(lidocaine 2.5% and prilocaine 2.5%) gel". The contents should be expressed as "1.7 g gel".

We are providing these comments to you before we complete our review of the entire application to give you preliminary notice of issues that we have identified. In conformance with the prescription drug user fee reauthorization agreements, these comments do not reflect a final decision on the information reviewed and should not be construed to do so. These comments are preliminary and subject to change as we finalize our review of your application. In addition, we may identify other information that must be provided before we can approve this application. If you respond to these issues during this review cycle, depending on the timing of your response, and in conformance with the user fee reauthorization agreements, we may not be able to consider your response before we take an action on your application during this review cycle.

If you have any questions, call Kimberly Compton, Regulatory Project Manager, at (301) 827-7432.

Sincerely,

{See appended electronic signature page}

Dale Koble, Ph.D.
Chemistry Team Leader for the
Division of Anesthetic, Critical Care, and
Addiction Drug Products, HFD-170
DNDC DNDC II, Office of New Drug Chemistry
Center for Drug Evaluation and Research

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/s/

Dale Koble
11/8/02 05:05:10 PM

MEMORANDUM OF TELECON

Date: March 7, 2002

Application Number: NDA 21-451
Drug: Oraqix Dental Gel

Between:
James Walker, Consultant on electronic issues, AstraZeneca
Nancy Smerkanick, Regulatory Consultant, AstraZeneca
Jean Supplee, Submissions Mgmt., AstraZeneca
Karenlee Voltz, Sr. Regulaotry Consultant, Dentsply
Bruce Manning, Sponsor Representative, Dentsply

Phone:
Sponsor: Dentsply.

And:
Gerald DalPan, M.D., Medical Officer
Dale Koble, Ph.D., Chemistry Team Leader
Nancy Chang, M.D., Anesthesia Team Leader
Yaron Harel, M.D., Medical Officer
Kim Compton, Project Manager

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

Subject: Oraqix-Filing Issues

The sponsor was contacted to discuss several clinical and chemistry issues that required attention prior to filing the application.

- Dr. Koble requested a list of all manufacturing and testing sites with CFN #s for the application. The sponsor referred Dr. Koble to the attachment to the form 356h. Dr. Koble, who was covering for the review chemist, Dr. Theodorakis, stated that the Division would look over this list and determine if it was sufficient.

- Dr. Koble inquired about the facility not ready for inspection. The sponsor stated that the issues remaining to be resolved before the site was ready for inspection were relatively minor and assured the Division that the site would be ready for inspection by April 1, 2002 and agreed to provide this assurance to the Division in writing.

- Dr. Koble stated that all the drug substance manufacturing sites would be required to meet current standards. He also stated that the Division would require specific references to the current manufacturing specifications, not simply a generalized reference to another NDA. The sponsor stated that they had already begun to compile such a listing and inquired if a

table of contents format would be acceptable. Dr. Koble stated that our preference would be to have the specifications for the drug substance, drug product and stability protocol in this NDA, but that at the very least a listing of submission dates, volume and page numbers in the referenced NDA would be acceptable. The sponsor stated they would supplement the NDA with the requested information.

- Dr. DalPan pointed out that several apparent abbreviations are used in the application such as "pocloc," and ".p" and requested that the sponsor clarify these unexplained terms. The sponsor stated that they would provide a list of codes for each table and clarifications for column headings as well.

- Dr. DalPan noted that there was no integrated listing of adverse events and other items in the application. The sponsor stated that they were unaware of this issue and would need to look into it. The sponsor agreed to get back to the Agency on this matter quickly.

- Dr. Harel noted that in the electronic portion of the submission, certain tables referred the reviewer to other tables, among other problems and noted that these were not in the acceptable format. Dr. DalPan requested that the sponsor re-examine all datasets and ensure that they are in compliance with the guidance for electronic submissions.

- Dr. DalPan requested that the sponsor re-examine the whole clinical section of the application and make certain that it is legible and all information is readily available, citing truncated columns and other unexplained inconsistencies. The sponsor stated that they would do so.

- The sponsor stated that their estimated timeline for completion of these tasks would be within 1 week, except for the ISS, which may take longer, but which they hoped to resolve inside the week as well.

