

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

21-451

MEDICAL REVIEW



FDA CENTER FOR DRUG EVALUATION AND RESEARCH

DIVISION OF ANESTHETIC, CRITICAL CARE, AND ADDICTION DRUG PRODUCTS
HFD-170, Room 9B-45, 5600 Fishers Lane, Rockville MD 20857

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DIVISION DIRECTOR REVIEW AND BASIS FOR APPROVAL ACTION

DATE: December 19, 2003

DRUG: Oraqix (lidocaine and prilocaine periodontal gel) 2.5%/2/5%

NDA: #21-451

NDA Code: Type 3S NDA

SPONSOR: Dentsply Pharmaceutical

INDICATION: For adults who require localized anesthesia in periodontal pockets during scaling and/or root planing

Dentsply Pharmaceutical has submitted an application for a local anesthetic periodontal gel product that is manufactured from drug substances that are produced by AstraZeneca AB, _____ located in Sweden. Oraqix (lidocaine and prilocaine periodontal gel) 2.5%/2/5% is a eutectic mixture of lidocaine and prilocaine that has been developed for to provide localized anesthesia in periodontal pockets for adults during scaling and/or root planing. It contains poloxamer excipients which show temperature-dependent gelation, such that the drug product is a low-viscosity fluid at room temperature, but forms an elastic gel at body temperature, such as when applied to a periodontal pocket. The concentrations of the active drug substances (lidocaine and prilocaine) in Oraqix are identical to the concentrations in the sponsor's drug product EMLA, a cream that has been approved for the production of local anesthesia of the skin and genital mucosa. EMLA is manufactured and distributed by AstraZeneca. As the studies submitted in this application were performed by AstraZeneca under their IND and the NDA was prepared for Dentsply by AstraZeneca, AstraZeneca is contractually obligated to assist Dentsply with regulatory matters through approval of the NDA. As such, Dentsply has referenced non-clinical and clinical data from the NDA for EMLA in support of the Oraqix application.

The original submission for this NDA was dated January 23, 2002. During the initial evaluation of the application the clinical review team determined that the studies submitted by the sponsor did document that the product appeared to be safe and effective when used according to the instructions in the clinical protocols. However, concerns were raised regarding the possibility that the product could be inadvertently injected into the periodontal tissues due to similarity of the Oraqix carpules to the standard carpules that contain solutions of local anesthetics used in the dental setting. The standard local anesthetic carpules are inserted in the same type of syringe that had been proposed for delivery of Oraqix. As the injection of Oraqix into the periodontal vasculature could result in embolization of gelatinous material, with resultant morbidity and even mortality, an approvable action was taken. The sponsor was required either to provide a complete safety assessment of Oraqix by injection, including relevant preclinical and clinical studies, or to provide adequate safeguards to prevent inadvertent injection of Oraqix.

In addition, the preclinical review team determined that there were outstanding genetic toxicology and reproductive toxicology issues. An approvable letter was issued on November 20, 2002 that included the following preclinical requirements:

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.

The sponsor submitted a complete response to the approvable letter on June 20, 2003.

Clinical Safety

Drs. Schultheis, Hyman and Chang have reviewed the materials submitted to address the safety concerns related to inadvertent injection of Oraqix. Dr. Chang's Team Leader Memo dated December 19, 2003, documents their conclusion that the dispenser and applicator redesign is sufficient to prevent inadvertent injection when used according to the instructions in the product label. This conclusion was based on the following findings:

- 1) the addition of a collar affixed to the carpule which prevents insertion into a standard dental injector;
- 2) the placement of a unique color band on the immediate container that will clearly distinguish this product from the other dental anesthetic products on the market; and
- 3) the addition of appropriate warnings to the package insert and to the package and container labeling.

Nonclinical Safety

Dr. Daniel Mellon completed a review of the studies submitted in response to the approvable letter. His review dated December 19, 2003, documents his conclusion that the studies submitted to address the potential clastogenicity of prilocaine do not demonstrate any chromosomal changes.

Dr. Mellon also reviewed the studies submitted to characterize the effects of lidocaine and prilocaine on reproduction. Segment II studies for lidocaine did not reveal evidence of teratogenicity. In a study designed to assess the toxic effects of prilocaine and vasopressin on embryo-fetal development in the rabbit, there was a single pup with spina bifida of a lumbar vertebra. This observation was in the low-dose group and no abnormalities occurred at the higher doses. Dr. Mellon notes that, "The low incidence of this malformation in the historical databases raised significant concern. Since this effect occurred in a low-dose animal and no other neural tube defects were noted in other animals, the effect does not appear to be treatment-related. As such, ...the study was sufficient to conclude that there was no evidence for prilocaine induced teratogenicity, under the conditions tested."

Two Segment III studies were performed with lidocaine alone. Dr. Mellon's review documents that neither study found evidence of peri- or postnatal developmental toxicity. In a third study, either lidocaine or prilocaine was administered. Although the study did not document developmental toxicity, Dr. Mellon notes that, "Technically, this study

does not fully address the post-natal development effects of prilocaine or lidocaine, since the F₁ generation was not tested for reproductive capacity, behavioral testing or reflex testing.”

Discussion

Although prilocaine is widely marketed and there has been extensive use over this local anesthetic over many years, it is not possible to fully assess the potential for reproductive toxicity without adequate preclinical data. Although I concur with Dr. Mellon’s conclusion that the single case of spina bifida in the Segment II studies does not appear to be drug induced based on its occurrence only in the low dose group, it is impossible to completely rule out the possibility of drug-related toxicity. Additionally, other agents that display sodium channel activity have documented teratogenicity, including neural tube defects (e.g. valproate). Therefore, it is important that an adequate preclinical evaluation of neurobehavioral development be performed in order to provide informative labeling. The sponsor has committed to performing a Segment III Reproductive Toxicology study on prilocaine in a single species in Phase 4 of development.

Action: Approval

Bob A. Rappaport, M.D.
Director
Division of Anesthetic, Critical Care and Addiction Drug Products
Office of Drug Evaluation II, CDER, FDA

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/s/

Bob Rappaport
12/19/03 08:47:48 PM
MEDICAL OFFICER



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HFD-170, ROOM 9B-45, 5600 FISHERS LANE, ROCKVILLE MD 20857

Medical Team Leader Memo

NDA #:	21-451
Sponsor:	Dentsply Pharmaceutical
Generic Name:	Lidocaine 2.5% and Prilocaine 2.5%
Proprietary Name:	Oraqix
Pharmacologic Class:	Local anesthetic
Purpose:	NDA response to approvable
Proposed Indication:	For adults who require localized anesthesia in periodontal pockets during scaling and/or root planing
Submission Date:	June 20, 2003
Clinical Reviewer:	Lester Schultheis, M.D., Ph.D.
Medical Team Leader	Nancy Chang, M.D.

BACKGROUND/SUMMARY

Refer also to the previous team leader memo and clinical review of the original NDA submission of January 23, 2002.

Oraqix (2.5% lidocaine, 2.5% prilocaine) Dental Gel is a eutectic mixture of lidocaine and prilocaine developed for a proposed indication of "localized anesthesia in periodontal pockets scaling and/or root planing". It contains poloxamer excipients which show temperature-dependent gelation, such that the drug product is a low-viscosity fluid at room temperature, but forms an elastic gel at body temperature, such as when applied to a periodontal pocket. It is intended for topical application to periodontal pockets.

The first cycle clinical review concluded that the product demonstrated efficacy and a reasonable level of safety when given according to the proposed indication. However, there was significant concern about the potential for inadvertent injection of this product as it was to be supplied in a standard dental cartridge that would be compatible with standard dental injector devices that are commonly used for injection of local anesthetics in the dental setting. As a result, on November 20, 2002 the division made an approvable action on this first submission, with the following issues to be resolved before an approval action could be taken (summarized and edited from the original approvable letter language):

1. Submit studies to address the genotoxic potential and the reproductive toxicity potential of prilocaine and lidocaine.
2. Submit a complete safety assessment of Oraqix by injection, including relevant preclinical and clinical studies. As an alternative to a safety assessment of the injection route, adequate safeguards to prevent inadvertent injection of Oraqix must be integrated into the labeling and design of the product and/or delivery system.

The current submission is a complete response to the approvable letter. In addition, safety updates were provided with this submission and again on 12/18/03, both stating that no new safety information has become available since the time of the original NDA submission. For assessment of the response to issue #1 above, refer to the pharmacology/toxicology review conducted by Dr. Mellon.

In response to issue #2, the sponsor has proposed the following:

1. The Oraqix cartridge has been modified by the addition of an exterior collar that prevents its insertion into a standard dental local anesthetic injector.
2. This modified cartridge is designed to fit into a novel reusable dispenser device.
3. Single use blunt applicator needles will be co-packaged with Oraqix. These blunt applicators will not fit onto a standard dental local anesthetic injector;

nor will standard needles be able to both fit onto the dispenser device and puncture the drug cartridge for delivery.

The sponsor elected not to study the safety of Oraqix by injection. Although many local anesthetics, including lidocaine and prilocaine, have been approved for use by injection, this product raises a unique safety concern because of its temperature-dependent gelation. If injection into the bloodstream might induce gelation, there would be potential risk of serious embolic events. Therefore, absent specific information on the safety of this product by injection, strong measures should be implemented to protect against inadvertent injection.

The proposed devices have undergone review by CDRH, and the devices have been determined to be acceptable from a CDRH perspective. Our own testing of these devices has confirmed that standard needles are not compatible with the new dispenser. Standard local anesthetic carpules will fit (though not securely) in the new dispenser in such a way that these drugs could be delivered with the new device. However, as the new dispenser device can only deliver with the blunt applicator supplied with Oraqix, the inadvertent use of standard local anesthetics (that have already been approved for injection) in these dispensers would most likely result in a topical administration that is not anticipated to constitute a significant risk to humans relative to the labeled indications for these drugs.

We have also confirmed that the new Oraqix cartridge with collar does not fit into standard dental injectors. The collar is affixed securely enough that it would not be anticipated to fall off with ordinary handling. However, the collar can be removed manually by a determined user without tools or extraordinary effort. With the collar removed, the cartridge can then fit into a standard dental injector.

This raises a lingering concern about the possibility that accidental injection of this product might still occur in a theoretical circumstance where an individual, such as a dental technician, might inappropriately remove the collars from Oraqix cartridges, and that these cartridges might mistakenly be placed in a standard dental injector. To counteract these concerns the sponsor has taken the following measures with respect to labeling of this product in accordance with the division's recommendations:

1. The package insert warns against injection in the header, the Precautions section, and the Dosage and Administration section.
2. Blister package labeling provides an illustration of the cartridge container with collar with a prominent statement "Do not remove collar".
3. Immediate container labeling displays a unique wide lavender color band with black cross-hatches. This band makes the container label distinct in several ways from those of existing dental local anesthetic products which currently follow a standard color coding system:
 - ◆ The primary band color is different from that of existing products
 - ◆ The cross-hatch pattern is unique to Oraqix
 - ◆ The band is wider than those found on standard local anesthetic cartridges

- ◆ The location of the band in Oraqix is such that the band may be visualized within a window found on many standard dental injectors. Standard local anesthetic cartridges have bands that are located on the opposite end of the cartridge.

With these changes, the Oraqix cartridge will be visually distinct from both the individual local anesthetic products currently available on the market, as well as the local anesthetic products as a group.

CONCLUSIONS/RECOMMENDATIONS

1. The Oraqix dispenser and applicator redesign is sufficient to prevent inadvertent injection of Oraqix when used with the dispenser.
2. Standard local anesthetic cartridges can be delivered using the Oraqix dispenser; however, this is not thought to constitute a significant clinical hazard.
3. The modified Oraqix cartridge with collar can not be used in a standard dental injector. However, the possibility of injection of Oraqix using a standard dental injector may still exist if the collar is inappropriately removed. Although the collars are secure enough that they are not likely to fall off inadvertently during normal handling, removal of collars can be accomplished manually without tools or extraordinary effort.
4. Package labeling and the product PI have prominently displayed wording warning against injection or removal of the cartridge collar.
5. The proposed immediate container labeling is readily distinguishable from existing local anesthetic products marketed in dental cartridges.
6. There is no previous experience with this type of product in this clinical setting of use upon which to predict the probability of the type of gross misuse that could result in a patient adverse event. The probability of a serious event related to Oraqix, even if it were injected, is also unknown.

Although the proposed redesign does not eliminate the possibility of accidental injection of Oraqix in the case of gross misuse or mishandling of the product, many safeguards at multiple levels have been incorporated into the design and labeling of the proposed Oraqix cartridge, dispenser, and applicator to protect against this possibility. It is impossible at this time to predict the magnitude of risk associated with the current design of this product. I believe the sponsor has made a reasonable and responsible effort to address and minimize the potential risk of injection, and I recommend approval.

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/s/

Nancy Chang
12/19/03 01:22:33 PM
MEDICAL OFFICER

John Kelsey
12/19/03 01:26:41 PM
MEDICAL OFFICER
I concur.

Lester Schultheis
12/19/03 04:43:54 PM
MEDICAL OFFICER

Fred Hyman
12/19/03 04:46:33 PM
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MEMORANDUM

SUBJECT: INTERNAL EVALUATION OF "PROPOSED MEASURES TO PREVENT ACCIDENTAL INJECTION OF ORAQIX™ 11/20/02"

THROUGH: BOB RAPPAPORT, MD (HFD-170)
ACTING, DIVISION DIRECTOR, DACCADP
AND
NANCY CHANG, M.D. (HFD-170)
TEAM LEADER, ANESTHESIA/CRITICAL CARE

FROM: LEX SCHULTHEIS, M.D., Ph.D., (HFD-170)

SUBJECT: Oraqix™ (lidocaine 2.5% and prilocaine 2.5%) Periodontal Gel
NDA 21451

DATE: JANUARY 6, 2003

RECOMMENDATIONS:

The Proposal to Prevent Inadvertent Injection of Oraqix (12/20/02) incorporates three features to prevent accidental injection of Dental Gel. First, the cartridge containing the drug is modified on its exterior by a collar that prevents it from being inserted into a standard dental syringe. The Oraqix cartridge may only be inserted into a unique dispenser specifically designed to hold the cartridge with a collar. The Oraqix dispenser may be able to accept standard dental cartridges for injection that do not have the collar, however another feature outlined below prevents their injection from the Oraqix dispenser. The applicator used to instill Oraqix into the dental pocket is a unique blunt tipped needle with a Luer-Lock hub. This applicator is distinguished from the standard dental needle used to inject local anesthetics from dental syringes by the absence of screw threads on the inside needle hub. A standard dental needle (with threads) will not fit the Oraqix dispenser, nor will the Oraqix applicator fit a standard dental syringe. Medical

needles with a Luer-Lock hub may fit the Oraqix dispenser, but they lack the double needle design required to puncture an Oraqix or injectable dental cartridge.

Background

As you noted in the Agency letter of November 20, 2002, it was suggested that “safeguards to prevent inadvertent injection “ are an acceptable option to address the safety of Oraqix™ delivery. Also as stated in section 4 of the same letter the Agency requested 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 entire current design.” We recognize that the injection system may be conceptual at this stage without even a functioning prototype, but for Agency approval we will need to examine a fully functional system.

Conclusions

The dispenser and modifications to the applicator and cartridge containing Dental Gel appear to be adequate precautions to prevent inadvertent injection of Oraqix. Final approval is pending physical examination of samples of the final products to be marketed by the Agency.

Lex Schultheis, M.D., Ph.D.
Nancy Chang, MD
Anesthesia Team Leader

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Nancy Chang, MD
Bob Rappaport, MD

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/s/

Lester Schultheis
1/7/03 04:10:57 PM
MEDICAL OFFICER

review of dispenser for oraqix

Nancy Chang
1/7/03 05:00:27 PM
MEDICAL OFFICER



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MEMORANDUM

FROM: NANCY CHANG (HFD-170)
TEAM LEADER, ANESTHESIA/CRITICAL CARE

SUBJECT: Oraqix Dental Gel, N21451
Medical Team Leader Summary

DATE: NOVEMBER 19, 2002

Background

Oraqix (2.5% lidocaine, 2.5% prilocaine) Dental Gel is a eutectic mixture of lidocaine and prilocaine developed for a proposed indication of "localized anesthesia in periodontal pockets for scaling and/or root planing". It contains poloxamer excipients which show temperature-dependent gelation, such that the drug product is a low-viscosity fluid at room temperature, but forms an elastic gel at body temperature, such as when applied to a periodontal pocket.

Clinical trials of Oraqix have demonstrated consistent, statistically significant reductions in pain associated with scaling and root planing compared to placebo, although these differences have generally been fairly small from a clinical perspective. The safety of Oraqix was evaluated in nearly 400 patients who were exposed to doses of Oraqix up to and including the maximum proposed dose of 8.5 g, corresponding to 5 cartridges of Oraqix. Pharmacokinetic data, including o-toluidine and methemoglobin levels, were obtained in patients exposed to the maximum recommended dose. These studies indicated that the potential for systemic toxicity from systemic exposure to the local anesthetics and their metabolites is low, and that local findings at the application site were generally mild or moderate reactions (e.g. irritation, edema, erythema) that resolved spontaneously during follow-up.

Oraqix is to be provided in cartridges that fit into a standard dental injector. These standard dental injectors are most often used for the injection of local anesthetics. Oraqix is to be packaged with a blunt tip applicator that will be fitted to the injector instead of a needle so that the product can be applied in periodontal pockets. During the course of review, the potential for inadvertent injection of the Oraqix product through a needle was identified as a major safety concern. The following discussion relies on review of materials submitted by the sponsor and also consultation with reviewers from the division of dental products.

Although there are other marketed dental products intended for topical application or application to periodontal pockets, none of these products are manufactured for use with the standard dental injector device. Products that are manufactured in cartridges compatible for use with the dental injector device are intended for injection through a needle. The safety of Oraqix following injection into tissues, including the

potential for systemic toxicity due to the excipients contained in Oraqix, has not been evaluated. In addition, the routine use of local anesthetics for major nerve blocks in dental practice carries a risk of intravascular injection. In addition to concerns of toxicity due to systemic exposure to the active and inactive ingredients of Oraqix, there is the additional concern that intravascular injection of Oraqix might result in embolization of gel particles, a potentially catastrophic event, particularly in the head and neck region. This potential risk has not been tested or otherwise evaluated.

The sponsor is aware of the potential for inadvertent injection that may occur because of the proposed delivery system. They are in the process of designing a new unique dispenser for Oraqix, but proposes that the risk of injection is minimized because of the physical resistance that would be encountered with attempts at injection through the 27 or 30 gauge needles that are standard in dental practice. They summarize data comparing extrusion forces for Oraqix versus water at 22°C and report that much higher extrusion forces are required with Oraqix. In addition, each Oraqix cartridge is separately packaged together with a blunt tip applicator to reduce the potential for mix-ups between Oraqix and standard local anesthetic cartridges.

Although high resistance to injection may discourage inadvertent injection by practitioners, practitioners also routinely encounter situations in which they will inject against high resistance, such as injections near bone, or situations when the injection needle or the cartridge-puncturing needle are bent. As long as Oraqix can be extruded through a 27 gauge needle by a human operator without extraordinary effort, the risk of inadvertent injection must still be present. Review of the sponsor's primary data testing extrusion pressures will need to be reviewed, along with "hands-on" testing by human operators will need to be evaluated to assess this risk. In addition, testing at temperatures other than 22°C may be appropriate if changes in viscosity with temperature variations might significantly affect extrusion pressures. In addition to variations in ambient temperatures at dental offices, the potential for storage of Oraqix cartridges at various temperatures must be considered.

The packaging of Oraqix in individual packets together with a blunt tip applicator may reduce the potential for inadvertent injection; however, it is standard practice in dental offices for dental cartridges to be taken out of their packaging materials and placed in drawers in the office. Cartridges are then laid out for use by a dental assistant, or handed to a dentist (in or out of the injector device) for use in a particular case. This clinical setting allows many points for potential bypass of the protection afforded by this packaging presentation.

In summary, this is a local anesthetic product that has some potential benefit to a limited population. However, this benefit appears to be relatively small, and this is clearly not a medically necessary product. On the other hand, there appears to be a real risk of inadvertent injection because of the proposed delivery system to be used for this product, which is one that is normally used for the injection of local anesthetics in the oral cavity, such as for major nerve blocks. The medical risks of injection of Oraqix into soft tissues have not been assessed. Neither have the risks of systemic exposure to Oraqix, which would occur to a higher degree from injection compared to topical application. Finally, injection of Oraqix for an intended major nerve block carries a risk of intravascular injection, with possible embolization of gel particles, a potentially catastrophic event.

The limited clinical benefit of this product does not justify the potential risks associated with accidental injection of Oraqix. Approval of this product will require a more complete assessment of the medical hazards of systemic exposure and possible intravascular injection of Oraqix, or it will require sounder safeguards against inadvertent injection.

Appendix

The Division of Medication Errors and Technical Support, Office of Drug Safety, has made the following recommendation on the proposed blister foil label for Oraqix:

We recommend revising the established name to read as follows:

Lidocaine and Prilocaine Gel
2.5%/2.5%

Their concern is based on the desire to keep the established name separate from the strength(s) of the active ingredients. To clarify the presentation and to address the concern expressed by DMETS, I would recommend the following presentation:

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

Nancy Chang, MD
Anesthesia Team Leader

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HFD-170:
Nancy Chang, MD
Bob Rappaport, MD

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/s/

Nancy Chang
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DIVISION DIRECTOR REVIEW AND BASIS FOR APPROVABLE ACTION

DATE: November 20, 2002

DRUG: Oraqix Periodontal Gel (lidocaine 2.5% and prilocaine 2.5% gel)

NDA: #21-451

NDA Code: Type 3S NDA

SPONSOR: Dentsply Pharmaceutical

INDICATION: Localized anesthesia in periodontal pockets for diagnostic procedures and treatment such as probing, scaling and/or root planing

Dentsply Pharmaceutical has submitted an application for a local anesthetic periodontal gel product that is manufactured from drug substances that are produced by AstraZeneca AB, _____ located in Sweden. Oraqix (2.5% lidocaine, 2.5% prilocaine) Dental Gel is a eutectic mixture of lidocaine and prilocaine that has been developed for a proposed indication of "localized anesthesia in periodontal pockets for diagnostic procedures such as probing, scaling and/or root planing." It contains poloxamer excipients which show temperature-dependent gelation, such that the drug product is a low-viscosity fluid at room temperature, but forms an elastic gel at body temperature, such as when applied to a periodontal pocket. The concentrations of the active drug substances (lidocaine and prilocaine) in Oraqix are identical to the concentrations in the sponsor's drug product EMLA, a cream that has been approved for the production of local anesthesia of the skin and genital mucosa. EMLA is manufactured and distributed by AstraZeneca. As the studies submitted in this application were performed by AstraZeneca under their IND and the NDA was prepared for Dentsply by AstraZeneca, AstraZeneca is contractually obligated to assist Dentsply with regulatory matters through approval of the NDA. As such, Dentsply has referenced

non-clinical and clinical data from the NDA for EMLA in support of the Oraqix application.

Review of the CMC portion of this application was completed by Michael Theodorakis, Ph.D. Review of the pharmacology and toxicology data presented in this application was completed by Timothy J. McGovern, Ph.D. Review of the clinical pharmacology and biopharmaceutics data in the application was completed by David Lee, Ph.D. A statistical review and evaluation was completed by Milton Fan, Ph.D. Consultation on this application was obtained from the Division of Dermatological and Dental Drug Products, the Division of Drug Marketing, Advertisement and Communications, and the Office of Drug Safety.

Efficacy for Oraqix has been established in three, placebo-controlled studies (B1, B2 and B3) in patients undergoing scaling and/or root planing (SRP). A detailed review of these studies was performed by the primary clinical reviewer for this product, Dr. Lester Schultheis. Dr. Nancy Chang, medical team leader for the anesthetic drug product group, provided oversight for Dr. Schultheis' evaluation, and has concurred with his conclusions and recommendations. In addition, Dr. Chang has summarized the review team's concerns regarding potential medication errors that could occur due to the similarity of the Oraqix packaging and delivery system to that of other non-eutectic local anesthetic products used in the dental office setting.

Studies B1 and B2 documented that statistically significantly lower pain levels were experienced during SRP by the Oraqix-treated subjects compared to the placebo-treated subjects. Pain was measured on a 100-mm visual analogue scale (VAS). The difference in VAS scores for the Oraqix and placebo subjects in Study B1 was 10 mm in median, 13 mm in mean, and 8 mm in Hodges-Lehmann estimate. The difference in median VAS scores for the Oraqix and placebo subjects in Study B2 was 8 mm in median, 6 mm in mean, and 5 mm in Hodges-Lehmann estimate. The protocol-specified expected effect size for these two trials was a difference of 15 mm. In addition, a statistically significant center effect was found in Study B2, with the significant overall effect driven entirely by Center 1.

