CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

21-486

MEDICAL REVIEW(S)

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 Tel:(301)443-3741

DIVISION DIRECTOR REVIEW AND BASIS FOR APPROVAL ACTION

DATE:	October 26, 2004
DRUG:	Lidocaine HCl 2% and Epinephrine 1:100,000 Solution for Topical Iontophoresis
NDA:	21-486
NDA Code:	Type 4S NDA
SPONSOR:	EMPI, Inc.
INDICATION:	For the iontophoretic production of local analgesia for superficial dermatological procedures such as venipuncture, shave removals and punch biopsies

EMPI, Inc. submitted NDA 21-486 in support of marketing approval for their lidocaine 2% solution with 1:100,000 epinephrine to be used with their approved Dupel iontophoretic topical delivery system. This NDA was submitted as a 505(b)(2) application with an indication for [redacted] and a dosing recommendation of up to 80 mA · minute. These two features of the application differed substantially from the RLD, Iontocaine. Iontocaine is only indicated for the production of local dermal analgesia by iontophoresis and only at a dose of 40 mA · minute. The sponsor was informed that they would be required to pay a user fee due to these differences. In order to not have to pay the user fee the sponsor agreed to change the indication [redacted] to be consistent with the RLD. Nevertheless, the application was not filed due to problems with the interpretability, completeness and legibility of the dataset. Significant problems with the quality of the data were again noted at the time of resubmission. The Division extended a number of offers to meet with appropriate representatives from the company in order to assure the quality of the data for review.

However, the sponsor turned down the Division's invitations, explaining that they were capable of making the necessary corrections in a timely manner.

Review of the CMC portion of this application was completed by Jila H. Boal, Ph.D. Review of the pharmacology and toxicology data presented in this application was completed by Adam M. Wasserman, 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 Lisa A. Kammerman, Ph.D. Consultation on this application was obtained from the Division of Drug Marketing, Advertisement and Communication and the Office of Drug Safety. The sponsor has submitted five studies in support of efficacy. A detailed review of these studies and of the safety of the product was performed by Arthur Simone, M.D., Ph.D. Nancy Chang, M.D. provided a supervisory clinical review.

Efficacy:

The sponsor submitted five single-site clinical studies in support of a finding of efficacy. Dr. Chang's Table 1, reproduced below, summarizes the clinical studies submitted with this application:

Table 1: Clinical Studies Overview

Type of Study	Study Number	Phase	Dose(s) mA·min	Deliv Electrode Size(s) Cm^2	Number of Treatments L=Tradename P=Placebo I=Iontocaine
PK	96-08.0	1	80	—	3 L
			80	10.1	3 L
			80	8.1	3 L
Shave Removal Punch Biopsy Analg Duration	97-07.0	2	40	—	7 L; 8 P
			80	8.1	9 L; 8 P
			80	—	8 L; 8 P
Shave Removal	99-02.0	3	40	8.1	20 L
			60		60 L; 20 P
			80		20 L; 20 P
Venipuncture Adult	99-07.0	3	20	8.1	60 L/P
			30		20 L/P
			40		20 L/P
Venipuncture Adult	00-1-03.0	3	20	10.1	30 L/P
					29 I/P
Dermal Irritation	01-1-06.0	1	80	8.1	48 L

The placebo treatments were identical to the Tradename treatments in terms of the electrode size and iontophoretic doses administered, but differed in that lidocaine was not present in the solution. Epinephrine was included in the placebo preparations.

Each of the efficacy trials was a double-blind study that compared the proposed product to placebo and/or an active control. A current of 4 mA was used in each of the studies. The duration of treatment ranged from 5 to 20 minute, corresponding to total doses ranging from 20 mA · minute to 80 mA · minute. The size of the electrodes ranged from 8.1 cm^2 to [redacted]

[redacted] The other four studies evaluated adults undergoing venipuncture (healthy volunteers), or undergoing punch biopsy (healthy volunteers) or shave removal of superficial skin lesions (seborrheic keratosis or benign nevocellular nevi).

In Phase 1 of Studies 97-07 and 99-02, patients were randomized to study drug or placebo. Within 10 minute of treatment, the subjects underwent needle prick testing for anesthesia. Subjects who reported pain were considered treatment failures and were not included in the second phase of the study. Subjects who requested supplemental analgesia during shave removals were also considered treatment failures. No supplemental analgesia was allowed for punch biopsy procedures. The primary efficacy outcome measure was a comparison of treatment failure rates.

In Study 97-07, none of the placebo subjects passed the pinprick test and, thus, there was no group in the second phase of the study that would allow a thorough comparison of the efficacy of Tradename to a control in the evaluation of analgesia in patients undergoing shave removal or punch biopsy. Of note, 33% of the Tradename-treated subjects also did not pass the pinprick test in this study, and 2 of 3 subjects eligible to request supplemental analgesia did so. However, a statistically significant treatment effect was found for the primary efficacy measure, treatment failure rates.

Study 99-02 consisted of two parts. The first part of the study was designed to identify the optimal dose for the second part of the study. Ninety percent of the placebo-treated subjects failed the pinprick test in Phase 1 of Part 1. Twenty-five percent, 10%, and 15% of the 40, 60 and 80-mA·minute Tradename groups, respectively, failed the pinprick test. In Phase 2, only one subject (treated with Tradename) required supplementary analgesia. There was a statistically significant treatment effect for the Tradename-treated subjects compared to the placebo-treated subjects on the primary outcome measure, treatment failure.

The 60-mA·minute dose was associated with the highest success, the lowest incidence of AEs, and the lowest VAS score (although not statistically significantly so) in Part 1, and was, therefore, selected for Part 2 of the study. In Phase 1 of Part 2, 92.5% of the active group passed the pinprick test, compared to 25% of the placebo group. Two patients in the active group required supplemental analgesia. There was a statistically significant

treatment effect for Tradename 60 mA · minute compared to placebo based on the primary outcome measure, treatment success. The secondary outcome measures were supportive of that result.

Studies 99-07 and 1-03 both evaluated venipuncture in healthy adult volunteers. In Phase 1of Study 99-07, subjects were administered either 20, 30 or 40-mA·minute doses on one arm and a matching placebo dose on the other arm. There was a statistically significant overall treatment effect on the primary outcome measure (VAS pain scale) for the Tradename groups compared to the placebo group. A statistically significant treatment difference was not found between the Tradename dose groups. The difference between Tradename and Placebo was statistically significant for the 20-mA·minute dose (95% confidence interval: -25.4, -8), but not for the other two doses.

In Phase 2 of 99-07, an additional 40 subjects were enrolled and evaluated in a confirmation of the sponsor's choice of the 20-mA · minute dose as optimal which they based on the results of Phase 1. (The 20-mA · minute dose resulted in the largest difference of the three doses when compared to placebo on the VAS in Phase 1.) Although the results of the primary outcome analysis did not show a statistically significant treatment effect for the 20-mA · minute dose compared to placebo, there was a two-fold difference in the VAS results, i.e., 24 versus 11 for placebo and lidocaine, respectively.

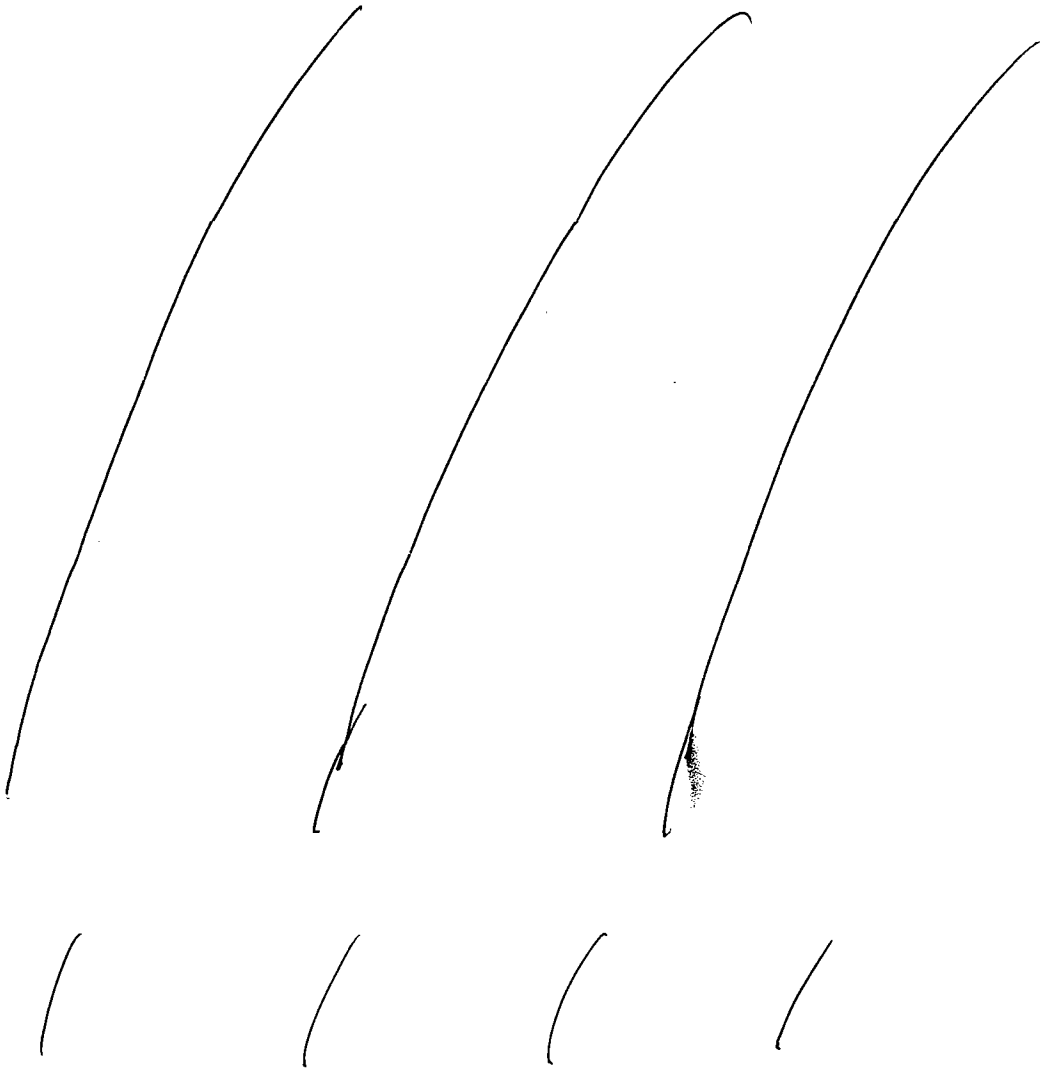
Dr. Kammerman raises concerns regarding the analysis performed by the sponsor for both phases of this study. She notes that the sponsor did not adjust for the fact that subjects were actually randomized three times: once to one of three treatment groups (for Phase 1 only), once to one of two treatment sequences (placebo applied to left arm and active comparator to right arm, or active comparator applied to left arm and placebo to right arm), and once to one of two sequences for blood draw (left then right arms or right then left arms). Nevertheless, when she reanalyzed the data using a linear model with appropriate terms, the difference between the Tradename and placebo groups remained statistically significant in both phases.

The secondary outcome measure, a global satisfaction score, was generally supportive of the primary outcome results.

Dr. Simone raises the concern that the VAS differences, while statistically significant, were small enough to be of questionable clinical significance. He also notes that the needle gauges used for the venipunctures were neither specified in the protocol, nor recorded in the CRFs. Finally, he expresses concern regarding the possibility that the placebo may have provided analgesia in a dose-dependent fashion. He bases this last speculation on a finding of decreasing VAS scores for increasing iontophoretic doses in the placebo-treated subjects. He notes that this unexpected effect could have resulted in the lower dose of the active drug falsely appearing to be more effective than the higher doses, and that, either the lidocaine is not contributing significantly to the efficacy, or only background noise is being captured and a clinically meaningful effect was not achieved.

Study 1-03 compared treatment with Tradename 20 mA · minute or Iontocaine 40 mA · minute, (each also compared to placebo), in a non-inferiority design, cross-over trial. At each of the two visits, subjects received an active treatment on one arm and a placebo treatment on the other. Although the comparison of the means between the two treatment groups was not statistically significant, the lower end of the 95% confidence interval on the treatment difference exceeded the protocol-specified delta of 10 points and, therefore, non-inferiority to Iontocaine was concluded. The secondary outcome measure, a global satisfaction score, was supportive of this finding.

Dr. Simone raises the same concern regarding the clinical significance for this study that he raised for Study 99-07. The treatment effect was small, less than 30 mm for the large majority of subjects. Additionally, he notes that the dose of Iontocaine (40 mA · minute) is half of the labeled dose for that product; and that the electrodes used in this trial were 25% larger than [redacted] possibly producing a weaker effect.



Clinical Safety:

The following conclusion is from Dr. Simone's clinical review addendum, page 3:

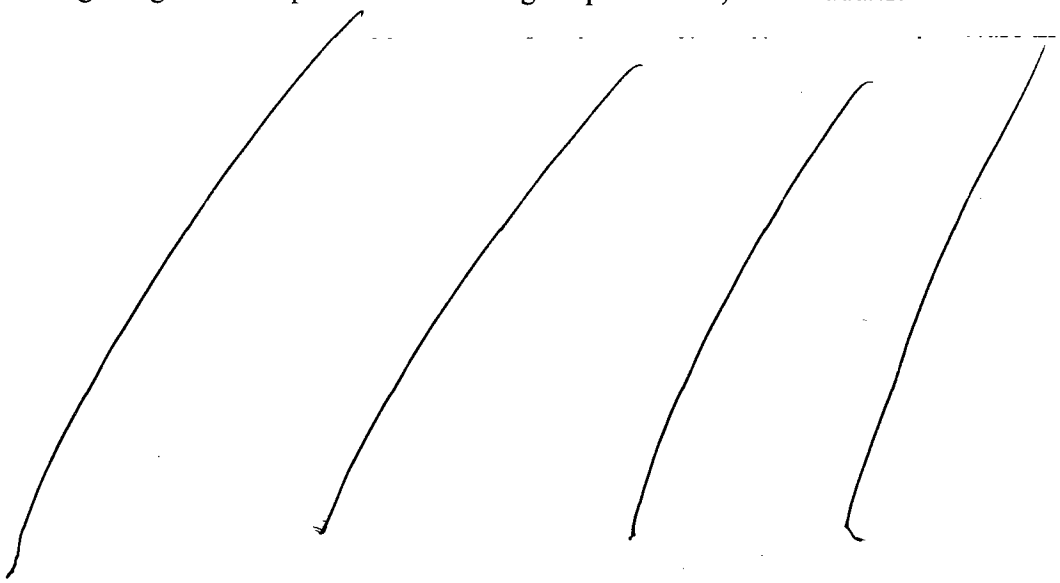
> In summary, the Empi iontophoretic drug product was associated with blanching and mild to moderate erythema. Adverse events were mostly mild; none were worse than moderate, and the nature and frequency of adverse events were consistent with those of the other approved iontophoretic lidocaine-epinephrine combination products. Adverse events generally resolved within two days although some persisted up to four days. Most adverse events required no treatment. Most frequently, the treatments consisted of discontinuing iontophoretic treatment due to pain or discomfort and supplementing the analgesia that was provided by the iontophoretic treatment.

Nomenclature:

The sponsor's original request for a Tradename received a "not-recommended" assessment from the Division of Medication Errors and Technical Support (DMETS). DMETS made this determination based upon look-alike and sound-alike confusion concerns related to other approved lidocaine containing products.

Discussion:

The sponsor has submitted one study that demonstrates the efficacy of Tradename in providing analgesia for venipuncture in adults and two studies that establish efficacy in providing analgesia for superficial dermatological procedures, also in adults.



An additional venipuncture study in adults was also flawed. That study compared Tradename to the RLD, but using a dose of Iontocaine that is half that of the dose listed in the approved label. The validity of this study, designed as a non-inferiority comparison, is thus brought into question.

The clinical and statistical review teams have also raised concerns regarding the validity of the studies submitted in support of efficacy for superficial dermatological procedures in adults. These concerns are primarily centered on the ability of the studies to provide assay sensitivity and the clinical significance of the results. While I recognize that the design of these studies raises some questions in regard to assay sensitivity, I am convinced that the results do support the effectiveness of Tradename in providing analgesia for these procedures. Most of the subjects who demonstrated anesthesia in the initial phase of the studies were able to tolerate procedures that would be expected to be quite painful. Although many of the placebo subjects were also able to tolerate these procedures, those subjects also experienced no discomfort during the first phase of the study, indicating a high degree of stoicism in the face of mild to moderate pain. While these results could indicate an absence of significant discomfort from the procedure and/or an absence of a substantial comparator group, I think that it is more likely that they represent evidence of a real effect in the less stoic subjects.

In addition, although the effect as measured by comparisons of the means of the results was small, this fact does not take into account the actual effect in individual patients. Clearly, some subjects experienced important levels of analgesia with Tradename, and, therefore, approval of this product will likely provide a clinically relevant effect for some patients, without any risk of clinically important safety concerns.

While the results of these studies may not fully address the questions raised by the review team, the weight of evidence provided in the application and the additional support provided by the RLD in this (b)(2) application, when assessed in light of the absence of any significant toxicity of the product, do allow a determination that Tradename will provide a reasonable level of effectiveness for some patients without significant risk of clinically relevant adverse events.

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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Bob Rappaport
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Clinical Review and Evaluation

NDA# (serial):	21-486 (N-000-BZ)
Drug Name (generic):	[not determined] Lidocaine HCl 2% and Epinephrine 1:100,000 Topical Solution for Iontophoresis)
Sponsor:	Empi, Inc.
Indication:	/ / /
Type of Submission:	Response to Request for Additional Information
Date of Submission:	October 11, 2004
Date of Receipt:	October 12, 2004 (CDER stamp date)
Reviewer:	Arthur Simone, MD, PhD
Project Manager:	Lisa Malandro
Review Date:	October 26, 2004

Background:

This submission was made in response to requests by the Division over the course of the review cycle in general and by email on August 20, 2004, in particular, to provide all adverse event information for all human subject studies in a single table. The table was to include the following information.