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/s/

Kimberly Compton
4/12/02 03:53:17 PM
CSO

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

IND 52,677

AstraZeneca LP
C/O New England Biomedical Research, Inc.
96 West Main Street
P.O. Box 809
Northborough, MA 01532

Attention: Bruce R. Manning
President

Dear Mr. Manning:

Please refer to the meeting between representatives of your firm and FDA on April 24, 2001. The purpose of the meeting was to discuss

The official minutes of that meeting are enclosed. You are responsible for notifying us of any significant differences in understanding regarding the meeting outcomes.

If you have any questions, contact me at (301) 827-7432.

Sincerely,

Kimberly A.Compton
Regulatory Project Manager
Division of Anesthetic, Critical Care, and
Addiction Drug Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

Enclosure

6 Page(s) Withheld

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

____ § 552(b)(4) Draft Labeling

6 § 552(b)(5) Deliberative Process

Withheld Track Number: Administrative- 2

SPONSOR MEETING MINUTES

Meeting Date: August 27th, 1998 9:00am to 10:30am

Location: Parklawn Building – 3rd Floor Conference Room "K"

IND Name: 52,677 Dental Gel 5% (Lidocaine/Prilocaine) - Oraqix™ Local Anesthetic for Topical Use in the Periodontal Pocket prior to Scaling and Root planing Procedures.

Sponsor: ASTRA USA

Type of Meeting: Guidance Meeting - Discuss Clinical Development Plan

Meeting Chair: Cynthia G. McCormick, M.D./Director

Minutes Recorder: Indira Kumar/ Regulatory Project Manager for Ken Nolan

FDA Attendees:	**Titles:**	**Offices:**
Cynthia G. McCormick, M.D.	Division Director	HFD-170
Bob Rappaport, M.D.	Deputy Director	HFD-170
Harold Blatt, DDS	Medical Reviewer/Anesthetic	HFD 170
Albinus D'Sa, Ph.D.	Team Leader/Chemistry	HFD-170
Michael Theodorakis, Ph.D.	Chemistry Reviewer	HFD-170
Dou Huey Jean, Ph.D.	Team Leader/Pharmacology	HFD-170
Kathleen Haberny, Ph.D.	Pharmacology Reviewer	HFD-170
Ramana Uppoor, Ph.D.	Team Leader/Clinical Pharm.	HFD-870
Suresh Doddapaneni, Ph.D.	Pharmacokineticist Reviewer	HFD-870
Jonathan Z. Ma, Ph.D.	Biostatistics Reviewer	HFD-170
Corinne P. Moody	Chief, Project Management Staff	HFD-170
Indira Kumar	Project Manager	HFD-170

External Attendees:	**Titles:**
Ingrid Bartinique, M.P.P.	Manager Regulatory Affairs/ASTRA USA
Randall Carpenter, M.D.	Director, Clinical Research/ASTRA USA
Angela Hee, D.M.D., M.P.H.	Assistant Director, Clinical Research/ASTRA USA
Murad Husain, R.Ph.	Associate Director Regulatory Affairs/ASTRA USA
Birgitta Flensburg, M, Pharm, Sci.	Regulatory Affairs/Sodertalje, Sweden
Goran Isaacson, D.D.S., Ph.D.	Medical Advisor, Clinical R&D/ Sodertalje, Sweden
Carin Junestrand, D.D.S.	Project Manager/ Sodertalje, Sweden
Stefan Lillieborg, M. Pharm.	Director, Clinical R&D/ Sodertalje, Sweden

Meeting Objective:

- To discuss the agenda items listed below.

Agenda:

1. To discuss the sponsor's meeting objectives:

Topic A: Adequacy of the Dental Gel 5% Clinical Program

- Program Highlights and Rationale for SP-DGA-0007 Phase 3 Study
- Feedback from the Division and Discussion

Topic B: Dosing Recommendation

- Rationale and Supportive Data
- Feedback from the Division and Discussion

Topic C: Combination Product Waiver

- Rationale: The EMLA Concept and Intrinsic Physicochemical Properties of Dental Gel 5%.

2. Any other business.

Discussion Points:

The sponsor gave a brief presentation on the background and clinical development plan on Dental Gel (Oraqix). The attached slides were used in their presentation – See Attachment A.