When these results were initially presented to the Division, the clinical relevance of the documented effect sizes was questioned. The sponsor hypothesized that, due to the low levels of pain experienced by many of the subjects in these two trials, it was not possible to document a robust effect size. In response to the Division's concern, the sponsor designed and performed a third placebo-controlled study (B3). For this study, an enrichment design was chosen that only allowed enrollment of patients who reported a score of greater than 30 mm on the VAS in response to mechanical probing of dental pockets. The median VAS score in the Oraqix-treated patients was 16 mm lower than that of the placebo-treated patients, and this difference was statistically significant. The mean difference was 11 mm and the Hodges-Lehmann estimate was 12 mm.

A post-hoc analysis performed by the sponsor evaluated the ratio of the median VAS scores in the Oraqix and placebo groups reported from the pooled results of Studies B1, 2 and 3. The results of this analysis documented an approximately 50% relative reduction in VAS scores associated with the use of Oraqix compared to placebo. An additional analysis evaluated logarithmically transformed data from the individual centers and computed a ratio of the VAS scores of the Oraqix group to the placebo group. This analysis also found an approximately 50% reduction in VAS scores for Oraqix compared to placebo. Both of these analyses appear to be supportive of the efficacy of Oraqix, but must be interpreted with caution as they were performed on a post-hoc basis and they pooled data across the three studies.

Patient Verbal Rating Scores (VRS) were analyzed as secondary endpoints in the three trials. These analyses were prespecified in the study protocols. This 5-point categorical scale described pain from “no pain” to “very severe pain.” Statistically significant reductions in the VRS for the Oraqix-treated patients compared to the placebo-treated patients were found in Studies B1 and B3, but not in Study B2.

Oraqix is applied to the gingival mucosa of dental pockets using a standard dental syringe that expels the drug from its glass carpule through a blunt-tipped needle that is packaged with the carpules. Each carpule contains 1.7 gm of periodontal gel and is fitted with a synthetic rubber plunger and diaphragm. When the back of the needle perforates the diaphragm, as the syringe plunger is depressed, drug is extruded through the blunt tip of the applicator needle into the dental pocket. Dosing in the clinical trials allowed for cumulative doses of up to 5 carpules per single treatment. However, relatively few patients were treated with the highest allowed dose. Approximately one carpule of gel was used per single quadrant of dentition.

In seven clinical studies, including a total of 391 patients exposed to Oraqix, there were no deaths, serious adverse events or adverse events that resulted in discontinuation. The most frequent adverse events documented in the Oraqix-treated patients were local reactions including discomfort, irritation, redness and edema. Systemic events that were associated with exposure to Oraqix in the clinical development program included “bad taste” and a slightly higher incidence of nausea compared with exposure to injected local anesthetic.

Of some concern, vesicle and ulcer formation occurred in 2 and 8 patients, respectively. The ulcers occurred in 5 Oraqix-treated patients and 3 placebo-treated patients in Study B1. Both of the subjects who developed vesicles were in Study A3, one of the biopharmaceutics studies. In a crossover study designed to assess tolerance to Oraqix treatment compared to treatment with lidocaine with epinephrine 1:200,000 injectable, no subject in either treatment group developed ulcers or vesicles. Ulcerations and vesicles were also not seen in any of the other studies. In addition, all of the events were rated mild to moderate, and that they all resolved spontaneously. Ulceration and vesicle formation do routinely occur in a small percentage of patients who have recently undergone SRP.

In the pharmacokinetic studies of Oraqix, the peak plasma levels of prilocaine and lidocaine, and their potentially toxic metabolites 2,6-xylylidine and o-toluidine, documented after the administration of the maximally proposed dose of drug product, were well below the levels that would be expected to be of clinical concern. The levels of methemoglobin documented in these studies were also well below those known to result in clinical toxicity.

One further safety concern centers on the similarity of the Oraqix carpules to the standard carpules that contain solutions of local anesthetics used in the dental setting. The standard local anesthetic carpules are inserted in the same type of syringe proposed for delivery of Oraqix. The clinical review team, including the dental consultants, has expressed concern that the similarity in these carpules will result in cases of inadvertent injection of Oraqix into the periodontal tissues. As the injection of Oraqix into the periodontal vasculature could result in embolization of gelatinous material, with resultant morbidity and even mortality, this concern was reported to the sponsor. The sponsor's response to this issue included their contention that 1) the packaging of their product, including warnings against injection and blister design, would prevent inadvertent administration, and that, 2) the resistance experienced by delivery of the gel product through the high-gauge needles used in dental practice would provide adequate warning to practitioners before the drug product could be delivered into the vasculature. However, as per Dr. Chang's review, it is standard practice in dental offices to remove local anesthetic carpules from their packaging and place them in a tray for convenience. Therefore, the warnings provided on the product packaging may not be adequate to prevent misuse. In addition, while a summary analysis was provided to support their hypothesis regarding the required pressures needed to inject Oraqix into the periodontal tissues, the actual data upon which this analysis was based was not submitted. It is not unusual in the dental setting for high resistance to be experienced during injection due to injection near bone, or due to situations in which the injection or cartridge-puncturing needle is inadvertently bent. Of note, the sponsor additionally reported in response to the above described concerns, that they are in the process of developing a reusable plastic cartridge-type drug delivery system that will not require the use of a standard syringe.

Although the core review team initially believed that there was a significant pediatric population that would benefit from the availability of treatment with Oraqix, further evaluation and research by the team and consultative input from the Division of Dermatologic and Dental Drug Products did not support this position. Thus, a waiver of pediatric development for this drug product has been recommended by the clinical team.

Nonclinical Safety

Two new acute toxicology studies were performed with lidocaine and prilocaine at maximally tolerated doses via the oral route of administration in rats. No unexpected

toxicities were noted at doses that resulted in higher plasma levels than would be expected in humans with the maximum proposed doses of Oraqix.

The following non-clinical studies were not submitted with this application and were not performed in support of the EMLA NDA:

- An *in-vitro* chromosome aberration study with prilocaine
- An *in-vivo* chromosome aberration study with prilocaine
- A fertility study with lidocaine
- Embryo-fetal development studies with prilocaine and lidocaine
- A pre- and post-embryo-fetal development study with lidocaine

Biopharmaceutics

As noted above, one pharmacokinetic study (A3) evaluated the plasma concentrations of lidocaine, prilocaine, 2,6-xylidine, o-toluidine, and methemoglobin, after administration of the highest recommended dose of Oraqix, 8.0-8.7 g. All of the plasma levels were considerably below the levels previously known to result in toxicity related to these substances.

Chemistry, Manufacturing and Controls

Although Dr. Theodorakis reported a series of potential deficiencies in his initial Oraqix review, those concerns were relayed to the sponsor and they were able to respond early enough in the review cycle in order to allow time for evaluation. Their response was reviewed by the CMC team and found to be acceptable.

Discussion

The sponsor has provided adequate evidence of the safety and efficacy of their drug product, Oraqix, for use in the setting of SRP. The indication must be limited to this setting as Oraqix has not been studied in the treatment of other dental procedures. However, due to concerns related to potential misuse of the product based on the similarity in packaging and appearance to injectable local anesthetics, and the potentially catastrophic events that could result from inadvertent injection of the product into the periodontal tissues and vasculature, this application cannot be approved at this time.

The sponsor has been informed of this decision and the concerns upon which it was based. The sponsor will need to make the necessary changes to the product packaging, warnings and delivery system to clearly differentiate it from injectable anesthetic drug products, even if a carpule were to be removed from the outer packaging.

In addition, the sponsor must submit acceptable data from certain nonclinical studies, as outlined above under **Nonclinical Safety**.

Action: Approvable

Bob A. Rappaport, M.D.
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REVIEW AND EVALUATION OF CLINICAL DATA

NDA #	21-451
Sponsor	Dentsply Pharmaceutical
Generic Name	Lidocaine 2.5% and Prilocaine 2.5%
Proprietary Name	Oraqix Periodontal Gel
Pharmacologic Class	Amide local anesthetics
Proposed Indication	Topical anesthesia for oral mucosa
Submission Date	January 23, 2002
Dosage forms	25 mg/mL each lidocaine and prilocaine thermosetting gel in 1.7mL dental cartridge
Strengths	25mg/mL lidocaine and 25mg/mL prilocaine
Route	topical
Clinical Reviewer	Lex Schultheis, M.D., Ph.D.
Statistical Reviewer	Milton Fan, Ph.D.
Completion Date	November 20, 2002

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Executive Summary

1. RECOMMENDATIONS

1.1 Recommended Action

Based upon the information submitted, Oraqix™ Periodontal Gel is approvable for its intended use “in adults for localized anesthesia in periodontal pockets for probing, scaling and/or root planning (SRP). Clinical trials have demonstrated a small, but statistically significant reduction in Visual Analog Scale (VAS) measurement of pain associated with SRP associated with the use of Periodontal Gel. Two out of three pivotal studies also demonstrated statistically significant reductions in Verbal Rating Scale (VRS) estimates of pain in patients receiving Periodontal Gel compared with patients receiving placebo gel for SRP. The active agents in Periodontal Gel have been approved for use in combination in the same concentration and proportion in EMLA® cream for topical application. The use of Periodontal Gel did not result in serious adverse events and appeared safe when used as directed.

A remaining concern is the similarity of the Oraqix cartridge to currently available dental cartridges for submucosal injection of local anesthetic. Both Oraqix and injectable anesthetic cartridges are inserted into a standard reusable syringe not supplied with the drug. The blunt needle supplied with Oraqix and sharp needles for injection both fit the same threaded tip of dental syringes. Because of the similarity of cartridge design and delivery, there is a potential for inadvertent injection of Oraqix into a submucosal blood vessel with possible systemic thrombus formation and embolization of gel.

2. SUMMARY OF CLINICAL FINDINGS

2.1 Overview of Clinical Program

The clinical development consisted of three phase 2 clinical pharmacology trials (A1, A2, A3) involving 52 subjects. Periodontal gel was administered in either a single dose or multiple doses and 11 subjects received the maximum recommended dose (8.5gm). These studies were designed to assess systemic uptake of lidocaine and prilocaine and plasma levels of the metabolites 2,6 xylydine from lidocaine and o-toluidine from prilocaine. The plasma concentration of methemoglobin was also monitored because the binding of o-toluidine oxidizes the ferrous of hemoglobin form to the ferric form thereby reducing its oxygen carrying capacity.

Three randomized, placebo controlled, double-blinded studies (B1, B2, B3) were conducted involving 337 patients. The placebo consisted of the solubilized poloxamer excipients without the active anesthetic ingredients. The placebo and active drug had different tastes, but no patients were exposed to both placebo and Periodontal Gel. In addition, to the placebo controlled studies, an open-label randomized crossover study (B4) compared preference for Periodontal Gel with injected local anesthetic (Xylocaine 2% with epinephrine) in 170 patients. An analytical study (B5) was performed by the

sponsor to reevaluate the results of B1 and B2 center by center because of possible variability in patient selection for the dental procedure used to evaluate Periodontal Gel.

The sponsor also provided a review of the medical literature surrounding EMLA® cream, because Periodontal Gel and EMLA® cream contain the same active agents (lidocaine and prilocaine) in the same proportion. Periodontal Gel differs from EMLA® cream in preparation because the intended use of Periodontal Gel requires limited flow properties after it is applied. The thermosetting property of Periodontal Gel enabling it to change from liquid to a gel as it warms from room to body temperature results from poloxameric excipients. The poloxamers (188 and 407) in Periodontal Gel have not been approved by the Agency for use in other products, but these or closely related chemically compounds have been tested in animal and human studies and been found to be safe and effective in the doses recommended for Oraqix.

2.2 Efficacy

Three randomized double-blind placebo controlled multicenter studies (B1, B2, and B3) were performed with the primary goal of comparing VAS scores in the Periodontal Gel and placebo gel recipients following SRP. A relative reduction of 15 mm on a 100 mm VAS (placebo-anesthetic treatment) was prospectively defined to constitute a "minimum clinically relevant difference" as a result of treatment. Statistically significant differences in VAS scoring were used to differentiate the anesthetic efficacy between patient groups receiving either Periodontal Gel or placebo. In the first two studies (B1, total n=122 and B2, total n= 130), measurements of central tendency in VAS (mean, median) were quite low even in the placebo group. This suggested that even though statistically significant differences in VAS appeared between placebo and study drug, the clinical relevance was marginal. The SRP procedure was simply not painful enough in the sample patient populations selected to demonstrate a substantial average reduction in pain. Some centers that enrolled patients with more extensive disease (deeper periodontal pockets) reported higher VAS scores in placebo and larger attenuation in the Periodontal Gel group. The third controlled study (B3, total n=85) attempted to select only patient who would experience clinically meaningful pain during SRP for comparison of Periodontal Gel to placebo gel by VAS. Patients were admitted to B3 if they reported pain greater than 30mm on VAS in response to mechanical probing. The median VAS in the Periodontal Gel group was 16 mm below that of the placebo group. Study B3 was the only pivotal study to meet prospective criteria for clinical as well as statistical significance in favor of Periodontal Gel in the primary outcome variable.

A post-hoc analysis of results performed by the sponsor from studies B1, B2 and B3 was contained in B5. This work evaluated the ratio of the median VAS reported from the pooled Periodontal Gel group to median VAS reported from the pooled placebo group. The findings of this analysis indicated about a 50% relative reduction in VAS associated with the use of Dental Gel. An additional analysis used logarithmic transformation of individual center data to compute a ratio of Dental Gel VAS to placebo

VAS with confidence intervals. These findings also estimated about a 50% reduction in VAS when Periodontal Gel was used. This work must be interpreted cautiously because a reduction in pain score expressed as a percent of a placebo score may appear more striking than it really is because the actual magnitude of discomfort with placebo was small.

Patient Verbal Rating Scores (VRS) were assessed as secondary endpoints in studies B1, B2 and B3. The VRS described the pain level felt by the patient during the SRP among 5 optional descriptions ranging from "no pain" to "very severe pain". Statistically significant differences were noted in favor of Periodontal Gel in the severity of pain reported typically during SRP and in the frequency with which the highest levels of pain were reported in B1. High levels of pain were an infrequent occurrence so that the greater number of patients with little discomfort dominated the median reported results. Fewer patients receiving Periodontal Gel reported high levels of pain compared with placebo, suggesting that Periodontal Gel mitigated discomfort among patients who were sensitive to the SRP procedure.

Study B2 revealed no statistically significant differences between VRS in placebo and Periodontal Gel groups. Both the placebo and Periodontal Gel groups reported the same number of patients having severe pain with SRP and the preponderance of patients reported pain at the low end of the scale.

Analysis of the VRS in Study B3 was remarkable for skewing of the Periodontal Gel group toward lower pain categories relative to the placebo group. In essence, a small number of placebo treated patients reported pain in the highest category, but none in the Periodontal Gel group reported pain at the highest level. Also a small number of patients in the Periodontal Gel group reported no pain with the SRP procedure, but none of the patients in the placebo group did so.

The collective findings of the placebo controlled B1-3 studies indicate that Periodontal Gel offered some relief to patients who were sensitive to the SRP procedure. Periodontal Gel treatment rarely abolished pain and was inadequate in others, however, for a subset of patients Periodontal Gel reduced the discomfort of the SRP procedure to a more tolerable level by statistical and clinical criteria.

Study B4 was an open label randomized crossover trial that compared patient preference for Periodontal Gel to local anesthetic injection in patients with known aversion to needle injections in their mouth. Most patients (70%) preferred Periodontal Gel compared to injected anesthetic (22%) and to those with no preference (8%), a finding biased by the patient selection criteria.

Secondary efficacy variables included pain associated with administration patient evaluation of satisfactory anesthesia during SRP, investigator's assessment of anesthesia, post-procedure discomfort, willingness to pay for anesthetic and willingness to return for the same treatment. The typical degree of discomfort associated with administration of Periodontal Gel was similar to that associated with injection. The quality of anesthesia

resulting from Periodontal Gel was inferior to injection, rated satisfactory by 80% of the patients who received Periodontal Gel and 96% of the patients who received local injections. Dentists performing SRP found statistically significant differences in operating conditions with satisfactory criteria met in 100% of the patients after injection, and in 76% of the patients receiving Periodontal Gel. Dental operating conditions was used as an index of adequacy of anesthesia. Post procedure discomfort was less in the Periodontal Gel group achieving a statistically significant difference. The economic analysis was not reviewed. Of the patients who expressed a preference for either injection or Periodontal Gel, 63% expressed willingness to return for SRP if they knew in advance that Periodontal Gel would be their anesthetic. Collectively these findings indicate that in treating patients with aversion to dental injections, Periodontal Gel was a satisfactory alternative with significant limitations.

2.3 Safety

The components of Periodontal Gel include lidocaine 2.5%, prilocaine 2.5% and prepurified poloxamers 188 and 407 as thermosetting agents with HCL. The maximum recommended dose per treatment is 5 cartridges equal to 8.5 gm Periodontal Gel containing 212.5 mg lidocaine and 212.5 mg prilocaine. The poloxamers had been approved for use in other products. Small changes in poloxamer concentration and in the purification process were made between clinical trials, but no clear changes in the adverse event profile or efficacy could be determined.

Lidocaine HCL is one of the most widely used amide agents for topical or conduction anesthesia. It is also approved as an antidysrhythmic. Agency approved lidocaine preparations (single active agent) for topical anesthesia include 2% jelly, 2.5-5 % ointment and 1,2 and 4 % aqueous solution. It is approved for use in adults and children over the age of 3 years. Toxic reactions (plasma levels 5000-6000ng/ml) may occur after topical administration of a single dose exceeding 300mg in healthy adults. Patients with hepatic insufficiency are at increased risk. Signs of toxicity include drowsiness, parasthesias, tinnitus and in high doses, convulsions and bradycardia with hypotension.

Prilocaine HCl is an amide local and conduction anesthetic similar to lidocaine, but is more rapidly metabolized and therefore a lower incidence of direct toxicity. Approved preparations of prilocaine as a single active agent include 0.1-3% solutions. It is approved for use in adults. Toxic reactions may occur after parenteral administration of doses exceeding 3-600 mg in adults with similar clinical signs as lidocaine. Patients with congenital or acquired conditions that produce abnormal high amounts of methemoglobin or restrict normal methemoglobin reductase activity may develop cyanosis after exposure to prilocaine.

EMLA® cream is a eutectic ointment of 2.5 % lidocaine and 2.5% prilocaine for local anesthesia of the skin. Plasma levels after application of 10 gm of EMLA to leg ulcers reached 840 ng/mL for lidocaine and 80 ng/mL for prilocaine.

Three pharmacokinetic studies (A1, A2, A3) with a total of 52 patients, three randomized double-blinded placebo controlled studies (B1, B2, B3) with a total of 337 patients and one open label crossover study (B4) of 170 patients with injected local anesthetic were used to develop a database of adverse events. There were 224 adverse events in 128 patients reported out of 559 patients studied.

The pharmacokinetic studies revealed that peak plasma levels of local anesthetics were reached within about 40 minutes after administration. Study A3 tested maximal recommended doses (5 cartridges) on 11 patients with the highest peak individual plasma levels recorded for lidocaine and prilocaine equal to 552ng/ml and 181 ng/ml respectively. An oral injection of 200mg dental anesthetic lidocaine can produce peak plasma levels of 2000ng/mL.

Plasma levels of a metabolite of lidocaine, 2,6 xylylidine and a metabolite of prilocaine, o-toluidine were also measured because of their individual and combined potential for toxic reactions. Both compounds were present in low concentrations with AUCinf ratios of 0.07-0.18 for 2,6 xylylidine/lidocaine and AUCinf ratio of 0.19-0.56 for o-toluidine/prilocaine.

Blood methemoglobin levels were monitored serially in each of the pharmacokinetic studies. Blood levels of methemoglobin at baseline ranged from 0 to 1.1% of total hemoglobin and rose to from 0.83 to 1.73% as the highest individually measured values. Clinical symptoms of hypoxemia typically require 10% of circulating hemoglobin be oxidized as methemoglobin.

Taken collectively, these studies indicate that the potential for systemic toxicity of Periodontal Gel appears similar to EMILA cream on the basis of pharmacokinetic data. These data suggest that the systemic manifestation of toxicity is unlikely unless adult patients have predisposing conditions or concurrent administration of medication impairs that metabolism. Use of concurrent amide anesthetics such as dental injections to supplement Periodontal Gel must be carefully considered to avoid exceeding toxic thresholds.

Pharmacokinetic studies poloxamers of the poloximers in Dental Gel were not investigated experimentally by the sponsor. Nor was clinical laboratory data collected to associate with adverse events to provide evidence of individual toxic reactions. Both poloxamers, 188 and 407 have been used in drug formulations to modify physical properties or to facilitate controlled release of active agents. Small changes in relative concentration of the poloxamers and the purification process were performed between clinical studies.

An evaluation of all seven clinical studies (A1-A3, B1-B3 and B4) indicates that the most frequent adverse events were local reactions at or near the site of application. These reactions including discomfort, irritation, redness and edema are common findings after SRP procedures. When specific comparison of local reactions was made between Periodontal Gel and injection, it was noted that Periodontal Gel was associated with

vesicle and ulcer formation in 10 patients, a finding not reported after injection. Placebo gel administration was also associated with local ulcer formation as an infrequent occurrence. Formation of local ulcers and vesicles may be a direct result of the poloxamers or a consequence of altered SRP technique because of topical anesthesia. They may be an unrelated incidental finding because of underlying pathophysiology. The local anesthetic injected in B4 was 2% Xylocaine® with epinephrine tartrate 12.5µg/mL (5.6 ug/mL free epinephrine), approved for use in Europe, but not in the United States. A similar local anesthetic 2% Xylocaine with epinephrine 1:200000 (5ug/mL free epinephrine), is approved in the United States and is in widespread application. Systemic adverse events associated with Periodontal Gel included bad taste and a slightly higher incidence of nausea than injected anesthetic. Most systemic events were of mild or moderate intensity and could not be causally related to Periodontal Gel. No subject died, required hospitalization or discontinued treatment because of an adverse event associated with Periodontal Gel. The studies seem adequate to indicate that Periodontal Gel may be used safely when applied as directed.

2.4 Dosing

Periodontal Gel is applied to the gingival mucosa of dental pockets using a standard (not provided) reusable dental syringe to expel the drug from its glass cartridge through a single use blunt tipped needle provided with the drug. Each cartridge containing 1.7 gm of Periodontal Gel is fitted with a synthetic rubber plunger and diaphragm. The back of the needle perforates the diaphragm as the plunger is depressed allowing the drug to exit through the blunt tip of the needle into the dental pocket.

About one cartridge of Periodontal Gel is used for a single quadrant of dentition. Cumulative doses up to 5 cartridges (maximum recommended dose) may be used if many teeth are treated in a single visit. The sponsor examined the range of doses and treatment scenarios likely to be used in clinical practice, but with relatively few patients at the maximum dose.

My safety review includes presentations of frequency and severity of adverse events related to the dose of Dental Gel administered. The data suggest that more adverse events occurred per patient and that the relative frequency of moderate to mild adverse events was higher with higher doses. The maximum dose was used under somewhat supernormal conditions with patients retaining the Dental Gel longer without rinsing their mouth than would be typical in actual practice. There were insufficient numbers of patients treated at the maximum dose to draw conclusions based upon statistical analysis of the adverse event reported at the maximum dose.

2.5 Drug-Drug Interactions

Administration of other local anesthetics especially of the amide type should be used with attention to the cumulative dose. Some antiarrhythmics have related structures and need to be considered when estimating the potential for additive effect. Patients

taking drugs or exposed to agents associated with drug-induced methemoglobinemia should be treated with caution.

2.6 Special Populations

No clinically significant drug-demographic interactions were noted in the efficacy or safety analyses. Both genders were well represented in the clinical studies without evidence of gender specific effects except that females reported that Dental Gel had an unpleasant taste more frequently than males. The age range of the subjects was appropriate to investigate use of the drug in adult patients with periodontal disease.

The racial composition of the placebo controlled clinical studies was mostly Caucasian (72%) with a smaller subset of African-Americans (23%) and small number of patients (5%) of other races. Some of the clinical trials were conducted outside the United States. It is most likely that race alone does not impact on the efficacy or safety of Periodontal Gel.

Children were not included in the clinical trials. Periodontal disease is found in adults. It is possible that SRP would be performed in small select pediatric populations, but the number of pediatric patients that would be exposed to Periodontal Gel is expected to be small.

No pregnant patients were studied. Newborns whose mothers are exposed to prilocaine may exhibit cyanosis from methemoglobinemia.

No patients with evidence of serious systemic disease or a history of serious systemic disease were studied. Patients with hepatic insufficiency, certain hemoglobinopathies or cardiopulmonary pathophysiology limiting oxygen carrying capacity and delivery may be at increased risk.

Clinical Review

1. INTRODUCTION AND BACKGROUND

1.1 Proposed Indications

Oraqix is indicated for adults who require localized anesthesia in periodontal pockets during scaling and/or root planning.