1. Subject ID and study number
2. Subject demographics including age, gender and race
3. Iontophoretic treatment (Lidopel, placebo, Iontocaine)
4. Iontophoretic dose – both nominal and actual delivered dose
5. Delivery electrode size
6. Site of treatment including placement site of return electrode
7. Adverse event – verbatim description and MEDDRA term
8. Site of adverse event
9. Severity of adverse event
10. Onset time of adverse event relative to iontophoretic treatment and dermatological procedure
11. Type of dermatological procedure
12. Duration of adverse event

13. Treatment provided for the adverse event

In addition, if the information was to be submitted in paper form, the data were to be sorted as follows.

- By subject
- By adverse event type
- By iontophoretic treatment
- By iontophoretic dose
- By study
- By subject demographics

Content of Submission:

The Sponsor provided a paper submission with tables sorted as requested. A total of 113 adverse events were listed in each of the tables. Adverse events were listed with verbatim descriptions and were classified as either "local dermatological" or other. There was no classification using MEDDRA terms or a similar classification system. (The Sponsor was excused from such classification of adverse events during a telecon with the Division.)

Comments:

The Sponsor's submission was compared to the ISS safety table created by this reviewer for assessing product safety in the NDA review with the following findings.

1. The Sponsor's submission did not include the 50 incidents of blanching which were recorded as adverse events in two of the clinical studies.
2. All non-blanching adverse events were identical between the Sponsor's submission and the reviewer safety table.
3. The Sponsor did not distinguish some adverse events by treatment drug used listed it as due to as "Empi Lidocaine, Placebo; Iontocaine, Placebo." This reviewer separated the treatments by onset time of adverse events and attributed them to active treatment or placebo, where appropriate, by working backwards from the data listings detailing which treatment was applied to each arm.
4. The iontophoretic dose for which adverse events occurred were the same between the two safety databases, but it should be noted that the NDA review used the actual dose delivered, not the nominal dose, in assessing safety. This resulted in three 40-mAmin nominal dose adverse events being reported as occurring at 20 mA·min (actual doses were [redacted] mA·min).
5. The race of one subject was erroneously recorded as Caucasian when it should have been listed as black in the reviewer's database. This was due to the id number, 11071, which was used in two different trials. The error in demographic data was not expected to influence the safety assessment as the majority of subjects were Caucasian females and too few minority subjects were evaluated in the studies to make meaningful comparisons

among groups.

Conclusions:

The datasets submitted by the Sponsor corroborate the reviewer constructed table used for the safety analysis in the NDA review. Based on the submission, the NDA review safety findings apply for the types and frequencies of adverse events that occurred as well as the iontophoretic doses, patch sizes and drug treatments with which they were associated. Comments in the NDA review regarding subject demographics are not significantly altered by the discrepancy noted above.

In summary, the Empi iontophoretic drug product was associated with blanching and mild to moderate erythema. Adverse events were mostly mild; none were worse than moderate, and the nature and frequency of adverse events were consistent with those of the other approved iontophoretic lidocaine-epinephrine combination products. Adverse events generally resolved within two days although some persisted up to four days. Most adverse events required no treatment. Most frequently, the treatments consisted of discontinuing iontophoretic treatment due to pain or discomfort and supplementing the analgesia that was provided by the iontophoretic treatment.

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/s/

Arthur Simone
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MEDICAL OFFICER

Modified as requested.

Bob Rappaport
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MEDICAL OFFICER

CLINICAL REVIEW

Application Type:	New Drug Application
Submission Number:	021-486
Submission Code:	N-000
Letter Date:	February 8, 2002
Stamp Date:	February 11, 2002
(Extended) PDUFA Goal Date:	October 26, 2004
Reviewer Name:	Arthur Simone, MD, PhD
Review Completion Date:	September 30, 2004
Established Name:	iontophoretic lidocaine 2% with epinephrine 1:100,000
(Proposed) Trade Name:	Lidopel
Therapeutic Class:	Local anesthetic
Applicant:	Empi, Incorporated
Priority Designation:	standard
Formulation:	transdermal system
Dosing Regimen:	single dose
Indication:	
Intended Population:	adults

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1 EXECUTIVE SUMMARY

1.1 Recommendation on Regulatory Action

Based on confounded efficacy results for the lower iontophoretic doses studied, i.e., 20 to 40 mA·min, an insufficient safety and efficacy database to support iontophoretic doses greater than 40 mA·min, limited characterization of pharmacodynamics, and a lack of data to satisfy the combination rule, an approvable action is recommended in response to this New Drug Application.

Responses to the deficiencies delineated in section 9.5 of this review in conjunction with additional data that adequately support efficacy and safety should be required and should be sufficient to support an approval action.

1.2 Recommendation on Postmarketing Actions

1.2.1 Risk Management Activity

This product has minimal to no abuse potential. Furthermore, it is likely that the use of this product would be limited to healthcare facilities, including the offices of private practitioners, and those home-care health providers who perform invasive therapies or blood collections. Therefore, risk management activity was not required as part of the development plan for this drug product.

1.2.2 Required Phase 4 Commitments

Pediatric studies assessing the safety and efficacy in children —
are required. All age groups — should be evaluated absent
justification for doing otherwise. The study plans should be submitted to the agency

1.2.3 Other Phase 4 Requests

None are recommended.

1.3 Summary of Clinical Findings

1.3.1 Brief Overview of Clinical Program

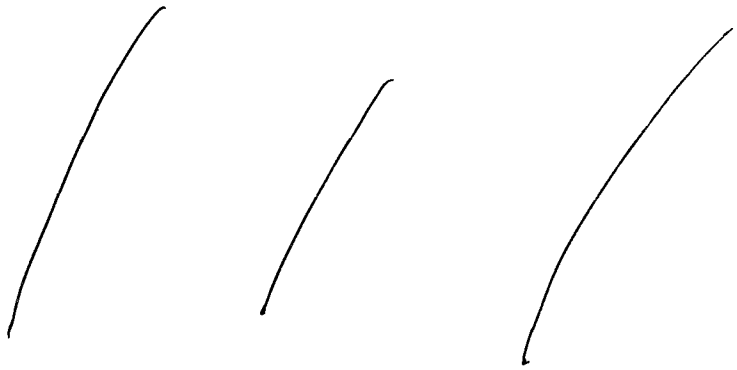
The Sponsor broadly based its clinical program on the one used by Iomed, Incorporated to support its NDA (20-530) for Iontocaine® which was approved in 1995 for the "production of local dermal analgesia by iontophoretic application of lidocaine 2% with epinephrine 1:100,000." For Lidopel, seven studies were conducted involving a total of 413 human subjects of whom, 325 received one or more iontophoretic treatments with Lidopel. A single Phase 1 study assessed pharmacokinetics associated with three different delivery patch sizes in a total of 9 subjects. A single Phase 2 study assessed efficacy with use for two types of dermatological procedures, comparing two delivery electrode sizes and two iontophoretic doses. A total of 48 subjects participated in the Phase 2 study. Phase 3 trials included one study of a single dermatological procedure, shave removals of superficial skin lesions, involving 140 subjects and three iontophoretic doses; one adult — venipuncture study involving 100 respectively; and a non-inferiority trial utilizing a single iontophoretic dose and comparing Lidopel to Iontocaine analgesia for 30 subjects undergoing venipuncture. A repeated-exposure study conducted on 12 subjects evaluated irritation associated with two sequential patch applications at two skin sites using a single iontophoretic dose.

1.3.2 Efficacy

Five clinical trials were used to assess the efficacy of Lidopel in providing analgesia for punch biopsies, shave removals of superficial dermatological lesions, and venipuncture. The trials which evaluated Lidopel use for punch biopsies and shave removals used a needle-prick test prior to the dermatological procedure to assess adequacy of analgesia. Use of the needle-prick test eliminated all of the control subjects scheduled to undergo punch biopsy in Study #97-07.0, the only study that examined punch biopsy procedures. No evidence was provided to relate passing or failing the needle-prick test with VAS pain scores associated with punch biopsies. Therefore, rendering a determination of efficacy in this setting was not possible. It should be noted that 33% of Lidopel-treated subjects in Study #97-07.0 failed to pass the needle-prick test.

Studies # 97-07.0 and 99-02.0 were the two trials in which analgesia for shave removals was evaluated. In Study 97-07.0, Lidopel was delivered via an electrode patch nearly [redacted] times as large as the [redacted] 8.1 cm^2 delivery electrode. The meaning of the results for this group of subjects was questionable as all the placebo-treated, control patients failed the needle-prick test. In that study, the need for additional analgesia (a possibility only for the shave removal procedures) also counted as a treatment failure. As 2 out of the 3 subjects who passed the needle-prick test and went on to have their shave biopsies requested additional analgesia, the minimal failure rate for Lidopel was 42%. In Study 99-02.0, patients undergoing shave removals were treated, in the first part of the trial, with either a 40, 60, or 80 mA·min dose of Lidopel or an 80 mA·min dose of placebo. Failure rates in that part of the study, including requests for additional analgesia, were 30%, 10% and 15% for the 40, 60 and 80 mA·min doses of Lidopel, respectively, and 90% for placebo treatment. The 60 mA·min dose was determined to be optimal for the procedure, however, in part two of the trial, there was no significant difference in the VAS scores for pain between Lidopel and placebo although there was a significant difference in global satisfaction for iontophoresis and the procedure which favored Lidopel,. Treatment failure rates for the second part of the study were 12.5 % for Lidopel and 75% for placebo. The results of these two studies, either taken alone or together, fail to provide a clear indication that Lidopel is superior to placebo in terms of its analgesic effect for the performance of shave biopsies.

The remaining three studies evaluated the use of Lidopel for analgesia during venipuncture. Part 1 of Study 99-07.0 evaluated analgesic effects of 20, 30 and 40 mA·min doses of both Lidopel and placebo. Lidopel treatment at 30 and 40 mA·min failed to significantly differ from placebo treatment in terms of VAS scores, and therefore, 20 mA·min was considered the optimal dose. In Part 2 of the study, 20 mA·min iontophoretic doses of Lidopel provided statistically significant more analgesia than placebo based on VAS scores, but the clinical significance of the difference, 13 mm out of a possible 100 mm, is questionable. A clinically significant difference between the treatments was not borne out by the global satisfaction scores which failed to differ significantly. Additionally, there was a significant difference in VAS scores associated with placebo treatments at 20 and 40 mA·min doses raising concerns of the validity of iontophoretically applied epinephrine as a placebo throughout the development program.



Study 00-1-03.0 was a non-inferiority trial that compared Lidopel and Iontocaine with placebo at an iontophoretic dose half that for which Iontocaine is labeled and using a delivery electrode for Lidopel which was 25% larger than [redacted] size. The meaning of the non-inferior finding is therefore of questionable value. It should be noted that in an ad hoc analysis of just the Lidopel and its corresponding placebo data indicated a statistically significant difference between the two treatment groups. This finding, in view of the delivery electrode used and the relatively small mean VAS difference between the treatments, is at best suggestive of a clinically relevant effect.

In summary, there was only a portion of one well-controlled study, part one of Study #99-07.0, which provided evidence of efficacy. Results from the other studies raised concerns regarding the validity of the placebo used throughout the clinical program, quality and quantity of the data collected, and the product's ability to provide adequate analgesia, based on failure rates, for superficial dermatological procedures.

1.3.3 Safety

At the time of this review, the Sponsor had not provided an integrated safety database. Therefore, a partial database was created from individual study CRTs. Analysis of this database indicated the most common adverse events to be blanching (not considered an adverse event by the Sponsor in all but the first two studies), burning/stinging sensation, erythema, pain and rash. Of these, only rash occurred significantly more frequently with Lidopel treatment than with placebo treatment, 5.5% versus 0.4%, respectively. Overall, the types of adverse events observed and their frequency of occurrence do not appear to substantially differ from that of either Iontocaine or LidoSite.

1.3.4 Dosing Regimen and Administration

Lidopel is administered using the Dupel® Iontophoresis System which provides a maximum iontophoretic current of 4 milliamps (mA) for up to a maximum of 40 minutes (min). This results in a maximum iontophoretic dose of 160 mA·min, which the Sponsor indicated was not clinically suitable for dermal analgesia due to the time required for the treatment. An 80 mA·min dose was the highest evaluated for safety and efficacy

1.3.5 Drug-Drug Interactions

No studies of drug-drug interaction potential were performed. Based on the approved Xylocaine® (lidocaine HCL and epinephrine Injection, USP) label, the following remarks may be made with regards to the Lidopel drug product.

The administration of local anesthetics containing epinephrine or norepinephrine to patients receiving monoamine oxidase inhibitors or tricyclic antidepressants may produce severe prolonged hypertension. Phenothiazines and butyrophenones may reduce or reverse the pressor effect of epinephrine, which may shorten the duration of analgesia. Concurrent use of these agents should generally be avoided. In situations when concurrent therapy is necessary, careful patient monitoring is essential.

1.3.6 Special Populations

The use of Lidopel was not assessed in any special populations

n fact, only healthy individuals presenting in non-emergent situations were recruited for all of the human subject trials. Based on limited systemic exposure to drug product expected with the use of Lidopel, clinical trials involving special populations, was not considered necessary by the Sponsor. Literature references of pediatric pharmacokinetics of lidocaine and an adult pharmacokinetic study with Lidopel were submitted to support the contention of limited systemic exposure for lidocaine. No data or references were submitted to substantiate limited systemic exposure to epinephrine.

A total of 23 subjects older than 65 years of age participated in the clinical trials; of these, two were older than 75 years of age.

The sponsor proposes to label Lidopel [redacted]

[redacted]

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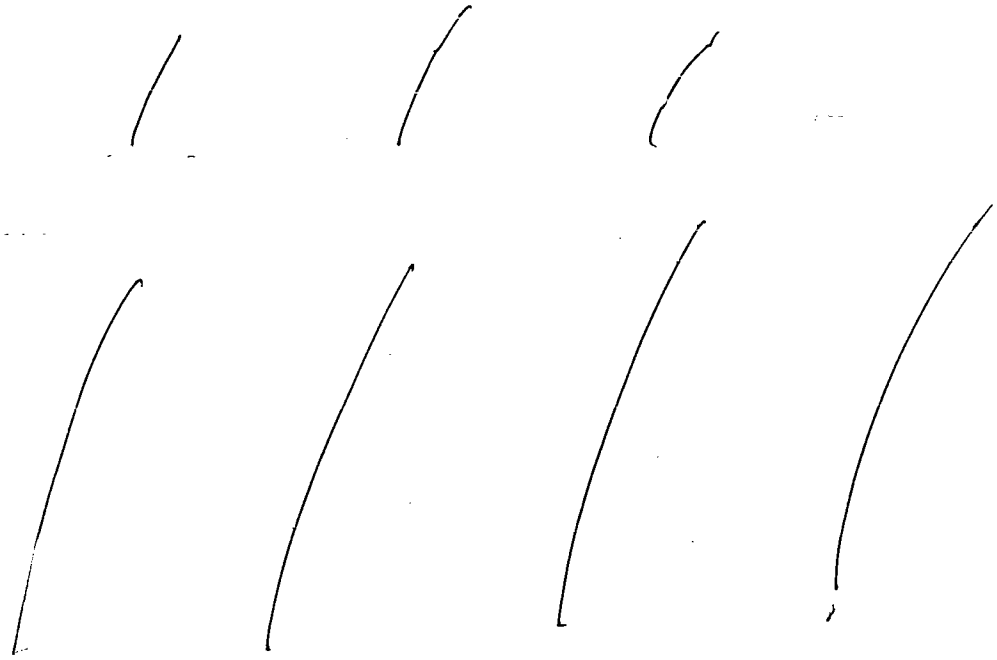
2 INTRODUCTION AND BACKGROUND

2.1 Product Information

This NDA was submitted for FDA approval to market a fixed combination drug product consisting of iontophoretically applied 2% lidocaine hydrochloride with epinephrine 1:100,000 (established name) under the proposed trade name: — idopel. The same drug combination has been approved under the trade name Iontocaine®. The two products differ in that they are administered by different, but similar, iontophoretic devices which use device-specific electrodes. Iontocaine is administered via the Phoresor Iontophoretic Drug Delivery System and the Anestrode™ Drug Delivery Electrodes; Lidopel is to be administered via Dupel® Iontophoresis System using Dupel® Iontophoresis Electrodes. Both delivery systems, including the electrodes, have been approved by FDA and provide an iontophoretic dose based on user-set iontophoretic currents applied for user-specified durations. In the case of Lidopel, the maximum label-recommended iontophoretic current is 4 mA – the device limit, and the maximum label-recommended duration — - the device limit is 40 minutes.

Lidopel is pharmacologically classifiable as a local anesthetic containing a sympathomimetic agent. The Sponsor's proposed indication and usage are as follows.



2.2 Currently Available Treatment for Indications

Multiple treatments for the indication of local dermal analgesia and/or analgesia are currently available. These include non-iontophoretically applied agents such as Xylocaine (lidocaine HCl) for infiltration, EMLA (lidocaine HCl 2.5% and Prilocaine 2.5%) cream and EMLA (lidocaine HCl 2.5% and Prilocaine 2.5%) disc for topical application, and the two approved iontophoretic products, Iontocaine (lidocaine HCl 2% and Epinephrine 1:100,000) delivered via the Phoresor® System and LidoSite™ Topical System (lidocaine HCl 10% and epinephrine 0.1%).