Topic C: Combination Product Waiver:

Rationale: The EMLA Concept and Intrinsic Physicochemical Properties of Dental Gel 5%.

It was agreed upon by the Division that the Combination Product Waiver would be granted to the Sponsor. (With further verification by Corinne Moody).

Chemistry:

- No outstanding issues at this time.

Pharmacology:

- No new preclinical animal toxicology studies were proposed at this time - Therefore there were no outstanding preclinical issues at this time.

- There was a concern regarding the label of the drug, referencing the CAC (Carcinogenicity Assessment Committee) recommendation that carcinogenicity of 2,6-xylidine is no longer required in the label. The Sponsor is measuring the plasma levels of 2,6-xylidine and o-toluidine in the SP-DGA-0006 Study. In keeping with the CAC recommendation, the Division recommended that the Sponsor removes 2,6-xylidine from the label and keeps the o-toluidine.

Statistics:

- The overall VAS score for pain intensity, which is considered as the primary efficacy endpoint would be measured at the end of the entire dental procedure which may involve more than one tooth. The sponsor plans to perform non-parametric statistical comparisons on the overall VAS score because it may not follow a normal distribution. The division recommended that ANOVA model also be used to explore potential risk factors, such as gender, age, number of teeth involved, etc.

- This is going to be a randomized, double-blind, placebo-controlled study. The study design looks reasonable in general given that the combination product waiver is granted to the sponsor. Sponsor may consider including the use of rescue medication in their secondary analysis plan.

Pharmacokinetics:

Topic B: Dosing Recommendation

- In the first pharmacokinetic study proposed (SP-DGA-0002) the doses were given up to 3.5 grams. Based on extrapolated data a maximum dose of 7 grams was proposed from a safety point of view. This appears reasonable as proposed for the upper end of the dose, however, a final dose recommendation cannot be made until the results of the Study SP-DGA-0006 has been reviewed.

- In the proposed study SP-DGA-0006, plasma levels should be sampled for a longer time (up to 8-10 hours to allow for calculation of AUC) instead of the proposed 4 hours, whereby only obtaining C_{max}.

Clinical:

Topic A: Adequacy of the Dental Gel 5% Clinical Program

The Sponsor has completed 4 studies (0002, 0003, 0004, and 0005) and will be conducting 2 studies (0006 (n = 12) in Sweden and 0007 (n = 80) in USA) in Fall, 1998. While the results of studies 0003 (n = 122) and 0004 (n = 130) are statistically significant, the treatment effect was small in both trials. It is believed that study 0007 (n = 80) to confirm the efficacy of Oraqix in patients who perceive SRP to be a painful procedure, would be more helpful in supporting the Sponsor's label.

- The Division recommended that the Sponsor eliminate patients in the proposed study SP-DGA-0007 who have received analgesics within a set amount of time because this may become a potential confounder and jeopardize the validity of the results.

- The Division also recommended that the Sponsor measure levels of methemoglobin in the proposed study SP-DGA-0006 and SP-DGA-0007.

- Although there is little evidence of periodontal diseases in children, the Division is concerned with any other dental procedures where this drug may have a pediatric indication.

Minutes Preparer: Indira Kumar / Regulatory Project Manager

Concurrence: Cynthia G. McCormick, MD/Director

cc:
Original IND 52,677

HFD-170/Division File
HFD-170/C.G. McCormick/B. Rappaport/H. Blatt
HFD-170/C. P. Moody/I. Kumar
HFD-170/A. D'Sa/M. Theodorakis
HFD-170/L. Jean/K. Haberny
HFD-170/R. Uppoor/S. Doddapaneni
HFD-170/T. Permutt/J. Ma

Drafted: I. Kumar 8-27-98, 8-12-99 11:35am
Final: C. P. Moody 8-12-99 11:00am
Filename: Minutes(DentalGel Oraqix 52677) 8-12-99

NDA/EFFICACY SUPPLEMENT ACTION PACKAGE CHECKLIST

Application Information			
NDA 21-451	Efficacy Supplement Type SE-	Supplement Number	
Drug: Oraqix (lidocaine and prilocaine periodontal gel) 2.5%/2.5%		Applicant: Dentsply Pharmaceutical	
RPM: Kim Compton		HFD-170	Phone # 301-827-7410
Application Type: (X) 505(b)(1) ( ) 505(b)(2)		Reference Listed Drug (NDA #, Drug name): Emla (lidocaine 2.5% and prilocaine 2.5%) Cream	