1.2 Milestones in Product Development

Lidocaine and prilocaine are well established local anesthetics of the amide type in use and are approved in a variety of formulations.

EMLA cream (NDA 19-941), a topical anesthetic product with identical active ingredients in the same concentration as Oraqix has been shown to be safe and effective on intact normal skin and on male genital skin and on female mucous membranes.

Important nonclinical studies in the development of Oraqix included a single local tolerance study on the oral/gingival mucosa of dogs. Single dose toxicity studies were performed with lidocaine and prilocaine alone to show safety margins to acutely toxic oral doses from accidental swallowing of Dental Gel. Mutagenic and carcinogenic effects of 2,6 xylydine and o-toluidine metabolites of lidocaine and prilocaine respectively were evaluated with respect to the dosage and route of administration of Dental Gel. A review of the published literature was performed on poloxamers, the excipients responsible for the thermosetting property of Dental Gel. (Dental Gel is a liquid at room temperature, but gels to a semisolid state at body temperature.)

Pharmacokinetic studies (A1, A2, A3) were performed in dental patients to benchmark plasma concentrations of lidocaine, prilocaine and their metabolites (2,6 xylydine and o-toluidine) in the dental application of scaling, probing and root planning (SRP). Blood concentrations of methemoglobin were collected also because o-toluidine is recognized as an oxidant of the normal form of ferrous hemoglobin.

Three randomized controlled clinical trials (B1, B2, B3) using thermosetting poloxamer gel without local anesthetics as placebo were performed to test efficacy of Oraqix Periodontal Gel in dental SRP. Post-hoc analysis of results from B1-3 was performed to evaluate possible center effects on measurements of efficacy. A randomized cross over study (B4) comparing anesthetic efficacy of Oraqix to local injected anesthetic was performed in patients requiring two SRP treatment sessions. Safety assessment of Oraqix used as directed was based upon clinical findings from studies A1-3 and B1-4.

1.3 Foreign Marketing

Oraqix (lidocaine 2.5% and prilocaine 2.5%) Periodontal Gel is not currently marketed anywhere in the world. A marketing application is being submitted in the European Union simultaneously with this New Drug Application.

2. FINDINGS FROM OTHER CHEMISTRY, PHARMACOLOGY

2.1 Chemistry

The active agents are the base forms of lidocaine 25mg/mL (Approved EMLA NDA Standard) and prilocaine 25 mg/mL (Approved EMLA NDA Standard) in an aqueous solution with poloxamers 188 (Purified AstraZenica) and 407 (Purified AstraZenica). Hydrochloric acid (qs) is used as a pH adjusting agent. The water is purified to Ph. Eur. and USP standards, not sterile. The poloxamers contribute thermosetting properties to Oraqix so that it is a liquid at room temperature and a semisolid gel at body temperature. A review of the manufacturing process did not reveal impurities or techniques that were related to adverse events. Quality control standards appeared appropriate.

2.2 Pharmacotoxicology

Two new acute toxicology studies were performed in rats with lidocaine and prilocaine administered orally at maximally tolerated doses. Toxicity was generally related to CNS effects that have been well characterized for high dose local anesthetics. Exposure to the anesthetic agents and their metabolic products, 2,6 xylidine and o-toluidine revealed plasma levels greater than anticipated after maximal dosing with Oraqix. A study in dogs with the initial formulation of poloxamers did not identify local irritation as a consequence of repeated application to the gingival sulcus.

Genetic testing with lidocaine and prilocaine did not reveal evidence of mutagenesis, however the study of prilocaine is incomplete.

3. HUMAN PHARMACOKINETICS AND PHARMACODYNAMICS

The active agents in Oraqix are lidocaine and prilocaine, members of the amide class of local anesthetics. Oraqix is applied directly into the periodontal pockets to provide local anesthesia for scaling and root planning in dentistry. The onset of anesthesia is about 30 seconds with a duration of action of 15-20 minutes. The peak plasma levels (median tmax) of lidocaine and prilocaine appear within 30 minutes after a single application of 0.9 to 3.5gms and 200 min after the maximum recommended dose of 8.5 gm applied in divided doses over 3 hours. Peak plasma concentrations are 0.17 and 0.08mg/L of lidocaine and prilocaine respectively after a single application of 0.9-3.5 gm Oraqix. Cumulative administration to the maximum recommended dose results in plasma levels of 0.28 mg/L lidocaine and 0.11 mg/L prilocaine. Both drugs have intermediate degrees of protein binding mainly to alpha 1 acid glycoprotein. Lidocaine is metabolized in the liver. Prilocaine is cleared in excess of hepatic blood flow purportedly by an extrahepatic mechanism. Lidocaine is metabolized by N-dealkylation and subsequent hydrolysis to 2,6-xylidine, which is excreted in the urine after conversion to 4-hydroxy-2-6-xylidine. Prilocaine is metabolized to o-toluidine and its hydroxylated metabolites. Methemoglobin formation from oxidation of ferrous hemoglobin by o-toluidine remained less than 2% for all patients studied, even with the maximum recommended dose of Oraqix. Application of Oraqix resulted in a mean terminal half-life of 3.6 hours for lidocaine and 2.8 hours for prilocaine.

4. DESCRIPTION OF CLINICAL DATA AND SOURCES

4.1 Sources of Clinical Data

The primary source of data was from the clinical trial programs for Oraqix. Other team members from the Anesthesia, Critical Care Division, Addiction Drug Product Division and members of the Dental and Dermatology Division provided critical consultation.

4.2 Overview of Clinical Trials

The individual reports from each clinical study were consulted first and the data therein compared with the electronic database. Analysis of data for the review was extracted directly from the electronic database. These data were compared with summary tables provided by the sponsor. Comparisons were made between Oraqix and EMLA cream using the articles supplied by the sponsor and independent review of the literature.

4.3 Postmarketing Experience

N/A

4.4 Literature Review

A selected review of the medical literature was performed focusing on local anesthetics especially of the amide type. Basic medical text references on hemoglobinopathies and methemoglobinemia were consulted. Review articles and labeling information on EMLA, lidocaine and prilocaine were examined.

5 CLINICAL REVIEW METHODS AND DATA INTEGRITY

5.1 Overview of How Review Was Conducted

Each clinical trial (A1-3, B1-4) was reviewed separately for efficacy and safety. Emphasis was placed on B3 as the pivotal study for efficacy. Study A3 was examined in particular because it evaluated the effect of maximal doses. Less emphasis was placed upon post-hoc analysis B5. Adverse events were grouped by type, dose and study to search for patterns related to severity and mechanism.

5.2 Overview of Materials Consulted in Review

NDA, electronically submitted tables and Clinical Report Forms. The consultation reports from the Dental and Dermatology division were vital references.

5.3 Evaluation of Data Quality and Integrity

The sponsor's tables and numerical data were compared with the electronic database and found to be internally consistent. Early questions numbers of AE and the numbers of patients reporting AE were successfully addressed by the sponsor. Some patients reported more than a single adverse event. Individual Clinical Report Forms were reviewed in cases of local ulcer and vesicle formation. The data presented by each study individually appeared to be referenced correctly and accurately in the summary manuscripts.

5.4 Compliance With Accepted Good Clinical Practices

Patients were adequately informed of their risks and alternatives by the informed consent documents. All patients had the option to withdraw from clinical studies without compromising their medical care. Internal Board Review was performed by the host institution for all studies. Studies were conducted in accordance with the Declaration of Helsinki and were consistent with Good Clinical Practice and applicable regulatory requirements.

5.5 Financial Disclosure

There were no financial disclosures that cast doubt on the veracity of the data or its method of collection. Some subinvestigators that participated in clinical studies prior to 1999 could not be located because of changes in employment to obtain information.

6. REVIEW OF EFFICACY

6.1 Findings vs. Labeling Claims

Oraqix has met criteria sufficient to qualify it as efficacious for the proposed indication. It is noted however, that the sponsor's label in **Clinical Studies** could mislead the practitioner by portraying Oraqix as a more powerful agent to relieve pain of SRP than it is.

"In all three studies did Oraqix provide significantly better anesthesia than placebo. In the two US studies, involving 122 and 80 patients each, were the placebo pain scores reduced by 54% (c.i. 35-83%) and 47% (c.i. 24-74%) respectively (B1, B3 and B5). In the third study, performed in 130 patients in Canada, was the placebo pain scores reduced by 50% (c.i. 25-100%) (B2 and B5). In all three studies were the anesthesia adequate to complete scaling and/or root planing of up to 15 minutes' duration, and the SRP could be completed without the need for any additional conventional anesthesia in almost all the patients treated with Oraqix."

The sponsor has chosen to present the ratio of Oraqix VAS score to placebo score for each placebo controlled study. While factually correct, this analysis does not reveal that for most patients, the pain from the dental procedure studied was at the low end of the VAS measurement tool. The use of post-hoc analysis understandably attempts to correct for

differences in patient selection and treatment between centers, however it may bias the conclusion in favor of Oraqix because the magnitude of pain measured by many patients was small. A more balanced representation of the local anesthetic capability of Oraqix is required to assist practitioners in matching the drug with patients who will derive the most benefit. Documenting the actual median pain scores for Oraqix and Placebo for each clinical study will enable practitioners to objectively evaluate the efficacy of the product in a more specific clinical setting. The sponsor also fails to point out that SRP was completed in patients receiving placebo without the need for additional conventional anesthesia.

The sponsor's discussion of B4, an open label crossover study comparing Oraqix to 2% Lidocaine plus epinephrine tartrate (12.5ug/mL) should not be included.

"Oraqix was compared to lidocaine 2%-epinephrine injection in conjunction with (manual and ultrasonic) scaling in one open-label, crossover study in Belgium in 170 patients who were bothered by the prospect of having a dental injection or its after-effects. Oraqix provided satisfactory anesthesia in the vast majority of the patients (80%), though statistically significantly less than lidocaine injection (96%). With Oraqix, significantly fewer patients were bothered by post-procedure problems such as numbness (15%) compared to lidocaine injection (66%). Most patients (70%) found Oraqix treatment preferable to lidocaine injection."

The study is biased because only patients with a known aversion to oral injection were enrolled. The injection product is also not approved for use in the United States.

The sponsor's label in **Overdosage** does not address the potential situation when an oral injection of local anesthetic may be needed to rescue a patient from pain inadequately mitigated by a maximum dose of Oraqix.

"Oraqix alone and used as recommended is not likely to cause toxic plasma levels of lidocaine and prilocaine (). However, if other local anesthetics are administered at the same time, e.g. topically or by dental injection, the toxic effects are additive and may cause an overdose with systemic toxic reactions."

A discussion of the plasma levels of drug after topical application of Oraqix compared with oral injection may offer important supplementary dosing guidance to clinicians.

The sponsor's discussion of **Adverse Events** was incomplete.

"Adverse events in clinical studies: Following SRP treatment with Oraqix in three placebo controlled studies, the most frequent symptoms were local reactions in the oral cavity

6.2 General Approach to Review of Efficacy

The pivotal clinical study for efficacy was B3. This multicenter randomized placebo controlled trial specifically recruited patients with known sensitivity to dental probing from a screening visit. It included 85 patients with 43 exposed to Oraqix. The primary outcome variable was the difference in VAS score between Oraqix and placebo treatment groups. Studies B1 (122 patients, 63 treated with Oraqix) and B2 (130 patients, 63 treated with Oraqix) were also evaluated for efficacy although the average magnitude of pain among these patients was smaller. The sponsor suggested that there may have been center effects in B1 and B2. The sponsor contends that patients with little sensitivity to SRP were recruited by some institutions thereby biasing the VAS to demonstrate little difference between Oraqix and placebo. To minimize the effect of center bias, a post hoc analysis was reported in B5. Study B4 was an open label cross over study (170 patients) comparing injection to Oraqix. This study was useful, but suffered from recruitment bias in that only patient who were injection averse were enrolled. Secondary efficacy variables (VRS) were reviewed, but emphasis was placed upon the sponsor's primary efficacy variable.

6.3 Individual Review of Studies (by indication)

6.3.1 Study B1: (SP-DGA-0003): A randomized, double-blind, placebo-controlled study to evaluate the efficacy of dental gel 5% (prilocaine 25mg/g and lidocaine 25 mg/g) for periodontal pocket anesthesia in conjunction with dental scaling and root planing.

Study Plan

The initial version of the protocol was dated 1/31/1997. An amendment was dated 4/10/1997 (amendment 1). The study was conducted between May 1997 and September 1997. The study was conducted as was pre-specified in the amended protocol. Source: original NDA submission, Vol. 1.26, pp 10, 65-66, 145.

Population, Design, and Objectives

Primary:

To determine the local anesthetic efficacy of dental gel 5% compared with placebo by means of assessing overall pain from SRP on a visual analogue scale (VAS)."

Secondary:

To determine the need for rescue anesthetic compared with placebo and to determine adverse events associated with the use of the dental gel."

Study Design:

The protocol was designed as a multicenter, randomized, parallel-group, double-blind, study comparing dental gel 5% and placebo gel. The study planned to enroll 120 evaluable patients, 60 in each arm. The study was conducted in 4-5 centers in the US. The study was comprised of one screening visit, one treatment visit, and a telephone follow-up.

Placebo-control design was selected to control for the lubricating effect of the excipients. Parallel-group was selected to avoid a carry-over effect of the pain perception, and to ensure blinding in face of a possible taste difference between dental gel 5% and the placebo gel.

“Inclusion Criteria:

Patients requiring periodontal SRP in at least one quadrant of the mouth that has not received SRP in the previous 12 months.

The selected quadrant shall include at least 5 natural teeth, at least 1 tooth of which should contain at least 1 pocket with a depth of 6 mm, and at least 2 other teeth each containing at least 1 pocket with depth of 5 mm.

Age at least 18 years.

Able to comprehend the VAS.

Written informed consent obtained.

Patient, in the opinion of the investigator, that are reasonably be expected to comply with the protocol.”

“Exclusion Criteria:

History of allergy, sensitivity, or any other form of reaction to local anesthetics of the amide type.

Receipt of an anesthetic or sedative in the 12 hours prior to probing/SRP.

Pregnancy and/or lactation (a negative pregnancy test is required in patients who are not postmenopausal or surgically sterile).

Significant disease and/or abnormalities (past or present) e.g. significant neurological, cardiovascular, renal, liver or blood disease, malignancy, psychiatric disorders, that would preclude SRP or the administration of a local anesthetic.

Ulcerative lesions in the oral cavity.

Abscesses or other acute infections in the oral cavity.

Patient requiring tooth extraction in the chosen quadrant.

Pathology in the oral cavity requiring immediate treatment.

Patient with dental implants in the chosen quadrant.

Patients with more than 8 teeth in the selected quadrant.

Previous history alcohol abuse.

Participation in a clinical study of an investigational drug within the previous 4 weeks.

Previous enrollment in the present study.”

Commentary: the 1997 version of the Case Report Forms (CRFs) contains identical sets of inclusion and exclusion criteria to the amended protocol. The amended protocol was followed as prospectively planned and written.

Patient withdrawal:

The study protocol states that patients will be free to withdraw from the study at any time if they wished. The investigator will be instructed to follow-up with them about their reasons, and inquires about adverse events. Patients will be withdrawn also if they met an exclusion criterion between the screening and the treatment visits. Patients can be withdrawn also at the discretion of the investigator at any time prior to study drug administration.

Scaling Procedure:

The study protocol states that the SRP procedure will be carried out manually. As far as possible, the same operator will perform all procedures in each center. The procedure will be made using sharp instruments of choice and with a technique and time sufficient for an adequate treatment result. The time at which the SRP (with dental gel) is started and finished per tooth and the time of first interruption due to pain will be recorded per tooth.

Study Drugs:

The study protocol states that the investigational drug and placebo will be produced and filled into 1.8-ml dental cartridges by Astra (Sweden).

Investigational Drugs:

Dental gel containing the active ingredient lidocaine 25 mg/g and prilocaine 25 mg/g, thermosetting agents, hydrochloric acid and purified water.

Placebo dental gel will contain thermosetting agents, sodium hydroxide and purified water.

Treatment Summary

Blinding: The investigators will be fully blinded to the identity of study drug they will administer to their patients. The sponsor and the Division were aware of a distinctive taste difference between the dental gel 5% and the placebo gel, which could not have been eliminated. As the study was not designed as a crossover trial, this fact has not compromised the study blinding.

At the screening visit, the investigators will enroll patients into the run-in phase of the study. Enrolled patients will require periodontal scaling root planning (SRP) in at least one quadrant of the mouth that had not been scaled/root planned within the previous 12 months. The selected quadrant will contain at least 5 natural teeth of which one will contain at least one probing site ≥ 6 mm, and at least two teeth each containing at least one site ≥ 5 mm. All teeth in the chosen quadrant will be scaled / root planed.

The patient will be seated in a dental chair. The quadrant will be selected per protocol. Cotton rods will be placed in the buccal fold of the selected quadrant and the teeth will be dried with compressed air before gel application. The location of hypersensitive teeth will be determined and recorded. Gel application will follow, using the dental cartridge system in which it is supplied, and administering it by means of a blunt needle. Gel application will start from the most posterior tooth of the selected quadrant, and follow sequentially to the more anterior tooth until the quadrant is finished.

The gel will be applied first at the gingival margin of the selected tooth and on the approximate surfaces of the adjacent teeth. After a waiting period of 30 seconds, the gel will be applied to the corresponding gingival pockets. The pockets will be filled until the gel becomes visible at the gingival margin. After a further 30 seconds, the SRP will commence. The procedure will be repeated on the following tooth sequentially. If the patient requests that the procedure will be interrupted due to pain, reapplication of the gel will take place and SRP had will resume after additional 30 seconds. A second interruption due to pain in the same tooth caused the patient to be classified as needing rescue anesthetic, and the patient's participation in the study ended.

At the end of the SRP of each tooth, the patient will report a VAS pain score. Five minutes after a quadrant will be finished the patient rated the overall pain using VAS followed by VRS. Both pain- scoring systems will precede any rescue anesthetic, if given. The total amount of study medication used will be recorded in all cases by visually assessing, down to the quarter of a cartridge, how much has been used. Possible adverse events will be monitored throughout the treatment period and at a follow-up visit 1 week \pm 3 days after the treatment visit.

Other treatment: Other medication, which is considered necessary for the patient's welfare, may be given the discretion of the investigator. No anesthetic or sedative may be taken for 12 hours prior to the application of dental gel. All medications administered will be recorded on the CRF.

Source: vol. 1.26, pp 73-77.

Assessments

Efficacy measurements included:

1. Primary: Overall (entire quadrant) Visual Analog Scale (VAS) with a left end point marked "no pain" and the right end-point marked "worst pain imaginable." After all teeth in the selected quadrant have been scaled / root planed, the patient will be given a VAS ruler and asked to indicate where on the scale it best described their pain from the overall procedure.
2. Secondary:
 - Overall Verbal Rating Scale (VRS): 5-point verbal rating scale (no, mild, moderate, severe, and very severe pain).

- Need for rescue anesthetic (rescue was given OR rescue was not given but SRP has been terminated secondary to intolerable pain).

Analysis Plan

The data sets to be analyzed will be based on different sets of patients depending on evaluability. These sets of patients will be referred to as the per- protocol (PP) and the all patients treated (APT) sets of patients. The APT database is based on all included patients except those who did not receive any study drug. A safety evaluation will be performed on all patients who have received study drug, that is the APT patients. The PP database is a subset of the APT data set obtained by excluding patients in the instance of major protocol violations. The main analysis of the efficacy variables will be based on the APT dataset. In addition, an analysis of the efficacy variables will be performed using the PP dataset.

The primary efficacy variable, the overall VAS pain score, will be compared between the two groups using a stratified Wilcoxon rank sum test, stratifying by center. The corresponding 95% CI and point estimate of the difference between the groups will also be evaluated. The test will be two-sided and statistical significance will be declared for an outcome with a $p \leq 0.05$. The proportion of patients needing rescue anesthesia will be used as a secondary efficacy variable. Comparison between treatment groups will be performed using a Mantel-Haenszel test. Other variables such as patients characteristics, overall VRS pain scores, time from start of scaling until end of scaling, interruption due to pain and time to first interruption and adverse events will mainly be evaluated by means of descriptive statistics (mean, median, standard deviation, minimum, maximum, etc.), frequency tables and graphs. Small centers, with fewer than 6 patients valid for analysis, may be pooled together with other small centers. Any decision regarding pooling of data from centers will be taken and documented before declaration of clean file and the breaking of treatment codes.

The minimum clinically relevant difference in the primary efficacy parameter, overall VAS score, to be detected is 15 mm. Assuming a SD of 25 mm, a sample size 59 evaluation patients per group is required in order to detect a statistical significant difference with a probability (power) of at least 90%. In these power considerations, a simple unstratified two-sample t-test with $\alpha = 0.05$ has been used under normality assumptions. This should provide a reasonable approximation for the sample size required for the stratified Wilcoxon test.

Source: vol. 1.26, pp 85-87

Study Conduct

The sponsor implemented the following quality assurance and quality control measures:

- On-site monitoring, both prior to study start and at the time of first patient enrollment.
- Continuous frequent monitoring visits of all sites.

- Availability of the monitor and the project manager between visits.
- Collection of original CRFs, with copies left on site.
- Dual data entry.
- Answering of all data clarifications or queries, with changes made to CRF initiated by staff at study site.
- Validity of all data for analysis and agreement on statistical analysis plan preceded the declaration of clean file.
- Declaration of clean file preceded randomization codes breaking and entry of these data to the database.

Source: vol.1.26, pp. 34-35.

Patient Disposition

122 patients were enrolled and were randomized. All 122 patients were valid for APT analysis, 119 patients were valid for PP analysis. 63 patients were allocated to treatment with dental gel 5%: 63 are valid for safety evaluation, 63 are valid for APT evaluation, 60 are valid for PP evaluation. 59 patients to treatment with placebo gel: 59 are valid for safety evaluation, 59 are valid for APT evaluation, and 59 are valid for PP evaluation. None of the 122 patients randomized discontinued treatment.

Table 6.1: number of patients by center [sponsor's table 1, vol. 1.26, pp. 21 (46)]

Center	Dental Gel 5% (APT/PP)	Placebo (APT/PP)	Total (APT/PP)
1	8/8	8/8	16/16
2	6/6	6/6	12/12
4	10/9	8/8	18/17
5	9/9	8/8	17/17
6	6/6	6/6	12/12
7	9/8	8/8	17/16
8	6/6	6/6	12/12
9	9/8	9/9	18/17

Protocol Deviations and Violations

Major Violations:

Three patients, all in dental gel 5% group, had major protocol violations and were excluded from the PP dataset:

- Patient #419 had an aphthous ulcer when entering the study. This was a violation of exclusion criterion 5.
- Patient #713 had herpes lesion on the lip when entering the study. This was a violation of exclusion criterion 5.

- In the selected quadrant patient #910 had one tooth with a pocket depth of ≥ 6 mm, but only one other tooth with a pocket depth of ≥ 5 mm. This was a violation of inclusion criterion 2.

Minor Violations:

The following violations were considered minor and therefore the patients were not excluded from any of the analyses:

- Patients were to be assigned consecutive patient numbers, as they were included into the study. However, patient #205 was included before patient #204 and patient # 424 was included before patient # 423.
- Patients #715 and 809 had history of alcohol abuse, which was a violation of exclusion criterion 11. However, since these patients had not abused alcohol for ten (#715) and seven (#809) years they were included in the PP dataset. This was decided upon prior to clean file and breaking of the treatment codes.

Commentary: These protocol violations are insignificant and have not influenced the study outcome.

Data Sets Analyzed

122 patients were enrolled and randomized. All 122 patients were valid for “all patients treated” (APT) analysis; none of the 122 patients randomized discontinued treatment. 3 patients had major protocol violations, 119 patients were valid for per-protocol (PP) analysis.

Source: vol. 1.26, pp 40-41.

Demographics/Group Comparability

Table 6.2: patient demographic data [modified from sponsor’s tables 2,3, vol. 1.26, pp. 24 (46)]

Parameter		Dental Gel 5% (N= 63)	Placebo (N= 59)	All (N=122)
Gender				
	Male	25	31	56
	Female	38	28	66
Race				
	Caucasian	42	37	79
	African-American	17	14	31
	Asian-American	3	7	10
	Other	1	1	2
Age				

	Mean (SD)	43 (11)	45 (12)	
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Table 6.3: Extent of Disease [modified from sponsor's table 4, 5, 6 vol. 1.26, pp 25 (46) – 26 (46)]:

Variable	Dental Gel 5% (N=63): Mean (SD)	Placebo (N=59): Mean (SD)
Mean Pocket depth (mm)	3.6 (0.5)	3.7 (0.5)
Proportion of Bleeding Pockets	0.4 (0.3)	0.4 (0.3)
Proportion of Hypersensitive Teeth	0.1 (0.2)	0.1 (0.2)
Mean Deepest Pocket depth (mm)	4.9 (0.8)	5.1 (0.7)
Proportion of Pockets 0-3 mm	0.56 (0.18)	0.54 (0.14)
Proportion of Pockets 4-6 mm	0.40 (0.15)	0.42 (0.15)
Proportion of Pockets > 6mm	0.04 (0.06)	0.04 (0.06)

Table 6.4: SRP Procedure [modified from sponsor's tables 7, 8 vol. 1.26, pp. 26 (46) – 27 (46)]:

Variable	Dental Gel 5%: Mean (SD)		Placebo Gel: Mean (SD)	
# of teeth/patient treated (protocol: 5-8 teeth)	6.3(1.6)	[N=63]	6.0 (2.1)	[N=59]
Time of SRP(min)/tooth	4.8 (2.8)	[N=398]	5.3 (3.3)	[N=356]

Commentary: The randomization has been successful. Both placebo and dental gel 5% groups were similar in the following parameters: race, ethnicity, extent of disease, number of teeth /patient treated. There was no significant difference among centers.