2.3 Availability of Proposed Active Ingredient in the United States

The active ingredients for Lidopel are, in general, widely available in the United States. Septodont, Incorporated, holds an ANDA (#84-048) for Octocaine® which is to be packaged as Lidopel. In terms of chemistry, manufacturing and controls Lidopel and Octocaine are identical; the only changes in the drug product proposed in the NDA are a change in proprietary name and the change in the route of administration from injection to topical iontophoretic administration. A letter of authorization to reference ANDA #84-048 was included in the NDA. Octocaine is manufactured by Novocol Pharmaceutical of Canada, Incorporated.

2.4 Important Issues With Pharmacologically Related Products

The more important issues regarding the use of local anesthetics and vasoconstrictors are those involving safety and are generally related to systemic exposure. With local anesthetics, the issues include the following.

1. Central nervous system reactions that range from CNS excitation with light-headedness, dizziness, paresthesias and acute anxiety at lower plasma levels to generalized tonic-clonic seizure activity, depression of conscious activity and respiratory arrest with profound depression of the medullary respiratory center at higher plasma concentrations.
2. Cardiac reactions including dose-dependent depression of myocyte activity with decreases in myocardial contractility beginning at doses that achieve sodium channel blockade. Life-threatening arrhythmias and cardiovascular collapse can occur at higher systemic exposures. Cardiac toxicity is related, in large part, to agent-specific kinetics of sodium channel block.
3. Allergic-type responses to local anesthetics range from contact hypersensitivity to anaphylactoid and anaphylactic reactions. The preservatives, methylparaben and metabisulfite, commonly used in multidose preparations may, independently of the local anesthetic, significantly increase the likelihood of an allergic-type response. Para-aminobenzoic acid (PABA), a metabolite of the ester local anesthetics, is commonly found in the environment and therefore, may serve as a significant source of allergic reactions as many patients present already sensitized to this compound.

Issues associated with vasoconstrictive agents include the following responses to topical and systemic exposures.

1. Decreased blood flow in tissues surrounding the site of locally administered vasoconstrictive agents may lead to ischemia and necrosis.
2. Vascular uptake of adrenergic agents can lead to plasma levels sufficient to result in tachycardia, hypertension, flushing, arrhythmia, myocardial ischemia, and possibly, myocardial infarction.

Combining a relatively short-acting local anesthetic with a vasoconstrictor may enhance the quality and duration of the block, and reduce the amount of local anesthetic required for a particular procedure. On the negative side, if the block significantly outlasts the procedure, it may pose a safety risk in that the patient may be unaware of trauma or injury to the anesthetized area, or of problems related to the block or procedure, such as nerve injury, that may be delayed in being diagnosed and/or treated.

2.5 Presubmission Regulatory Activity

The original IND for the Lidopel system was submitted by Empi, Inc. on December 12, 1997 and was assigned IND number 54,731.

Two pre-IND meetings were held. At the first meeting, on July 16, 1996, two points were raised by the Division.

1. A PK study should be performed.
2. Clinical studies should incorporate at least two clinical procedures.

On May 19, 1997, the Division indicated that mutagenicity data would be required for an NDA, but that literature-based evidence might be acceptable.

The second pre-IND meeting was held on May 21, 1997. At that time, the following points were raised by the Division.

1. A 14-day dermal irritation study in rabbits should be submitted in support of an IND.
2. Six subjects would be sufficient in the PK study.
3. An enrollment of 300 subjects (total for active and placebo treatments combined) could be sufficient for the clinical trials.

In a 1998 review of a Phase II study protocol, the Division commented that using the difference in proportion of treatment failures between active and placebo treatments was acceptable as a primary endpoint. The Division was also willing to accept the use of a pinprick test as an initial assessment of analgesia, i.e., a failed pinprick test would constitute treatment failure and a passed pinprick test would allow the subject to undergo the planned procedure. The Division also accepted the use of a request by a subject for additional analgesia as an indication of treatment failure.

The End-of Phase II (EOP2) meeting was held with the Division on June 30, 1999. The following issues were addressed.

1. Regarding submission of the new drug application under 505 (b)(2), Dr. McCormick informed the sponsor of the following:
   - The Agency needed to know in what aspects this product differed form the listed product (drug/device combination). If there were specific aspects of the device that were substantially different (chemistry, electrodes, electrical current), the differences were to be identified. In that case, clinical studies of safety or efficacy, or both would be necessary.
   - If there were no identifiable differences, a therapeutic equivalence trial might be needed.
   - The sponsor needed to provide data to substantiate the claim that this was a 505(b)(2) application.

2. Drs. McCormick and Ma (biostatistics reviewer) made the following comments in response to whether 200 subject exposures would be adequate to support the safety and efficacy of Lidopel and an approval of the NDA.
   - Dr. McCormick responded that it would depend on how this product differed from the existing product. If there were significant differences that raise specific safety concerns, then a database of approximately 300 patients would be more appropriate. If there were no appreciable differences, then the requirements under Generic regulations would apply.
   - Dr. Ma suggested that uneven sample sizes might be considered so as to increase patient exposure to the active treatment.
3. Dr. Ma responded to the Sponsor's request that the Division find acceptable the study design for the Phase 3 study #99-02.0, "Anesthetic Effect of 2% Lidocaine HCL and Epinephrine 1:100,000 Delivered via the Dupel Iontophoresis System to Subjects Undergoing Shave Removals".
   - It was not clear from the protocol how the optimum effective dose would be determined in the Part I of Study 99-02.0 and whether that minimum effective dose would be the optimal dose level the sponsor would eventually market. It was indicated that, a dose that merely differs statistically significantly from placebo is not necessarily the one that provides the most clinically satisfactory outcomes.
   - The definition of treatment failure also contained subjects who could not tolerate the iontophoretic procedure. These subjects could be different from those who failed due to inadequate analgesia and it would be desirable to examine how they distributed across treatment groups.
4. Related to the same protocol, the Sponsor asked does the Agency agree that the end points are adequate to achieve the stated objectives?
   - Dr. McCormick responded that pain rating should be a primary instead of a secondary endpoint.
   - It was also noted by Dr. McCormick that the minimum effective dose is usually determined in Phase I or II and not in a Phase 3 trial as proposed.
5. The Sponsor asked if the Agency agreed that the proposed comparison of placebo treatment versus active treatment was acceptable?
   - Dr. McCormick responded that it was adequate, but added that the Sponsor should consider using a 3rd arm consisting of the existing listed iontophoretic product, in one of the studies, to demonstrate therapeutic equivalence.
6. The Sponsor requested that the Division confirm the acceptability of the study design for the Phase 3 study #99-07.0, "Phase 3 study on Anesthetic Effect of 2% Lidocaine HCL and Epinephrine 1:100,000 delivered via the Dupel Iontophoresis System to Subjects Undergoing Venipuncture".
   - Dr. McCormick responded that it was acceptable.
   - Dr. Ma noted that the protocol gave conflicting statements about what was to be the primary efficacy endpoint. Page 9 of the protocol stated the VAS pain score was primary, but page 27 stated that the satisfaction rating was.

In a letter to the Sponsor, stamped March 10, 2000, the Division provided comments concerning two Phase 3 protocols. Among those comments were the following.

1. Provide the analytical methods used for compatibility and stability under iontophoretic conditions.
2. Provide reliable data on mutagenicity.
3. Provide reliable data on reproductive toxicity including fertility, early embryonic development through implantation, fetal development, post-natal development and maternal function.
4. Carcinogenicity studies are not required.
5. Patients with various skin types and pigmentations should be included in the trials.
6. An adequate number of patients over the age of 75 years should be included in clinical studies.
7.
8.
9. Systemic exposure should be characterized in adults following repeated use of the system at the same site and following repeated use at different skin sites.
10. Patients should be reevaluated at 48 – 72 hours after treatment for hypersensitivity reactions.

A pre-NDA meeting was held with the Division on July 20, 2001. At the meeting, Dr. Rappaport stated that the overall development plan appeared to be adequate and that there were probably no major concerns, but without complete electrode information, a full assessment of the proposed plan to evaluate dosing and administration was not possible. The following comments were made by the Division in response to the Sponsor's meeting package.

1. Evaluation of repeat dosing required that the repeated dose should be tested immediately, not 7 days later.
2. The proposed clinical trials appeared to be adequate and well controlled.
3. The number of subjects to be evaluated could be potentially too small: 51 subjects receiving 80 mA·min doses and 35 subjects receiving 60 mA·min doses.
4. The duration of the anesthetic effect should be determined. The Sponsor indicated that duration had been assessed and found to be on the order of 30 minutes which was felt to be sufficient for the types of procedures to be studied.
5. The number of subjects and doses studied for each type of procedure should be clearly outlined. The sponsor stated that the 20 mA·min dose was intended for use with venipuncture and that up to a ——— dose could be used for shave procedures.
6. The CMC portion of the NDA needed to be complete either by submission of the information in the NDA, or by reference to other applications submitted to FDA.

The following preliminary list of information to be included in the NDA was provided.

a. For the ANDA drug product provide the following in the NDA (if possible) and a specific reference (submission date, volume number, page number) to the ANDA:
   - Drug substance specifications
   - Drug product specifications
   - Expiration dating period for the drug product
   - Current sites (and CFN #s) of drug substance/drug product manufacturing and testing (for inspection)

b. Provide specifications for impurities in the ANDA drug substance and drug product in accordance with ICH [update to the ANDA may be necessary].

c. Provide acceptance specifications to be used by EMPI for the ANDA drug product, a description of the protocol that will be used to label the product with the correct expiration date, etc.

d. Provide the name, address, and CFN# for the facility to be used by EMPI for labeling the drug product obtained from the ANDA holder.

e. Provide detailed identification of the investigational formulations, iontophoretic devices, and electrodes used in the clinical trials; including certificates of analysis for the ANDA drug product, device/electrode production numbers, clinical protocol numbers, etc. Any differences between the ANDA product or the 510(k) products studied in the clinical investigations and the to-be-marketed products should be indicated and justifications/data provided to support the suitability of the changes in terms of drug product performance.

f. Provide studies demonstrating acceptable drug delivery for the drug product at the extremes of the ANDA drug product specifications (e.g., pH).

g. Provide a specification for drug delivery and a regular schedule for testing of this attribute.

h. Provide a description of how changes in the ANDA drug product or the iontophoretic device/electrode will be controlled, documented, and reported to the Agency (e.g., the letter of authorization from the ANDA holder should include a suitable commitment concerning changes in the ANDA).

The sponsor stated that the information stated in (a) could be provided and that the ANDA was approved in approximately 1980 and that there was only one supplier of the drug product and substance to the sponsor. Dr. Koble reminded the sponsor that this application will need to meet current standards regarding impurities and ICH guidelines. Regarding point (g), an *in vitro* release test for drug delivery, Dr. Koble informed the sponsor that we could discuss this point further and advised them to propose a test that we would evaluate for acceptability. The sponsor stated that since the drug product and the device are

not sold together they are not tied together. Dr. Koble stated that since the product will be labeled for use with this device the sponsor will need to demonstrate that the drug is delivered as stated. Dr. Duffy stated that the sponsor should investigate any variation regarding application of the drug to the electrode, i.e., are naïve practitioners (based on the labeling alone) able to apply the drug solution appropriately. Dr. Koble went on to say that the sponsor may need to have some type of validation to demonstrate that there is not significant variation of technique or provide the Agency with justification why such a validation would not be necessary based on how the product works (i.e., application of the product is "foolproof"). Regarding point (h), Dr. Koble stated that any changes to the ANDA would need to be communicated to our Division. The sponsor stated that they could create a protocol to accommodate this need. Dr. McCormick reminded the sponsor that regarding any future changes, safety is always of paramount concern.

7. Statistical analyses would be reviewed with the NDA, but SAS format for the datasets is preferable.
8. Submissions in electronic format are highly preferred and encouraged, to facilitate the review process. The following points should be followed.
    a. *"Providing Regulatory Submissions in Electronic Format"* [guidance on the web].
    b. Dataset sizes should be < 25MB/file - if not, they should be divided into smaller datasets.
    c. Each subject should have a single unique identification for the whole application.
    d. All date variables should use the same format.
    e. Time, including treatment start and stop times, and dates should be
        - based on start of study treatment,
        - show duration of treatment, and
        - be expressed in minutes, hours, or days as appropriate.
    f. Each dataset should include study, center, treatment assignment, subject identification, and subjects' sex, age, and race. Text should be used for these variables in addition to codes.
9. Provide the CRFs for subjects who discontinued due to an adverse event. The Division reserves the right to request any and all CRFs during the review process.
10. Provide a detailed description of the studies (including description and validation of the analytical methods) performed to generate the compatibility and stability of the drug product under iontophoretic conditions. Dr. Koble referred the sponsor to detailed CMC comments sent to the sponsor early in the IND review process.
11. The sponsor sought agreement with the Division to submit the NDA and address the multiple-dose information later in a supplement. Dr. McCormick agreed that this was acceptable to the Division.

On February 8, 2002, the Sponsor submitted the new drug application (NDA) which was assigned the reference number 21-486.

On October 21, 2002, the Sponsor was issued a reminder that they had not submitted the required annual report for the IND which was due in February of that year.

2.6 Other Relevant Background Information

The appropriate user fee was not submitted with the NDA on February 8, 2002. The application was therefore deemed incomplete by the Agency and was not accepted for filing. The Sponsor was notified of this on February 28, 2002, and was also informed that the receipt date for the submission would be the date the review division was notified that the user fee payment was received by the bank.

On April 18, 2002, the Sponsor sent a letter to the Agency stating its case for not paying a user fee: the NDA referenced a drug product that contains the same molecular entity and the same indication for use as a drug product that has already been approved by FDA. Jane Axelrad, Associate Director for Policy, CDER, responded with the following comments on September 26, 2002.

Under section 736(a) of the Federal Food, Drug and Cosmetic Act (the Act), a human drug application submitted on or after September 1, 1992, is subject to an application fee. As defined in section 735(1)(B) of the Act, the term "human drug application" includes an application for approval of a new drug submitted under section 505(b)(2) after September 30, 1992, which requests approval of –

(i) a molecular entity which is an active ingredient (including any salt or ester of an active ingredient), or

(ii) an indication for a use, that had not been approved under an application submitted under section 505(6).

If either condition (i) or (ii) above applies, a 505(b)(2) application is subject to an application fee.

Empi's 505(b)(2) application for a drug product containing both lidocaine and epinephrine was not subject to an application fee under the first condition above because Iontocaine, approved December 21, 1995, is the same combination of molecular entities as Empi's proposed product.

As for the second condition, FDA indicated that a plain reading of the statute, section 735 (1)(B) of the Act, as supported by the legislative history leads to the conclusion that any change in the package insert labeling for a 505(b)(2) application that would fall under 21 CFR 201.57(c) would be a new "indication for a use." Based on this interpretation, the following analysis was performed to determine whether Lidopel meets this definition of "indication for a use."

1 Page(s) Withheld

✓ Trade Secret / Confidential

_____ Draft Labeling

_____ Deliberative Process

In addition, Lidopel's package insert labeling references a maximum dosage of 80 mA·min The Dosage and Administration section states in relevant part.:

In the application at issue here, Empi was requesting a new higher dosing recommendation of 80 mA·min. FDA believed that this important relevant modification of dosage was a new "indication for a use" as described under 21 CFK 201.57(c). For example, 21 CFR 201.57(c)(3)(i) states in part:

> ... If the information is relevant to the recommended interval between doses, the usual duration of treatment, *or any modification of dosage,* it shall be stated in the "Dosage and Administration" section of the labeling and referenced in this section.
>
> (Emphasis added by FDA.)

Because the Lidopel application which is a new claim and also included a new higher dosing recommendation, Empi's application for Lidopel was considered to have new "indications for a use." Therefore, Empi's Lidopel application meets the second condition for a human drug application submitted under section 505(b)(2) of the Act and is subject to a fee."

If Empi wished to avoid paying the user fee, they were advised to revise the proposed labeling of their product to remove the indication

On October 15, 2002, the Sponsor resubmitted the proposed labeling with a change in indication to "" The Dosage and Administration instructions were also revised to state that " The Agency was willing to accept the application for review without a user fee.

A teleconference was held on December 9, 2002, between representatives of Empi, Inc. and the FDA Division of Anesthetics, Critical Care and Addiction Drug Products. During this teleconference, the Division cited the following regulatory and "legibility" issues with the NDA that could prevent filing of the NDA if not resolved by the filing deadline.

1. Integrated safety summary data tables (the one included in the NDA was lacking several key elements such as patient demographics, treatment group, extent of

exposure, temporal relationship between treatment and adverse event, or severity, duration, outcome, and action taken, if any, of each adverse event).

2. Integrated safety and efficacy data by race, gender and age.
3. Data presentations that were incomplete, inaccurate or inadequately defined including:
    a. Column headers that do not match data definition tables or which are not defined on data definition tables.
    b. Truncated text.
    c. Entries that on their face appear to be illogical or incorrect. These included data entries that included a seemingly impossible number of significant digits (VAS scores and temperatures), dates such as 1899 and 2028, and entries such as –7 that were not defined.

The Division stressed its concern about the interpretability and reliability of the data, based on the number of findings already made during a cursory review. The Division informed the Sponsor that the filing deadline for this application would occur on Friday, December 13, 2002. The Division suggested that the elements required by regulation be addressed and the electronic database be subjected to a complete quality control (QC) process for legibility and accuracy, and that this QC process should be documented for Agency review. A submission was requested by the close of business on Wednesday, December 11, 2002, if the sponsor wished to have the submission considered and reviewed prior to the filing decision. Additionally, the Division stated that the electronic database was very difficult to work with and requested that the Sponsor refer to the guidance for electronic submissions.

The Sponsor indicated that they would not be able to provide the Division with the documents required by the regulations by Wednesday, December 11, 2002, but would get back to the Division with their intentions. Additionally, the Sponsor stated that they were concerned that many of these issues could have been addressed had the Division informed them earlier.