❖ Application Classifications:	
• Review priority	(X) Standard ( ) Priority
• Chem class (NDAs only)	**4S**
• Other (e.g., orphan, OTC)	
❖ User Fee Goal Dates	-November 22, 2002 (cycle 1) **-December 19, 2003 (cycle 2)**
❖ Special programs (indicate all that apply)	(X) None Subpart H ( ) 21 CFR 314.510 (accelerated approval) ( ) 21 CFR 314.520 (restricted distribution) ( ) Fast Track ( ) Rolling Review
User Fee Information	
• User Fee	(X) Paid
• User Fee waiver	( ) Small business ( ) Public health ( ) Barrier-to-Innovation ( ) Other
• User Fee exception	( ) Orphan designation ( ) No-fee 505(b)(2) ( ) Other
❖ Application Integrity Policy (AIP)	
• Applicant is on the AIP	( ) Yes (X) No
• This application is on the AIP	( ) Yes (X) No
• Exception for review (Center Director's memo)	
• OC clearance for approval	
❖ Debarment certification: verified that qualifying language (e.g., willingly, knowingly) was not used in certification and certifications from foreign applicants are co-signed by U.S. agent.	(X) Verified
❖ Patent	
• Information: Verify that patent information was submitted	(X) Verified
• Patent certification [505(b)(2) applications]: Verify type of certifications submitted	**N/A** 21 CFR 314.50(i)(1)(*i*)(A) ( ) I ( ) II ( ) III ( ) IV 21 CFR 314.50(i)(1) ( ) (ii) ( ) (iii)
• For paragraph IV certification, verify that the applicant notified the patent holder(s) of their certification that the patent(s) is invalid, unenforceable, or will not be infringed (certification of notification and documentation of receipt	( ) Verified

of notice).	
❖ Exclusivity (approvals only)	
• Exclusivity summary	**X**
• Is there an existing orphan drug exclusivity protection for the active moiety for the proposed indication(s)? *Refer to 21 CFR 316.3(b)(13) for the definition of sameness for an orphan drug (i.e., active moiety). This definition is NOT the same as that used for NDA chemical classification!*	( ) Yes, Application #_____ **(X)** No
❖ Administrative Reviews (Project Manager, ADRA) *(indicate date of each review)*	
General Information	
❖ Actions	
• Proposed action	**(X)** AP ( ) TA ( ) AE ( ) NA
• Previous actions (specify type and date for each action taken)	**AE on November 20, 2002 (cycle 1)**
• Status of advertising (approvals only)	**(X)** Materials requested in AP letter ( ) Reviewed for Subpart H
❖ Public communications	
• Press Office notified of action (approval only)	**(X)** Yes ( ) Not applicable
• Indicate what types (if any) of information dissemination are anticipated	( ) None ( ) Press Release ( ) Talk Paper ( ) Dear Health Care Professional Letter
❖ Labeling (package insert, patient package insert (if applicable), MedGuide (if applicable)	
• Division's proposed labeling (only if generated after latest applicant submission of labeling)	**X**
• Most recent applicant-proposed labeling	**X**
• Original applicant-proposed labeling	**X**
• Labeling reviews (including DDMAC, Office of Drug Safety trade name review, nomenclature reviews) and minutes of labeling meetings *(indicate dates of reviews and meetings)*	**DDMAC did not write a review, but did OK the draft label sent to the sponsor 12/17/03 and in the previous cycle.**
• Other relevant labeling (e.g., most recent 3 in class, class labeling)	
❖ Labels (immediate container & carton labels)	
• Division proposed (only if generated after latest applicant submission)	
• Applicant proposed	**X**
• Reviews	**X (ODS)**
❖ Post-marketing commitments	
• Agency request for post-marketing commitments	
• Documentation of discussions and/or agreements relating to post-marketing commitments	
❖ Outgoing correspondence (i.e., letters, E-mails, faxes)	**X**
❖ Memoranda and Telecons	**X**
❖ Minutes of Meetings	
• EOP2 meeting (indicate date)	**N/A-see "Guidance Meeting" below**
• Pre-NDA meeting (indicate date)	**X- 4/24/01**
• Pre-Approval Safety Conference (indicate date; approvals only)	