Treatment Compliance

The treating dentist (the investigator) was responsible for the drug administration.

Unplanned Analyses

Study B5, reviewed below, was a post-hoc reanalysis of studies B1-3.

Sponsor's Efficacy Results

Primary Efficacy Variables

The primary efficacy variable was defined in the protocol as the global VAS pain score (measured at the end of dental treatment of the whole quadrant). The analysis plan in the protocol for all variables was descriptive statistics (mean, median, standard deviation, minimum, maximum).

Tables 6.5, 6.6 and 6.7 present these data.

Table 6.5: Overall VAS pain scores during SRP [modified from sponsor's table 9, vol. 1.26, pp 28(46)]:

Group	Center	N	Min	1st Quartile	Median	Q3	Max
Dental Gel 5%	1	8	0	3.5	6.0	11.0	30
	2	6	0	0.0	7.5	8.0	12
	4	9	0	0.0	0.0	5.0	9
	5	9	0	6.0	16.0	20.0	27
	6	6	0	0.0	3.0	19.0	23
	7	8	7	15.5	23.0	35.5	48
	8	6	6	8.0	21.5	25.0	41
	9	8	0	1.0	4.5	15.0	34
	All	60	0	2.5	7	19	48
	Placebo	1	8	4	7.5	15.5	32.5
2		6	0	0.0	4.5	10.0	20
4		8	0	0.0	11.5	15.0	64
5		8	0	4.5	10.5	21.0	49
6		6	0	4.0	8.0	22.0	35
7		8	32	35.5	46.5	63.0	72
8		6	2	17.0	22.0	66.0	94
9		9	0	20.0	35.0	60.0	86
All		59	0	5.0	17.0	38.0	94

The sponsor points out in the discussion that the median VAS score in the dental gel 5% group was 7 mm, while the *median VAS score* in the placebo group was 17 mm which are statistically significantly different ($p < 0.0005$) (see table 6.5). The sponsor notes that in the placebo group there was a large center variation in VAS pain scores, with median scores ranging from 4.5 mm to 46.4 mm. In dental gel 5% group the variation was smaller, medians ranging from 0 mm to 23 mm (table 6.5).

The difference between the dental gel group median VAS score and the placebo gel median VAS score was only 10 mm. The original IND (as well as this study protocol) had defined the target VAS difference that will be considered clinically meaningful to be at least 15 mm (or 15% of the 100mm VAS scale). The difference achieved by comparing the median VAS scores in the two arms is smaller than this pre-specified threshold by 5 mm.

As the sponsor pre-specified that the analysis will be done using the Wilcoxon non-parametric comparison, the choice of the median as the representative statistical parameter for the group comparison seems appropriate.

Table 6.6: Overall VAS pain scores during SRP [modified from sponsor's table 9, vol. 1.26, pp. 28(46)]:

Group	Center	N	Mean	SD
Dental Gel 5%	1	8	8.9	9.6
	2	6	5.8	4.8
	4	9	2.4	3.8
	5	9	13.3	9.2
	6	6	8.0	10.2
	7	8	25.4	13.7
	8	6	20.5	12.8
	9	8	9.4	12.4
	All	60	11.6	12.0
	Placebo	1	8	20.0
2		6	6.5	7.7
4		8	14.6	21.1
5		8	15.1	15.7
6		6	12.8	13.3
7		8	49.4	15.8
8		6	37.2	35.2
9		9	40.6	30.3
All		59	25.4	24.7

The numbers are similar when we examine the *mean VAS scores* presented in table 6.6. The difference between the two study arms is 25.4 mm - 11.6 mm = 13.8 mm. This value also does not surpass the pre-specified 15-mm difference between the dental gel arm and the placebo arm. There are equally compelling arguments to support the choice of the mean as the representative statistical parameter for the group comparison: the sample size calculations in the original protocol were done based on the mean values of both study arms.

Table 6.7: Overall VAS pain scores during SRP, test of treatment differences between arms [sponsor's table 10, vol.1.26, pp. 28 (46)]:

Variable	Lower CI limit	Hodges-Lehmann point estimate	Upper CI limit	P-Value (two sided) Ho: no treatment difference
Overall VAS Score during SRP	2.00	8.00	13.00	< 0.0005

In the pooled analysis, stratified by center, the *Hodges-Lehmann point estimate* of treatment difference was 8 mm (95% CI: 2.0, 13.0). The pre-specified difference of 15 mm falls outside the 95% CI. The variation was greater in the placebo group.

Secondary Efficacy Variables

Two secondary efficacy variables were defined in the study protocol.

1. Overall Verbal Rating Scale (VRS): 5-point verbal rating scale (no, mild, moderate, severe, and very severe pain). See data in table 6.8.

Table 6.8: Overall VRS pain scores: frequency (percent) [sponsor's table 11, vol. 1.26, pp. 31 (46)]

Group	Dental Gel 5%:	Placebo
No Pain	22 (35)	12 (20)
Mild Pain	35 (55)	26 (44)
Moderate Pain	5 (8)	14 (24)
Severe Pain	1 (2)	6 (10)
Very Severe Pain	0 (0)	1 (2)

The sponsor's analysis: combining the categories of no pain and mild pain yields 90% in dental gel 5%, 64% in placebo group. In the dental gel 5% group only one patient reported severe pain, while 6 patients (10%) reported severe pain in the placebo group. The overall VRS pain score was statistically significantly lower in the dental gel 5% group than in the placebo group (P = 0.001)

Commentary: This secondary outcome variable supports the effectiveness of the active drug compared to placebo.

2. Need for rescue anesthetic (rescue was given OR rescue was not given but SRP has been terminated secondary to intolerable pain): See data in table 6.9.

Table 6.9: Number of patients with first and second interruption (s) due to pain: frequency (%) [sponsor's table 12, vol. 1.26, pp. 32 (46)]

Group	Dental Gel 5% (N=63)	Placebo (N=59)
1 st interruption	49 (12%)	42 (12%)
2 nd Interruption	7 (2%)	10 (3%)

The sponsor's analysis: in the dental gel 5% group 7 out of 63 (11%) patients needed rescue anesthetic, that is, they had a second interruption due to pain or had a rescue medication. In the placebo group the corresponding figure was 10 out of 59 (17%) patients. In both groups the first interruption was seen in 12% of the teeth.

According to the sponsor's analysis, there was no indication that extent of disease (bleeding, pus, hypersensitivity and pocket depth) influenced the VAS pain scores in the dental gel 5% group.

Source: vol.1.26, pp 45-55.

Discussion of Efficacy Findings

The data of study B1 supports dental gel 5% efficacy. The median overall VAS score in the active drug arm is statistically significant lower than the median overall VAS score in the placebo arm. The size of this difference, 10 mm (or 10%) falls short of the pre-specified 15 mm difference. Intention-to-treat analysis performed by Dr. Fan demonstrated that the statistical difference remained unchanged even when the three excluded patients were added back to the analysis. In the ITT analysis, the median difference between the overall VAS in both study arms remains 10 mm, while the mean difference is slightly reduced from 13.8 mm (in the per protocol analysis) to 13.2 mm. The clinical significance of this difference needs to be carefully considered, in light of the drug's benefits for the patient (non-invasive local analgesia), the drug's safety profile, and the previous finding of safety and efficacy in EMLA.

6.3.2 Study B2 (SP-DGA-0004): A randomized, double-blind, placebo-controlled study to evaluate the efficacy of dental gel 5% for periodontal pocket anesthesia in conjunction with dental scaling and root planing.

Study Plan

The initial version of the protocol was dated 1/31/1997. An amendment was dated 4/10/1997 (amendment 1). The study was conducted between May 1997 and September 1997. The study was conducted as was pre-specified in the amended protocol. Source: original NDA submission, vol. 1.29, pp 71, 114.

Population, Design, and Objectives

Primary:

To determine the local anesthetic efficacy of dental gel 5% compared with placebo by means of assessing overall pain from SRP on a visual analogue scale (VAS)."

Secondary:

"To determine the need for rescue anesthetic compared with placebo and to determine adverse events associated with the use of the dental gel."

Study Design:

The protocol was designed as a multicenter, randomized, parallel-group, double-blind, study comparing dental gel 5% and placebo gel. The study planned to enroll 120 evaluable patients, 60 in each arm. The study was conducted in 6 centers in Canada. The study was comprised of one screening visit, one treatment visit, and a telephone follow-up.

Placebo-control design was selected to control for the lubricating effect of the excipients. Parallel-group was selected to avoid a carry-over effect of the pain perception, and to ensure blinding in face of a possible taste difference between dental gel 5% and the placebo gel.

"Inclusion Criteria:

Patients requiring periodontal SRP in at least one quadrant of the mouth that has not received SRP in the previous 12 months.
The selected quadrant shall include at least 5 natural teeth, at least 1 tooth of which should contain at least 1 pocket with a depth of at least 6 mm, and at least 2 other teeth each containing at least 1 pocket with depth of at least 5 mm.
Age at least 18 years.
Able to comprehend the VAS.
Written informed consent obtained.
Patients, in the opinion of the investigator, who can reasonably be expected to comply with the protocol."

"Exclusion Criteria:

History of allergy, sensitivity, or any other form of reaction to local anesthetics of the amide type.
Receipt of an anesthetic or sedative in the 12 hours prior to probing/SRP.
Pregnancy and/or lactation (a negative pregnancy test is required in patients who are not postmenopausal or surgically sterile).
Significant disease and/or abnormalities (past or present) e.g. significant neurological, cardiovascular, renal, liver or blood disease, malignancy, psychiatric disorders, that would preclude SRP or the administration of a local anesthetic.
Ulcerative lesions in the oral cavity.
Abscesses or other acute infections in the oral cavity.
Patient requiring tooth extraction in the chosen quadrant.
Pathology in the oral cavity requiring immediate treatment.
Patient with dental implants in the chosen quadrant.
Patients with more than 8 teeth in the selected quadrant.
Previous history alcohol abuse.
Participation in a clinical study of an investigational drug within the previous 4 weeks.
Previous enrollment in the present study."

Commentary: the 1997 version of the Case Report Forms (CRFs) contains identical sets of inclusion and exclusion criteria to the amended protocol. The amended protocol was followed as prospectively planned and written.

Patient withdrawal:

The study protocol states that patients will be free to withdraw from the study at any time if they wish. The investigator will be instructed to follow-up with them about their reasons, and inquires about adverse events. Patients will be withdrawn also if they meet an exclusion criterion between the screening and the treatment visits. Patients can be withdrawn also at the discretion of the investigator at any time prior to study drug administration.

Scaling Procedure:

The study protocol states that the SRP procedure will be carried out manually. As far as possible, the same operator will perform all procedures in each center. The procedure will be made using sharp instruments of choice and with a technique and time sufficient for an adequate treatment result. The time at which the SRP (with dental gel) is started and finished per tooth and the time of first interruption due to pain will be recorded per tooth.

Study Drugs:

The study protocol states that the investigational drug and placebo will be produced and filled into 1.8-ml dental cartridges by Astra (Sweden).

Investigational Drugs:

Dental gel containing the active ingredient lidocaine 25 mg/g and prilocaine 25 mg/g, thermosetting agents, hydrochloric acid and purified water (the to-be-marketed product). Placebo dental gel will contain thermosetting agents, sodium hydroxide and purified water (not the to-be-marketed product).

Treatment Summary:

Blinding: The investigators will be fully blinded to the identity of study drug they will administer to their patients. The sponsor and the Division were aware of a distinctive taste difference between the dental gel 5% and the placebo gel, which could not have been eliminated. As the study was not designed as a crossover trial, this fact has not compromised the study blinding.

At the screening visit, the investigators will enroll patients into the run-in phase of the study. Enrolled patients will require periodontal scaling root planning (SRP) in at least one quadrant of the mouth that had not been scaled/root planned within the previous 12 months. The selected quadrant will contain at least 5 natural teeth of which one will contain at least one probing site ≥ 6 mm, and at least two teeth each containing at least one site ≥ 5 mm. All teeth in the chosen quadrant will be scaled / root planed.

The patient will be seated in a dental chair. The quadrant will be selected per protocol. Cotton rods will be placed in the buccal fold of the selected quadrant and the teeth will be dried with compressed air before gel application. The location of hypersensitive teeth will

be determined and recorded. Gel application will follow, using the dental cartridge system in which it is supplied, and administering it by means of a blunt needle. Gel application will start from the most posterior tooth of the selected quadrant, and will be followed with SRP at this tooth. The procedure will continue sequentially to the more anterior tooth until the quadrant is finished.

The gel will be applied first at the gingival margin of the selected tooth and on the approximate surfaces of the adjacent teeth. After a waiting period of 30 seconds, the gel will be applied to the corresponding gingival pockets. The pockets will be filled until the gel becomes visible at the gingival margin. After a further 30 seconds, the SRP will commence. The procedure will be repeated on the following tooth sequentially. If the patient requests that the procedure will be interrupted due to pain, reapplication of the gel will take place and SRP had will resume after additional 30 seconds. A second interruption due to pain in the same tooth caused the patient to be classified as needing rescue anesthetic, and the patient's participation in the study ended.

At the end of the SRP of each tooth, the patient will report a VAS pain score. Five minutes after a quadrant will be finished the patient rated the overall pain using VAS followed by VRS. Both pain- scoring systems will precede any rescue anesthetic, if given. The total amount of study medication used will be recorded in all cases by visually assessing, down to the quarter of a cartridge, how much has been used. Possible adverse events will be monitored throughout the treatment period and at a follow-up visit 1 week \pm 3 days after the treatment visit.

Other treatment: Other medication, which is considered necessary for the patient's welfare, may be given the discretion of the investigator. No anesthetic or sedative may be taken for 12 hours prior to the application of dental gel. All medications administered will be recorded on the CRF.

Source: vol. 1.29, pp. 8 (30) – 13 (30).

Assessments

Efficacy measurements included:

3. Primary: Global (mouth quadrant) Visual Analog Scale (VAS) with a left end point marked "no pain" and the right end-point marked "worst pain imaginable." After all teeth in the selected quadrant have been scaled / root planed, the patient will be given a VAS ruler and asked to indicate where on the scale it best described their pain from the overall procedure.
4. Secondary:
 - Overall Verbal Rating Scale (VRS): 5-point verbal rating scale (no, mild, moderate, severe, and very severe pain).

- Need for rescue anesthetic (rescue was given OR rescue was not given but SRP has been terminated secondary to intolerable pain).

Analysis Plan

The data sets to be analyzed will be based on different sets of patients depending on evaluability. These sets of patients will be referred to as the per- protocol (PP) and the all patients treated (APT) sets of patients. The APT database is based on all included patients except those who did not receive any study drug. A safety evaluation will be performed on all patients who have received study drug, that is the APT patients. The PP database is a subset of the APT data set obtained by excluding patients in the instance of major protocol violations. The main analysis of the efficacy variables will be based on the APT dataset. In addition, an analysis of the efficacy variables will be performed using the PP dataset.

The primary efficacy variable, the overall VAS pain score, will be compared between the two groups using a stratified Wilcoxon rank sum test, stratifying by center. The corresponding 95% CI and point estimate of the difference between the groups will also be evaluated. The test will be two-sided and statistical significance will be declared for an outcome with a $p \leq 0.05$. The proportion of patients needing rescue anesthesia will be used as a secondary efficacy variable. Comparison between treatment groups will be performed using a Mantel-Haenszel test. Other variables such as patients characteristics, overall VRS pain scores, time from start of scaling until end of scaling, interruption due to pain and time to first interruption and adverse events will mainly be evaluated by means of descriptive statistics (mean, median, standard deviation, minimum, maximum, etc.), frequency tables and graphs. Small centers, with fewer than 6 patients valid for analysis, may be pooled together with other small centers. Any decision regarding pooling of data from centers will be taken and documented before declaration of clean file and the breaking of treatment codes.

The minimum clinically relevant difference in the primary efficacy parameter, overall VAS score, to be detected is 15 mm. Assuming a SD of 25 mm, a sample size 59 evaluation patients per group is required in order to detect a statistical significant difference with a probability (power) of at least 90%. In these power considerations, a simple unstratified two-sample t-test with $\alpha = 0.05$ has been used under normality assumptions. This should provide a reasonable approximation for the sample size required for the stratified Wilcoxon test.

Study Conduct

The sponsor implemented the following quality assurance and quality control measures:

- On-site monitoring, both prior to study start and at the time of first patient enrollment.
- Continuous frequent monitoring visits of all sites.
- Availability of the monitor and the project manager between visits.

- Collection of original CRFs, with copies left on site.
- Dual data entry.
- Answering of all data clarifications or queries, with changes made to CRF initialed by staff at study site.
- Validity of all data for analysis and agreement on statistical analysis plan preceded the declaration of clean file.
- Declaration of clean file preceded randomization codes breaking and entry of these data to the database.

Source: vol. 1.29, pp. 17 (51) – 18 (51)

Patient Disposition

131 patients were enrolled and were randomized. One patient discontinued prior to treatment, 130 patients were valid for APT analysis, 127 patients were valid for PP analysis. 64 patients were allocated to treatment with dental gel 5%: 63 are valid for safety evaluation, 63 are valid for APT evaluation, 62 are valid for PP evaluation. 67 patients to treatment with placebo gel: 67 are valid for safety evaluation, 67 are valid for APT evaluation, and 65 are valid for PP evaluation. None of the 131 patients randomized discontinued treatment.

Table 6.1: number of patients by center [adapted from the sponsor's table 1, vol. 1.29, pp. 22 (51)]

Center	Dental Gel 5% (APT/PP)	Placebo (APT/PP)	Total (APT/PP)
1	12/12	13/13	25/25
2	16/15	17/15	33/30
3	8/8	8/8	16/16
4	15/15	15/15	30/30
5	6/6	8/8	14/14
6	6/6	6/6	12/12

Protocol Deviations and Violations

Major Violations:

Three patients, 2 in the placebo group (#207, #222) and 1 in the dental gel 5% group (#205), had a major protocol violations and were excluded from the PP dataset. Patient 505 did not receive any study drug and hence, was not valid for any analysis.

- For patients 205 and 222, the SRP procedure continued after the second interruption due to pain.

- Patient #207 was participating in another clinical trial.
- Patient 505 had received SRP in chosen study quadrant during the last 12 months. This was a violation of inclusion criterion 1. The patient was withdrawn from the study prior to treatment and was not treated with any study drug.

Minor violations:

Patients were to be assigned consecutive numbers, as they were included into the study. However, 9 patients from center 1 were not assigned consecutive numbers (they were recruited by phone and were assigned a patient number upon arriving at the center). Occasionally, patients were not treated consecutively according to their patient number. This was considered a minor violation, and these patients were not excluded from the analysis.

Data Sets Analyzed:

131 patients were enrolled and randomized. One patient was discontinued before treatment. The other 130 patients were valid for “all patients treated” (APT) analysis; none of the 130 patients randomized discontinued treatment. 3 patients had major protocol violations, 127 patients were valid for per-protocol (PP) analysis.

Demographics/Group Comparability

Table 6.2: patient demographic data [adapted from the sponsor’s tables 2, 3, vol. 1.29, pp. 25 (51)]

Parameter		Dental Gel 5% (N= 63)	Placebo (N= 67)	All (N=130)
Gender				
	Male	26	30	56
	Female	37	37	74
Race				
	Caucasian	57	63	120
	African-American	2	4	6
	Asian-American	2	0	2
	Other	2	0	2
Age				
	Mean (SD)	48 (12)	48 (13)	

Table 6.3: Extent of Disease [adapted from sponsor tables 4, 5, 6, vol. 1.29, pp 26 (51) – 27 (51)].

Variable	Dental Gel 5% (N=63):	Placebo (N=67):
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	Mean (SD)	Mean (SD)
Mean Pocket depth (mm)	3.5 (0.5)	3.6 (0.5)
Proportion of Bleeding Pockets	0.5 (0.3)	0.5 (0.3)
Proportion of Hypersensitive Teeth	0.1 (0.2)	0.1 (0.2)
Mean Deepest Pocket depth (mm)	4.9 (0.8)	4.9 (0.7)
Proportion of Pockets 0-3 mm	0.55 (0.16)	0.56 (0.18)
Proportion of Pockets 4-6 mm	0.41 (0.14)	0.41 (0.15)
Proportion of Pockets > 6mm	0.03 (0.06)	0.04 (0.06)

Table 6.4: SRP Procedure [sponsor tables 7, 8 vol. 1.29, pp 27(51) – 28(51)]:

Variable	Dental Gel 5%: Mean (SD)		Placebo Gel: Mean (SD)	
# of teeth/patient treated (protocol: 5-8 teeth)	6.3(1.3)	[N=63]	6.5 (1.6)	[N=67]
Time of SRP(min)/tooth	3.4 (2.2)	[N=409]	3.4 (2.5)	[N=436]

Commentary: The randomization has been successful. Both placebo and dental gel 5% groups were similar in the following parameters: race, ethnicity, extent of disease, number of teeth /patient treated. There was no significant difference among centers.

Treatment Compliance

The treating dentist (the investigator) was responsible for the drug administration.

Sponsor's Efficacy Results

Primary Efficacy Variables

The primary efficacy variable was defined in the protocol as the global VAS pain score (measured at the end of dental treatment of the whole quadrant). The analysis plan in the protocol for all variables was descriptive statistics (mean, median, standard deviation, minimum, maximum).

Table 6.5: Overall VAS pain scores during SRP [adapted from sponsor's table 9, vol.1.29, pp 29 (51)].

Group	Center	N	Min	1st Quartile	Median	Q3	Max
Dental Gel 5%	1	12	0	0.0	2.0	13.5	60
	2	16	0	1.0	5.0	15.0	30
	3	8	3	5.5	11.5	31.0	85
	4	15	0	0.0	10.0	20.0	53
	5	6	0	2.0	19.0	35.0	53

	6	6	0	0.0	0.0	2.0	2
	All	63	0	0	5.0	20.0	85
Placebo	1	13	0	15.0	38.0	50.0	68
	2	17	0	3.0	10.0	15.0	40
	3	8	5	18.0	31.5	53.5	79
	4	15	0	2.0	6.0	18.0	44
	5	8	0	1.5	8.0	23.0	42
	6	6	1	2.0	14.5	30.0	35
	All	67	0	4.0	13.0	30.0	79

The sponsor points out in the discussion that the median VAS score in the dental gel 5% group was 5 mm, while the *median VAS score* in the placebo group was 13 mm ($p = 0.015$) (see table 6.5). The sponsor notes that in the placebo group there was a large center variation in VAS pain scores (in 2/6 centers placebo did better than dental gel 5%), with median scores ranging from 6 mm to 38 mm. In dental gel 5% group the variation was smaller, medians ranging from 0 mm to 19 mm (table 6.5).

The sponsor does not mention that the difference between the dental gel group median VAS score and the placebo gel median VAS score was only 8 mm, the original IND (as well as this study protocol) had defined the target VAS difference that will be considered clinically meaningful to be at least 15 mm (or 15% of the 100mm VAS scale). The difference achieved by comparing the median VAS scores in the two arms is smaller than this pre-specified threshold by 7 mm (or 46%). As the sponsor pre-specified that the analysis will be done using the Wilcoxon non-parametric comparison, the choice of the median as the representative statistical parameter for the group comparison seems appropriate.

Table 6.6: Overall VAS pain scores during SRP [adapted from sponsor's table 9, vol.1.29, pp 29 (51)].

Group	Center	N	Mean	SD
Dental gel 5%	1	12	11.9	20.2
	2	16	8.7	9.2
	3	8	23.0	27.9
	4	15	13.9	17.2
	5	6	21.3	20.6
	6	6	0.7	1.0
	All	63	12.8	17.9
Placebo	1	13	34.4	22.0
	2	17	10.8	10.2
	3	8	36.3	24.8
	4	15	10.9	12.0
	5	8	13.4	15.4
	6	6	16.2	14.1
	All	67	19.2	19.2

The numbers are similar when we examine the *mean VAS scores* presented in table 6.6. The difference between the two study arms is 19.2 mm – 12.8 mm = 6.4 mm. This value also does not surpass the pre-specified 15-mm difference between the dental gel arm and the placebo arm. There are equally compelling arguments to support the choice of the mean as the representative statistical parameter for the group comparison: the sample size calculations in the original protocol were done based on the mean values of both study arms.