On December 11, 2002, a teleconference was again held between representatives of Empi, Inc. and the Division of Anesthetics, Critical Care and Addiction Drug Products. The Sponsor was informed that there were major flaws in the application that had not been corrected and which would not allow the application to be filed. The following items were discussed and provided to the Sponsor in a "Refuse to File" letter dated December 13, 2002.

1. The current integrated summary of safety (ISS) does not present data in a reviewable format. The table that presents adverse events across studies does not contain key information required for the review of this integrated data set. For example, there is no information included about patient demographics, treatment group, extent of exposure or temporal relationship between treatment and adverse event. Nor has information been provided regarding severity, duration, outcome, and action taken for each adverse event.

2. There is no presentation of data analyzed by gender, race, age, and other relevant subgroups in the integrated summary of efficacy (ISE) or ISS. There is text describing the conclusions of your analysis, but the data are not included.
3. The clinical database is not reviewable as submitted. Even on superficial review, the database was found to be scattered with entries that were illogical or undefined. Many of the column headers were undefined or did not correspond to those defined in the data definition tables. There were also instances in which data entries were truncated. There was at least one instance in which data appeared to be missing entirely, e.g. data from at least one patient did not appear in some of the data tables for the study.
4. The format of the electronic database was not consistent with the "Guidance for Industry: Providing Regulatory Submissions in Electronic Format —General Considerations," "Guidance for Industry: Regulatory Submissions in Electronic Format; New Drug Applications" and "Example of an Electronic New Drug Application Submission." The format used made meaningful review difficult at best.

The Division indicated its concern that these items were not resolved quickly as the Division had seen these types of issues before and has worked with Sponsors to correct them. The Division encouraged the Sponsor to meet with the review team to discuss the problems and the ways to resolve them so that the next submission could be filed. The Sponsor questioned if the corrective actions could be taken during the review cycle. The Division stated that due to the PDUFA timelines, it would not be acceptable to the Division to receive the required documents after filing, as it shortened the time available for review of the application. The Division stated that the Sponsor would receive a refuse to file letter by the close of business on Friday, December 13, 2002. The Sponsor was informed that they could resubmit at any time; however, the Division strongly recommended that they meet with the review team and look at the electronic database together prior to resubmission. The Sponsor questioned whether the letter would itemize all the issues. The Division replied that the regulatory requirements would be itemized in a global sense; however, each individual mistake would not be listed. Additionally, the Division stated that there were many smaller issues which should be discussed. The Division encouraged the Sponsor to access application reviews and electronic submissions guidances which are available on the FDA website in order to better understand the review process. The Sponsor stated that they would contact the Division in the beginning of January to arrange a conference call to discuss the status of the application and the Sponsor's intentions for resubmission.

On February 20, 2003, the Sponsor and the Division presented their cases before the FDA Refuse to File Review Committee. The committee supported the Division's decision. Dr. Rappaport met separately with the Sponsor after the meeting and offered again to work with them to facilitate the filing of the NDA.

On July 29, 2003, the sponsor submitted data in response to the Refusal to File action. This was followed by a teleconference with the Division on April 2, 2003, to discuss the data and a path forward for the application. The Division stated that there were significant improvements made to the data. On initial review, the data appeared to meet minimum filing requirements. The Division, however, noted the following:

1. Some data fields were still populated with bullets. The Division requested that those fields were to be populated with an appropriate descriptor (i.e., if data is missing state that it is missing). The Division also suggested that if a field can be filled, it should be.
2. Adverse event times were missing. The Sponsor should have provided those data, or an explanation for their absence, prior to resubmission of the NDA. The sponsor was also advised to provide fields describing variables such as onset and duration of events. Alternatively, the fields could be formatted for calculations of elapsed times.
3. The adverse event tables met the minimum regulatory requirements; however, they could be combined into a more comprehensive file across studies since each table contained only a few broad categories.

A teleconference was held on September 4, 2003, to discuss problems with the electronic submission dated August 12, 2003. The following issues were raised at that time.

1. The Division had previously stated it was having problems interpreting the contents of the data sets, specifically, DATA9707, DATA9902, DATA9914 and DATA00103. The problems encountered included the following:
   - AE_TIME values were not meaningful in DATA9707 and DATA9902.
   - In DATA9914 some data were meaningful; however, the "2" value used in RES_TIME and AE_TIME was not.
   - RES_DATE values of "01/03/1960" were not meaningful.
   - RES_TIME values and DURADAYS values were not meaningful.

   Since that time, the Division was able to locate the appropriate data dictionaries and resolve most, but not all of these problems. The Sponsor clarified that some of the still uninterpretable numbers were SAS formatted date/time values that were expressed in seconds past midnight. Other data that were expressed as military time were formatted as character strings. The Sponsor stated that the Division should be able to re-program the data sets; however, the Division stated that the data sets should have been submitted in a legible format consistent with that listed in the data dictionaries, and that it was the Sponsor's responsibility to program the data sets in a manner that is legible and reviewable. The current format prevented the reviewer from analyzing times to onset, resolution times and durations. It would be preferable if the data could be formatted to allow such data analysis, but at a minimum, the primary data must be legible and interpretable without the need for further manipulation or programming by the reviewer.
2. The Division also requested a comprehensive table of contents. The current submission referred to sections of the original February, 2003 submission and updated or replaced others, but there was no single updated table of contents

linking the appropriate sections of the original submission with those of all subsequent submissions. The lack of a comprehensive table of contents was a filing issue.

3. The Division also noted that the lack of an integrated safety database that merged all of the databases. The Sponsor stated they were unable to provide this as it would constitute a monumental task and that some of the data were not compatible. The Division stated that to the extent scientifically feasible, a comprehensive database of all safety data should be included as part of the ISS. Scientific justification for excluding particular studies could be offered, but where possible, all data should be integrated. The Division noted that combining the safety data from all studies requires a significant amount of time and results in a substantial volume of material, but noted also that this was a requirement of all sponsors.

The Sponsor stated that they tried to make review of the NDA easier for the FDA by submitting the electronic version of the datasets, but that an electronic integrated safety database may not be feasible. The Division stated that they have offered several times in the past to work with the Sponsor with regards to what would be required in the NDA submission, regardless of format, including an invitation to come to the Agency and work directly with the review team. The Sponsor stated that they thought the best way to help the Division was to submit the information electronically instead of a paper copy. The Division reiterated that an electronic submission was strongly encouraged but not required. The offer to come to the Agency and work directly with the review team was again extended, but the Sponsor stated they would regroup at this time.

Another teleconference was held on September 16, 2003, to further clarify some of the points made at the teleconference on September 4 of that year. In particular, Dr. Rappaport reiterated that three things discussed during the September 4, 2003 teleconference needed to be resolved before the application could be filed.

1. The ISS should be integrated unless the Sponsor can provide a scientific rationale explaining why the data cannot be integrated.
2. The Sponsor must provide a comprehensive table of contents.
3. The Sponsor must fix the illegible data points even if the format prevents the Division from manipulating the data. The data format should be consistent throughout the ISS.

Mr. Yingling stated they were surprised with the points raised in the September 4, 2003 teleconference. Based on a discussion with the Division during the April 2, 2003 telecon, the Sponsor was under the impression that their submission would be acceptable. Thus, they submitted the application on July 29, 2003, and thought the issues were resolved. Dr. Rappaport stated that there was apparent miscommunication at the April 2, 2003 teleconference as the discussion was centered on improvements in the data presentation which was a different issue from an integrated ISS. Dr. Rappaport again stated that if the Sponsor cannot integrate the data, than a rationale for not doing so should be provided.

Dr. Rappaport reminded the Sponsor that the rationale may be unacceptable to the Division and could lead to a non-approvable action for the application. Mr. Yingling stated he would talk with the Sponsor, clarify these issues with them and contact the Division concerning their plans to resolve these filing issues.

On September 26, 2003, the Division had not received all the materials necessary to consider the July 29, 2003, submission a complete response to the deficiencies outlined in the refuse-to-file letter. In a teleconference held with the Sponsor, the Division indicated that there was not adequate time to thoroughly review the required additional materials should they be submitted, and therefore, the Division had made the decision to consider the July 29, 2003 submission as a minor amendment to NDA 21-486. The Division stated that the receipt of the additional required materials would be considered as a complete response to the refusal to file, and that their receipt would initiate the review clock. These materials arrived September 26, 2003.

On December 9, 2003, the NDA was determined by the Division to be sufficiently complete to permit a substantive review and it was filed with the following potential review issue forwarded to the Sponsor.

> "The database contains a fairly small number of exposures to Lidopel at each dose tested. The adequacy of the database for a determination of safety and efficacy at the appropriate dose(s) will be the subject of ongoing review."

On June 8, 2004, the Division received a submission dated June 7, 2004 which contained substantial amounts of data and constituted a major amendment to the application. The receipt date was within 3 months of the user-fee goal date, and therefore, the Division extended the PDUFA goal date by three months to provide time for a full review of the submission. The extended user fee goal date was October 26, 2004.

3 SIGNIFICANT FINDINGS FROM OTHER REVIEW DISCIPLINES

3.1 CMC (and Product Microbiology, if Applicable)

Lidopel 1.8 mL solution is packaged in a cartridge [redacted], for single use. The drug product does not contain a microbial preservative. The packaging design and closure system are identical to that of the approved Octocaine® product. Lidopel has a 20-months expiration dating period when stored in its commercial container closure system. The expiration dating was supported by the stability data in the ANDA 84-048 for Octocaine (approved prior to Jan 1, 1982).

The Dupel® Buffered Iontophoresis Electrode System consists of a drug delivery electrode and a return electrode. The electrodes are designed for single application use. There are multiple sizes and shapes of drug delivery electrodes to accommodate placement at different body sites and use with different drug products. The return electrode is available in only one size but is compatible for use with all drug delivery electrode sizes. Both electrodes have buffering capability to maintain the surface pH between 4 and 8 for iontophoretic doses of up to 160 mA·min. The delivery electrode is packaged without medication. Prior to the iontophoretic treatment, an appropriate amount of Lidopel is introduced through a syringe to the delivery electrode as per the device label instructions. At the same time, the surface of the return electrode is dampened with 1-2 drops of water for injection. CDRH has concluded that the device and the electrodes are safe with respect to material of construction, mode of operation, and performance characteristics.

The outstanding CMC deficiencies with respect to Lidopel, at the time of this review, are listed below and were provided to the Sponsor in a letter dated August 24, 2004, and discussed during a teleconference on September 1, 2004.

I. In reference to the drug substances specifications:
   A. Provide the following revised specifications for lidocaine hydrochloride.
      1. Individual drug-related unspecified impurity or degradation product: NMT [redacted]
      2. Total impurity: NMT [redacted]
      3. [redacted] NMT [redacted]
   B. Provide the following revised specifications for epinephrine.
      1. [redacted] NMT [redacted]
      2. [redacted] NMT [redacted]
      3. Individual drug-related unspecified impurity: NMT [redacted]
      4. Total known: NMT [redacted]
      5. Total unknown: NMT [redacted]
II. In reference to the Lidopel. drug product specifications:
   A. Revise the specifications for the degradation products of lidocaine and epinephrine in the drug product as follows:

1. Individual unspecified and unidentified degradation products of lidocaine: NMT — or — whichever is lower.
2. Individual unspecified and unidentified degradation products of epinephrine: NMT — or — whichever is lower.

3.2 Animal Pharmacology/Toxicology

The following information is taken from the executive summary of the primary pharmacology/toxicology reviewer's evaluation of the NDA.

The principal concern with iontophoretic administration of Lidopel is the possibility of local dermal irritation which can take the form of erythema, eschar formation, edema and/or frank burning of the dermal and epidermal layers of the skin to which the electrode containing the drug product is applied. Due to the wide clinical experience with lidocaine and lidocaine/epinephrine-containing drug products and the decision of the sponsor to submit as a 505(b)(2) referencing Iomed Iontocaine which is an iontophoretically delivered lidocaine/epinephrine-containing drug product, the sponsor was only required to conduct a dermal irritation study in the rabbit. Results of this study demonstrated that 14-day exposure to a dose of 2% lidocaine/1:100,000 epinephrine delivered at a rate (80 mA·min) higher than that indicated for clinical use (40 mA·min) produced significant erythema and milder edema which first appeared as a slight irritation (primarily erythema) on approximately Day 5 of dosing and continued with worsening severity through the duration of the study. Full recovery from dermal irritation after cessation of drug administration was observed to occur though in several cases complete resolution required 3-7 days. No evidence of dermal irritation was noted in any animal on the first day of dosing and irritation was considered barely perceptible on the second day of administration. Histopathologic assessment of the skin of animals with mild to moderate dermal irritation scores obtained at the conclusion of the treatment period revealed evidence of inflammation, hypertrophy and necrosis of the epidermis and edema of the dermis. Toxicokinetic evaluation of systemic exposure to lidocaine after iontophoretic administration of Lidopel resulted in barely detectible plasma lidocaine concentrations using — methods (LLOQ = — µg/mL) in a minority of animals with all values being ≤ —, µg/mL while the values of the remaining plasma samples was below the LLOQ. Thus, extremely low levels of systemic lidocaine exposure were noted in all animals at all time-points after administration of Lidopel with this method.

4 DATA SOURCES, REVIEW STRATEGY, AND DATA INTEGRITY

4.1 Sources of Clinical Data

The following table summarizes the documents utilized in the course of the review of this NDA. The submission dated September 26, 2003, contains the comprehensive Table of Contents which specifies the archival source for each component of the NDA. Submissions to the NDA dated prior to September 26, 2003, which were not included in the comprehensive Table of Contents were not considered for review purposes. Data tables submitted in paper format were transcribed to Microsoft Excel and JMP 4 compatible SAS files for the purposes of data analysis, verification of Sponsor's findings, and data exploration.

Table 4.1-1 Items Evaluated in the Clinical Review

Item	Date	Description
Divisions Files: I54731	various	Correspondence and minutes of interactions with sponsor
I 54,731 (N031YY)	11/22/02	Annual report
I 54,731 (N033YY)	03/21/03	Annual report
I 54,731 (N034YY)	4/30/04	Annual report
N 21-486 (N000)	02/08/02	initial NDA submission – FDA refused to file
N 21-486 (N000AR)	10/15/02	NDA summary and labeling information
N 21-486 (N000BZ)	07/29/03	Revised ISS, ISE, data tables and dictionaries, user fee
N 21-486 (N000RS)	09/26/03	Revised table of contents
N 21-486 (N000SU)	04/01/04	120-day safety update
N 21-486 (N000BZ)	05/21/04	Response to clinical and statistical requests for additional information
N 21-486 (N000BZ)	06/07/04	Response to clinical and statistical requests for additional information
N 21-486 (N000BZ)	06/23/04	Resubmission of SAS data sets
N 21-486 (N000BZ)	08/16/04	Response to clinical and statistical requests for additional information
N 21-486 (N000BZ)	9/3/04	Response to clinical and statistical requests for additional information
N 20-530	NA	Iontocaine NDA clinical review
N 21-504	NA	LidoSite Topical System® NDA clinical review

4.2 Tables of Clinical Studies

The table below summarizes the human subject trials conducted in support of the application. Included in the table is a breakdown, by study, of the number of treatments administered for each test drug with each iontophoretic dose and delivery patch size.

Table 4.2-1 Table of Clinical Studies

Type of Study	Study Number	Phase	Iontophoretic Dose(s) mA·min	Electrode Size(s) Cm^2	Number of Treatments L=Lidopel P=Placebo I=Iontocaine
Pharmacokinetic	96-08.0	1	80	—	3 L
			80	—	3 L
			80	8.1	3 L
Dermatological	97-07.0	2	40	—	7 L; 8 P
			80	8.1	9 L; 8 P
			80	—	8 L; 8 P
Dermatological	99-02.0	3	40	8.1	20 L
			60		60 L; 20 P
			80		20 L; 20 P
Venipuncture - Adult	99-07.0	3	20	8.1	60 L/P
			30		20 L/P
			40		20 L/P
Venipuncture - Adult	00-1-03.0	3	20	10.1	30 L/P
					29 I/P
Dermal Irritation	01-1-06.0	1	80	8.1	48 L

4.3 Review Strategy

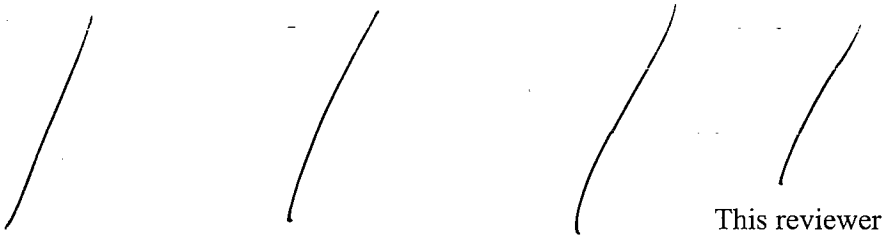
The review began by determining that all applicable items of the clinical section were included and that the NDA was suitable for filing. During the most recent review for filability of the submission, multiple deficiencies were still noted. The greatest deficiency remained the lack of a fully integrated summary of safety and, in particular, ISS data tables to be used in the review process. After discussions with the Sponsor and the submission of revised some revised materials, the Division determined that the deficiencies appeared to be sufficiently remedied as to allow initiation of a meaningful review. An ISS data table for analysis and review was to be generated by this reviewer.

Data from the four Phase-3 pivotal trials, the controlled Phase-2 clinical trial, and those uncontrolled trials that contributed to the findings of efficacy were reviewed in detail. This included review of trials using varying delivery electrode patch sizes and iontophoretic doses. The safety review consisted of a review of the Integrated Summary of Safety (ISS) data that was provided by the Sponsor, verification and additional analyses of the ISS database where possible, review of the case report forms and case report tabulations, and an attempt at creating an ISS database for analysis. Creation of the database was not possible with the data tables provided by the sponsor due to data not available in the NDA, e.g., whether adverse events occurred at the site of the delivery or return electrode. In addition, the construction of the database required the concatenation and manipulation of multiple tables from each study. As these tables were submitted in printed rather than electronic format, the time requirement exceeded the resources available. The Sponsor was again asked, and agreed, to create the table, which at the time of this review was still pending.