• Other	-Guidance Meeting- 8/27/98 -Internal Meeting- 8/21/00 -Post-action Guidance Meeting 3/19/03
❖ Advisory Committee Meeting	
• Date of Meeting	N/A
• 48-hour alert	
❖ Federal Register Notices, DESI documents, NAS, NRC (if any are applicable)	
Summary Application Review	
❖ Summary Reviews (e.g., Office Director, Division Director, Medical Team Leader) *(indicate date for each review)*	DD-X (Nov 20, 2002- cycle 1) and (Dec 19, 2003-cycle 2) TL-X (Nov 20, 2002- cycle 1) and (Dec 19, 2003-cycle 2)
Clinical Information	
❖ Clinical review(s) *(indicate date for each review)*	X (November 20, 2002)
❖ Microbiology (efficacy) review(s) *(indicate date for each review)*	X (November 14, 2002)
❖ Safety Update review(s) *(indicate date or location if incorporated in another review)*	Included in Clinical Review (see above)
❖ Pediatric Page (separate page for each indication addressing status of all age groups)	X
❖ Statistical review(s) *(indicate date for each review)*	X (October 9, 2002)
Biopharmaceutical review(s) *(indicate date for each review)*	X (November 19, 2002)
❖ Controlled Substance Staff review(s) and recommendation for scheduling *(indicate date for each review)*	N/A
❖ Clinical Inspection Review Summary (DSI)	
• Clinical studies	N/A
• Bioequivalence studies	
CMC Information	
❖ CMC review(s) *(indicate date for each review)*	X (Nov 8, 2002, addenda, Nov 19, 2002-cycle 1) and (Dec 10, 2003, addenda Dec 17, 2003- cycle 2)
❖ Environmental Assessment	
• Categorical Exclusion *(indicate review date)*	See11/8/02 CMC Review #1, Pg. 96
• Review & FONSI *(indicate date of review)*	
• Review & Environmental Impact Statement *(indicate date of each review)*	
❖ Micro (validation of sterilization & product sterility) review(s) *(indicate date for each review)*	N/A
❖ Facilities inspection (provide EER report)	Date completed: (X) Acceptable ( ) Withhold recommendation
❖ Methods validation	( ) Completed (X) Requested ( ) Not yet requested

Nonclinical Pharm/Tox Information	
❖ Pharm/tox review(s), including referenced IND reviews *(indicate date for each review)*	**X** (Nov 18, 2002; addenda, Nov 20, 2002-cycle 1) and **(December 19, 2003-cycle 2)**
❖ Nonclinical inspection review summary	
❖ Statistical review(s) of carcinogenicity studies *(indicate date for each review)*	
❖ CAC/ECAC report	

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/s/

Kimberly Compton
12/22/03 04:19:57 PM

NDA/EFFICACY SUPPLEMENT ACTION PACKAGE CHECKLIST - cycle 1

Application Information			
NDA 21-451	Efficacy Supplement Type SE-	Supplement Number	
Drug: Oraqix (lidocaine 2.5% and prilocaine 2.5%) Periodontal Gel		Applicant: Dentsply Pharmaceutical	
RPM: Kim Compton		HFD-170	Phone # 301-827-7410
Application Type. (X) 505(b)(1) ( ) 505(b)(2)		Reference Listed Drug (NDA #, Drug name): Emla (lidocaine 2.5% and prilocaine 2.5%) Cream	