Table 6.7: Overall VAS pain scores during SRP, test of treatment differences between arms [adapted from sponsor’s table 10, vol. 1.29, pp 32 (51)]

Variable	Lower CI limit	Hodges-Lehmann point estimate	Upper CI limit	P-Value (two sided) Ho: no treatment difference
Overall VAS Score during SRP	0.00	4.00	10.00	< 0.015

In the pooled analysis, stratified by center, the *Hodges-Lehmann point estimate* of treatment difference was 4 mm (95% CI: 0.0, 10.0). The pre-specified difference of 15 mm falls outside the 95% CI.

Trend observed that deeper pockets were associated with more pain in placebo, but not the Oraqix treatment group.

Secondary Efficacy Variables

Two secondary efficacy variables were defined in the study protocol.

1. Overall Verbal Rating Scale (VRS): 5-point verbal rating scale (no, mild, moderate, severe, and very severe pain). See data in table 6.8.

Table 6.8: Overall VRS pain scores: frequency (percent) [adapted from the sponsor’s table 11, vol. 1.29, pp 32 (51)]

Group	Dental Gel 5%:	Placebo
No Pain	23 (37)	17 (25)
Mild Pain	26 (41)	34 (51)
Moderate Pain	11 (17)	13 (19)
Severe Pain	3 (5)	3 (5)
Very Severe Pain	0 (0)	0 (0)

The sponsor’s analysis: using the Spearman rank correlation coefficient there was a statistically significant correlation between the overall VAS and VRS pain scores, with a correlation coefficient value of 0.79 ($p < 0.0005$).

Commentary: There does not seem to be a clear difference in VRS between the study arms.

2. Need for rescue anesthetic (rescue was given OR rescue was not given but SRP has been terminated secondary to intolerable pain): See data in table 6.9.

Table 6.9: Number of teeth with first and second interruption (s) due to pain: frequency (%) [adapted from the sponsor's table 12, vol. 1.29, pp 35 (51)]

Group	Dental Gel 5% (N=409)	Placebo (N=436)
1 st interruption	22 (5%)	36 (8%)
2 nd Interruption	5 (1%)	7 (2%)

Sponsor's note: due the small number of patients needing rescue anesthetic, no formal statistical tests were performed.

Discussion of Efficacy Findings in Study B2 (SP-DGA-0004)

The data of study B2 supports the efficacy of dental gel 5%, compared to the placebo-gel (median VAS pain score was 5 mm in dental gel 5% and 13 mm in the placebo group $p=0.015$). The pre-specified difference in VAS pain score of 15 mm between the treatment arms was not met in this study, in any of the three statistical variables assessed. The median scores of the two arms are compared ($13 - 5 = 8$ mm). The mean scores of the two arms are compared ($19.2 - 12.8 = 6.4$ mm). The Hodges-Lehmann point estimate found a difference between the study arms of 4.0 (95% CI: 0.0, 10.0). These data were significantly influenced by a very high variability in the placebo arm VAS pain scores (median scores ranging between 6.0–38.0 mm). In the dental gel 5% the group variation was smaller: median ranging from 0.0-19.0 mm. One secondary outcome measure (VRS score) showed no difference between the study arms. Another secondary outcome variable (amount of rescue anesthesia) showed a trend of fewer rescue treatments required in the dental gel 5% arm.

Centers 7 and 9 reported higher median pain VAS pain scores (46.6 and 35.0) than the others associated with differences of 22 and 30 mm between Oraqix and placebo. These data suggest that in patients who exhibit more pain, Oraqix exceeded the 15mm predefined threshold for clinical efficacy.

As all protocol violations happened in center 2, this reviewer has calculated the median VAS score in this center and found it to be 5 mm for dental gel 5%, 9 mm for placebo (lower overall VAS difference between the study arms when compared to the whole study population). Median VAS score in all other study centers (excluding center 2) was calculated to be 5 mm in the dental gel 5% arm, 15.5 mm in the placebo arm (higher overall VAS difference between the study arms when compared to the whole study population).

6.3.3 Study B3 (SP-DGA-0007): A randomized, double-blind, placebo-controlled study to evaluate the efficacy of lidocaine, prilocaine dental gel 5% for periodontal pocket anesthesia in conjunction with dental scaling and root planing in pain-sensitive patients.

Study Plan

The initial version of the protocol was dated 7/8/1998. Amendments were dated 8/31/1998 (amendment 1) and 5/9/2000 (amendment 2). The study was conducted between 8/8/2000 and 2/21/2001. The study has been conducted as was pre-specified in amended study protocol.

Population, Design, and Objectives

The protocol-specified objectives were:

“Primary:

To determine the local anesthetic efficacy of dental gel 5% compared with placebo by means of assessing overall pain from SRP on a visual analogue scale (VAS) in pain-sensitive patients.”

“Secondary:

1. To determine the local anesthetic efficacy of dental gel 5% compared with placebo by means of assessing overall pain from SRP on a verbal rating scale (VRS) in pain-sensitive patients.
2. To determine the need for rescue anesthetic in the dental gel 5% group compared with the placebo group.
3. To compare the dental gel 5% and the placebo groups in regard to the mean VAS pain score from teeth where the deepest probing site is ≥ 6 mm.
4. To compare the dental gel 5% and the placebo groups in regard to the mean VAS pain score from teeth where the deepest probing site ≤ 5 mm.
5. To assess adverse events.”

Study Design:

The protocol was designed as a multicenter, randomized, parallel-group, double-blind, study comparing dental gel 5% and placebo gel. The study planned to enroll 80 evaluable patients, 40 in each arm. The study was conducted in 4-5 centers in the US, and aimed to enroll 12-24 patients in each center. The study was comprised of one screening visit, one treatment visit, and a telephone follow-up. The probing carried out to screen for pain sensitivity and the SRP at the treatment visit had to be performed by the same operator (in order to avoid SRP being perceived as less painful during the treatment visit due to a gentler technique exercised by a different operator).

Placebo-control design was selected to control for the lubricating effect of the excipients. Parallel-group design was selected to avoid a carry-over effect of the pain perception, and to ensure blinding in face of a possible taste difference between dental gel 5% and the placebo gel.

“Inclusion Criteria:

Patients requiring periodontal SRP in at least one quadrant of the mouth that has not received SRP in the previous 6 months.
Patient with 5-8 natural teeth in the selected quadrant.
Age at least 18 years.
Able to comprehend the VAS.
Patient, in the opinion of the investigator, who can reasonably be expected to comply with the protocol.
Written informed consent obtained.
Patient reporting VAS pain score of ≥ 30 mm upon probing.
The selected quadrant contains at least 2 teeth each with at least 1 probing site ≥ 5 mm and at least 1 other tooth with at least 1 probing site ≥ 6 mm.”

“Inclusion criteria 1-6 must be fulfilled before enrolled patients were entered into the run-in. Inclusion criteria 7-8 must be fulfilled before enrolled were randomized. The patients selected for inclusion in this study were representative of pain-sensitive patients. Not all patients enrolled were randomized.”

“Exclusion Criteria:

History of allergy, sensitivity, or any other form of reaction to local anesthetics of the amide type.
Receipt of an anesthetic or sedative in the 12 hours prior to probing/SRP.
Significant disease and/or abnormalities (past or present) e.g. significant neurological, cardiovascular, renal, liver or blood disease, malignancy, psychiatric disorders, that would preclude SRP or the administration of a local anesthetic.
Ulcerative lesions in the oral cavity.
Acute infections or pathology in the oral cavity requiring immediate treatment.
Patient requiring tooth extraction in the quadrant selected for treatment.
Patient with dental implants in the quadrant selected for treatment.
Current alcohol or drug abuse.
Participation in a clinical study of an investigational drug within the previous 4 weeks.
Previous enrollment in the present study.”

The sponsor states: “The exclusion criteria must be checked before patient entry into the study. Exclusion criterion 1 is a contraindication. Exclusion criterion 2,4,5 and 8 are important since they may have an undue influence on the primary efficacy criterion of pain assessment. The remaining exclusion criteria are included in order to enhance the interpretation of the study.”

In the 2000 version of the Case Report Forms (CRFs), inclusion criteria 1-6 from the protocol are listed as the initial inclusion criteria (criteria 1-6 functioned as a screening tool). After Probing and pain assessment takes place inclusion criteria 7,8 are assessed.

Exclusion criteria in the 2000 version of the CRF are identical to those in the protocol. In summary, the amended protocol was followed as prospectively planned and written.

Patient withdrawal:

The study protocol states that patients will be free to withdraw from the study at any time if they wished. The investigator will be instructed to follow-up with them about their reasons, and to inquire about adverse events. Patients will be to be withdrawn also if they met an exclusion criterion between the screening and the treatment visits. Patients can be withdrawn also at the discretion of the investigator at any time prior to study drug administration.

Reasons for selecting the study population: "In order to verify that Dental Gel 5% provides sufficient pain control in patients who perceive the SRP procedure to be painful, the patient population in this study will include only pain sensitive patients."

Commentary: studies B1 and B2 which were concluded earlier in the drug development process showed a small effect size, which fell beneath the goal specified in the original IND of 15 mm difference in VAS scores between Dental Gel 5% and placebo. The Division had communicated to the sponsor that an enrichment design might be helpful in showing a more robust effect.

Scaling Procedure:

The study protocol states that the SRP procedure will be carried out manually. As far as possible, the same operator will perform all procedures in each center. The procedure will be made using sharp instruments of choice and with a technique and time sufficient for an adequate treatment result. The time at which the SRP (with dental gel) is started and finished per tooth and the time of first interruption due to pain will be recorded per tooth.

Study Drugs:

The study protocol states that the investigational drug and placebo will be produced and filled into 1.7-ml dental cartridges by Astra (Sweden).

Investigational Drugs:

Dental gel containing the active ingredient lidocaine 25 mg/g and prilocaine 25 mg/g, thermosetting agents, hydrochloric acid and purified water.

Placebo dental gel will contain thermosetting agents, sodium hydroxide and purified water.

Treatment Summary

Blinding: The investigators will be fully blinded to the identity of study drug they will administer to their patients. The sponsor and the Division were aware of a distinctive taste

difference between the dental gel 5% and the placebo gel, which could not have been eliminated. As the study was not designed as a crossover trial, this fact has not compromised the study blinding.

Enrollment and randomization procedure: At the screening visit, the investigators enrolled patients into the run-in phase of the study. After an informed consent has been obtained, inclusion criteria 1-6 and none of the exclusion criteria were fulfilled, the patient was assigned an enrollment code. Enrolled patients required periodontal scaling root planning (SRP) in at least one quadrant of the mouth that had not been scaled/root planned within the previous six months. The selected quadrant had to contain 5-8 natural teeth. Enrolled patients were screened for pain sensitivity, by probing the buccal side of the elected quadrant, using force sufficient to measure the depth of the pockets and cause bleeding. Patients reporting pain scoring >30 mm upon probing on a 100 mm VAS scale (inclusion criterion 7), and with at least two teeth each containing at least one site with a pocket depth greater than or equal to 5 mm, and at least one other tooth containing at least one probing site ≥ 6 mm (inclusion criterion 8) they were assigned a patient number and entered into the treatment phase. Patient numbers formed the basis for randomization and therefore had to be consecutive at each center. Withdrawn or non-evaluable patients were replaced, using the lowest available patient number. Each patient chart recorded pockets depths pockets with bleeding on probing (6 sites/tooth) and the presence of hypersensitive teeth. The sites in which the pockets depth were checked were: mesiobuccal, buccal, distobuccal, mestolingual, lingual and distolingual.

The treatment visit took place 2 days – 4 weeks after the screening visit. Based on the randomization results, patients received either dental gel 5% or placebo gel prior to SRP. The gel was applied by means of a standard dental-cartridge system with a blunt applicator, starting at the most posterior tooth of the selected quadrant. The gel was first applied on the gingival margin around the selected tooth and the adjacent teeth. After waiting 30-45 seconds, the gel was applied to the gingival pockets, filling them until it becomes visible at the gingival margin. The SRP procedure could start after an additional 30-45 seconds. The procedure was repeated sequentially from a more posterior tooth in the quadrant to the next anterior one. If the patient requested an interruption due to pain, one reapplication of the gel per tooth was allowed. A second interruption due to pain in the same tooth caused the patient to be classified as needing rescue anesthetic, and the patient's participation in the study ended.

At the end of the SRP of each tooth, the patient reported a VAS pain score. Five minutes after a quadrant was finished the patient rated the overall pain using VAS followed by VRS. Both pain- scoring systems preceded any rescue anesthetic, if given. If the patient's treatment plan included one quadrant, treatment was allowed to be completed during one session. If the patient's treatment plan included more than one quadrant, the second quadrant could not be treated until after the follow-up phone call, 24-72 hours later.

The investigator recorded on the CRF the amount of gel administered, rounded to the nearest quarter of a cartridge (a cartridge is 1.8 ml and contains 1.7g gel). The timeline of the SRP and the gel application for each tooth was also recorded on the CRF.

Assessments

Efficacy measurements included:

2. Primary: Overall (entire quadrant) Visual Analog Scale (VAS) with a left end point marked “no pain” and the right end-point marked “worst pain imaginable.”
3. Secondary:
 - Overall Verbal Rating Scale (VRS): 5-point verbal rating scale (no, mild, moderate, severe, and very severe pain).
 - VAS scores per single tooth.
 - Need for rescue anesthetic (rescue was given OR rescue was not given but SRP has been terminated secondary to intolerable pain).

Analysis Plan

All variables will be evaluated by means of descriptive statistics (mean, median, standard-deviation, minimum, maximum), frequency tables and graphs as appropriate. The main analysis of the data will be based on the intention to treat (ITT) database (all randomized patients). A second database will be analyzed in addition is the per-protocol (PP) subset of the ITT database. The PP database will be created from the ITT database, after exclusion of major protocol violations. The overall VAS and the overall VRS scores will be compared between the two groups using a stratified Wilcoxon rank-sum test stratified by center. The corresponding 95% confidence interval and Hodges-Lehmann point estimate (HL estimate) of the difference between the groups will also to be evaluated. The test will be two-sided and statistical significance will be declared for an outcome with a $p < 0.05$. The proportion of patients needing rescue anesthetic in the treatment groups will be compared using a Mantel-Haenszel test. Descriptive statistics will be used to evaluate patients characteristics, extent of disease, previous scaling/root planning, time from start of SRP until the end of scaling of each tooth, interruption due to pain and time to first interruption, adverse events. Subgroup analysis: deepest pockets (teeth with probing ≥ 6 mm) will be analyzed separately than shallow pockets (teeth with probing ≤ 5 mm). Centers with fewer than six patients will be pooled with other small centers (decision will be made prior to code breaking). Missing data will be assumed to have happened at random, allowing to a reduced sample size. The influence of the following variables on VAS will be assessed by descriptive statistics: extent of disease, SRP time/tooth, upper/lower jaw, tooth location and patient's sex. Sample size will be calculated to be 39 evaluable patients per group based on the following assumptions: difference of VAS pain score = 15 mm, SD = 20 mm, $\alpha = 0.05$, power = 90%.

Study Conduct

The sponsor implemented the following quality assurance and quality control measures:

- On-site monitoring, both prior to study start and at the time of first patient enrollment.

- Continuous frequent monitoring visits of all sites.
- Availability of the monitor and the project manager between visits.
- Collection of original CRFs, with copies left on site.
- Dual data entry.
- Answering of all data clarifications or queries, with changes made to CRF initialed by staff at study site.
- Validity of all data for analysis and agreement on statistical analysis plan preceded the declaration of clean file.
- Declaration of clean file preceded randomization codes breaking and entry of these data to the database.

Patient Disposition

113 patients were enrolled, 26 failed screening, and the other 87 met inclusion criteria. Two patients withdrew their consent and did not return for treatment visit, and therefore 85 were randomized. All 85 patients were valid for ITT analysis, 80 patients were valid for PP analysis. 43 patients were randomized to treatment with dental gel 5%: 43 are valid for safety evaluation, 43 are valid for ITT evaluation, 40 are valid for PP evaluation. 42 patients were randomized to treatment with placebo gel: 42 are valid for safety evaluation, 42 are valid for ITT evaluation, and 40 are valid for PP evaluation. None of the 85 patients randomized discontinued treatment.

Table 6.1: Number of patients per center [modified from sponsor's table 1, vol. 1.31, pp. 21(51)]

Center	Dental Gel5% (ITT/PP)	Placebo (ITT/PP)	Total (ITT/PP)
2	9/8	8/7	17/15
4	10/10	10/10	20/20
5	12/10	12/11	24/21
6	12/12	12/12	24/24

Protocol Deviations and Violations

Major Violations:

Dental Gel 5% group:

- Patient 203 had one tooth with a pocket depth > 6 mm, but only one other tooth with a pocket depth > 5 mm. This was a violation of inclusion criterion 8.
- In patient 502 the upper right hand quadrant was chosen for screening of pain sensitivity at visit 1. However, between visits 1 and 2 a crown fell off tooth #4 and therefore an alternative quadrant was chosen for gel and SRP treatment.
- In patient 516 a crown fell off during SRP, creating a treatment scenario of only four teeth treated with investigational product. This was a violation of inclusion criterion 2.

Placebo Gel group:

- Patient 205 had one tooth with a pocket depth > 6 mm, but only one other tooth with a pocket depth > 5 mm. This was a violation of inclusion criterion 8.
- Patient 501 endodontic involvement was diagnosed in retrospect (during SRP). This was a violation of exclusion criterion 5.

Minor Violation:

Dental Gel 5% group:

- Two patients (206, 622) were assigned patient numbers in visit 1, instead of during visit 2.
- Patients 402, 411, 415 had their AE follow-up outside of the 24-72 hour window – they were 1-2 days late.
- In patient 401 the VAS scores were mistakenly rounded to the nearest 10-mm (recorded as 0: the original values had therefore to be between 0-4 mm). They were edited later to be 2 mm.
- Patient 409 received SRP in quadrant 3 immediately after study treatment in quadrant 4. This was a violation of protocol, as it could have increased the risk of having local reactions in the oral cavity. However, this violation did not affect the efficacy evaluation, and patient was not excluded.

Commentary: These protocol violations are insignificant and have not influenced the study outcome.

Data Sets Analyzed

113 patients were enrolled, 87 met inclusion criteria, 85 were randomized. All 85 patients were valid for intention to treat (ITT) analysis; none of the 85 patients randomized discontinued treatment. 5 patients had major protocol violations, 80 patients were valid for per-protocol (PP) analysis.

Commentary: analysis of PP dataset did not yield different results than analysis of the ITT dataset.

Demographics/Group Comparability

Table 6.2: patient demographic data [modified from sponsor's table 2, 3, 4 vol. 1.31, pp 23 (51) – 24 (51)]

Parameter	Dental Gel 5% (N= 43)	Placebo (N=42)	Total (N=85)	Not Randomized (N=28)
Gender				
Male	15	19	34	14
Female	28	23	51	14
Race				
Caucasian	20	23	43	22
African-American	22	17	39	5

	Asian-American	1	2	3	0
	Other	0	0	0	1
Ethnicity					
	Hispanic	1	2	3	0
	Non-Hispanic	42	40	82	28
Age					
	Mean (SD)	46 (11)	47 (14)		49 (10)
	Min	21	21		21
	1st Quartile	39	37		45
	Median	46	48		48
	Q3	54	54		56
	Max	71	77		68
Time of Previous SRP					
	6-11 months ago	5 (12%)	4 (10%)		
	1-2 years ago	12 (28%)	11 (26%)		
	3-4 years ago	4 (9%)	1 (2%)		
	≥ 5 years ago	9 (21%)	8(19%)		
	Never	13 (30%)	18 (43%)		

Table 6.3: Extent of Disease [modified from sponsor's table 6, 7, 8, vol. 1.31, pp 25(51) – 26 (51)]

Variable	Dental Gel 5% (N=43): Mean (SD)	Placebo (N=42): Mean (SD)
Mean Pocket depth (mm)	4.0 (0.7)	3.9 (0.9)
Proportion of Bleeding Pockets	0.5 (0.3)	0.5 (0.3)
Proportion of Hypersensitive Teeth	0.3 (0.2)	0.3 (0.3)
Mean Deepest Pocket depth (mm)	5.5 (1.0)	5.4 (1.1)
Proportion of Pockets 0-3 mm	0.45 (0.21)	0.46 (0.20)
Proportion of Pockets 4-6 mm	0.48 (0.19)	0.47 (0.17)
Proportion of Pockets > 6mm	0.06 (0.08)	0.07 (0.10)

Table 6.4: SRP Procedure [modified from sponsor's table 9, 10 vol. 1.31, pp 26 (51) – 27 (51)]

Variable	Dental Gel 5%: Mean (SD)	Placebo Gel: Mean (SD)
# of teeth/patient treated (protocol: 5-8 teeth)	6.5 (1.0) [N=43]	6.1 (2.2) [N=42]
Time of SRP(min)/tooth	3.6 (2.3) [N=280]	3.8 (2.4) [N=258]

Commentary: The randomization has been successful. Both placebo and dental gel 5% groups were similar in the following parameters: race, ethnicity, extent of disease, number of teeth /patient treated. There was no significant difference among centers.

Table 6.5: VAS pain scores upon probing (during the screening visit) [modified from sponsor's table 5, vol. 1.31, pp 24 (51)].

Group	N	Mean	SD
Dental Gel 5%	43	61.6	17
Placebo	42	62.7	17.8
Withdrawals Before Randomization	2	69	12.7
Screening Failures	26	17.6	7.8

Treatment Compliance

No problems related to treatment compliance were reported.

Unplanned Analyses

Study B5 was a post-hoc reanalysis of the data from studies B1-3 and is reviewed in more detail below.

Sponsor's Efficacy Results

Primary Efficacy Variables

The primary efficacy variable was defined in the protocol as the overall VAS pain score (measured at the end of dental treatment of the whole quadrant). The analysis plan in the protocol for all variables was descriptive statistics (mean, median, standard deviation, minimum, maximum). Tables 6.6, 6.7 and 6.8 present these data.

Table 6.6: Overall VAS pain scores during SRP: [modified from sponsor's table 11, vol. 1.31, pp 28 (51)]

Group	Center	N	Min	1st Quartile	Median	3rd Quartile	Max
Dental Gel 5%	2	9	3	5	8	21	23
	4	10	0	2	7	39	50
	5	12	3	8.5	19.5	35	46
	6	12	0	0	5	18	83
	All	43	0	3	11	22	83
Placebo	2	8	3	3	26	35	59
	4	10	3	3	22	38	100
	5	12	3	3	35	40.5	47
	6	12	5	5	19	37.5	63
	All	42	3	3	27	38	100

The sponsor points out in the discussion that the median VAS score in the dental gel 5% group was 11 mm, while the *median VAS score* in the placebo group was 27 mm, a difference of 16 mm (see table 6.6). The protocol had defined the target VAS difference

that would be considered clinically meaningful to be at least 15 mm (or 15% of the 100mm VAS scale). The difference achieved by comparing the median VAS scores in the two arms surpasses this pre-specified threshold by 1mm. The two-sided p-value calculated is 0.004 – a significant difference between the two arms [null hypothesis (Ho): no treatment difference]. As the sponsor pre-specified that the analysis will be done using the Wilcoxon non-parametric comparison, the choice of the median as the representative statistical parameter for the group comparison seems appropriate.

Table 6.7: Overall VAS pain scores during SRP: [modified from sponsor’s table 11, vol. 1.31, pp 28 (51)].

Group	Center	N	Mean	SD
Dental Gel 5%	2	9	12.0	8.6
	4	10	16.7	19.2
	5	12	21.6	15.3
	6	12	17.5	27.8
	All	43	17.3	19.2
Placebo	2	8	24.9	19.1
	4	10	33.0	30.9
	5	12	31.0	13.5
	6	12	24.5	19.6
	All	42	28.5	20.9

The numbers are different, however, when we examine the *mean VAS scores* presented in table 6.7. Here the difference between the two study arms is 28.5 mm – 17.3 mm = 11.2 mm, which does not reach the pre-specified 15% difference in VAS scores. There are equally compelling arguments to support the choice of the mean as the representative statistical parameter for the group comparison: the sample size calculations in the original protocol were done based on the mean values of both study arms.

Table 6.8: Overall VAS pain scores during SRP, test of treatment differences between arms: [modified from sponsor’s tables 12, 14, 16 vol. 1.31, pp. 28 (51) - 32 (51)]

Variable	Lower CI limit	Hodges-Lehmann point estimate	Upper CI limit	P-Value (two sided) Ho: no treatment difference
Overall VAS Score during SRP	4.00	10.00	19.00	0.004
Mean VAS Score / tooth, in teeth ≥ 6mm	1.0	6.5	14.5	0.017
Mean VAS Score / tooth, in teeth ≤ 5 mm	0.2	3.8	8.5	0.043

Finally, the *Hodges-Lehmann point estimate* shows only 10-mm difference (95% CI: 4.0, 19.0).