At times during the review process, questions regarding various aspects of the Sponsor's data gathering and analysis or of the data itself were forwarded to the sponsor. A clinical site investigation was conducted at the , which was the site responsible for the Findings of that investigation are summarized in this review.

4.4 Data Quality and Integrity

The Division of Scientific Investigations (DSI) conducted a clinical site investigation for



This reviewer participated in the investigation and performed the following:

1. Reviewed all source data material for completeness and accuracy in collecting information and preparing it for transcription to the Case Report Forms (CRFs).
2. Reviewed case report forms for accuracy of transcription from source records.
3. Calculated
4. Calculated
5. Verified assessment of

6. Calculated [redacted]
doses).

Findings from the clinical site investigation included the following.

1. The protocol stated that " [redacted]
2. The protocol required [redacted]
3. Several parents did not fill out the [redacted]
4. [redacted]
5. There were several out-of-window follow ups, e.g., subject # [redacted]
6. The [redacted] transcribed the wrong number on a [redacted] form, and there were corrections on the case report forms, e.g., subject [redacted].

4.5 Compliance with Good Clinical Practices

The Sponsor has asserted that "all clinical studies of Lidopel™ conducted by or sponsored by Empi, Inc. were conducted in compliance with the regulations for Institutional Review Boards (21 CFR 56) and Informed Consent (21 CFR 50), as well as state and local requirements for the conduct of clinical trials." [NDA Section 8, p. 149]

As the "studies were reviewed by the applicable IRBs in accordance with the FDA's IND regulations and consent was obtained from participating subjects [redacted], the studies were completed in accordance with FDA regulations for Good Clinical Practice and the Helsinki Agreement for Ethical Principles for Medical Research Involving Human Subjects." [NDA Amendment 003, March 16, 2004, p.5]

4.6 Financial Disclosures

In compliance with 21CFR §54.4, Certification and Disclosure Requirements, Empi, Incorporated submitted certification on the financial interest and arrangements of the clinical investigators who enrolled subjects into the covered clinical studies of Lidopel. The Sponsor noted that two of the studies they conducted, Studies #96-08.0 and #97-07.0, were completed prior to February 2, 1998 and therefore, were not covered by these

requirements. The remaining five studies were conducted by investigators who were certified to not have participated in any financial arrangement with Empi, Incorporated and not have received significant payments as defined in 21 CFR §54.2(f). The Sponsor also certified that each investigator "did not disclose any proprietary interests in the product or a significant equity in the sponsor as defined in 21 CFR §54.2(b)."

Based on the information provided, there are no financial reasons for questioning the integrity of the data submitted.

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ON ORIGINAL

5 CLINICAL PHARMACOLOGY

5.1 Pharmacokinetics

Study 96-08.0 evaluated systemic lidocaine levels in adults following an 80 mA·min iontophoretic dose of Lidopel administered via an 8.1, — cm^2 delivery electrode. Three subjects were evaluated for each delivery patch size. The patches were applied to the forearm on a randomly selected side. Blood samples were collected from the contralateral side prior to iontophoretic treatment, at the conclusion of the iontophoretic treatment, and at 0.25, 0.5, 1, 2, 4, and 6 hours after the conclusion of the iontophoretic treatment.

Prior to and for two hours after the iontophoretic treatment, all subjects had lidocaine plasma concentrations of 0.00 ng/mL (the Sponsor reported a LQC of 2 ng/mL for the GCMS used in this study). At four hours after the iontophoretic treatment, two subjects had levels of — and — ng/mL. At six hours after the treatment, the subject with a 4-hour plasma level of — ng/mL had a level of 0.00 ng/mL. The subject with a — ng/mL plasma level had a level of — ng/mL. A subject (#04 — with no detectable plasma level of lidocaine before 6-hours post-treatment had a level of — ng/mL at six hours. No follow-up plasma levels were performed on the two subjects that had detectable levels at six hours after the iontophoretic treatment. The Sponsor reported that the plasma level of — ng/mL came from a subject who had the blood sample taken from the same side as the iontophoretic treatment, in violation of the protocol. All plasma concentrations of lidocaine associated with the iontophoretic treatment were below the reported therapeutic range of 1.5 to 6.0 mcg/mL. Subject number 04 —, who experienced detectable levels of lidocaine at 4 and 6 hours, received treatment with the largest delivery electrode — cm^2; subject #0? — who had the lowest detectable lidocaine level, received treatment with the 8.1 cm^2 delivery electrode; the delivery electrode used for subject #0? —, the only other subject with a detectable lidocaine level, was the largest. —

No studies were conducted to assess plasma levels of lidocaine following multiple simultaneous iontophoretic treatments or sequential treatments at a single site. Plasma levels of epinephrine were not assessed in any of the human subject studies.

5.2 Pharmacodynamics

No pharmacodynamic studies were conducted by the Sponsor in support of this NDA. In most of the trials, the clinical procedure or needle-prick testing began within 10 minutes of the end of the iontophoretic treatment. No assessment was made within that time period or shortly thereafter to determine if the level of analgesia waxed, waned or remained unchanged. In Study 97-07.0, the needle-prick test was repeated one-half hour after the iontophoretic treatment to assess the continuance of analgesic effect. Of those tested, 69% passed the needle-prick test. No further assessment of the level of analgesia or characterization of the level and duration of the analgesic profile was made. The Sponsor indicated that the dermatological procedures for which Lidopel was likely to be used were less than one-half hour duration.

5.3 Exposure-Response Relationships

As detectable serum levels of either epinephrine or lidocaine were not expected to occur with this product when used as directed, exposure-response relationships are based on the iontophoretic dose administered.

All clinical assessments of Lidopel were made on relatively healthy subjects. With the exception of the skin lesions scheduled for shave removal, the delivery and return electrodes were placed on intact, normal-appearing skin. Single applications of 20, 30, 40, 60 and 80 mA·min iontophoretic doses were evaluated for safety and efficacy in adults. [redacted] A study of dermal irritation assessed only skin appearance following two consecutive 80 mA·min doses to the same skin site in two locations, one arm and the contralateral thigh, on adult volunteers.

The clinical trials indicated no clear exposure-response relationship in terms of efficacy or safety. In the trials involving shave removals and punch biopsies, the data suggest a lower failure rate, based on the needle-prick test, with higher iontophoretic doses. In one of the venipuncture trials, the lowest iontophoretic dose of Lidopel appeared to be most efficacious.

6 INTEGRATED REVIEW OF EFFICACY

6.1 Indication

The most recent version of the proposed package insert, dated June 14, 2004, gives the following indication.

6.1.1 Methods

Three types of procedures were studied to assess dermal analgesia provided by Lidopel: punch biopsies, shave removals of superficial dermatological lesions, and venipuncture. Study 97-07.0 and 99-02.0 compared the analgesic efficacy of Lidopel and placebo (Lidopel without lidocaine) at various iontophoretic doses, 40, 60 and 80mAmin, for the two superficial dermatological procedures. Study 99-07.0 evaluated efficacy of providing analgesia for venipuncture in adult subjects. This study compared Lidopel with placebo (Lidopel without lidocaine) and also evaluated multiple iontophoretic doses, 20, 30 and 40 mA·min. Study 00-1-03.0 compared Lidopel and Iontocaine with placebo (Lidopel without lidocaine) for providing analgesia for venipuncture in adults. This non-inferiority trial evaluated a single iontophoretic dose of 20 mA·min.

6.1.2 General Discussion of Endpoints

The Sponsor used four endpoints to assess the efficacy of Lidopel:

1. failure rate compared to placebo for providing sufficient unsupplemented analgesia for shave removal of superficial skin lesions,
2. VAS scores for pain compared with placebo for shave removal of skin lesions, punch biopsies, and venipuncture,
3. global satisfaction scores for the iontophoretic treatment and dermatological intervention whenever VAS scores were assessed,
4. differences in VAS scores versus placebo for pain of venipuncture between Lidopel and Iontocaine.

The use of failure rate for providing adequate analgesia was based in part on studies submitted in support of efficacy for the Iontocaine NDA. These studies, like the ones reviewed here, included assessment of analgesia using a needle-prick test before performing the dermatological procedure and assessment of procedural pain using VAS scores. The Sponsor included excerpts of the clinical reviews for the Iontocaine NDA in Appendix 8-8 of the NDA. These excerpts included the concerns the reviewer had with the use of needle-prick testing and the treatment unblinding that occurred with its use. The Division, however, did concur with the Sponsor that use of failure rates, needle-prick testing, and counting requests for supplemental analgesia as a treatment failure were acceptable assessments of efficacy.

The use of VAS scores to assess pain and categorical global satisfaction scores have been validated in adults.

The non-inferiority trial conducted by the Sponsor offered not only a valid means of assessing efficacy, but an opportunity to make at least a superficial comparison with the innovator product, Iontocaine. The choice of a 20 mA·min iontophoretic dose for the study, however, confounded the results as Iontocaine is approved only for 40 mA·min treatments.

6.1.3 Study Design

The Sponsor took two approaches to evaluating efficacy. First was assessment of treatment failures. This method was utilized in Study # 97-07.0 and #99-02.0, and defined treatment failure as one or more of the following:

1. inability to tolerate the specified iontophoretic dose;
2. elicitation of pain at one or more of the sites tested by needle prick following iontophoretic treatment;
3. request for supplemental analgesia during the dermatological procedure – valid only for subjects undergoing shave removal procedures.

Subjects who "failed" were discontinued from the study; those who "passed" were further evaluated using secondary endpoints for rating pain with the procedure and global satisfaction with the iontophoretic treatment and dermatological procedure. Pain was assessed using a 100 mm Visual Analog Scale (VAS) score with which "0" indicated no pain and "100" indicated severe pain. Global satisfaction was rated with an 11-point categorical satisfaction score in which "0" indicated no satisfaction and "10" indicated complete satisfaction.

The second method for assessing efficacy involved using a 100 mm VAS score to measure the pain associated with venipuncture as the primary endpoint. In studies #99-07.0, —, and #00-1-03.0, the VAS scores associated with Lidopel treatment were compared to that of placebo or, in the case of study #00-1-03.0, placebo and Iontocaine. Global satisfaction scores as measured with an 11-point categorical satisfaction score were used as a secondary endpoint in each of these studies.

For studies #97-07.0 and #99-02.0, a significantly lower failure rate with Lidopel than with placebo constituted a "win" in terms of efficacy. In studies #99-07.0 and — significantly lower VAS scores with Lidopel constituted a "win." Study #00-1-03.0 was designed as a non-inferiority trial in which differences in VAS scores between Lidopel and placebo were compared to those between Iontocaine and placebo.

In each of the clinical trials, blinding, randomization, identification of endpoints, and prospective formulation of a statistical analysis plan were adequate to minimize bias. In studies #97-07.0 and #99-02.0, subjects underwent a needle-prick test to assess adequacy of analgesia prior to undergoing either a punch biopsy or shave removal of a superficial skin lesion. The needle-prick test resulted in most, and in some cases all, of the placebo-treated patients being discontinued from the study and effectively unblinded the investigator. Although this might have introduced bias in the last part of the study, i.e., the actual dermatological procedure, the majority of the treatment failures occurred in this part of the studies, and where supplemental analgesia was provided, the responder analysis results were not significantly altered.

There were two concerns as regards the efficacy results involving the use of iontophoretically administered epinephrine as a placebo. First, validation of iontophoretically applied epinephrine as a placebo was not provided. A similar placebo was used in studies which supported the approval of Iontocaine, however those studies did not include iontophoretic doses in excess of 40 mA·min as were used in this NDA. The concern regarding this placebo treatment is that it may alter blood flow to the nerves within the dermis producing either a hypo- or a hypergesic effect. This concern is supported by the changes in VAS scores noted for placebo in study #99-07.0 where the scores decreased with increasing iontophoretic dose. Second, in study #99-02.0, placebo was only administered at 80 mA·min and then compared to active treatments administered at 40, 60, and 80 mA·min.

In the non-inferiority trial, two design issues impact on the adequacy of the trial for supporting efficacy. First, the delivery electrode patch that was used in the study was 10.1 cm^2 which has 25% more surface area than the — 8.1 cm^2 patch which was used in the other Phase 3 trials. In theory, the larger patch should provide a less concentrated dose of drug over a larger surface area and produce a less dense block. The use of a larger patch would be expected therefore to reduce analgesia and possibly reduce adverse events associated with the drug product and/or the iontophoretic current. The second design issue with this study is that the iontophoretic dose selected, 20 mA·min, is the "optimal" dose for Lidopel, but only half the labeled dose for Iontocaine. As indicated by the primary clinical reviewer in NDA review for Iontocaine (which was included in Appendix 8-8 of the Lidopel NDA), two efficacy studies of Iontocaine indicated that approximately 20% of subjects did not receive sufficient analgesia with Iontocaine at doses of 20 and 30 mA·min to pass the equivalent of the Lidopel needle-prick test. Thus the significance of a non-inferior determination is of questionable clinical value.

6.1.4 Efficacy Findings

The table below provides a breakdown of the Lidopel treatments administered in the clinical trials. The table divides the treatments based on the size of the delivery electrode patch, the nominal iontophoretic dose administered, and the procedure for which the treatment was administered.

Table 6.1-1 Lidopel treatments by dose, procedure and delivery electrode size

	Delivery Electrode Patch Size (cm^2)							
	8.1					10.1		
Iontophoretic Dose	20 mA·min	30 mA·min	40 mA·min	60 mA·min	80 mA·min	20 mA·min	40 mA·min	80 mA·min
Shave removal			20	60	20		8	
Punch biopsy					7			9
Venipuncture – adult	60	20	20			30		
Column Totals	**100**	**20**	**50**	**60**	**27**	**30**	**8**	**9**

The table demonstrates the breadth of the trial designs as well as a relative paucity of data supporting final dosing requirements. In short, these results are more representative of Phase 2 dosing explorations than pivotal trials. Detailed reviews of each of the five

clinical trials are provided in the Appendix, Section 10.1, of this review; summaries of the methods, efficacy findings, and deficiencies for each study are included here. The trials were all single-site, randomized and controlled. The Sponsor identified one of the trials as a Phase 2 study and the others were classified as Phase 3.

Study 97-07.0: This Phase 2 trial was the only one used to assess analgesia for punch biopsies. In addition, the trial was used to assess two different delivery electrode patch sizes, 8.1 and — cm^2, and two different iontophoretic doses, 40 and 80 mA·min for both patch sizes and 80 mA·min alone for the 8.1 cm^2 patch. Both shave removals of skin lesions and punch biopsies were evaluated. The placebo, as for all the clinical trials, consisted of iontophoretically administered Lidopel solution that was formulated without lidocaine, i.e., the placebo was an iontophoretic dose of epinephrine. Unless noted otherwise, the placebo was administered at the same iontophoretic dose and with the same size delivery electrode as the active/Lidopel treatment. The table below indicates which patches and iontophoretic doses were used with which procedures.

Table 6.1-2 Procedures, doses and patch sizes for Study 97-07.0

		Delivery electrode patch size (cm^2)	
		8.1	—
Iontophoretic Dose (mA·min)	40		Shave removal (n^1=15)
	80	Punch biopsy (n^1=17)	Punch biopsy (n^1=16)

[1]The n includes 8 subjects who received placebo treatment.

Failure rates between placebo and Lidopel were compared as the primary efficacy endpoint. Failure included inability to tolerate the full iontophoretic dose, pain with a needle-prick test before the procedure, and request for supplemental analgesia during the procedure (applicable only in the case of shave removals). Subjects who underwent their dermatological procedures rated their pain and global satisfaction.

Of the subjects receiving Lidopel treatments, 33% (8/24) failed the needle-prick test while 100% (23/23) of subjects receiving the placebo treatment failed. Lidopel failures by dose and patch size were 33% (3/9) of those with the large patch and 80 mA·min dose, 63% (5/8) of those with the large patch and 40 mA·min dose. Of the subjects receiving the small patch and the 80 mA·min dose, 0% (0/7) failed the test.

Only three of those subjects who passed the needle-prick test could be assessed for the need for additional analgesia, i.e., only three subjects underwent shave removals. Two of these three subjects required supplemental analgesia. Therefore, in all, 42% (10/24) of subjects receiving Lidopel treatments experienced treatment failures. The large patch and 40 mA·min dose of Lidopel were associated with a failure rate of 88% (7/8); the large patch and 80 mA·min dose resulted in a 33% (3/9) failure rate; the small patch and 80 mA·min dose had no treatment failures (0/7). It should be noted that the 0% failure rate

was associated with punch biopsy procedures which precluded the use of additional analgesia; therefore, the 0% failure rate represents the lower limit for the true failure rate.

This trial was used to assess duration of analgesia. One half hour after the iontophoretic treatment, those subjects who passed the first needle-prick test and required no supplemental analgesia were retested with the needle-prick test. Thirteen of the 14 subjects who should have been evaluated were, and of those, 69% (9/13) passed the repeat test. No assessment of whether analgesia sufficient for dermatological procedures was performed, and no further characterization of the analgesic time profile was made.

