CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

21-451

APPROVAL LETTER

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: Karenlee Modric,
Director, Regulatory Affairs and Quality Assurance

Dear Ms. Modric:

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

We acknowledge receipt of your submissions dated February 1, March 8, and 14, April 1, May 17, June 24 and 27, July 17, August 16, and 26, September 20, October 15, November 11, 13, 18 and 21, and December 20, 2002, February 12, March 28 and 31, April 14, 15 and 30, May 2, June 19, July 24, September 17, November 21, and December 11, 12, and 18, 2003.

The June 19, 2003, submission constituted a complete response to our November 20, 2002, action letter.

This new drug application provides for the use of Oraqix (Lidocaine and prilocaine periodontal gel) 2.5%/2.5% for adults who require localized anesthesia in periodontal pockets during scaling and/or root planing.

We have completed our review of this application, as amended, and it is approved, effective on the date of this letter, for use as recommended in the attached labeling (package insert) and labeling submitted December 12, 2003 (immediate container and carton labels) with the minor revisions noted below.

The final printed labeling (FPL) must be identical to the enclosed labeling (text for the package insert), and the labeling submitted December 12, 2003 (immediate container and carton labels) with the following minor revisions.

1. On the Immediate Carton (foil blister) labels:

   Switch the location of the phrase "Rx Only" with the phrase "1.7 g" ("1.7 g" currently appears on the line with the word "Use" and it appears that this might be an instruction

to "use 1.7 g"). Also, add the word "gel" after the phrase "1.7 g" (e.g., to read "1.7 g gel").

2. On the Immediate Container (Cartridge) label:

   Right adjust the phrase "1.7 g" and add the word "gel" following it so it is clear that the 1.7 g refers to the amount of gel in the cartridge and it is separated from the word "Use" as much as possible.

3. In the Package Insert:

   a. Convert the "max" portion of the phrases "Cmax" and "Tmax" to subscripts.

   b. Ensure that all references to the brand name Oraqix are followed by the appropriate symbology (e.g.,®) consistently throughout the labeling.

   c. Update the duration of action of the anesthetic effect range from the current 25-75% quartile to the 10-90% range.

4. In all Oraqix labeling:

   a. Ensure that the newly agreed upon established name ["Oraqix (lidocaine and prilocaine periodontal gel) 2.5%/2.5%"] is consistently used throughout the labeling.

   b. Adjust the fonts or other appropriate features accordingly (not simply the point size of the typeface, since different fonts have different prominences, etc.) so that the established name *appears* at half the prominence of the brand name. We note that in the current versions, different fonts are utilized so that even though the point sizes listed appear to be in the appropriate ratio, the sizes of the letters do not allow for the appropriate prominence of the established name.

Marketing the product with FPL that is not identical to the approved labeling text may render the product misbranded and an unapproved new drug.

Please submit the copies of final printed labeling (FPL) electronically, according to the guidance for industry titled *Providing Regulatory Submissions in Electronic Format - NDA* (January 1999). Alternatively, you may submit 20 paper copies of the FPL as soon as it is available but no more than 30 days after it is printed. Please individually mount ten of the copies on heavyweight paper or similar material. For administrative purposes, this submission should be designated "FPL for approved NDA 21-451." Approval of this submission by FDA is not required before the labeling is used.

We remind you of your postmarketing study commitment in your submission dated December 19, 2003. This commitment is listed below.

Complete a Segment III Reproductive Toxicology study on prilocaine in a single species as described in the ICH-S5A Guidance to Industry. The adverse effects to be assessed will include measurements of altered growth and development and functional deficits in the offspring,

including behavior, maturation (puberty) and reproduction (F1). Sensory functions, reflexes and behavioral responses will be assessed in the F1 generation.

Protocol Submission:	by May 2004
Study Start:	by July 2004
Final Report Submission:	by July 2005

We also remind you of your agreements to the following:

1. Provide, on at least an annual basis, all reports of product misuse, product defects (e.g. defective collars), device failures, or other events that may relate to the potential for accidental injection of Oraqix. Submit such information even if no adverse occurrences are observed.

2. Provide a plan for education of practitioners during the rollout of Oraqix. This educational program should include instruction on the proper use of Oraqix, particularly with respect to the need to avoid injection of Oraqix.