Secondary Efficacy Variables

Three secondary efficacy variables were defined in the study protocol.

1. Overall Verbal Rating Scale (VRS): 5-point verbal rating scale (no, mild, moderate, severe, and very severe pain). See data in table 6.9.

Table 6.9: Overall VRS pain scores: frequency (percent) [(modified from sponsor’s table 17, vol. 1.31, pp 33 (51))]

Group	Dental Gel 5%:	Placebo
No Pain	6 (14)	0 (0)
Mild Pain	24 (56)	20 (48)
Moderate Pain	13 (30)	18 (43)
Severe Pain	0 (0)	3 (7)
Very Severe Pain	0 (0)	1 (2)

The VRS scores show slightly higher frequency of no pain and mild pain in the dental gel 5% as compared with placebo. Conversely, severe pain and very severe pain were observed only in the placebo group. The sponsor reported that the overall VRS pain score was significantly lower statistically ($p=0.003$) in the Dental Gel group than in the placebo gel group. The Agency statistical team reported similar findings ($p<0.0023$). When the VRS categories of ‘no pain’ were combined with ‘mild pain’ by the Agency statistical team, Dental Gel reduced pain compared to placebo with marginal statistical significance ($p<0.0485$).

2. VAS scores per tooth (by tooth location): See data in table 6.10.

Table 6.10: VAS scores per tooth (by tooth location) [modified from sponsor’s table 20, vol. 1.31, pp 36 (51)]

Group	Dental Gel 5%:		Placebo:	
	Mean (SD)	[N]	Mean (SD)	[N]
Molars	14.7 (17.7)	[N=42]	24.3 (21.9)	[N=42]
Premolars	13.5 (19.7)	[N=41]	21.7 (18.9)	[N=37]
Incisors	13.4 (14.7)	[N=40]	18.0 (15.5)	[N=33]
Canines	11.8 (14.2)	[N=40]	15.8 (15.1)	[N=35]

Commentary: 7-11 mm VAS scores difference between the dental gel 5% group and the placebo group in the molar and the premolar subgroups. Other subgroups showed smaller

differences, although VAS scores were consistently higher in the placebo group compared to the dental gel group.

3. Need for rescue anesthetic (rescue was given OR rescue was not given but SRP has been terminated secondary to intolerable pain): See data in table 6.11.

Table 6.11: Number of patients with first and second interruption (s) due to pain: frequency (%) [modified from sponsor's table 18, vol. 1.31, pp 35 (51)]

Group	Dental Gel 5% (N=43)	Placebo (N=42)
1 st interruption	12 (28%)	18 (43%)
2 nd Interruption	2 (5%)	7 (17%)

Commentary: the need for rescue medication appears to have occurred with slightly higher frequency in the placebo group than in the dental gel group. This difference is statistically insignificant (p values 0.1774 for first interruption, 0.0887 for second interruption by fisher's exact test).

Table 6.12: Mean VAS pain score/tooth, by the deepest probing site. See data in table 6.12. [modified from sponsor's tables 11-16, vol. 1.31, pp 28 (51) – 32 (51)]

Variable	Dental Gel 5% (N=43)	Placebo (N=42)
≥ 6 mm	17 (16.8)	25.6 (21.5)
≤ 5 mm	12.4 (14.9)	16.8 (14.8)

Commentary: the VAS scores are slightly lower in the dental gel 5% group, but the differences between the dental gel 5% and the placebo group are very small (8mm in the ≥ 6 mm pockets, 4 mm in the ≤ 5 mm pockets).

The data of study B3 support the efficacy of dental gel 5%, compared to the placebo gel. The pre-specified difference in VAS pain score of 15 mm between the treatment arms was met in this study, if the median scores of the two arms are compared (27 – 11 = 16 mm) (P = 0.004). If the mean scores of the two arms are compared, however, the difference between the two arms falls below the pre-specified 15 mm difference: (28.5 – 17.3 = 11.2 mm). The Hodges-Lehmann point estimate found a difference between the study arms of 10.0 (95% CI: 4.0, 19.0). From these three descriptive statistical variables, two (mean, Hodges-Lehmann point estimate) are beneath the pre-specified difference of 15% and the third (median) surpasses it by a razor-thin margin (16%). The statistical finding of a 15 mm difference between groups is therefore not robust, despite the fact that the p values are consistently below 0.05 (i.e. the active and placebo groups are statistically significantly different from one another). The determination of efficacy will have to rely on assessment of the clinical significance of the differences between the two study arms.

6.3.4 Study B4 (SP-DGA-0005) A two period, crossover, randomized, open study to evaluate patient preferences for anesthetic method using non-injection Lidocaine,

prilocaine Dental Gel 5% and injection of Xylocaine 2%-adrenaline in conjunction with scaling and/or root planing.

Findings vs. Labeling Claims

The sponsor was informed during drug development by the Agency that an open-label study would not be considered acceptable for an efficacy trial. Study B4 is presented in abbreviated form only.

Study Plan

The study was conducted between September 2000 and December 2000.

Population, Design and Objectives

Primary:

To investigate the patient's preferred anesthetic method, locally applied dental gel 5% vs. injection of Xylocaine 2% adrenaline, in conjunction with periodontal SRP.

Secondary:

To compare the two anesthetic methods with reference to the patients' and the investigator's assessments of the quality of the anesthesia and their satisfaction of it, including the patients' willingness to return (WTR) and willingness to pay (WTP) extra for dental gel 5%. Adverse events were also evaluated.

Study Design:

Multicenter, two-period, crossover randomized, open-label, trial of local application of dental gel 5% in the periodontal pockets and injection of Xylocaine 2% adrenaline in conjunction with SRP.

Patients who are bothered by injections and scheduled for injection anesthesia in conjunction with SRP procedure in all four quadrants will be included.

Two treatment visits are included, one week apart, followed by a follow-up phone call 24-48 hours after each visit. Each patient will be treated with dental gel 5% and subjected to SRP in the upper and the lower quadrant in one side of the mouth at one visit and with injection anesthesia in the quadrants of the other side of the mouth at one visit.

Treatment Summary

Assessments

Primary:

- The patient's preferred anesthetic method (patients will be offered the option of selecting either one of the two anesthesia modes and a no preference option).

Secondary:

- The investigator's judgement regarding the ability to perform an adequate treatment (after the completion of both visits).

- The patients' filled questionnaire regarding the pain and discomfort secondary to anesthesia (filled immediately after the treatment) and the impact on daily life activities in the evening following the treatment (at least 4 hours after the treatment).
- The patients' willingness to return and willingness to pay extra for dental gel 5%.

Patient Disposition:

170 patients were randomized. 84 received dental gel 5% during visit 1 (42 left side, 42 right side) and 86 received injection during visit 1 (43 left side, 43 right side). The patients crossed over in visit 2. No patient was discontinued after visit 1, one patient was discontinued after visit 2. 169 patients have completed the study. Thirteen patients had major protocol violations and were excluded from PP analysis. Available for safety analysis 170 patients, for ITT analysis 170, for PP analysis 157.

Primary Efficacy Results

Results:

Table 1: Patient's preference [adapted from sponsor's table 10, vol. 1.35, pp. 42 (82)]

Study Center	N (patients)	Dental Gel 5%	Injection of Anesthesia	No Preference
1	23	14 (50.9%)	8 (34.8%)	1 (4.3%)
2	21	18 (85.7%)	2 (9.5%)	1 (4.8%)
3	20	10 (50.0%)	8 (40.0%)	2 (10.0%)
4	23	16 (69.6%)	4 (17.4%)	3 (13.0%)
5	13	7 (53.9%)	5 (38.5%)	1 (7.7%)
6	22	19 (86.4%)	2 (9.1%)	1 (4.6%)
7	21	18 (85.7%)	2 (9.5%)	1 (4.8%)
8	14	8 (57.1%)	4 (28.6%)	2 (14.3%)
Total	157 (100%)	110 (70.1%)	35 (22.3%)	12 (7.6%)

Table 1 shows that 70% of the patients preferred dental gel 5%, 22% preferred injection anesthesia, and 8% did not express a preference ($p < 0.0005$).

Sponsor's Secondary Efficacy Results

The main reason for choice of dental gel 5% was "less numbness following procedure". The main reason for choice of injection anesthesia was "less pain and other discomfort". The data, which summarizes the investigator's judgement regarding the ability to perform an adequate treatment, there was a significant difference ($p < 0.0005$) in favor of injection anesthesia. Following injection, this ability was rated as satisfactory or very satisfactory for 100% of the patients. The corresponding figure after dental gel 5% treatment was 76%. The patients' pain and discomfort secondary to anesthesia was similar in both anesthetic methods. Patients' rating of satisfaction from anesthesia was significantly ($p < 0.0005$) in favor of injection anesthesia. 96% of the patients rated it as satisfactory or very

satisfactory. The corresponding figure for dental gel 5% was 80%. Post-procedural discomfort was found statistically significant ($p < 0.0005$) in favor of dental gel 5%. 56% of all patients responded to the dental gel 5% treatment as not being bothered or hardly bothered at all. The corresponding figure for injection anesthesia was 38%. The question of willingness to pay extra was put to all patients preferring dental gel 5% to injection anesthesia. 109 PP patients answered this question: 66 (61%) said "yes", 43 (39%) said "no". The question of willingness to return for another treatment if they knew they would be offered dental gel 5% was put to all patients who expressed preference of mode of anesthesia (patients who expressed no preference were excluded from this question). 142 patients answered this question: 107 (75%) preferred dental gel 5%, 35 (24%) patients preferred injection anesthesia.

Source: vol. 1.35, pp. 42 (82) – 65 (82).

This study suggests that while lidocaine injection provides better analgesia, patients prefer Oraqix, and that post-procedural discomfort is better after Oraqix. This study can not be blinded, and had to be conducted open-label. The study's efficacy conclusions must therefore be interpreted with caution. It is still interesting to know that a significant majority of pain sensitive patients, while acknowledging that injected anesthesia provides them superior pain control, would prefer dental gel 5% over the injectable anesthesia once they have experienced both. This study does not support Oraqix efficacy. There is only one comparator, and Oraqix was less effective analgesic than the comparator. However, neither does it disprove the efficacy of Oraqix?

7. INTEGRATED REVIEW OF SAFETY

7.1 Findings vs. Labeling Claims

The sponsor's proposed label comments on frequency of adverse events in 3 placebo controlled clinical studies (B1-3), where the placebo groups were exposed to Dental Gel that did not contain local anesthetic. It does not reference adverse events from B4, a comparison between Dental Gel and injected local anesthetic. The table of application site disorders presented in the adverse event section of the label is also drawn from only Studies B1-3. This may lead the reader to assume that ulcers or vesicle formation noted in the table are unrelated to the product, because the incidence of these events was similar in the active and placebo groups. In contrast, ulcer or vesicle formation was not observed after the use of injected Xylocaine® with epinephrine tartrate 12.5µg in study B4. This formulation of lidocaine with epinephrine is not approved for use by the Agency although it is similar to formulations of lidocaine with epinephrine that are approved for use in the United States. Although the absence of local ulcer formation after injection may possibly be a result of sampling error, these data suggest that local ulcers may be a consequence of the vehicle used for Dental Gel the mechanics of administration of Dental Gel. Local ulcers may be a consequence of modified SRP technique because of lower effectiveness of Dental Gel compared to injected Xylocaine (leading to differences in dental technique), or to other differences such as obscuration of the field due to Dental Gel. A comparison of

adverse events between local anesthetic injection and application of Dental Gel as observed in B4 should be included in this section of the label.

It is also noted that adverse event data were not reported from studies A1-3. These studies were primarily pharmacokinetic in nature, but A3 was the only study performed with the sponsor's highest recommended dose. It was interesting to note that every patient (n=11) in A3 experienced an adverse event with 6/11 patients reporting local reactions and 3/11 patients reporting a total of 7 local reactions that required greater than one week to resolve. The A1-3 studies were not controlled and represented early experience with the drug and its application technique so the frequency of adverse reactions may not be representative. Despite these limitations, documentation of adverse events with the highest recommended dose should be available on the label to offer the best guidance to practitioners.

The sponsor's assertion that most adverse events associated with use of Dental Gel are local, and mild to moderate in nature appears valid. There were no systemic adverse reactions in the findings of the studies as reported that could be attributed with high likelihood to Dental Gel.

7.2 Adequacy of Exposure and Safety Assessment

Safety data come from four Phase 3 studies, three Phase 2 studies and review of the published literature on EMLA® cream, prilocaine and lidocaine. A total of 559 patients participated in studies with 391 patients exposed to Dental Gel.

Table 1: The Clinical Program [modified from the sponsors' table 1, vol. 1.19, pp. 14 (39)]

Study Number	Patients – (Dose Range, gm) Dental Gel 5%	Patients- (Dose Range, gm) Placebo	Total Patients
A1 (SP-DGA-0001)	30 (0.1-0.7)	0	30
A2 (SP-DGA-0002)	11 (0.9-3.5)	0	11
A3 (SP-DGA-0006)	11 (8.0-8.7)	0	11
B1 (SP-DGA-0003)	63 (0.4-2.1)	59 (0.4-2.6)	122
B2 (SP-DGA-0004)	63 (0.4-4.3)	67 (0.4- 5.1)	130
B3 (SP-DGA-0007)	43 (0.9-2.6)	42 (0.4-3.4)	85
B4 (SP-DGA-0005)	170 (1.3-6.8)	0	170
Total	391	168	559

In all studies, Dental Gel was administered by dental syringe attached to a blunt needle applicator. In early studies, A1-2 Dental Gel was supplied by the sponsor in _____ into a syringe by the investigator. In later studies, A3 and B1-4, Dental Gel was supplied in its to-be-marketed form (prefilled glass cartridges each containing 1.7 gm of study drug preparation, supplied with blunt needle applicator). Dental Gel contained Xylocaine 2% (25 mg/g lidocaine base) with prilocaine (25 mg/g base) in an _____ in thermosetting purified poloxamers 188 and 407. Placebo cartridges contained only the thermosetting poloxamers 188 and 407 and _____

Three studies (A1-A3) measured the plasma level of active agents and their metabolites in a total of 52 patients with incrementally larger doses used in each study. Patients in study A3 (n=11) were treated with 4.7-5 cartridges (about 212.5 mg lidocaine and 212.5 mg prilocaine) and retained the administered Dental Gel in dental pockets for 154-201 minutes. These patients were exposed to the maximum recommended dose for a much longer period than is typical for an SRP procedure (less than 20 minutes). Even if no rinsing of the Dental Gel occurred after each tooth, the total time that the patient is exposed to Dental Gel undergoing SRP would be expected to be much less than the time of exposure used in A3.

The plasma profiles of lidocaine, prilocaine, 2,6 xylidine and o-toluidine were measured as primary objectives with methemoglobin measured as a secondary objective. Signs and symptoms of systemic toxicity with lidocaine and prilocaine are restlessness, circumoral parasthesia, tinnitus, tremors, shivering, sedation, and in very high doses, convulsions. The peak plasma concentrations of lidocaine and prilocaine (mean \pm SD and (range)) in A3 were 284 ± 122 (157-552) ng/mL and 106 ± 45 (53-181) ng/mL, values below the threshold for initial signs of CNS toxicity (5000-6000 ng/mL). The compounds 2,6 xylidine and o-toluidine are metabolites of prilocaine. In A3, systemic exposure of patients to 2,6-xylidine and o-toluidine was also low compared with parent compounds with individual AUC_{inf} ratios of 0.07-0.18 and 0.19-0.56 respectively. Doses in excess of 600 mg prilocaine administered intravenously results in excessive binding of these metabolites to hemoglobin to form methemoglobin and thereby cause peripheral cyanosis. (Local Anesthetics in AMA Drug Evaluations pp.373-394 Copyright ©1983 American Medical Association)

In normal individuals methemoglobin is typically about 1% of the total hemoglobin concentration. In the absence of anemia or other systemic disease, clinical signs of cyanosis correspond to methemoglobin levels greater than 1.5mg/dL or (15%). Symptoms of fatigue, headache, tachycardia and weakness develop when methemoglobin levels exceed 20-30%. ("Poisoning and Drug Overdosage" Christopher H. Linden; Michael J. Burns in Harrison's Textbook of Medicine Ed. Eugene Braunwald, Anthony S. Fauci, Kurt J. Isselbacher, Dennis L. Kasper, Stephen L. Hauser, Dan L. Longo, J. Larry Jameson pp.1096-7133.(ch396) Copyright ©2001-2002 The McGraw-Hill Companies) In A3, methemoglobin levels measured before application of Dental Gel ranged between 0.0-1.1% and rose slightly to 0.83-1.73%. There was no reported evidence of cyanosis or respiratory failure among the adverse events in any study (A1-3, B1-4) and the low plasma levels of methemoglobin and prilocaine metabolites after administration of the highest doses of Dental Gel studied argue against this as being likely.

All plasma measurements appeared to be acquired frequently enough and over sufficient duration to capture the peak plasma levels and the return to baseline.

Safety evaluation of appropriateness of the sponsor's recommended maximum allowed dose requires evidence of efficacy at sub-maximal doses to avoid compelling practitioners to exceed maximum dosing in order to provide patient with sufficient analgesia to complete a procedure. Study B4, a randomized crossover study of 170 patients with low pain tolerance to SRP compared efficacy of Dental Gel to injected Xylocaine 2% with epinephrine tartrate 12.5 μ g, a common dental anesthetic regimen in Europe. The range of Dental Gel administered in B4 was ¾ to 4 cartridges, 20% below the maximum recommended dose (5 cartridges) for all patients. The sponsor's

recommendation for the maximum allowed dose is consistent with their expected use of the product. Each study enrolled a similar number of adult males and females. Pregnant women were not included in any of the studies. No patients with hepatic or renal impairment were studied. Patients with a history of severe preexisting systemic disease (neurological, cardiovascular, renal, liver, blood disease or malignancy, psychiatric disorder, allergy to local (amide) anesthetics, active substance abuse) were excluded from participation. Recently exposed patients to sedation, anesthesia or dental procedures or oral ulceration were also excluded.

The ethnic diversity was limited, including primarily Caucasians (n=461) and African-Americans (n=80), a small number of Asians (n=16) and other racial groups (n=2). No statistical comparisons were presented, but there did not appear to be an over-representation of serious or severe adverse events in any of the populations studied. One of the most serious adverse events to be anticipated is methemoglobinemia in a patient with limited blood-oxygen carrying capacity or delivery. Certain ethnic populations have a higher incidence of hemoglobinopathies that can limit oxygen carrying capacity; however, measured concentrations of methemoglobin were low.

No patients withdrew from clinical study because of an adverse event.

Patients were interviewed by personal visit 1 week \pm 3 days (B1, A3), by telephone 24-48 hours (A1-2, B2, and B4) or by telephone 24-72 hours (B3) after treatment. Peak plasma levels of drugs and metabolites had passed after less than 250 minutes in all patients so that the interview occurred after peak systemic exposure to Dental Gel. Standardized questions were asked to describe complaints referred to the oral cavity and general somatic symptoms. Adverse events were categorized by seriousness (effect on general health) and severity (intensity of distress).

7.3 Methods for Review of Safety

The safety evaluation was reviewed from the ISS provided in the original NDA submission (vol. 1.19). and the complete tables of all reported adverse events. The 120 day safety update revealed no new occurrences of adverse events.

Deaths

No patient died.

Non-Fatal Serious Adverse Events

No serious adverse events were reported.

Adverse Events Leading to Study Discontinuation

No patient discontinued the investigational product due to an AE in any of the seven clinical studies listed in table 1.

7.4 Safety Findings from Clinical Studies

Overall Evaluation of Adverse Events

The numbers and categorizations of adverse events as reported in the Amendment to NDA 21,451 March 14, 2002 were compared with the tabulations of adverse events for

each individual study. There were 118 (30%) AE's in the group of 391 patients exposed to dental gel 5% and 45 (27%) AE's in the group of 168 patients exposed to placebo gel. There were 61 (36%) AE's in the group of 170 patients exposed to the injectable Xylocaine 2% with epinephrine tartrate 12.5µg.. The great majority of the AE's were application site reactions (72/118 (61%) in the dental gel group, 47/61 (77%), in the injected lidocaine group and 26/45 (58%) in the placebo group). The placebo consisted of thermosetting gel (poloxamers 188 and 407) infiltrated into the dental pocket.

AE by System

Table 2: number (percentage) of patients with AEs displayed by SOC and preferred term, in the whole clinical program [sponsor's table 3, vol. 1.19, pp. 19 (39) – 20 (39)]

SYSTEM ORGAN CLASS Preferred Term	Dental gel 5% (N=391)	Placebo gel (N=168)	Xylocaine (N=170)
MUSCULO-SKELETAL SYSTEM DISORDERS			
Arthralgia		1 (1)	
Arthropathy	1 (0)	1 (1)	
Myalgia	1 (0)	2 (1)	
CENTRAL & PERIPHERAL NERVOUS SYSTEM DISORDERS			
Dizziness	1 (0)	1 (1)	1 (1)
Headache	8 (2)	3 (2)	5 (3)
SPECIAL SENSES OTHER, DISORDERS			
Taste Perversion	8 (2)	1 (1)	
PSYCHIATRIC DISORDERS			
Insomnia		1 (1)	
GASTRO-INTESTINAL SYSTEM DISORDERS			
Anus Disorder	1 (0)		
Constipation	1 (0)		
Nausea	3 (1)		1 (1)
Pharynx Disorder	1 (0)		
Tooth Disorder	1 (0)		
METABOLIC AND NUTRITIONAL DISORDERS			
Hypoglycemia			1 (1)
CARDIOVASCULAR SYSTEM DISORDERS			
Pallor	1 (0)		
HEART RATE AND RHYTHM DISORDERS			
Palpitation	1 (0)		

Tachycardia			1 (1)
RESPIRATORY SYSTEM DISORDERS			
Coughing		1 (1)	
Pharyngitis	1 (0)		
Respiratory Infection	2 (1)		1 (1)
Rhinitis		2 (1)	
PLATELET, BLEEDING & CLOTTING DISORDERS			
Bleeding Post Vessel Puncture	1 (0)		
URINARY SYSTEM DISORDERS			
Polyuria	1 (0)		
REPRODUCTIVE DISORDERS, FEMALE	1 (0)		
Dysmenorrhea			
BODY AS A WHOLE – GENERAL DISORDERS			
Accident and/or Injury	2 (1)	2 (1)	
Fatigue	3 (1)		2 (1)
Flu-Like Disorder	2 (1)		
Pain	1 (0)	1 (1)	1 (1)
Rigors (Chills)	1 (0)		
APPLICATION SITE DISORDERS			
Anesthesia local	2 (1)		
Application Site Edema	2 (1)	1 (1)	
Application Site Reaction	52 (13)	20 (12)	
Injection Site Abscess		1 (1)	
Injection Site Pain			45 (26)
Injection Site Reaction			1 (1)
TOTAL	78 (20)	32 (19)	52 (31)

Some of these events that occurred only in the active group (nausea, palpitation, flu-like disorder, rigors) might deserve closer examination if you haven't already.

Some patients reported more than a single adverse event. Accidents reported in the dental Gel group included a single automobile accident and a puncture wound of the foot caused by a metal. Musculoskeletal complaints in the Dental Gel group included soreness after water skiing. Associated with the Dental Gel group were systemic adverse events of undetermined etiology included menstrual cramps, polyuria, palpitations, pallor, constipation and skin slippage from the anus. Most adverse events in all groups were related to the application site in the form of inflammatory reactions and discomfort.

Application Site AE

Table 3: Number (percent) of patients with AE: Application site [sponsor's table 4, vol.1.19, pp. 20 (39)]

SYSTEM ORGAN CLASS Low Level Term	Dental Gel 5% (N=391)	Placebo (N=168)	Xylocaine (N=170)
APPLICATION SITE DISORDERS			
Anesthesia local	2 (1)		
Application site bleeding		2 (1)	
Application site burning	1 (0)		
Application site irritation	4 (1)	3 (2)	
Application site local pain	17 (4)	4 (2)	
Application site numbness	9 (2)		
Application site pruritus		1 (1)	
Application site pulsation	2 (1)	1 (1)	
Application site redness	4 (1)		
Application site soreness	16 (4)	8 (5)	
Application site ulcer	5 (1)	3 (2)	
Application site vesicles	2 (1)		
Application site edema	2 (1)	1 (1)	
Application site reaction	4 (1)	1 (1)	
Injection site abscess		1 (1)	
Injection site pain			45 (26)
Injection site reaction			1 (1)
TOTAL	55 (14)	21 (13)	46 (27)

The types of local reactions were similar between the Dental Gel group and the placebo group. The most common symptoms in both groups were soreness and pain in the treated area. There were a small number of patients exhibiting consisting of local ulcer or vesicle formation among the Dental Gel subjects (2%) and the placebo subjects (2%). The injectable Xylocaine ® plus epinephrine group (which was only studied in the open-label active-control study B4) had number of patients (26%) reporting injection site pain. Application site pain and soreness were seen in lower incidence in both the Dental Gel group (9%) and placebo group (8%). Masking of local adverse reactions to Dental Gel may have occurred as a result of trauma from SRP. Neither ulcers nor vesicles were reported in subjects after treatment with Xylocaine ® 2% with epinephrine tartrate 12.5µg. These findings suggest that ulcer or vesicle formation were a consequence of either contact with the gel or the technique of application.