Study 99-02.0: This Phase 3 study was conducted in two parts. The first part consisted of a double-blinded, randomized, placebo-controlled comparison of three iontophoretic doses of Lidopel used to provide dermal analgesia for shave removals of skin lesions. The three iontophoretic doses of Lidopel included 40, 60 and 80 mA·min; the placebo was an iontophoretically-administered 80 mA·min dose of 1:100,000 epinephrine. A delivery electrode with an 8.1 cm^2 surface area was used throughout the study. Following iontophoretic treatment, analgesia was assessed with needle-prick testing. Those patients who passed the needle-prick test underwent their procedure. Patients who failed the needle-prick test or who required supplemental analgesia were considered treatment failures, the primary endpoint. Those who had their procedures assessed their pain levels and global satisfaction with treatment as secondary endpoints. The iontophoretic dose shown to be most effective and safe was to be used in the second part of the study. The second part consisted of comparing Lidopel with placebo, both administered at the same iontophoretic dose, for providing analgesia during shave removals of skin lesions. The protocol and endpoints were otherwise the same as in the first part of the study.

In part one of the study, all of the Lidopel treatments fared significantly better than the placebo when it came to passing the needle-prick test, and none of the Lidopel treatments did significantly better than the others. When the success rate combining both the results for the needle-prick test and the need for extra analgesia was considered, only that of the 40mAmin dose diminished. When the assessments of a patient, who had taken analgesics, in violation of entry criteria, are disregarded, there was no difference among the three dose groups and placebo for either VAS scores or global satisfaction scores.

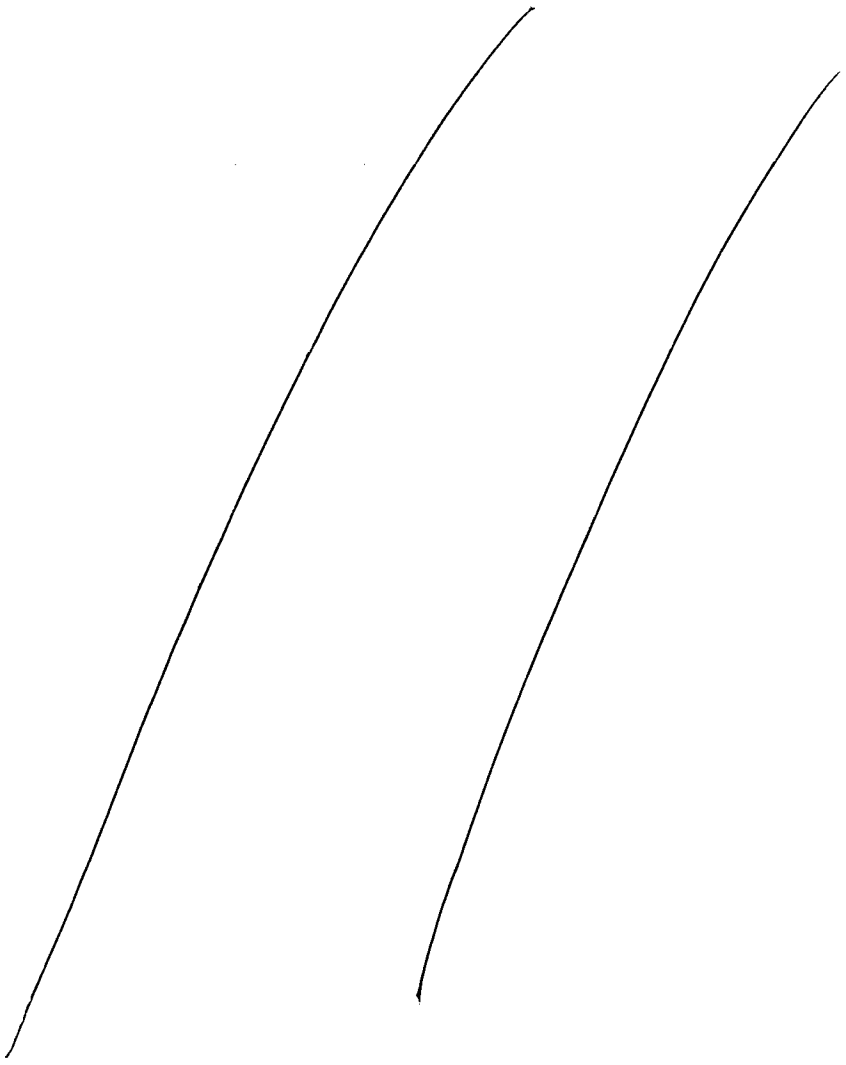
Based on the success rates and numbers of adverse events for each Lidopel dose, it was determined that 60 mA·min was the optimal dose for the dermatological procedure, and the dose to be further studied in part two.

In the second part of the study, the success rate was better with Lidopel than placebo both for passing the needle-prick test and the need for additional analgesia. In this part of the study, there was no significant difference in the VAS scores between Lidopel and placebo

treatments although there was a significant difference in global satisfaction scores between the two groups.

Study 99-07.0: This was a single-center, randomized, double-blinded, placebo-controlled, Phase III trial which evaluated the analgesic effects of Lidopel compared to placebo in adults undergoing venipuncture. Each subject received both a placebo and Lidopel treatment simultaneously, one on each arm. The placebo consisted of an iontophoretic treatment with epinephrine. The study was conducted in two phases. The first phase was to assess which of three iontophoretic doses, 20, 30 or 40 mA·min, provided the best analgesia, and the second was a repeat of the protocol with additional subjects using only the optimal iontophoretic dose as found in phase one.
Based on VAS scores for pain, the combined iontophoretic doses of Lidopel provided significantly more analgesia than the combined placebo treatments. There were however no significant differences in pain levels among the iontophoretic doses when VAS scores for Lidopel treatments were compared to those of the corresponding placebo treatments. Therefore, the lack of adverse events occurring with the 20 mA·min dose led the Sponsor to conclude that a 20 mA-min iontophoretic dose provided the optimal treatment and to use this dose in the second phase of the study. The data from the second phase were combined with the equivalent data from the first phase, i.e., all subjects who received an iontophoretic dose of 20 mA·min, and analyzed *en masse*. With this approach, the Sponsor observed a significant difference in analgesia between the Lidopel and placebo treatments. The magnitude of the difference between active and placebo treatments in the second phase was similar to that in the first.

The clinical significance of the mean of differences in VAS scores was questionable as the magnitudes were so small: 17, 5 and 6 mm for the 20, 30 and 40 mA·min doses, respectively. Global satisfaction scores were therefore used to gain perspective. In the first phase of the study, there was a difference favoring Lidopel treatment when the data from all three iontophoretic dose groups were combined. Although there was no comparison of satisfaction scores performed within each iontophoretic dose group, the greatest difference occurred in the 20 mA·min dose group, 1.2 (out of a possible 10), which was 12 and 4 times that observed in the 30 and 40 mA·min dose groups, respectively. The second phase of the study however, indicated there was no significant difference in subject satisfaction between Lidopel and placebo at this iontophoretic dose. The data suggest that, in the setting of venipuncture, Lidopel does not provide clinically more meaningful analgesia, based on VAS and global satisfaction scores, than placebo treatment at iontophoretic doses of 20, 30 or 40 mA·min.



Study 00-1-03.0: This non-inferiority study compared the pain perceived by adults undergoing bilateral blood draws from the antecubital fossae following iontophoretic treatment on one arm with one of two active treatments (Lidopel or Iontocaine) and placebo (epinephrine delivered through the same type of iontophoretic device as used for the active treatment) on the opposite arm. Subjects presented for two treatment sessions so as to be exposed to both active treatments and two placebo treatments. An iontophoretic dose of 20 mA·min was used throughout the study. VAS scores were used to assess pain and an 11-point global satisfaction score was used to assess overall satisfaction with the treatment and blood draw.

The results of the study led to the rejection of the null hypothesis, i.e., that the devices differed in analgesia provided. This result is confounded by the iontophoretic dose used, 20 mA·min, as it is half the dose for which Iontocaine is labeled. An additional concern with the study was related to the delivery patch electrode size utilized. A 10.1 cm^2 electrode patch was used for the two active treatments; however, the Lidopel patch evaluated in the other Phase 3 trials is 8.1 cm^2. The difference in surface area when using the same iontophoretic dose could result in a less effective block for the treatment with the larger patch due to the less concentrated application of local anesthetic to the skin. In this instance, the Lidopel treatments may have been less effective than if the 8.1 cm^2 had been used.

Viewing this study only as a comparison of Lidopel and placebo , however the data indicated that use of Lidopel resulted in lower VAS scores than use of placebo, means (standard deviations): 8.6 (10.4) and 17.7 (20.8), respectively. The difference was statistically significant, paired Student's t test: p=0.025. This result is pending confirmation by the statistics team, but the two means are relatively small and indicate that the clinical difference between the two treatments is minimal.

A last consideration for this product was efficacy in terms of success of venipuncture. By combining the data from the three venipuncture studies, it was possible to discern whether or not iontophoretic treatment with epinephrine or epinephrine-containing local anesthetic caused a significant reduction in successful blood draws. The table summarizes the findings. Lidopel appears no different from placebo in terms of successful blood draws and somewhat better than Iontocaine (administered at half the labeled dose). Success rates of 95% with one or two attempts at venipuncture would be satisfactory for a phlebotomist using accepted methods of analgesia.

Table 6.1-3 Success with venipuncture following iontophoretic treatment

Study	Treatments (n)	Success on 1st attempt n (%)			Success on 2nd attempt n (%)			Unsuccessful blood draws n (%)		
		L*	P*	I*	L	P	I	L	P	I
00-1-03	Lidopel (30) Placebo (59) Iontocaine (29)	24 (80)	54 (92)	25 (86)	2 (7)	2 (3)	1 (3)	4 (13)	3 (5)	3 (10)
99-07	Lidopel (100) Placebo (100)	90 (90)	92 (92)		4 (4)	4 (4)		6 (6)	4 (4)	

*L = Lidopel; P = placebo; I = Iontocaine

6.1.5 Clinical Microbiology

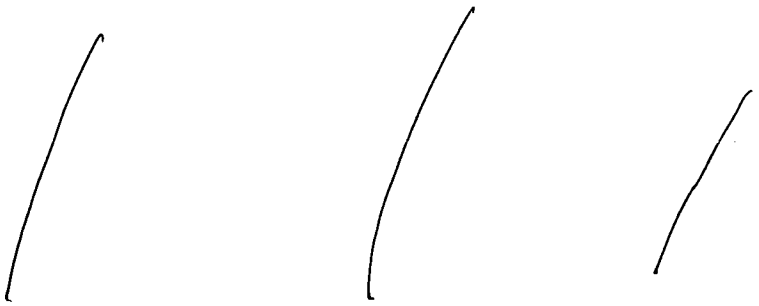
This section is not applicable as the drug product is not an antimicrobial.

6.1.6 Efficacy Conclusions

The efficacy of Lidopel was studied under a variety of conditions but in a nonsystematic fashion. The result was data which were, at times, impossible to put into context in terms of dosing requirements and electrode size for different dermatological procedures and patient populations. Specifically, the following items hindered, and, in some cases, precluded the determination of efficacy.

1. An 8.1 cm^2 delivery electrode patch was not evaluated in one of the Phase 3 trials (Study 00-1-03.0).
2. The non-inferiority trial (Study 00-1-03.0) used an iontophoretic dose of 20 mA·min which was determined to be the optimal dose for Lidopel but was only half the labeled dose for Iontocaine. In the absence of efficacy data for Iontocaine at that dose, the significance of the non-inferior finding of this study is unclear.
3. Punch biopsies were studied in only one trial which, due to its design, resulted in no appropriate comparator group for the 7 subjects who actually underwent the

procedure following an 80 mA·min Lidopel dose via an 8.1 cm^2 delivery electrode. All placebo subjects failed the needle-prick test. Five other subjects in that study also underwent their punch biopsies following an 80 mA·min dose of Lidopel but via a — cm^2 delivery electrode. There was no significant difference in VAS scores for these two groups.

4. Shave biopsies were studied in two clinical trials, Study 97-07.0 and Study 99-02.0. In the first of those trials, only 2 subjects underwent their procedure. They received a 40 mA·min dose of Lidopel via a — cm^2 delivery electrode. As with their punch-biopsy counterparts, there was no comparator group.
5. In study 99-02.0, the first part of the study indicated Lidopel at doses of 40, 60 and 80 mA·min had significantly fewer failures with the needle-prick test and significantly lower VAS scores than an 80 mA·min dose of epinephrine when used for performing shave biopsies. There was no significant difference in either needle-prick failure rates or VAS scores among the active groups. In the second part of the study, in which a 60 mA·min dose of Lidopel was compared to a 60 mA·min dose of placebo for the same procedure, significantly more Lidopel-treated patients passed the needle-prick test, however there was no significant difference in the VAS scores between the two groups.
6. Study 99-07.0 evaluated analgesic effects of 20, 30 and 40 mA·min doses of Lidopel and placebo for venipuncture in Part 1 of the study. Lidopel treatment at 30 and 40 mA·min failed to significantly differ from placebo treatment in terms of VAS scores, and therefore, 20 mA·min was considered the optimal dose. In Part 2 of the study, with 20 mA·min iontophoretic dosing, Lidopel treatment provided statistically significant more analgesia than placebo treatment based on VAS scores, but the clinical significance of the difference, 13 mm out of a possible 100 mm, is questionable. The lack of significant difference in global satisfaction scores at the 20 mA·min dose also raises questions about the clinical significance of the drug's effect. Additionally, there was a significant difference in VAS scores associated with placebo treatments at 20 and 40 mA·min doses.
7. 

In summary, limited data suggest that there might be a difference in analgesia produced by Lidopel and an equivalent iontophoretic dose of epinephrine when used for shave biopsies and venipuncture. A 60 mA·min dose might be effective for shave

biopsies in adults. The validity of the placebo treatment is uncertain and could be masking the true effectiveness of the Lidopel treatments. Lack of specification and/or recording of needle size in the venipuncture studies precluded an important consideration for efficacy. Lack of efficacy data for Iontocaine at half its labeled dose, limits the usefulness of the non-inferiority trial. Adequate characterization of the depth (physical and sensory) and duration of analgesia with Lidopel has not been provided.

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7 INTEGRATED REVIEW OF SAFETY

7.1 Methods and Findings

In addition to data from clinical trials, the Sponsor submitted literature findings and FDA medical reviewer's notes for the Iontocaine NDA submission in support of the safety of iontophoretically administered lidocaine and epinephrine.

7.1.1 Deaths

No deaths occurred in any of the human subject studies of Lidopel.

7.1.2 Other Serious Adverse Events

No serious adverse events were reported for any of the human subject studies of Lidopel.

7.1.3 Dropouts and Other Significant Adverse Events

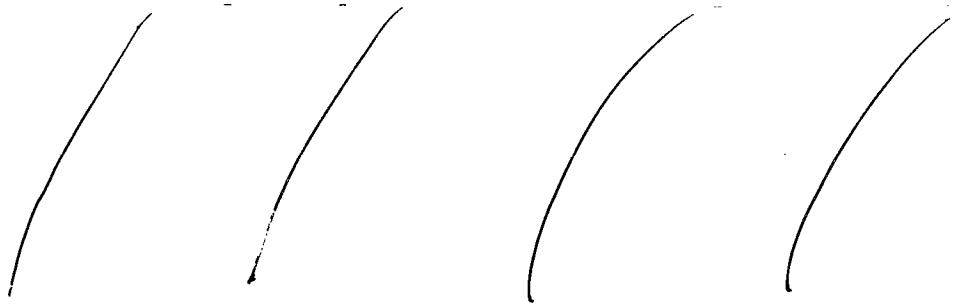
7.1.3.1 Overall profile of dropouts

Of the — subjects enrolled in the clinical studies, , and — subjects were withdrawn due to adverse events.

Subject #203 — withdrew from Study #97-07.0 after 90 seconds of iontophoretic treatment due to a burning sensation under the delivery electrode. Subject #030-008 who was participating in Study #00-1-03.0 was withdrawn by the investigator following the first of the two treatment visits due to reported numbness in the right arm from the forearm to the hand and an achy right shoulder. These symptoms were on the

side that had received an iontophoretic treatment but were attributed to the subject's arthritis

In all of the human subject studies, a total of — participants were unable to complete their iontophoretic treatments because of discomfort, pain, or burning sensations. —



7.1.3.2 Adverse events associated with dropouts

Adverse events reported for the subjects who dropped out or were withdrawn from the study included blanching at the iontophoretic site for subject #20? —. in study 97-07.0 and for subject #030-008 in study 00-1-03.0, shoulder pain and numbness in the forearm and hand on the side given the placebo treatment. The shoulder pain and arm numbness for subject #030-008 were attributed to arthritis. No resolution time was reported for this subject for either event; and the subject did not participate in the second phase of the study.

The nine subjects who were not able to tolerate the full iontophoretic treatment gave the following reasons: four reported itching or painful scratching, three reported burning sensations, one reported pain and one just cried and ask that the electrodes be removed. Seven of the nine treatments were placebo; the other two were Lidopel treatments.

7.1.3.3 Other significant adverse events

All reported adverse events were described as mild or moderate and, generally, were similar to those seen with other iontophoretic products. None were considered to be significant in terms of their nature, duration, or need for treatment.

7.1.4 Other Search Strategies

Adverse events were evaluated in terms of demographic frequency and relationship to subject's skin type, iontophoretic dose, and iontophoretic drug administered. No special search strategies were utilized in the course of this review although an integrated safety database had to be created from the individual study data tables provided. The safety database was used to conduct the analyses not performed by the Sponsor, but requested by the Division.

7.1.5 Common Adverse Events

In all, 361 iontophoretic treatments of Lidopel, 247 treatments with placebo and 29 treatments of Iontocaine were administered for a total of 637 iontophoretic treatments. The Sponsor reported that 113 adverse events occurred in total across all studies and treatments. These events reported were either mild (85%) or moderate (15%) in severity. All but one adverse event were reported to have resolved; one of the mild events, petechia, was described as having "insufficient follow up." Most of the adverse events, 79%, resolved without intervention; discontinuation of iontophoretic therapy was required in 7% of cases, and therapeutic or medical intervention was required in 14% of cases.