Submit clinical protocols to your IND for this product. Submit nonclinical and chemistry, manufacturing, and controls protocols and all study final reports to this NDA. In addition, under 21 CFR 314.81(b)(2)(vii) and 314.81(b)(2)(viii), you should include a status summary of each commitment in your annual report to this NDA. The status summary should include expected summary completion and final report submission dates, any changes in plans since the last annual report, and, for clinical studies, number of patients entered into each study. All submissions, including supplements, relating to these postmarketing study commitments must be prominently labeled "Postmarketing Study Protocol", "Postmarketing Study Final Report", or "Postmarketing Study Correspondence."

All applications for new active ingredients, new dosage forms, new indications, new routes of administration, and new dosing regimens are required to contain an assessment of the safety and effectiveness of the product in pediatric patients unless this requirement is waived or deferred. We are waiving the pediatric study requirement for ages 0-5 years and deferring pediatric studies for ages 6-17 years for this application.

In addition, submit three copies of the introductory promotional materials that you propose to use for this product. Submit all proposed materials in draft or mock-up form, not final print. Send one copy to this division and two copies of both the promotional materials and the package insert directly to:

Division of Drug Marketing, Advertising,
and Communications, HFD-42
Food and Drug Administration
5600 Fishers Lane
Rockville, MD 20857

Please submit one market package of the drug product when it is available.

We have not completed validation of the regulatory methods. However, we expect your continued cooperation to resolve any problems that may be identified.

We remind you that you must comply with reporting requirements for an approved NDA (21 CFR 314.80 and 314.81).

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.
Director
Division of Anesthetic, Critical Care and
Addiction Drug Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

Enclosure

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

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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: Lee A. Zagar
Director, Quality and Regulatory Affairs

Dear Mr. Zagar:

Please refer to your new drug application (NDA) dated January 22, 2002, received January 22, 2002, 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 acknowledge receipt of your submissions dated February 1, March 8, and 14, April 1, May 17, June 24 and 27, July 17, August 16, and 26, September 20, October 15, November 11, 13, and 18, 2002.

We have completed our review of this application, as submitted, with draft labeling, and it is approvable. Before the application may be approved, however, it will be necessary for you to:

1. Submit the following studies to address the genotoxic potential of prilocaine:

   a. an *in vitro* test with cytogenetic evaluation of chromosomal damage with mammalian cells or an *in vitro* mouse lymphoma tk assay.

   b. an *in vivo* test for chromosomal damage using rodent hematopoietic cells. This study is requested as a previously submitted *in vivo* mouse micronucleus assay did not demonstrate sufficient toxicity at the highest dose tested.

2. Submit the following studies to address the reproductive toxicity potential of prilocaine:

   a. a fertility study with lidocaine.

   b. embryo-fetal development studies in rabbits with lidocaine and prilocaine.

   c. pre- and post-natal development studies with lidocaine and prilocaine.

3. Submit a complete safety assessment of Oraqix by injection, including relevant preclinical and clinical studies is required. This should include assessment of local toxicit(ies), assessment of systemic exposure to the active and inactive ingredients in Oraqix, and an assessment of the safety of these systemic exposure(s). This safety evaluation should also address the potential for accidental intravascular injection of Oraqix.

4. As an alternative to requirement #3, adequate safeguards to prevent inadvertent injection of Oraqix must be integrated into the labeling and design of the product and/or delivery system. Data intended to support the safety of the current design against inadvertent injection must account for variations in viscosity that may occur with variations in ambient temperature and/or storage conditions of Oraqix. These data must also take into account the entire range of needle sizes that might reasonably be used in the current injector device. The division would also request that samples of the entire injection system, including Oraqix cartridges, needles in the entire range of applicable sizes, and injectors be submitted with any such justification of the safety of the current design.

5. Submit a draft package insert and blister, carton, and container labels modified to reflect the following comments, and the revisions noted in the attached marked-up draft. Further labeling comments will be provided once the aforementioned deficiencies are adequately addressed.

   a. Revise the established name to read as follows:

      Oraqix (lidocaine 2.5% and prilocaine 2.5%) Periodontal Gel

   d. Relocate the net quantity statement so that it does not appear in conjunction with the proprietary name. In addition decrease the size of the net quantity statement so that is not larger than the product strength.

If additional information relating to the safety or effectiveness of this drug becomes available, revision of the labeling may be required.

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

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

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

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

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

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

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

/s/

Bob Rappaport
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