AE Severity

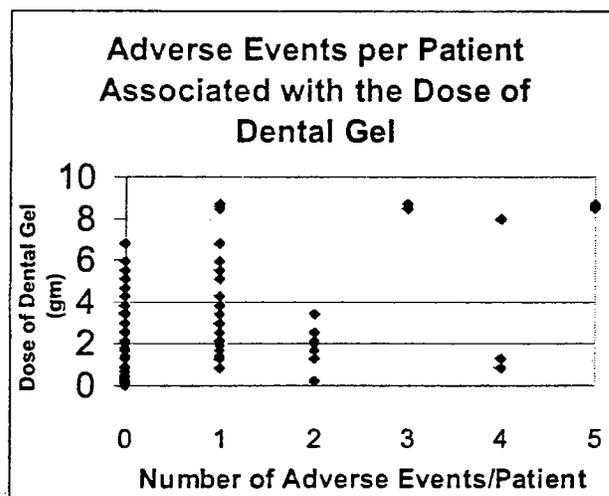
The great majority of all AE's were of either mild or moderate intensity. Fifty-nine (15%) out of 391 patients exposed to dental gel 5% and 25 (15%) out of 168 patients exposed to placebo reported at least one mild AE. Seventeen (4%) of patients exposed to Dental Gel 5% and 7 (4%) of all patients exposed to placebo reported a moderate AE. Two (0.35%) of all 559 patients reported a severe AE. One patient had reported a severe fatigue starting 3h after administration and lasting 2 days, and another patient reported severe bad taste lasting approximately half an hour, resulting from Dental Gel overflow to the tongue. The patient reporting severe fatigue, a 51 year old Caucasian female, received

only ¾ of a cartridge (1.35 gm Dental Gel). This represents a very low dose, well below the amount needed to exceed toxic thresholds for direct local anesthetic effects or methemoglobin formation to account for symptoms of fatigue. No systemic adverse event could be attributed to toxic levels of drug or metabolite based upon the doses administered. Adverse events related to local injection of Xylocaine 2% with epinephrine were generally related to pain on injection, local effects or mild systemic symptoms such as headache.

AE by Dose

A higher frequency of local reactions (mild-moderate) were seen when the Dental Gel dose was > 3.4 g gel (18/80 = 23%) as opposed to the frequency seen when the dose was 1.7 – 3.4 g gel (15 / 133 = 11%) or when the dose was 0 - 1.7 g gel (22 / 178 = 12%). The sponsor comments that the higher dose Dental Gel was used mainly in studies A3 and B4, where the number of treated teeth was also higher than in other studies. The sponsor's argument is that the higher rate of local reactions was due, at least in part, to the procedure and not Dental Gel. The sponsor did not conduct a study to directly compare adverse events in subjects receiving the highest dose Dental Gel vs. placebo gel so the etiology of increased frequency of local reactions was not completely resolved. The B4 study does allow some outcome anticipation if dental practice were to reflect substitution of Dental Gel for an injection anesthetic for the SRP. The frequency of local reactions was less with high dose Dental Gel when compared with injection, but the nature of the local reactions observed reflected a possible inflammatory process not seen after injection.

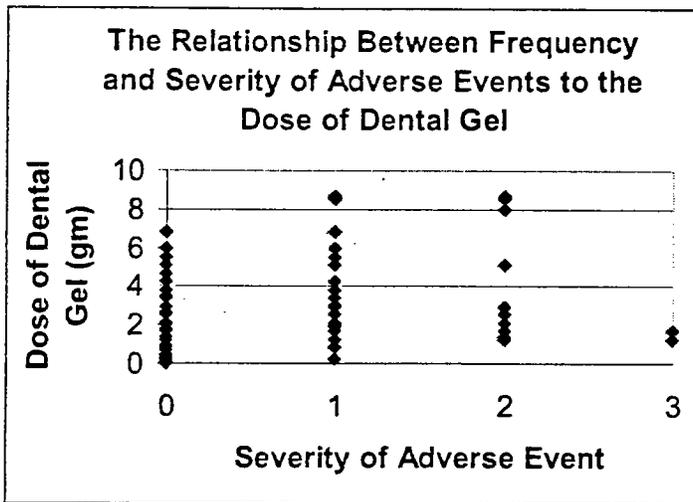
Some patient who had adverse events experienced more than one. As part of this review the dose of Dental Gel administered was compared with the number of adverse events per patient.



Each point on the graph above references a patient who reported having adverse events. This depiction suggests that the highest doses of administered Dental Gel were associated with a higher number of adverse events per patient. These findings are biased by Study A3 where every patient received the highest recommended dose of Dental Gel for a

lengthy period. All patients in A3 reported adverse events with about half of those patients reporting multiple adverse events. Multiple reported adverse events might be alternate descriptors of the same pathophysiologic process.

We also compared the frequency of occurrence of adverse events and the severity of adverse event reported with the dose of Dental Gel administered.



The severity of adverse event is coded on the horizontal axis using the same scale as the sponsor’s adverse event table. No adverse events are referenced as “0”, mild as “1”, moderate as “2” and severe adverse events as “3”. Each point on the graph refers uniquely to a patient reporting at least one adverse event. The most severe adverse event was recorded for patients reporting multiple adverse events. These data suggest that severity was not strongly related to the administered dose. The highest doses administered did appear to account a larger fraction of the moderate adverse events than they did among the mild adverse events. The severe adverse events reported were associated with small doses of Dental Gel. These findings are biased by the impact of Study A3 with its small sample of patients exposed to a high dose of Dental Gel and all of its subjects reporting adverse responses.

The limited data at the highest dose renders statistical analysis impractical, however, there is a suggestion that maximal dosing of Dental Gel may be associated with a higher incidence of multiple adverse events and moderate rather than mild severity.

7.5 Description of Patient Demographics

Drug – Demographic Interactions

Age

Twenty-two out of 391 patients exposed to dental gel 5% were > 65 years old, 6 of whom > 75 years. Table 4 shows the distribution of AE by age.

Table 4: AE's by age, in number (percent) of patients. Each patient is counted only once per preferred term (all studies) [sponsor's table 12, appendix to the ISS, vol. 1.19, pp. 20 (37) – 21 (37)]

SYSTEM ORGAN CLASS Preferred Term	18.0 – 64.9 years			65 or more years		
	Dental gel 5% N=369	Placebo gel N=151	Xylocaine N=159	Dental gel 5% N=22	Placebo gel N=17	Xylocaine N=11

Appears This Way
On Original

MUSCULO-SKELETAL SYSTEM DISORDERS						
Arthralgia					1 (6)	
Arthropathy	1 (0)				1 (6)	
Myalgia	1 (0)	2 (1)				
CNS & PNS DISORDERS						
Dizziness	1 (0)	1 (1)	1 (1)			
Headache	8 (2)	3 (2)	4 (3)			1 (9)
SPECIAL SENSES OTHER< DISORDERS						
Taste perversion	7 (2)	1 (1)		1 (5)		
PSYCHIATRIC DISORDERS						
Insomnia		1 (1)				
GASTRO-INTESTINAL SYSTEM DISORDERS						
Anus Disorder	1 (0)					
Constipation	1 (0)					
Nausea	3 (1)		1 (1)			
Pharynx disorder	1 (0)					
Tooth Disorder	1 (0)					
METABOLIC & NUTRITIONAL DISORDERS						
Hypoglycemia			1 (1)			
CARDIOVASCULAR DISORDERS, GENERAL						
Pallor	1 (0)					
HEART RATE & RHYTHM DISORDERS						
Palpitation	1 (0)					
Tachycardia			1 (1)			
RESPIRATORY SYSTEM						
Coughing		1 (1)				
Pharyngitis	1 (0)					
Respiratory infection	2 (1)		1 (1)			
Rhinitis		2 (1)				
PLATELET, BLEEDING & CLOTTING DISORDERS						
Bleeding post vessel puncture	1 (0)					
URINARY SYSTEM DISORDERS						
Polyuria	1 (0)					
REPRODUCTIVE DISORDERS, FEMALE						
Dysmenorrhea	1 (0)					
BODY AS A WHOLE – GENERAL DISORDERS						
Accident and/or Injury	2 (1)	2 (1)				
Fatigue	3 (1)		2 (1)			
Flu-like disorder	2 (1)					
Pain	1 (0)	1 (1)	1 (1)			
Rigors (chills)	1 (0)					
APPLICATION SITE DISORDERS						
Anesthesia local	2 (1)					
Application site edema	2 (1)	1 (1)				
Application site reaction	48 (13)	19 (13)		4 (18)	1 (6)	
Injection site abscess		1 (1)				
Injection site pain			42 (26)			3 (27)
Injection site reaction						1 (9)
TOTAL	74 (20)	30 (20)	48 (30)	4 (18)	2 (12)	4 (36)

No significant pattern differentiates the patient > 65 from the younger patient's AE profile. The small number of patients >65 does not allow conclusions about the incidence and severity of adverse events in the patient sub-population > 65 years old. The incidence of serious systemic disease and periodontal disease increases in older individuals. Decreased renal, hepatic or cardiovascular function may impair clearance of the local anesthetics in Dental Gel or its metabolites, however, prior studies of EMLA cream on intact skin do not indicate higher plasma levels in geriatric patients compared to non-geriatric patients. Older individual may particularly benefit from less invasive and more benign anesthetics. It is a limitation of the reported clinical studies that more patients from the elderly population were not recruited.

Race

Table 5: AE by race, in number (percent) of patients. Each patient is counted only once per preferred term (all studies) [from sponsor's table 13, appendix to ISS, vol. 1.19, pp. 22 (37) – 23 (37) The term "Noncaucasian" was stricken because it does not identify a race.]

SYSTEM ORGAN CLASS Preferred Term	Caucasians N=461			Black =80, Oriental=16, Other = 2 (N=98)		
	Dental gel 5%	Placebo gel	Xylocaine	Dental gel 5%	Placebo gel	Xylocaine

**Appears This Way
On Original**

MUSCULO-SKELETAL SYSTEM DISORDERS						
Arthralgia		1 (1)				
Arthropathy	1 (0)	1 (1)				
Myalgia	1 (0)	2 (2)				
CNS & PNS DISORDERS						
Dizziness	1 (0)	1 (1)	1 (1)			
Headache	7 (2)	3 (2)	4 (2)	1 (2)		1 (2)
SPECIAL SENSES OTHER DISORDERS						
Taste perversion	8 (2)	1 (1)				
PSYCHIATRIC DISORDERS						
Insomnia		1 (1)				
GASTRO-INTESTINAL SYSTEM DISORDERS						
Anus Disorder	1 (0)					
Constipation				1 (2)		
Nausea	3 (1)		1 (1)			
Pharynx disorder	1 (1)					
Tooth Disorder	1 (0)					
METABOLIC & NUTRITIONAL DISORDERS						
Hypoglycemia			1 (1)			
CARDIOVASCULAR DISORDERS, GENERAL						
Pallor	1 (0)					
HEART RATE & RHYTHM DISORDERS						
Palpitation	1 (0)					
Tachycardia			1 (1)			
RESPIRATORY SYSTEM						
Coughing		1 (1)				
Pharyngitis	1 (0)					
Respiratory infection	2 (1)		1 (1)			
Rhinitis					2 (5)	
PLATELET, BLEEDING & CLOTTING DISORDERS						
Bleeding post vessel puncture	1 (0)					
URINARY SYSTEM DISORDERS						
Polyuria	1 (0)					
REPRODUCTIVE DISORDERS, FEMALE						
Dysmenorrhea				1 (2)		
BODY AS A WHOLE - GENERAL DISORDERS						
Accident and/or Injury	2 (1)	2 (2)				
Fatigue	3 (1)		2 (1)			
Flu-like disorder	2 (1)					
Pain	1 (0)	1 (1)	1 (1)			
Rigors (chills)	1 (0)					
APPLICATION SITE DISORDERS	2 (1)					
Anesthesia local	1 (0)	1 (1)		1 (2)		
Application site edema	49 (15)	13 (10)		3 (6)	7 (16)	
Application site reaction		1 (1)				
Injection site abscess			44 (27)			1 (20)
Injection site pain			1 (1)			
Injection site reaction						
TOTAL	72 (21)	23 (19)	50 (30)	6 (11)	9 (20)	2 (40)

The disproportionate number of Caucasians and African-Americans to other races in the studies reported makes it difficult to exclude potential association, by race, of adverse reaction to Dental Gel. Some of the studies conducted outside the United States (A1: Sweden, A2: Sweden, A3: Sweden, B2: Canada, B4: Belgium,) may be subject to racial patient selection bias because ethnic diversity does not parallel that of our own country. The table depicting the relationship of adverse events by race is not stratified completely, however, the numbers of subjects and adverse events from other races when compared to Caucasians and African-Americans is very small. There is no compelling data to suggest that individuals would be at particular risk of serious or severe adverse events based upon racial origins alone, but the data presented cannot rule out this possibility. It is well known that people with inherited as well as acquired hemoglobinopathies and depressed oxygen carrying capacity are potentially at increased risk of adverse events from methemoglobin formation from metabolism of prilocaine.

Gender

Table 6: AE by gender, in number (percent) of patients. Each patient is counted only once per preferred term (all studies) [sponsor's table 14, appendix to ISS, vol. 1.19, pp. 24 (37) - 25 (37)]

SYSTEM ORGAN CLASS Preferred Term	Males = 247			Females = 312		
	Dental gel 5%	Placebo gel	Xylocaine	Dental gel 5%	Placebo gel	Xylocaine

Appears This Way
On Original

MUSCULO-SKELETAL SYSTEM DISORDERS						
Arthralgia		1 (1)				
Arthropathy		1 (1)		1 (0)		
Myalgia		1 (1)		1 (0)	1 (1)	
CNS & PNS DISORDERS						
Dizziness	1 (1)		1 (1)		1 (1)	
Headache	4 (2)	1 (1)	2 (2)	4 (2)	2 (2)	3 (3)
SPECIAL SENSES OTHER< DISORDERS						
Taste perversion	1 (1)	1 (1)		7 (3)		
PSYCHIATRIC DISORDERS						
Insomnia		1 (1)				
GASTRO-INTESTINAL SYSTEM DISORDERS						
Anus Disorder	1 (1)					
Constipation				1 (0)		
Nausea	1 (1)			2 (1)		1 (1)
Pharynx disorder				1 (0)		
Tooth Disorder	1 (1)					
METABOLIC & NUTRITIONAL DISORDERS						
Hypoglycemia						1 (1)
CARDIOVASCULAR DISORDERS, GENERAL						
Pallor	1 (1)					
HEART RATE & RHYTHM DISORDERS						
Palpitation				1 (0)		
Tachycardia						1 (1)
RESPIRATORY SYSTEM						
Coughing		1 (1)				
Pharyngitis	1 (1)					
Respiratory infection	2 (1)					1 (1)
Rhinitis		1 (1)			1 (1)	
PLATELET, BLEEDING & CLOTTING DISORDERS						
Bleeding post vessel puncture	1 (1)			1 (0)		
URINARY SYSTEM DISORDERS						
Polyuria				1 (0)		
REPRODUCTIVE DISORDERS, FEMALE						
Dysmenorrhea						
BODY AS A WHOLE - GENERAL DISORDERS						
Accident and/or Injury	2 (1)	2 (3)				
Fatigue	1 (1)			2 (1)		2 (2)
Flu-like disorder	1 (1)			1 (0)		
Pain	1 (1)				1 (1)	1 (1)
Rigors (chills)				1 (0)		
APPLICATION SITE DISORDERS						
Anesthesia local				2 (1)		
Application site edema	1 (1)			1 (1)	1 (1)	
Application site reaction	18 (11)	5 (6)		34 (15)	15 (17)	
Injection site abcess			12 (15)		1 (1)	33 (38)
Injection site pain			1 (1)			
Injection site reaction						
TOTAL	26 (16)	11 (14)	15 (18)	52 (23)	21 (24)	37 (42)

A higher frequency of adverse events emerging from application site disorders was reported for females than for males. The proportion of adverse events by gender was

similar for Dental Gel, placebo gel and Xylocaine (with epinephrine) injection. The differential preponderance of adverse events was largely related to an increased frequency of local reactions among females.

AE Timing

The most frequent AE's started on the treatment day and included soreness, numbness, irritation, and pain at the application or injection site, bad taste and headache. Systemic adverse events by absorbed anesthetic or their metabolites would be expected to coincide with plasma peak values (C_{max}). Most of the reported studies (A1, A2, B1-4) exposed patients to Dental Gel by sequential administration around one tooth at a time followed by rinsing, just as would be expected in common dental practice. The total period of treatment was about 45 minutes. In A3 Dental Gel was instilled into all dental pockets (median 27 teeth) and was not rinsed for 3 hours. The pharmacokinetic analysis of A3 revealed plasma peak values occurring at 180-200 minutes for lidocaine and prilocaine. Metabolites of prilocaine (o-toluidine and 2, 6 xylydine reached their maxima at 280-320 minutes. These times coincide with the duration of exposure. By 600 minutes all of these agents had returned to their pretreatment baseline. Methemoglobin levels remained less than 2% throughout the study period. Based upon these pharmacokinetic findings it is reasonable to expect that most adverse events related to Dental Gel would present on the day of exposure. Immune-mediated inflammatory processes would take a longer period to fully develop, however the studies reported would not be able to detect mild inflammatory processes attributable to Dental Gel because of the overwhelming effect of SRP trauma.

Laboratory Findings

No laboratory testing was performed for reported adverse events, and no routine laboratory testing was done, except for PK sampling.

Extent of Laboratory Testing in the Development Program

The sponsor states: "in view of the long-term experience and well-known characteristics of lidocaine and prilocaine, together with the comparatively low systemic exposure associated with the periodontal gel, vital signs, ECG and standard clinical laboratories values have not been assessed in these studies." The cause of "tachycardia" reported in a patient injected with Xylocaine ® with epinephrine tartrate 12.5µg and "palpitations" in a patient administered who received Dental Gel could not be elucidated from the data provided. We agree that cardiac rhythm or serious hemodynamic effects would not be expected from Dental Gel in the setting for its proposed use. The drugs at the doses administered are unlikely to result in measurable changes in vital signs or laboratory values. Selection of Studies and Analyses for Overall Drug-Control Comparisons

7.6 Selected Studies and Analyses for Overall Drug-Control Comparisons

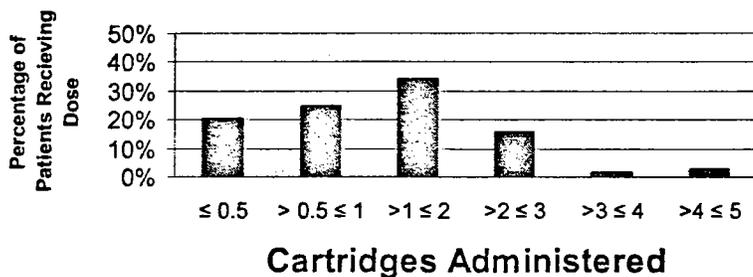
The pharmacokinetic studies (A1-A3) reflected the plasma concentrations of local anesthetics and toxic metabolites meeting or exceeding the dosing range of Dental Gel likely to be encountered in clinical practice when Dental Gel is used as the sole anesthetic

for SRP. Study A3 exposed patients to the recommended maximum dose of Dental Gel for a longer period than would be likely in actual dental use. It is noteworthy that only a small number of patients (n= 11) were so treated and they all reported adverse reactions (mild –moderate). Most of the reported adverse reactions were site related to the SRP procedure. Toxic plasma levels of anesthetic, metabolites or methemoglobin were never approached in any reported study. No patients with predisposing conditions to impaired metabolism or delayed excretion of Dental Gel or its metabolites were studied. The cumulative effect on plasma concentrations of injected local anesthetics as a rescue treatment after Dental Gel application was not independently investigated. Plasma concentrations in the setting of misuse such as topicalization of the entire oral cavity were similarly not investigated.

Placebo controlled studies appeared generally adequate in design and reflected generally similar adverse events from placebo gel and Dental Gel. Most adverse events were local and related to the site of application. A small number of adverse events appeared systemic in nature including: nausea, headache, gastrointestinal complaints, cardiovascular symptoms, musculoskeletal disorders and polyurea, dysmenorrhea and flu-like symptoms. The systemic adverse events reported only a single time among all the 559 patients studied that came from the Dental Gel group were not related to exceptionally high exposure to the drug, advanced age or concurrent disease. These events, including dysmenorrhea, polyuria and pallor were mild in nature and could neither be related nor excluded as a complication of Dental Gel administration. Interpretation of small numbers of adverse events such as two cases of “flu-like symptoms” occurring exclusively in the Dental Gel group is not possible because of the small numbers of these findings. Musculo-skeletal adverse events were reported from a small number of patients in both the placebo gel and Dental Gel groups. These events appeared well localized to specific joints or muscle groups sometimes associated with a known precipitating trauma. Gastrointestinal system disorders reported in the Dental Gel group, but not the placebo gel group covered a wide range of findings from anal skin slippage to a dislodged dental cap. Within the gastrointestinal adverse event list were three cases of nausea (1%) not reported after placebo (0%). Direct systemic effects cannot be excluded, but it is also possible that nausea was related to the unpleasant taste of Dental Gel, also reported more frequently as an adverse event in the Dental Gel group (2%) compared with placebo gel (1%).

As seen in the figure below, most of the data collected from the clinical studies (A1-3, B1-4) is associated with doses of Dental Gel appropriate for SRP of one or two quadrants of the mouth. Each cartridge containing 1.7 gm of Dental Gel is designed to cover a single dental quadrant. There were very few patients studied at the maximum recommended dose (5 cartridges) although the few patients that were studied were thoroughly exposed for longer than would be typical in clinical practice.

Frequency of Dose/ Patient in Clinical Studies n=391



**Appears This Way
On Original**

Local adverse events comparing Dental Gel to placebo gel were obtained from the results of the studies B1-B3. The dosing range extended from 0.4 to 8.7 gm for Dental Gel and from 0.4 to 5.1 gm for placebo gel. These doses cover the recommended range. The type of site related adverse events were similar between Dental Gel and placebo gel. With the exception of redness and vesicle formation the local events noted in the Dental Gel group were also represented in the placebo gel group. Oral ulcer and vesicle formation may occur in patients without periodontal disease, however these findings were observed in the patients near the treatment sites. The proximity of the lesions to the locus of treatment suggests a causal relationship that may be related to contact with Dental Gel or placebo gel. Ten patients out of 559 studied developed small ulcers or vesicles of mild to moderate severity. The table below relates the dose administered, the drug and the type of lesion.

Adverse Event	Drug	Grams	Cartridges	Study	Patient ID
Appl.Site,Ulcer	Dental Gel	1.7	1	B1	106
Appl.Site,Ulcer	Placebo	1.7	1	B1	108
Appl.Site,Ulcer	Dental Gel	0.85	0.5	B1	109
Appl.Site,Ulcer	Dental Gel	0.85	0.5	B1	208
Appl.Site,Ulcer	Placebo	0.85	0.5	B1	428
Appl.Site,Ulcer	Dental Gel	0.85	0.5	B1	706
Appl.Site,Ulcer	Dental Gel	1.275	0.75	B1	708
Appl.Site,Ulcer	Placebo	0.85	0.5	B1	808
Appl.Site,Vesicles	Dental Gel	8	4.7	A3	203
Appl.Site,Vesicles	Dental Gel	8.7	5	A3	204

Although the reported number of occurrences is small, they may represent a low incidence of a topical inflammatory reaction imparted by the formulation in Dental Gel.

Dental Gel was also compared with local injection of Xylocaine® with epinephrine tartrate 12.5µg/mL for safety. The formulation of lidocaine used for this study conducted in Belgium includes a low dose of epinephrine as a vasoconstrictor to control bleeding. A similar formulation approved for use in the United States includes epinephrine HCL in a concentration of 5 µg/mL (1:200000). Occasional post-injection headache has been attributed to systemic absorption of epinephrine. The apparently

higher dose of epinephrine in the formulation used in B4 is a consequence of the higher gram molecular weight of epinephrine tartrate compared with epinephrine HCL. The incidence of headache was similar in groups receiving Dental Gel and injected local anesthetic. Other systemic adverse events reported after administration of Dental Gel, but not injected local anesthetic included musculoskeletal disorders, taste perversion, pallor, polyuria, dysmenorrhea, accidents, and flu symptoms. Gastrointestinal disorders were more frequent in the Dental Gel than in the injection site group. Nausea, the only gastrointestinal disorder to occur in the Dental Gel and injection group, occurred with about the same incidence in both groups. The gastrointestinal adverse events that were unique to the Dental Gel group were individual cases. Individual examination of musculo-skeletal disorders and accidents from the adverse event table could not exclude, but did not suggest a relationship to Dental Gel.