The NDA, as originally submitted and subsequently amended, did not provide a breakdown of adverse events based on treatment type (Lidopel, placebo, Iontocaine), electrode associated with the event (drug/placebo-containing delivery electrode or return electrode), iontophoretic dose, onset time relative to iontophoretic treatment, duration of event, and subject demographics associated with each event. At the time of this review, the Sponsor was preparing an amendment to redress this issue. In the interim period, a summary of all adverse events with no distinction for treatment, electrode, or iontophoretic dose is presented below. In addition, adverse event data tables were constructed *de novo* utilizing the data listings from the NDA.

7.1.5.1 Eliciting adverse events data in the development program

The Sponsor focused on dermatological adverse events at the sites of electrode placement. The clinical trial protocols required investigator assessment of the sites prior to and following iontophoretic treatment as well as follow-up assessments when dermatological changes were noted. Specifically, a visual inspection of the delivery and return electrode sites was to have been performed by the Investigator or a designee immediately after the iontophoretic treatment was completed. All but the earliest two protocols indicated "the presence of blanching and/or mild erythema are not considered

adverse events, however, their occurrence will be recorded on the appropriate CRF." Any "other clinically significant changes of the skin occurring from the iontophoretic treatment should be recorded as an adverse event." Follow up consisted of telephone calls two to three days after the procedure questioning the subjects on the condition of the treatment site. Further evaluation by an Investigator, which required a return to clinic, was to be done if the Investigator deemed it appropriate. Guidelines were not provided for what constituted need for further assessment. Erythema was graded from 0 to 4 based on the definitions below; only grades three and higher were to be recorded as adverse events. In addition to the above, only spontaneous reporting of adverse events by the subjects and adverse events noted by the investigative staff were recorded in the CRFs and treated or followed as was deemed appropriate by the investigator.

Table 7.1-1 Grading of erythema at the site of delivery and return electrodes

Grade	Rating	Definition
0	None	No erythema
1	Barely	Very slight or barely perceptible
2	Mild	Well defined
3	Moderate	Moderate to severe
4	Marked	Severe (beet red) to slight eschar formation (injury in depth)

7.1.5.2 Appropriateness of adverse event categorization and preferred terms

Adverse events were only listed verbatim from the CRFs. Preferred terms were not used by the Sponsor as they did not have dictionary access. In addition, adverse events were not categorized by system. As there were relatively few adverse events, the Division accommodated the Sponsor by assigning the preferred terms and categorizing the events during conduct of the review.

7.1.5.3 Incidence of common adverse events

Among all the treatments, i.e., Lidopel, placebo and Iontocaine, the following adverse events occurred with a frequency of greater than 1%: burning, itching, bruising, pain, petechiae and erythema. Blanching was a common occurrence but was considered by the Sponsor as an expected response to treatment rather than an adverse event.

7.1.5.4 Common adverse event tables

Table 7.1-2 Common Adverse Events

Adverse Event	Incidence (based on number of treatments)					
	Lidopel		Placebo		Iontocaine	
Blanching[1]	26/33	(79%)	24/24	(100%)	N/A	
Burning	6/361	(1.7%)	6/247	(2.4%)	3/29	(10%)
Bruising	3/361	(0.8%)	2/247	(0.8%)	2/29	(7.0%)
Erythema[2]	9/361	(2.5%)	10/247	(4.0%)	0/29	(0%)
Itching	5/361	(1.4%)	4/247	(1.6%)	0/29	(0%)
Pain	9/361	(2.5%)	3/247	(1.2%)	0/29	(0%)
Rash	20/361	(5.5%)	1/247	(0.4%)	0/29	(0%)

[1]The Sponsor considered blanching an adverse event (AE) in studies 96-08.0 and 97-07.0 only. After that it was considered "a normal, temporary loss of skin color due to the vasoconstriction caused by epinephrine" and was no longer documented as an AE. The denominator was adjusted to reflect the number of subjects actually evaluated.

[2]Erythema was recorded as an adverse event only if it was considered "moderate to severe" with severe defined as "beet redness to slight eschar formation (injury in depth)." Erythema that was "very slight," "barely perceptible," or "well defined" was not considered an adverse event.

7.1.5.5 Identifying common and drug-related adverse events

Adverse events identified in the table above may have been caused by the application of an iontophoretic current, iontophoresis of epinephrine or lidocaine, or a combination of any or all of the above. All placebo treatments consisted of an iontophoretically applied dose of epinephrine 1:100,000. The lack of a drug-free placebo in which an iontophoretic current was applied, a current-free placebo in which the delivery patch containing drug product was applied, and a current-free, drug-free patch being applied to the skin precludes the determination of the etiology of the AEs described above. The table below consists of data from this NDA and the product labels for Iontocaine and LidoSite. It demonstrates the similarity of adverse events, both in nature and frequency of occurrence, among the three drug products and placebos.

Table 7.1-3 Comparison of Adverse Events for Lidopel, LidoSite and Iontocaine

Adverse Event	Frequency with Treatment [%]*					
	Active			Placebo		
	Lidopel	LidoSite	Iontocaine	Lidopel w/o lidocaine	LidoSite w/o lidocaine	LidoSite w/o current
Pain/burning	4.2	2.4	5	3.6	5.8	0
Rash	5.5	4.9	1	0.4	0	0
Burns	0	1.4	N/A	0	0.3	0
Subcutaneous hematoma	0.8	0.3	N/A	0.8	0.3	0
Vasoconstriction	0	0.3	N/A	0	0.6	0
Erythema	2.5	0.1	N/A	4.0	0	0
urticaria	0.3	0.1	6	0	0	0
paresthesia	0.3	N/A	3	0	N/A	N/A
Taste perversion	0	N/A	1	0	N/A	N/A
blanching	79	N/A	N/A	100	N/A	N/A

*N/A = no data available

7.1.5.6 Additional analyses and explorations

The Sponsor provided a distribution of adverse events based on iontophoretic dose. Although it was not possible to discern dose dependency of individual adverse events, there appeared to be some dose dependency for events that the Sponsor deemed to be related to the study drug or device. The following table summarizes the Sponsor's findings.

Table 7.1-4 Distribution of Adverse Events by Iontophoretic Dose (based on Table 64 on p96 of Attachment 5 of July 29, 2003 submission)

Iontophoretic Dose (mA·min)	Total number of treatments (n)	Treatments with AEs (n)	Drug or Device Related AEs (n)	Percent AEs related to drug/device (%)
20	179	30	22	12
30	40	2	0	0
40	91	15	9	10
60	80	24	12	15
80	129	39	30	23

The Sponsor also provided a similarly generic approach to evaluating adverse events to subject demographics including skin type. There were four classes of skin type defined as follows.

Type I – always burns easily, never tans
Type II – always burns easily, tans minimally
Type III – burns moderately, tans gradually
Type IV – burns minimally, always tans

The table below summarizes these findings.

Table 7.1-5 Distribution of Adverse Events by Subject Demographics (based on Tables 54, 55, 66, 67, 68 and 69 of Attachment 5 of July 29, 2003 submission)

Demographic	Demographic subgroup	Total treated (n)	Number with adverse events (n)	Percent with adverse events (%)
Gender	Male	148	28	19
	Female	265	59	22
Age				
	18-65 years	316	67	21
	> 65 years	23	2	9
Race	Caucasian	362	75	21
	Black	21	2	10
	Hispanic	18	7	39
	Asian	5	1	20
	Others	7	2	29
Skin Type[1]	I	19	4	21
	II	81	20	25
	III	148	26	18
	IV	138	29	21
	Not available	27	8	30

[1]Skin type data was not collected for the subjects enrolled in Study #96-08.0 and for the first 18 subjects in Study #99-02.0.

7.1.6 Less Common Adverse Events

Most of the less common adverse events were very unlikely to be related to the iontophoretic treatment, e.g., menses, diarrhea and upper respiratory infections. Some of the events however were consistent with elevated systemic epinephrine, e.g., headache, diaphoresis and near syncope, although onset, duration and vital sign measurements

suggest that these episodes were not directly due to the iontophoretic treatment. None of the less common adverse events were described by the Sponsor as serious.

7.1.7 Laboratory Findings

7.1.7.1 Overview of laboratory testing in the development program

Laboratory testing was not included by the Sponsor in the development program, either preclinical or clinical, except with the pharmacokinetics trial,11 nor was it requested by the Division in communications with the Sponsor. The justification for this course of action included the limited systemic exposure to drug product that was expected to occur with the iontophoretic doses used in the clinical trials and the body of knowledge available from approved products containing lidocaine and/or epinephrine and from the literature.

7.1.7.2 Selection of studies and analyses for drug-control comparisons of laboratory values

Not applicable to this NDA.

7.1.7.3 Standard analyses and explorations of laboratory data

Not applicable to this NDA.

7.1.7.4 Additional analyses and explorations

Not applicable to this NDA.

7.1.7.5 Special assessments

Not applicable to this NDA.

7.1.8 Vital Signs

7.1.8.1 Overview of vital signs testing in the development program

Vital sign assessment included noninvasive measurement of blood pressure, heart rate, respiratory rate, and temperature. Vital signs were generally assessed prior to and within minutes after iontophoretic treatment. In Study #97-07.0, vital signs were also recorded one-half hour after the iontophoretic treatment, and in Study #01-1-06.0, a second set of vital signs was recorded one hour following treatment.

7.1.8.2 Selection of studies and analyses for overall drug-control comparisons

The data provided by the Sponsor related to systemic absorption of lidocaine following a single iontophoretic treatment with Lidopel, combined with data from the literature indicate that insufficient amounts of lidocaine are systemically absorbed so as to affect hemodynamics and patient vital signs. No evidence was provided to address the issue of systemic absorption of epinephrine during or following iontophoretic treatments. In all of the clinical trials involving Lidopel, the comparator, if one was used, contained epinephrine in the same concentration as Lidopel. Therefore, an assessment of a controlled comparison was not possible.

Although the Sponsor did not submit a rationale for not evaluating epinephrine exposure, a reasonable argument could be made that a clinically-significant systemic exposure to epinephrine would result in increases in systolic and diastolic blood pressure as well as heart rate. In addition, for the same iontophoretic dose, an epinephrine-placebo treatment should result in greater epinephrine exposure than a Lidopel treatment. Therefore, comparison of vital signs for the two treatment groups could provide an indication of clinically significant epinephrine exposure. The vital sign data was analyzed from this perspective as described in section 7.1.8.3 below.

7.1.8.3 Standard analyses and explorations of vital signs data

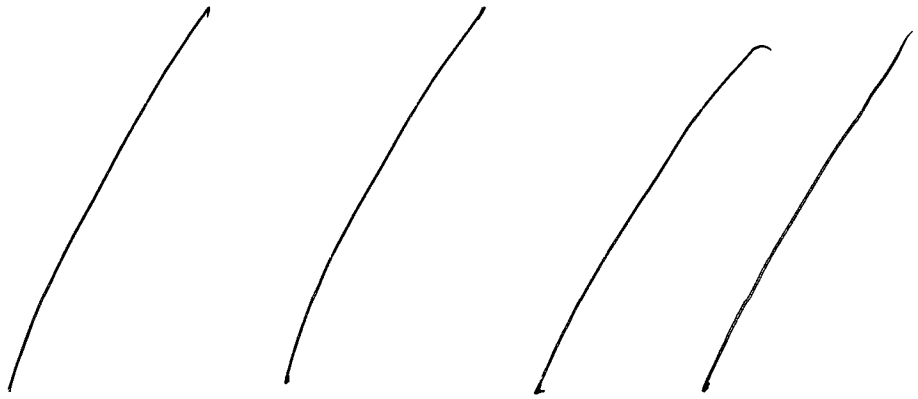
The sponsor reported general vital sign findings for individual studies and an analysis of vital signs for studies 97-07.0 and — There were no changes in vital signs that were considered clinically significant by the Sponsor, and in Study 97-07.0, there was found to be no evidence of a treatment group or drug effect on vital signs based on a repeated measures analysis of variance.

Vital sign analysis for the purpose of this review was limited to descriptive statistics and assessment of changes in vital signs before and after iontophoretic treatment for placebo and Lidopel treated subjects. The data were considered in three groupings: summary adult data from Studies #97-07.0, #99-02.0, #99-07.0 and #00-1-03.0 [redacted], and repeat dose data from Study #01-1-06.0. As noted by the Sponsor for individual studies, respiratory rate and temperature did not change significantly when evaluated across all studies. Therefore, only the hemodynamic vital signs, systolic and diastolic blood pressures and heart rate, were considered for further evaluation.

The table below provides summary information of adult vital sign data from four of the studies. There were no changes in systolic or diastolic blood pressures or heart rate that suggest either a safety concern or a systemic response to epinephrine. These findings are limited to the time point studied which, according to the protocols, was immediately following iontophoretic treatment. It is interesting to note that mean values for all three parameters declined after Lidopel treatment but increased with placebo treatment. Whether this might be related to greater epinephrine exposure with placebo is not determinable, but the difference is relatively small and would not be expected to be of clinical consequence.

Table 7.1-6 Analysis of vital sign data from adult trials

Vital Sign	Pre-treatment		Post-treatment		Change: Post - Pre	
	Mean (SD) [min, max]		Mean (SD) [min, max]		Mean (SD) [min, max]	
	Placebo (n=64)	Lidopel (n=130)	Placebo (n=64)	Lidopel (n=130)	Placebo (n=64)	Lidopel (n=130)
Systolic BP (mmHg)	119.5 (11.7) [94, 150]	121.4 (13.2) [90, 155]	121.0 (11.8) [100, 148]	117.0 (12.8) [88, 154]	1.6 (6.8) [-18, 18]	-4.6 (4.9) [-22, 0]
Diastolic BP (mmHg)	76.6 (9.3) [60, 100]	77.0 (10.2) [32, 94]	79.4 (9.4) [58, 102]	76.9 (10.5) [48, 102]	2.8 (5.2) [-10, 14]	-0.3 (7.0) [-16, 16]
Heart Rate (bpm)	73.2 (8.8) [56, 92]	73.6 (9.1) [52, 100]	74.1 (7.8) [56, 102]	17.2 (9.8) [44, 102]	0.9 (6.9) [-18, 28]	-1.6 (6.7) [-18, 28]



The vital sign data from Study #01-1-06.0 are presented in the table below. This study presents a limited worst-case scenario in terms of patient exposure to repeated doses of Lidopel as well as simultaneous applications of two Lidopel treatments. The study permits a crude assessment of systemic absorption of epinephrine. As no data has been provided by the Sponsor, it is not certain when peak systemic levels of epinephrine are likely to occur following iontophoretic administration. Similarly, it is not known how long systemic exposure to iontophoretically-applied epinephrine persists following treatment. The data from this study indicate that in the minutes and at one hour following repeat 80 mA·min iontophoretic treatments of Lidopel at two sites, there are no vital sign changes to suggest a clinically significant level of systemic absorption of epinephrine. In fact, there is a significant decrease in both systolic blood pressure and heart rate at both post-treatment time points.

Table 7.1-8 Vital sign analysis for Study #01-1-06.0

Vital Sign	Pre-treatment	Post-treatment	1 hour Post-treatment	Change: Post- vs. Pre-treatment	Change: 1 hr. Post- vs. Pre-treatment
	Mean (SD) [min, max]	Mean (SD) [min, max]	Mean (SD) [min, max]	Mean (SD) {p-value[1]}	Mean (SD) {p-value[1]}
Systolic BP (mmHg)	137.6 (20.1) [112, 177]	121.3 (12.4) [103, 139]	126.0 (22.7) [98, 169]	-16.3 (15.6) {0.004}	-11.6 (18.1) 0.049}
Diastolic BP (mmHg)	75.3 (14.0) [54, 96]	71.3 (10.6) [55, 84]	71.2 (11.9) [53, 86]	-3.9 (8.2) {0.125}	-4.1 (8.6) {0.128)
Heart Rate (bpm)	76.8 (12.6) [60, 101]	67.3 (7.5) [55, 77]	66.6 (10.4) [53, 85]	-9.4 (7.3) {0.001}	-10.2 (5.6) {<0.001}
Resp. Rate (bpm)	14.7 (3.1) [10, 20]	14.8 (3.0) [10, 20]	13.5 (2.8) [9, 18]	0.1 (2.0) {0.889}	-1.2 (4.2) {0.356}

[1]P-values were generated by the Sponsor using the paired, two-sided Student's t- test and were verified by this reviewer.

7.1.8.4 Additional analyses and explorations

None were conducted by the Sponsor and none were performed by the reviewer.

7.1.9 Electrocardiograms (ECGs)

7.1.9.1 Overview of ECG testing in the development program, including brief review of preclinical results

ECG testing was not included by the Sponsor in the development program, either preclinical or clinical, nor was it requested by the Division in communications with the Sponsor. The primary justification for this course of action was the limited systemic exposure to drug product that was expected to occur with the iontophoretic doses used in the clinical trials. Although the Sponsor did evaluate plasma levels of lidocaine following a single iontophoretic treatment, plasma levels of epinephrine were never assessed, and lidocaine levels following repeated or multiple simultaneous iontophoretic treatments were not evaluated.

7.1.9.2 Additional analyses and explorations

None were performed by the Sponsor or by the reviewer.

7.1.10 Immunogenicity

Not applicable to this NDA.

7.1.11 Human Carcinogenicity

As noted in the Pharmacology-Toxicology review, the sponsor was not required, according to ICH M3 guidance, to conduct carcinogenicity assessments for lidocaine or epinephrine as they are not to be used continuously for >6 months.

Previous evaluation of lidocaine with epinephrine has been conducted by the National Toxicology Program and results suggested that lidocaine itself is not associated with enhanced carcinogenic risk though dosing has been assessed as being inadequate.

A metabolite of lidocaine, 2,6-xylidine, is a known and potent rat carcinogen although the Anesthetics and Life Support Drugs Advisory Committee determined that the differences in metabolism between rats and humans as well as the acute use of this product results in a low carcinogenic risk for humans.