❖ Application Classifications:	
• Review priority	(X) Standard ( ) Priority
• Chem class (NDAs only)	**4S**
• Other (e.g., orphan, OTC)	
❖ User Fee Goal Dates	**November 22, 2002**
❖ Special programs (indicate all that apply)	(X) None Subpart H ( ) 21 CFR 314.510 (accelerated approval) ( ) 21 CFR 314.520 (restricted distribution) ( ) Fast Track ( ) Rolling Review
❖ User Fee Information	
• User Fee	(X) Paid
• User Fee waiver	( ) Small business ( ) Public health ( ) Barrier-to-Innovation ( ) Other
• User Fee exception	( ) Orphan designation ( ) No-fee 505(b)(2) ( ) Other
❖ Application Integrity Policy (AIP)	
• Applicant is on the AIP	( ) Yes (X) No
• This application is on the AIP	( ) Yes (X) No
• Exception for review (Center Director's memo)	
• OC clearance for approval	
❖ Debarment certification: verified that qualifying language (e.g., willingly, knowingly) was not used in certification and certifications from foreign applicants are co-signed by U.S. agent.	(X) Verified
❖ Patent	
• Information: Verify that patent information was submitted	(X) Verified
• Patent certification [505(b)(2) applications]: Verify type of certifications submitted	**N/A** 21 CFR 314.50(i)(1)(*i*)(A) ( ) I ( ) II ( ) III ( ) IV 21 CFR 314.50(i)(1) ( ) (ii) ( ) (iii)
• For paragraph IV certification, verify that the applicant notified the patent holder(s) of their certification that the patent(s) is invalid, unenforceable, or will not be infringed (certification of notification and documentation of receipt of notice).	( ) Verified

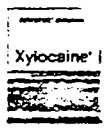
❖ Exclusivity (approvals only)	
• Exclusivity summary	**N/A**
• Is there an existing orphan drug exclusivity protection for the active moiety for the proposed indication(s)? *Refer to 21 CFR 316.3(b)(13) for the definition of sameness for an orphan-drug (i.e., active moiety). This definition is NOT the same as that used for NDA chemical classification!*	( ) Yes, Application #_____ **(X)** No
❖ Administrative Reviews (Project Manager, ADRA) *(indicate date of each review)*	
General Information	
❖ Actions	
• Proposed action	( ) AP ( ) TA **(X)** AE ( ) NA
• Previous actions (specify type and date for each action taken)	
• Status of advertising (approvals only)	( ) Materials requested in AP letter ( ) Reviewed for Subpart H
❖ Public communications	
• Press Office notified of action (approval only)	( ) Yes **(X)** Not applicable
• Indicate what types (if any) of information dissemination are anticipated	( ) None ( ) Press Release ( ) Talk Paper ( ) Dear Health Care Professional Letter
❖ Labeling (package insert, patient package insert (if applicable), MedGuide (if applicable)	
• Division's proposed labeling (only if generated after latest applicant submission of labeling)	**X**
• Most recent applicant-proposed labeling	
• Original applicant-proposed labeling	**X**
• Labeling reviews (including DDMAC, Office of Drug Safety trade name review, nomenclature reviews) and minutes of labeling meetings *(indicate dates of reviews and meetings)*	**DDMAC did not write a review, but did OK the draft label sent to the sponsor 11/20/02.**
• Other relevant labeling (e.g., most recent 3 in class, class labeling)	
❖ Labels (immediate container & carton labels)	
• Division proposed (only if generated after latest applicant submission)	
• Applicant proposed	**X**
• Reviews	**X (ODS)**
❖ Post-marketing commitments	
• Agency request for post-marketing commitments	
• Documentation of discussions and/or agreements relating to post-marketing commitments	
❖ Outgoing correspondence (i.e., letters, E-mails, faxes)	**X**
❖ Memoranda and Telecons	**X**
❖ Minutes of Meetings	
• EOP2 meeting (indicate date)	**N/A-see "Guidance Meeting" below**
• Pre-NDA meeting (indicate date)	**X- 4/24/01**
• Pre-Approval Safety Conference (indicate date; approvals only)	
• Other	**-Guidance Meeting- 8/27/98** **-Internal Meeting- 8/21/00**