Study B4 demonstrated a qualitative difference to the type of application site disorder to Dental Gel vs injected local anesthetic with a slightly smaller incidence of local adverse events overall. Pain of injection was different in character than discomfort with superficial reactions from instilled Dental Gel. Study B4 appeared to be a reasonable predictor of adverse events that could be expected if Dental Gel were to substitute for the alternative typically now employed.

7.7 120-Day Safety Update

There were no outstanding adverse events reported at 120 days.

7.8 Safety of EMLA Cream

Lidocaine 2.5% and Prilocaine 2.5% are the active ingredients in EMLA, a product which is approved in the US (December 30, 1992) as well as in > 60 other countries worldwide.

Four Astra- sponsored studies of EMLA on the oral mucosa involved 70 patients. No AE's were reported in these studies. One study included an assessment of lidocaine and prilocaine plasma concentrations, which were below toxic levels, and MetHb, which was within normal limits. In addition, six studies describing safety data of oral mucosa use of EMLA have been published in the literature. The only AE reported were 2 patients reporting burning sensation on application and few patients reporting a bad taste. Two of the studies measured plasma lidocaine and prilocaine, with all the results below toxic levels.

Fourteen clinical studies evaluated the use of EMLA cream for superficial minor surgery in genital mucous membranes and as pretreatment for local infiltration anesthesia, involving 707 patients. 628 patients received single dose 5% EMLA cream application, out of whom 378 (60%) were females. 157 patients received a single dose of 10g, and 25 patients also received top-up doses, resulting in doses between 10-15g. The primary AE's reported were application site reactions: redness (20.9%), burning sensation (16.7%) and edema (10.3%) – all mild/moderate. No SAE's were reported in these studies, and no patient discontinued secondary to an AE.

8. DOSING, REGIMEN, AND ADMINISTRATION ISSUES

The safety and efficacy of Oraqix was evaluated in nearly 400 patients, however only 11 patients were evaluated at the maximum recommended dose (8.5gm). The patients treated with the maximum dose were subjected to longer exposure than would be typical in clinical practice. All the supernormally treated reported mild to moderate adverse reactions that were self limited.

The injector assembly for Oraqix is identical to that used for submucosal injection dental procedures. There exists a possibility that a medication error may result in submucosal or even vascular injection of Oraqix.

9. USE IN SPECIAL POPULATIONS

9.1 Concurrent Systemic Disease

Administration of other local anesthetics especially of the amide type should be used with attention to the cumulative dose and the potential for exceeding maximum recommended doses. Antiarrhythmics such as tocainide and mexiletine have related structures and need to be considered when estimating the potential for additive effect.

Patients with hemoglobinopathies or certain enzyme deficiencies are at a greater risk for Methemoglobinemia. Patients taking drugs or exposed to agents associated with drug-induced methemoglobinemia should be treated with caution. Agents known to induce methemoglobinemia include sulfonamides, acetaminophen, acetanilid, aniline dyes, benzocaine, chloroquine, dapsone, naphthalene, nitrates, nitrofurantoin, nitroglycerin, nitroprusside, pamaquine, para-aminosalicylic acid, phenacetin, phenobarbital, phenytoin, primaquine and quinine.

9.2 Adequacy of By-Gender Investigation and Analyses

Pregnant women were not studied.

Elderly Population

In the Oraqix clinical program, 33/559 (6%) patients were between the ages 65-74 and 6/559 (1%) were 75 years or older. No overall differences in safety profile were noted between the elderly population and the whole study population (see table 4).

The sponsor points out that safety data is available from 20 clinical studies of EMLA cream and EMLA anesthetic disc, in which geriatric patients were included. The sponsor concludes that AE severity and frequency were found to be similar in geriatric and non-geriatric patients.

9.3 Pediatric Program Evaluation

Pediatric patients were not studied, as periodontitis is primarily an adult disease. For this reason, the sponsor has requested a waiver from pediatric studies. This will be granted, based also on consultation with medical reviewers in the dental drug division that the number of pediatric patients who can benefit is small and that the available data from adults may be extrapolated to the relevant pediatric population.

9.3 Abuse Liability

This product does not pose abuse liability concern

CONCLUSIONS, RECOMMENDATIONS AND LABELING

Oraqix has been shown to be safe and effective as an anesthetic for topical use in dental scaling and root planning. The efficacy of Oraqix is largely based upon statistical differences in pain scoring compared with placebo. The actual clinical impact in pain relief may be quite modest, but does appear to have application to adult patients who are particularly sensitive to the procedure, but are averse to having local injections.

The risk to patients from Oraqix appears small provided that it is used with good clinical judgement in patient selection. Appropriate clinical vigilance to avoid medication errors is also required and to insure correct route of administration.

Lex Schultheis, M.D., Ph.D.
Medical Officer

Nancy Chang, MD
Medical Team Leader

Bob Rappaport, MD
Acting Division Director

cc: Division File
Original NDA
HFD-170: Rappaport, etc.

This is a representation of an electronic record that was signed electronically and
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/s/

Lester Schulthers
11/20/02 07:16:31 PM
MEDICAL OFFICER

Nancy Chang
11/20/02 07:18:34 PM
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Bob Rappaport
11/20/02 07:27:49 PM
MEDICAL OFFICER



Memorandum

DATE: October 7, 2002

FROM: Fred Hyman, D.D.S. M.P.H., Dental Officer, HFD-540

THROUGH: John Kelsey, D.D.S., M.B.A., Dental Team Leader, HFD-540

THROUGH: Jonathan Wilkin, M.D., Division Director, HFD-540

TO: Kim Compton, Project Manager, HFD-170

SUBJECT: Consult to the Division of Anesthetic, Critical Care and Addiction Drug Products, HFD-170 for NDA 21-451, Oraqix™ Periodontal Gel (2.5% prilocaine, 2.5% lidocaine)

HFD-540 Consult #345

Introduction and Regulatory Background

Oraqix™ Periodontal Gel 5% is a eutectic¹ oil-in-water mixture of 2.5% lidocaine and 2.5% prilocaine. The active ingredients in Oraqix are identical to those in EMLA® cream, which was first approved in 1992 as NDA19-941 for “use on normal intact skin for local analgesia.” EMLA® Anesthetic Disc, a single-dose topical adhesive system, was approved in 1998 as NDA 20-962. The EMLA Disc contains the same active ingredients as EMLA cream, but is packaged in a cellulose sponge that is saturated with 1 gm of the cream, a single dose unit. On January 28, 2000, the additional indication “for use on genital mucous membranes for superficial minor surgery and as a pretreatment for infiltration anesthesia” was added to EMLA cream. In contrast to EMLA, either in its cream form, or the anesthetic disc, however, Oraqix has been formulated as a thermoreversible gelling system, which is a low-viscosity fluid at room temperature and becomes an elastic gel after introduction into the periodontal pocket. The use of EMLA cream for scaling is unsuitable because 1) it does not remain at the application site due to its low viscosity and 2) its opaque color makes visibility difficult in the periodontal pockets.

¹ According to the submission, the “eutectic oil-in-water” mixture creates a microemulsion consisting of micelles that solubilize the active ingredients. The release of these ingredients from the micelles is rapid and the penetration of lidocaine and prilocaine molecules into the gingival mucosa is quick and effective.

Other related dental anesthetics that are currently marketed include Hurricaine®, a 20% benzocaine gel approved for transient topical anesthesia on all accessible mucous membranes, and DentiPatch™, a topically applied patch of lidocaine that was approved in 1996 as NDA 20-575 for pre injection-site anesthesia.

Oraqix is proposed for use as a local anesthetic in periodontal pockets for _____, scaling and /or root planing in adult patients. There is a need for an effective, injection-less form of local anesthesia for scaling and root planing (SRP) because patients do not like needles or pain, yet periodontal disease is widely prevalent. In a 1989 NIDCR national survey, 47% of adult males and 39% of females exhibited at least one site with gingivitis, the mildest form of periodontal disease, as demonstrated by bleeding on probing. Even mild periodontal disease may require SRP for treatment. In numerous studies, dental patients report a dislike for injection of a local anesthetic, but want to avoid feeling discomfort in dental procedures where pain is likely to result. Oraqix is to be used in periodontal pockets during procedures such as SRP for patients who require analgesia. The periodontal pockets are to be filled with the Oraqix by means of a blunt-tipped applicator provided together with the gel, until the gel becomes visible at the gingival margin. If the effect wears off during the procedure, Oraqix can be reapplied up to a maximum recommended dose of five cartridges at one treatment session.

Summary of NDA Submission

This NDA was submitted to the Division of Anesthetic, Critical Care, and Addition Drug Products (HFD-170) on January 22, 2002. The Clinical portion consists of 28 volumes, which contains integrated summaries of efficacy and safety, as well as detailed study reports. These include the full study reports for four sets of trials labeled A, B, C, and D. Trials B1, B2 and B3 are pivotal clinical trials; B4 is an open label study to evaluate subject preferences of gel to injection; and B5 is not a clinical trial, but rather a further analysis of B1, B2 and B3. Studies A1, A2 and A3 are clinical pharmacology and pharmacokinetics studies that evaluate anesthetic onset of the gel and plasma levels for safety. Studies D1 and D2 examined consumer preferences, including subject attitudes and willingness to pay for treatment. Miscellaneous studies C1, C2, C3, C4, C6, C7, C8, C9 and C 10 are study reports that were conducted in the past with EMLA cream, and were submitted for supporting documentation. The focus of this consult is the review of pivotal trials B1, B2 and B3 for safety and efficacy, and studies A1, A2, and A3 for safety.

Requested Information in the Current Consult:

In correspondence dated May 17, 2002, HFD-170 requested a consult from the Dental Team in HFD-540 to review the NDA from a dental perspective with five questions in mind. In this section of the review, these five questions will be restated and answered. Following this section, comments and recommendations will be made to the sponsor's proposed labeling, as well as several other related miscellaneous comments.

Please note that it is not the intent of this consult to provide recommendations for regulatory action of this drug. HFD-540 is providing thorough answers to the questions

posed in the consult in a way that reflects the expertise of a clinical reviewer who is familiar with dental drugs and procedures. This includes opinions on the clinical significance of treatment and actual use in clinical practice. However, since the indication of this drug is to reduce pain associated with a dental procedure, rather than to treat or prevent any dental disease, the regulatory decision will need to be in accordance with the policies of HFD-170. A review of the minutes of the sponsor meetings with HFD-170 reveals prior discussions about criteria for approval that did not involve HFD-540.

1. *Is the study design appropriate?*

Response:

This multiple dose, double blind, randomized placebo-controlled, parallel group, multi-center study is well designed and capable of meeting the sponsor's objectives. Fortunately, there was no ethical concern to prevent including a placebo group for this trial, which is important in trials utilizing a subjective endpoint such as discomfort. These subjective endpoints often demonstrate a very high placebo effect (30-50%), making it difficult to demonstrate efficacy without a placebo group. The use of parallel groups as opposed to cross-over design minimized the potential for loss of blinding and any carryover effect from the drug. One design flaw that will be discussed in further detail later in this review is that the inclusionary and exclusionary criteria in studies B1 and B2 did not screen for subjects who experienced sufficient susceptibility to pain resulting from dental scaling procedures to have required this anesthetic agent. As a result, those two studies did not achieve the 15% reduction in pain levels that was the sponsor's goal.

2. *Do you agree with the safety and efficacy endpoints?*

Response:

Efficacy Endpoints:

The remarks in this section of the consult will provide an opinion about some difficulties associated with the sponsor's choice of their endpoint; however, prior to the submission of the NDA, HFD-170 had conducted discussion with the sponsor about the endpoints. At a pre-NDA meeting between HFD-170 and the sponsor on April 24, 2001, the clinical reviewer, Dr. Hal Blatt, and the Division Director, Dr. Cynthia McCormick acknowledged that studies B1 and B2 had a smaller than desired effect size. According to the minutes, "Drs. Blatt and McCormick emphasized that Study 007 [later known as B3] is critical for the application." As will be discussed in this section, the sponsor's secondary outcome variable (percentage of subjects who reported "no pain" or "mild pain") might have been a better choice for primary outcome variable than the VAS pain scale, as the former has built-in clinical significance for the dental practitioner. The VAS for pain requires greater subjectivity to determine the critical amount of reduction and is dependent upon other factors such as the level of initial pain.

The primary efficacy endpoint in all three trials is the subjects' self-assessed measurement of pain on a 100-mm VAS scale that ranges from "no pain" on the left to "worst pain imaginable" at the extreme right. The primary efficacy variable was compared between the test group and the placebo group using a rank sum test, stratified by center. The sponsor had prespecified that a difference of 15 mm. would be considered a clinical success, although it appears from the meeting minutes that the 15-mm improvement in pain scores was a goal for the sponsor, rather than an agreed-upon minimum for approval. Although the sponsor showed statistical significance in all three pivotal trials, they were only able to show a difference of 15 mm. in one of these studies.

The inability of the sponsor to meet a 15-mm. VAS improvement in two of the three studies requires further examination during the review process. In hindsight, the sponsor was unrealistic and overestimated the degree of pain that a typical patient would experience for a scaling procedure. In study B1, the average subject in the placebo group reported a median overall VAS of 17 mm. and in study B2, the median overall number was 13 mm. With an average of 13 –17 mm. on the VAS scale with a placebo, it is clearly impossible to reach a 15-mm. improvement. Although both B1 and B2 showed statistically significant differences in the VAS (Study B1: 17mm. in the placebo group vs. 7 mm. in the Oraqix group and Study B2: 13 mm. in the placebo group vs. 5 mm. in the Oraqix group), neither reached a 15 mm. difference. However, in Study B3, the sponsor recruited only subjects who reported 30 mm. on the VAS during a trial SRP upon screening, and they were able to demonstrate greater than 15-mm. improvement with statistical significance during the trial. In Study B3, the placebo group reported 27 mm. during the trial, and the Oraqix group reported 11 mm. In typical practice, the results from B3 are more realistic as dentists will only use the product during procedures that they know or suspect will cause the patient measurable pain.

There are two secondary efficacy measurements – overall verbal rating scale and the need for rescue anesthetic. The 5-point VRS is the comparison of percentages of subjects who report "no pain" or "mild pain" during the procedure on a verbal rating scale that ranges from "no pain" to "very severe pain". Both measurements are made after all teeth in the selected quadrant have been scaled/root planed.

For this proposed usage, the VRS secondary endpoint is more descriptive than the VAS primary outcome and has more interpretive value for the average dental clinician. Whereas the numbers from the VAS are difficult to interpret, the percentage of subjects who report pain or mild pain is clinically meaningful and easy to interpret. In terms of pain relief and prevention, achievement of "no pain" or "mild pain" is the clinician's goal; the comparison of those who reported that level on test product versus placebo allows for an educated decision about use. The VRS results showed that in studies B1 and B3, there were statistically significant differences between the test and placebo groups as follows:

B1: Placebo: 64%; Oraqix group: 90%
B3: Placebo: 48%; Oraqix group: 70%

In study B2, the placebo group had an overall score of 76% and the Oraqix 78%, which did not reach statistical significance in its difference.

Recommendations are made in the labeling section of this consult to incorporate these results into the revised label, should the drug be approved.

Safety

The safety data were obtained from seven studies conducted in four countries – Belgium, Canada, Sweden and the US. A total of 559 subjects were evaluated for safety, of which 391 were exposed to Oraqix and 168 to the placebo gel. Each subject was examined for general appearance of the oral cavity before and after administration of Oraqix. The sponsor intentionally did not collect vital signs, ECG, or standard clinical laboratory values due to their belief that lidocaine and prilocaine have been well studied in the past and there is low systemic exposure associated with Oraqix. Rather, they conducted pharmacokinetic studies in which they demonstrated that plasma levels of lidocaine, prilocaine and their metabolites are well under levels that are known to be unsafe.

Pharmacokinetic study A3, which was conducted to evaluate plasma concentrations of lidocaine, prilocaine, *o*-toluidine, and methemoglobin (metHB) revealed that all values were well below toxic levels. Following administration of the highest recommended dose of Oraqix, the plasma concentrations of lidocaine and prilocaine were well below toxic levels, and *o*-toluidine was significantly below those known to have mutagenic effects *in vitro*. Since the metabolites of *o*-toluidine are known to potentially induce formation of metHB, the metHB values were assessed in 11 subjects who received 8.0 –8.7 g Oraqix. All had normal values of below 2% whereas at least 10% metHb is needed before clinical signs of methemoglobinemia are seen.

The most frequent AEs in all seven studies were local reactions in the oral cavity, occurring at low and similar frequencies (approximately 20%) after exposure to Oraqix and placebo. These symptoms, which included burning, irritation, bleeding, numbness, redness, and pain, are consistent with local irritations normally found after SRP procedures. Events reported by System Organ Class do not provide a signal of any systemic events associated with the use of Oraqix. All events were non-serious, mostly of mild to moderate intensity. In addition, no subject died for any reason, and no subject discontinued treatment with the investigational product due to an AE in any study.

From a standpoint of the dental review team, the safety evaluation has been sufficient to demonstrate the safe use of this product if used as directed. There are no local reactions that give a signal of causal association with Oraqix, and pharmacokinetic evaluation revealed low levels of absorption with resulting safe

2 Page(s) Withheld

2 § 552(b)(4) Trade Secret / Confidential

 § 552(b)(4) Draft Labeling

 § 552(b)(5) Deliberative Process

Indications and Use:

A revision has been provided for this section to help clarify that not all patients will benefit from Oraqix and that procedures milder than SRP have not been studied. Also note that "root planing" is misspelled in the proposed label.

Currently proposed wording:

"Oraqix is indicated in adults for localized anesthesia in periodontal pockets for _____, scaling and/or root planing (sic)."

Recommended Revision:

"Oraqix is indicated for adults who require localized anesthesia in periodontal pockets during scaling and/or root planing."

Adverse Reactions:

The first statement in this section is:

"No adverse reactions that could be ascribed to Oraqix have been reported."

Similarly, later in that same section, under the subsection, "Adverse Events in Clinical Studies" it states:

Although true, this leads the clinician to believe that there is no relationship. With small numbers, it is equally likely that there may be some relationship. An alternative would be to eliminate the first statement, and either eliminate the current statement, or revise it to:

Overdosage

In this section, the first sentence is one that the clinicians was referred to from the Warnings and Precautions section regarding the additive effect of injectible local anesthetic agents in combination with Oraqix. Since it is not uncommon to combine blocks with infiltration for more profound soft tissue anesthesia during dental procedures, it will be of more value to the average dental clinician to be specific about the maximum safe levels when used in combination, rather than requiring the dentist to go to another source to locate this information. In addition, the Hurracaine label mentions methylene blue as the recommended treatment for methHB, which is absent on this proposed label.

Additional Comments:

1. This drug is a combination of two drugs, prilocaine and lidocaine. In accordance with FDA's combination policy, the sponsor must demonstrate that each component makes a contribution to the overall product. HFD-170 has already agreed to accept the combination policy demonstration from the earlier EMLA approvals to fulfil that requirement.
2. Although the product was only tested on one quadrant during the clinical trials, there is no reason to believe that use of the product for SRP on the entire mouth would be less effective. As long as the five syringe maximum is maintained, the additional teeth subjected to SRP should not pose a safety issue. As with any dental procedure, however, it is the responsibility of the dentist to assess if the procedure is causing undue fatigue or other physical or emotional stress when deciding the time constraints on any procedure.
3. The syringe and cartridge system for administering Oraqix should be evaluated since it is unique as compared to syringes for injection or syringes for irrigation. Either HFD-170's assigned CMC reviewer or FDA's Center for Device Evaluation and Radiological Health, Dental Devices Branch could review the syringe and cartridge system.

cc: HFD-540/Dental Consult File
HFD-540/DD/Wilkin
HFD-540/DTL/Kelsey
HFD-540/DO/Hyman/Gilkes
HFD-540/PM/Kozma-Fornaro

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/s/

Fred Hyman
10/28/02 11:19:25 AM
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John Kelsey
10/29/02 09:14:52 AM
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Jonathan Wilkin
11/3/02 11:00:22 AM
MEDICAL OFFICER

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

DATE: September 27, 2002

FROM: John V. Kelsey, D.D.S., M.B.A.
 Dental Team Leader, Division of Dermatologic and Dental Drug
 Products (HFD-540)

THROUGH: Jonathan Wilkin, M.D.
 Director, Division of Dermatologic and Dental Drug Products
 (HFD-540)

SUBJECT: Consult Request for NDA 21-451, Pediatric Waiver Request for
 Oraquix™ Periodontal Gel

TO: Kimberly Compton, Project Manager, Division of Anesthetic,
 Critical Care and Addiction Drug Products (HFD-170)

Dental Officer's Review of NDA 21-451
Pediatric Waiver Request – 2nd

Drug: Oraquix Periodontal Gel
(lidocaine 2.5% and prilocaine 2.5%)

Consult Number: 353

Sponsor: DENTSPLY Pharmaceutical

Submission Date: July 12, 2002

Received Date: July 16, 2002

Review Date: August 1, 2002

Proposed Indication: Local anesthesia
in periodontal pockets for dx procedures

CSO: MJ Kozma-Fornaro

Pharmacologic Category: Dental
anesthetic

Background:

This is a follow-up consult to a consult provided to the Division of Anesthetic, Critical Care and Addiction Drug Products (HFD-170). The original consult, which was completed December 26, 2001, addressed a pediatric waiver request from AstraZeneca

LP, for IND 52,677. AstraZeneca subsequently sold this product to DENTSPLY Pharmaceutical, which has submitted an NDA (21-451) for the product.

This product is a local anesthetic gel to be used to anesthetize the gingiva in patients undergoing periodontal procedures (e.g., scaling and root planing). The material sent by HFD-170 for review is an NDA amendment from DENTSPLY Pharmaceutical, which provides additional data about the prevalence of periodontal disease in children and asks the Agency to reconsider its denial of the pediatric waiver request in light of this new data. The new data comes from databases of procedures performed in private dental practices maintained by the American Dental Association and Delta Dental of Pennsylvania.

Discussion:

A pre-NDA meeting of the Sponsor and HFD-170 was held on 4/24/01. At that meeting the Sponsor asked if the Division could be expected to grant a pediatric waiver for the product. Dr. Hal Blatt, a dentist assigned to HFD-170 at that time, responded that the product would likely be valuable in a number of indications that affected children and said that the product should be studied in children to age 6. The specific pediatric indications mentioned by Dr. Blatt were:

The Sponsor's response to Dr. Blatt's comments were prepared by Steven Adair, DDS, MS, Director of Advanced Education, Department of Pediatric Dentistry, Medical College of Georgia.

He argued that juvenile periodontitis is a relatively rare disease. He estimated that 80,000 children in the U.S. have the condition and argued that all of those will not seek treatment. He further argued that scaling and curettage is not universally employed to treat this condition. The scaling and curettage would be the aspect of treatment for which the anesthetic gel would be useful. He also argued that, "delaying treatment for the sake of enrolling the patient in a clinical trial would jeopardize the periodontal health of some patients and would pose an unacceptable risk." He noted that, "when required, there are other means available to obtund the discomfort of scaling and curettage." Finally he reported that scaling may actually prove harmful to patients.

He concluded that the limited number of patients would make it difficult to conduct a clinical trial in these patients.

This reviewer responded that in fact 80,000 may be a low estimate, as it is based on the disease prevalence in whites. Blacks and Hispanics are reported to have much higher

Reviewer's Comment: This reviewer is not aware of physiological differences between adults and children age 6 and above that would be expected to use this product that would be expected to result in a different response between the groups. Similar products have been widely used in both adults and children with no apparent differences in efficacy. Considerations of safety and labeling issues will be left to the reviewers in HFD-170.

Conclusion:

It is this reviewer's opinion that efficacy data on Oraquix from adults can be extrapolated to the pediatric population in which this product would be expected to be used (age 6 and above). A waiver of pediatric efficacy studies can be granted on that basis. Consequently, the data in the current submission concerning the number of children who are treated for periodontal indications has not been reviewed. Safety considerations regarding use of this product in children and related labeling issues will be left to HFD-170.

Recommended Regulatory Action:

It is the opinion of this reviewer that a pediatric waiver request should be granted based on the fact that adult data for Oraquix can be extrapolated to the pediatric population down to age 6.

John V. Kelsey, DDS, MBA

cc: NDA 21-451
HFD-540/Div File
HFD-540/TL/Kelsey
HFD-540/DO/Gilkes/Hyman
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/s/

John Kelsey
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9/29/02 03:00:24 PM
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