❖ Advisory Committee Meeting	
• Date of Meeting	**N/A**
• 48-hour alert	
❖ Federal Register Notices, DESI documents, NAS, NRC (if any are applicable)	
Summary Application Review	
❖ Summary Reviews (e.g., Office Director, Division Director, Medical Team Leader) *(indicate date for each review)*	**DD-X (November 20, 2002)** **TL-X (November 20, 2002)**
Clinical Information	
❖ Clinical review(s) *(indicate date for each review)*	**X (November 20, 2002)**
❖ Microbiology (efficacy) review(s) *(indicate date for each review)*	**X (November 14, 2002)**
❖ Safety Update review(s) *(indicate date or location if incorporated in another review)*	**Included in Clinical Review (see above)**
❖ Pediatric Page (separate page for each indication addressing status of all age groups)	**N/A**
❖ Statistical review(s) *(indicate date for each review)*	**X (October 9, 2002)**
❖ Biopharmaceutical review(s) *(indicate date for each review)*	**X (November 19, 2002)**
❖ Controlled Substance Staff review(s) and recommendation for scheduling *(indicate date for each review)*	**N/A**
❖ Clinical Inspection Review Summary (DSI)	
• Clinical studies	**N/A**
• Bioequivalence studies	
CMC Information	
❖ CMC review(s) *(indicate date for each review)*	**X (November 8, 2002, addenda, November 19, 2002)**
❖ Environmental Assessment	
• Categorical Exclusion *(indicate review date)*	**See11/8/02 CMC Review, Pg. 96**
• Review & FONSI *(indicate date of review)*	
• Review & Environmental Impact Statement *(indicate date of each review)*	
❖ Micro (validation of sterilization & product sterility) review(s) *(indicate date for each review)*	**N/A**
❖ Facilities inspection (provide EER report)	Date completed: (X) Acceptable ( ) Withhold recommendation
❖ Methods validation	( ) Completed (X) Requested ( ) Not yet requested
Nonclinical Pharm/Tox Information	
❖ Pharm/tox review(s), including referenced IND reviews *(indicate date for each review)*	**X (November 18, 2002; addenda, November 20, 2002)**
❖ Nonclinical inspection review summary	
❖ Statistical review(s) of carcinogenicity studies *(indicate date for each review)*	
❖ CAC/ECAC report	

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

/s/

Kimberly Compton
11/22/02 05:05:28 PM



DENTSPLY
PHARMACEUTICAL

DENTSPLY Pharmaceuti
Concord Executive Center
3427 Concord Road
York, PA 17402
(717) 757-0200
Fax (717) 757-4402

January 9, 2002

Food and Drug Administration (360909)
Mellon Client Service Center
Room. 670
500 Ross St.
Pittsburgh, PA 15262-0001

Re: FDA NDA 21-451, User Fee Payment for Oraqix™ (lidocaine 2.5% and prilocaine 2.5%) Periodontal Gel New Drug Application, User Fee ID Number 4225

Dear Sir or Madam:

Enclosed herewith is our check in the amount of $313,320 which we understand will be the established FDA User Fee for New Drug Applications containing clinical data in 2002. This amount is tendered for our upcoming New Drug Application for Oraqix™ based on a telephone conversation on January 9, 2002 between our Mr. Bruce Manning and Mr. Michael Jones of FDA. Mr. Jones advised that this established fee would be published in the Federal Register in the near future. If this information should prove incorrect, please invoice us for the balance due or refund the excess.

Please acknowledge receipt of this fee at your earliest convenience by return pre-paid UPS. A completed air bill and return UPS envelope is enclosed for your convenience.

If there are any questions on this procedure, please contact the undersigned immediately.

Thank you for your early processing of this payment.

Sincerely,

Lee A. Zagar
Director, Quality and Regulatory Affairs.

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION

Form Approved: OMB No. 0910-0297
Expiration Date: February 29, 2004.

USER FEE COVER SHEET

See Instructions on Reverse Side Before Completing This Form

This form must be signed and accompany each new drug or biologic product application and each new supplement. See exceptions on the reverse side. If payment is sent by U.S. mail or courier, please include a copy of this completed form with payment. Payment instructions and fee rates are posted on CDER's website: http://www.fda.gov/cder/pdufa/default.htm

1. APPLICANT'S NAME AND ADDRESS

[illegible]TSPLY Pharmaceutical
[illegible] Concord Road
[illegible], PA 17402

2. TELEPHONE NUMBER (Include Area Code)

(717) 757-0200

3. PRODUCT NAME

Orajel™ (lidocaine 2.5% and prilocaine 2.5%) Periodontal Gel

4. BLA SUBMISSION TRACKING NUMBER (STN) / NDA NUMBER

N021451

5. DOES THIS APPLICATION REQUIRE CLINICAL DATA FOR APPROVAL?

☒ YES ☐ NO

IF YOUR RESPONSE IS "NO" AND THIS IS FOR A SUPPLEMENT, STOP HERE AND SIGN THIS FORM.

IF RESPONSE IS 'YES', CHECK THE APPROPRIATE RESPONSE BELOW:

☒ THE REQUIRED CLINICAL DATA ARE CONTAINED IN THE APPLICATION.

☐ THE REQUIRED CLINICAL DATA ARE SUBMITTED BY REFERENCE TO:

_____
(APPLICATION NO. CONTAINING THE DATA).

6. USER FEE I.D. NUMBER

4225

7. IS THIS APPLICATION COVERED BY ANY OF THE FOLLOWING USER FEE EXCLUSIONS? IF SO, CHECK THE APPLICABLE EXCLUSION.

☐ A LARGE VOLUME PARENTERAL DRUG PRODUCT APPROVED UNDER SECTION 505 OF THE FEDERAL FOOD, DRUG, AND COSMETIC ACT BEFORE 9/1/92
(Self Explanatory)

☐ A 505(b)(2) APPLICATION THAT DOES NOT REQUIRE A FEE
(See item 7, reverse side before checking box.)

☐ THE APPLICATION QUALIFIES FOR THE ORPHAN EXCEPTION UNDER SECTION 736(a)(1)(E) of the Federal Food, Drug, and Cosmetic Act
(See item 7, reverse side before checking box.)

☐ THE APPLICATION IS A PEDIATRIC SUPPLEMENT THAT QUALIFIES FOR THE EXCEPTION UNDER SECTION 736(a)(1)(F) of the Federal Food, Drug, and Cosmetic Act
(See item 7, reverse side before checking box.)

☐ THE APPLICATION IS SUBMITTED BY A STATE OR FEDERAL GOVERNMENT ENTITY FOR A DRUG THAT IS NOT DISTRIBUTED COMMERCIALLY
(Self Explanatory)

8. HAS A WAIVER OF AN APPLICATION FEE BEEN GRANTED FOR THIS APPLICATION?

☐ YES ☒ NO

(See item 8, reverse side if answered YES)

9. SIGNATURE OF AUTHORIZED COMPANY REPRESENTATIVE	TITLE	DATE
[signature]	Lee A. Zagar Director, Quality & Regulatory Affairs	1/9/02

(4/91)

Created by: PSC Media Arts (301) 443-3454 EF

New Drug Application NDA 21-451
User Fee Cover Sheet

018-001-045

USER FEE VALIDATION SHEET

NDA # 21-451 Supp. Type & # N000 UFID # 4225
(e.g., N000, SLR001, SE1001, etc.)

1. (YES) NO User Fee Cover Sheet Validated? MIS_Elements Screen Change(s):

2. (YES) NO **APPLICATION CONTAINS CLINICAL DATA?**
(Circle **YES** if NDA contains study or literature reports of what are explicitly or implicitly represented by the application to be adequate and well-controlled trials. Clinical data do not include data used to modify the labeling to add a restriction that would improve the safe use of the drug (e.g., to add an adverse reaction, contraindication or warning to the labeling).

REF **IF NO CLINICAL DATA IN SUBMISSION, INDICATE IF CLINICAL DATA ARE CROSS REFERENCED IN ANOTHER SUBMISSION.**

3. YES (NO) **SMALL BUSINESS EXEMPTION**

4. YES (NO) **WAIVER GRANTED**

5. YES (NO) **NDA BEING SPLIT FOR ADMINISTRATIVE CONVENIENCE (other then bundling).**
If **YES**, list all NDA #s, review division(s) and those for which an application fee applies.

NDA #	Division		
N_____	HFD-_____	Fee	No Fee
N_____	HFD-_____	Fee	No Fee

6. (YES) NO **BUNDLING POLICY APPLIED CORRECTLY? No Data Entry Required**
(Circle **YES** if application is properly designated as one application or is properly submitted as a supplement instead of an original application. Circle **NO** if application should be split into more than one application or be submitted as an original instead of a supplement. If **NO**, list resulting NDA #s and review division(s).

N/A

NDA #	Division	NDA #	Division
N_____	HFD-_____	N_____	HFD-_____

7. P (S) **PRIORITY or STANDARD APPLICATION?**

[signature] 2/12/02 Pamela Jean 2/12/02
PM Signature / Date CPMS Concurrence Signature / Date

2/14/00