7.1.12 Special Safety Studies

Special safety studies were neither proposed by the Sponsor nor requested by the Division.

7.1.13 Withdrawal Phenomena and/or Abuse Potential

Withdrawal phenomena have not been reported for either lidocaine or epinephrine at the doses or dosing regimens expected to be used with this drug product even in the anticipated "worst case scenarios." Abuse potential is expected to be minimal based on the long historical experience the Agency has with lidocaine and epinephrine when used alone and in combination with each other.

7.1.14 Human Reproduction and Pregnancy Data

The sponsor did not conduct reproductive and developmental toxicology studies but offered the following as evidence that iontophoretically administered lidocaine and epinephrine pose no significant risk in terms of reproduction and pregnancy.

1) The previous Agency findings of human safety for lidocaine/epinephrine drug products currently marketed.
2) Publicly available information derived from:
    a. Iomed Iontocaine® NDA 20-530
    b. Data from other lidocaine/epinephrine products
    c. Data in the published literature
3) The low levels of systemically available lidocaine or epinephrine expected after iontophoretic application of the Lidopel® drug solution to human skin.

7.1.15 Assessment of Effect on Growth

Due to the limited systemic exposure to Lidopel and the limited acute nature of its clinical use, assessment of Lidopel's effects on growth was not required and was not conducted.

7.1.16 Overdose Experience

Overdose with Lidopel can take two forms. First, excessive or inappropriate use, such as multiple simultaneous applications or use on abraded or injured skin, could theoretically result in systemic toxicity related to lidocaine and/or epinephrine. Second, repeat applications to the same skin site may cause tissue injury. Study 01-1-06.0, evaluated dermal irritation following a repeat application of Lidopel at the same site for simultaneous applications at two sites. The study utilized the highest iontophoretic dose, 80 mA·min. There was no evidence of overdose of either form, systemic or local, based on vital sign data, adverse event reports and visual assessment of application sites.

7.1.17 Postmarketing Experience

Lidopel is not marketed in the United States or foreign countries. There is however, safety information available on a similar product, Iontocaine® which iontophoretically delivers the same combination of lidocaine and epinephrine and is marketed in the United States.

Iontocaine® uses a 40 mA·min maximum iontophoretic dose which is in the midrange of doses studied with the Lidopel product, thus it would be expected to have a similar safety profile. According to the package insert, adverse events occurring with Iontocaine® include urticarial reaction (approximately 6%) primarily under the dispersive electrode, rash (1%) and burning sensation (5%) under the dispersive electrode, paresthesia (3%), and taste perversion (1%). Abrasion, application site reaction, ecchymosis, petechia, hypesthesia, dizziness, pain, postural dyspnea, and redness lasting greater than 24 hours occurred in <1% of the subjects. In all but one instance, these reactions did not interfere with the iontophoresis treatments.

The Iontocaine® package insert also states that animal studies showed that a single application of the product can cause erythema and edema, and that multiple applications could cause acanthosis, hyperkeratosis, inflammatory response, hemorrhage and/or necrosis involving only the epidermis and the papillary dermis. These lesions resolved after one week.

7.2 Adequacy of Patient Exposure and Safety Assessments

7.2.1 Description of Primary Clinical Data Sources (Populations Exposed and Extent of Exposure) Used to Evaluate Safety

7.2.1.1 Study type and design/patient enumeration

Table 4.2-1 above presents a breakdown of the clinical trial used to evaluate the safety and efficacy of Lidopel in humans. The table provides the Phase, nature, enrollment numbers, iontophoretic doses and delivery electrode patch information for each of the trials. The first table below provides a breakdown of exposures for each of the drug products, Lidopel, placebo, and Iontocaine, by iontophoretic dose and delivery electrode size. The second table below provides a comparison of exposures to Lidopel based on the iontophoretic dose and the size of the delivery electrode used.

Table 7.2-1 Extent of exposure by drug product, iontophoretic dose and delivery electrode size

Drug	Total Exposures	Exposures by Iontophoretic Dose (mA·min)					Exposures by Electrode Size (cm^2)			
		20	30	40	60	80	8.1	10.1	—	—
Lidopel	361	130	20	57	60	94	310	30	3	18
Placebo	247	138	20	33	20	36	172	59	0	16
Iontocaine	29	29	0	0	0	0	0	29	0	0

Table 7.2-2 Exposures to Lidopel by iontophoretic dose and delivery electrode size

Iontophoretic Dose (mA·min)	Exposures by Delivery Electrode Size			
	8.1 cm^2	10.1 cm^2	— cm^2	— cm^2
20	100	30	0	0
30	20	0	0	0
40	50	0	0	7
60	60	0	0	0
80	80	0	3	11

7.2.1.2 Demographics

The table below provides a breakdown of subject demographics for the clinical trials. There were significantly more females than males enrolled in the trials, but sufficient numbers of both were evaluated to adequately assess this demographic for safety and efficacy. In terms of age, race and skin type, too few individuals who were either over the age of 65 years - especially over the age of 75 years, were non-Caucasian, or had skin type I were evaluated to adequately determine either safety or efficacy in those categories.

Table 7.2-3 Clinical trial subject demographics – entire safety database

Demographic	Demographic subgroup	Total subjects treated (n)
Gender	Male	148
	Female	265
Age	[illegible]	[illegible]
	[illegible]	[illegible]
	18-65 years	317
	> 65 years	20
Race	Caucasian	362
	Black	21
	Hispanic	18
	Asian	5
Skin Type[1]	I	19
	II	81
	III	148
	IV	138
	Not collected	27

[1]Skin type data was not collected for the subjects enrolled in Study #96-08.0 and for the first 18 subjects in Study #99-02.0.

7.2.1.3 Extent of exposure (dose/duration)

All trials, with the exception of Study #01-1-06.0, utilized a single application of Lidopel with a single iontophoretic dose. The patches and current were applied long enough to deliver the nominal iontophoretic dose required by the study. The maximum time of exposure to iontophoretic current was on the order of 20 minutes, the time required to deliver an 80 mA·min iontophoretic dose. In study #01-1-06.0, each of 12 adult subjects had two simultaneous 80 mA·min applications of Lidopel, one on an antecubital fossa and the other on the contralateral thigh. Once the treatment was over, the patches were removed, the sites were assessed for irritation, and a second simultaneous treatment was applied to both of the sites. No assessment of analgesia was made in this study, and no assessment of blood levels of the drug product was made.

From a clinical perspective, it is anticipated that a product such as this may be applied simultaneously at multiple sites, generally no more than two, and possibly sequentially with little time lapsing between applications. Efficacy evaluation for these situations would provide clinically useful information regarding possible rescue of an insufficient analgesic effect following a single treatment at one site. Potentially, the second treatment could have greater effect perhaps due to reduced skin impedance or less effect due to conditions such as possible current injury. Evaluation of safety for these situations is important as exposure to additional drug product and repeat exposure at the same site

may result in sufficient systemic exposure of lidocaine and/or epinephrine as to have untoward clinical effects especially in vulnerable populations such as small children or debilitated older adults. Although Study#01-1-06.0 assessed localized dermatological effects of these types of exposures, further evaluation including active assessment for systemic toxicity and measurements of plasma levels of lidocaine and epinephrine should be done. Characterization of the depth and duration of analgesia associated with repeat applications at the same skin site should also be performed.

7.2.2 Description of Secondary Clinical Data Sources Used to Evaluate Safety

7.2.2.1 Other studies

No studies other than those described above were submitted for the evaluation of safety.

7.2.2.2 Postmarketing experience

There is no postmarketing experience with Lidopel. The safety experience associated with Iontocaine is cited elsewhere in this review.

7.2.2.3 Literature

Literature cited by the Sponsor was primarily directed at supporting efficacy. One article by Ashburn et al., assessed adverse events, vital sign data and serum lidocaine levels following a 40 mA·min dose of 2% lidocaine and 1:100,000 epinephrine in adults using the Iomed system. Their findings were similar to the Sponsor's in the following ways.

1. There were no detectable levels of lidocaine ($\geq$ 0.1 mcg/ml) immediately after iontophoretic treatment and again at 30, 60 and 120 minutes after treatment.
2. All vital signs were within normal limits.
3. All but one patient had blanching, all but 2 had erythema.
4. Less common adverse events included petechiae and paresthesias.

A PubMed literature search resulted in no additional materials compared to those provided by the Sponsor.

7.2.3 Adequacy of Overall Clinical Experience

The Sponsor was advised that evaluation of Lidopel in a minimum of 300 subjects might be sufficient to allow a determination of safety and efficacy. At the Pre-NDA meeting, a concern was expressed that the final number of subjects might be too small considering the nature of the protocols. In all 325 subjects underwent a total of 361 iontophoretic treatments with Lidopel. The following deficiencies in the extent of exposure limited the assessment of safety.

1. Data from the trials assessing Lidopel efficacy for shave removals and punch biopsies suggested that the iontophoretic dose most likely to be efficacious was 80 mA·min. This dose of Lidopel was assessed in 37 subjects, 29 of whom received it with the [redacted] 3.1 cm^2 delivery electrode. [redacted]
2. The majority of the subjects in the clinical trials were Caucasian females. Although females outnumbered males by 2:1 in the adult trials, a sufficient number of males, 116, [redacted] ere treated with Lidopel for an assessment of safety at the lower iontophoretic doses. The 99 non-Caucasian subjects were predominantly of Hispanic ethnicity and were too few in numbers to assess safety, or efficacy, at any particular iontophoretic dose.
3. Despite advice from the Division to include a significant number of subjects over the ages of 65 and 75 years, only 21 subjects over the age of 65 years were exposed to Lidopel treatment, and of those, only 2 were over the age of 75 years.
4. Only subjects who were in relatively good health were enrolled in the clinical trials.

In terms of safety, the Agency's safety experience with Iontocaine could supplement the data from the clinical trials, however, Iontocaine was approved only for a 40 mA·min iontophoretic dose leaving a paucity of evidence of safety at the higher doses.

7.2.4 Adequacy of Special Animal and/or In Vitro Testing

The dermal irritation study in rabbits submitted by the sponsor was sufficient, per the Pharmacology-Toxicology review team, to address the concerns for potential dermal irritation that were raised at the Pre-IND meeting.

7.2.5 Adequacy of Routine Clinical Testing

Routine clinical testing was limited to vital sign collection. The timing of vital sign assessment was important as it was the only quantitative assessment that could be related to systemic absorption of epinephrine. No evidence was provided, and none could be found in the literature, to indicate either an absence of systemic absorption or the timing of peak serum levels relative to iontophoretic treatment. Vital signs were not collected during the iontophoretic procedure to assess hemodynamic derangements that may occur with the pain, burning or itching that were experienced by some subjects and which were severe enough to stop the iontophoretic treatment.

7.2.6 Adequacy of Metabolic, Clearance, and Interaction Workup

Metabolism, clearance and interaction of lidocaine and epinephrine were not studied by the Sponsor and were not required by the Division as systemic levels were expected to be so low as to not be detectable or to be sufficiently low that knowledge of these processes from other approved epinephrine-containing lidocaine products should be applicable.

7.2.7 Adequacy of Evaluation for Potential Adverse Events for Any New Drug and Particularly for Drugs in the Class Represented by the New Drug; Recommendations for Further Study

The evaluation for adverse events was lacking in two regards. First, the sponsor opted to discount blanching as an adverse event after the first two clinical trials, in part, because the frequency with which it occurred led the Sponsor to describe it as an expected response to treatment. Second, there was no proactive assessment for signs and/or symptoms related to possible systemic effects of epinephrine.

7.2.8 Assessment of Quality and Completeness of Data

The Sponsor, at the time of this review, had not submitted a complete, integrated, safety database as previously requested. The data analysis conducted for this review was based on a partial data table created with data from the individual studies. Submission of the Sponsor's integrated database is pending.

Some of the data relevant to adverse events was missing from the trials. In particular, the electrode associated with the adverse event was not always specified, and the size needle used for venipuncture was neither prescribed by the study protocols nor consistently documented in the CRFs. Blanching was recorded as an adverse event in two studies then specifically identified by the Sponsor as not being an adverse event in the remaining studies. It was to have been noted in the CRFs but not included in individual study analyses or lists of adverse events.

A data dictionary was not utilized for systematic classification of adverse events.

7.2.9 Additional Submissions, Including Safety Update

No additional safety data was submitted other than the IND annual reports dated March 21, 2003, and April 30,2004, (IND submissions: N-033-YY and N-034-YY) and the 120-day safety update to the NDA, dated April 1, 2004, (submission: N000SU) which indicated there was no previously unreported safety information to be provided for evaluation.

7.3 Summary of Selected Drug-Related Adverse Events, Important Limitations of Data, and Conclusions

The adverse events reported in the clinical trials were neither life threatening nor serious. The nature and frequency of the events were consistent with those reported for other iontophoretically applied lidocaine and epinephrine products. Because the placebo treatment in all of the clinical trials consisted of iontophoretically applied epinephrine, it is not possible to distinguish whether some of the events were related to the iontophoretic current, the presence of epinephrine, the presence of lidocaine, or some combination of the above. In addition, the site of the adverse event, i.e., whether at the application site of the delivery or return electrode, was not clearly identified in some instances. The table below summarizes the adverse events for both Lidopel and placebo treatments.

Table 7.3-1

Adverse Event	Incidence in Clinical Trials	
	Lidopel	Placebo
Blanching[1]	26/33 (79%)	24/24 (100%)
Burning	6/361 (1.7%)	6/247 (2.4%)
Bruising	3/361 (0.8%)	2/247 (0.8%)
Erythema[2]	9/361 (2.5%)	10/247 (4.0%)

Adverse Event	Incidence in Clinical Trials	
	Lidopel	Placebo
Itching	5/361 (1.4%)	4/247 (1.6%)
Pain	9/361 (2.5%)	3/247 (1.2%)
Rash	20/361 (5.5%)	1/247 (0.4%)

[1]The Sponsor considered blanching an adverse event (AE) in studies 96-08.0 and 97-07.0 only. After that it was considered "a normal, temporary loss of skin color due to the vasoconstriction caused by epinephrine" and was no longer documented as an AE. The denominator was adjusted to reflect the number of subjects actually evaluated.

[2]Erythema was recorded as an adverse event only if it was considered "moderate to severe" with severe defined as "beet redness to slight eschar formation (injury in depth)." Erythema that was "very slight," "barely perceptible," or "well defined" was not considered an adverse event.

In addition to the limitations described above for interpreting the adverse event data, there were too few subjects in the following categories to be able to discern differences in occurrence among subgroups.

- Race: only 44 non-Caucasians were included in all of the studies
- Age: only 20 subjects were 65 years of age or older
- Skin Type: only 19 subjects had type I skin which "always burns easily; never tans."

In summary, the data provided by the Sponsor to date have not been in a format amenable to a full analysis of adverse events; therefore, tables were constructed *de novo* using some of the data that were contained in the abridged data sets provided for each study. Based on analysis of this data, there is a small amount of evidence that the frequency of adverse events correlates to iontophoretic doses with more adverse events occurring at higher doses. The safety data provided by the clinical trials appear to be consistent with those seen with approved iontophoretic lidocaine and epinephrine products, however, there is no safety information from previously approved products that applies directly to the iontophoretic doses for which there is some evidence of efficacy, 20 mA·min for venipuncture and 80 mA·min for dermatological procedures. The data that is available from this NDA is insufficient to comment on demographic distribution of adverse events in populations that are either non-Caucasian, over age 65 years old, or have type I skin.

7.4 General Methodology

7.4.1 Pooling Data Across Studies to Estimate and Compare Incidence

7.4.1.1 Pooled data vs. individual study data

The Sponsor expressed concern regarding the validity of pooling safety data across studies for the following reasons.

1. Iontophoretic doses ranged from 20 mA·min to 80 mA·min and included 30, 40, and 60 mA·min doses.
2. While all studies that evaluated safety and effectiveness compared Lidopel to placebo or an alternate Lidopel dose, one study, #00-1-03.0, was a cross-over study in which two treatments were compared, Lidopel versus placebo and Iontocaine versus placebo.
3. Clinical procedures varied by study and included dermatological procedures and venipuncture.
4. Study enrollment was not balanced for gender, race, ethnicity, and skin type and these subgroups, therefore, were not equally represented across studies.
5.
6. Two studies considered blanching as an adverse event, in the others it was considered an expected response to the epinephrine and recorded but not documented as an adverse event.
7. Randomization procedures differed by study, e.g., subject, limb, order of device use.

While the concerns are legitimate, the Sponsor was to combine data from all the clinical trials and create a single dataset that included subject ID, demographics, adverse events, iontophoretic dose, drug, and procedure. The Sponsor stated such a dataset was not possible to create and instead submitted data sets for each trial individually. Data were combined to the degree possible and considered in the context of the studies from which they were collected. This was achieved by considering the iontophoretic doses used and the procedure for which the treatment was administered.

7.4.1.2 Combining data

As of the time of this review, an integrated safety database had not been provided by the Sponsor. A database was created using submitted data from individual studies. This database contained study number, subject identification, adverse event description, device, drug, iontophoretic dose, and subject demographic information. This database

was used for adverse event analysis. A separated table was constructed using subject identification, drug, iontophoretic dose and vital sign data to assess possibly significant systemic exposure to epinephrine.

7.4.2 Explorations for Predictive Factors

7.4.2.1 Explorations for dose dependency for adverse findings

The following table indicates that, overall, adverse events occurred more frequently with higher iontophoretic doses. This data is confounded by the decision made by the Sponsor to not include blanching as an adverse event in all but two of the clinical trials. In the two trials in which it was assessed as an adverse event it occurred with 79% of the Lidopel treatments and with 100% of the placebo treatments.

Table 7.4-1 Incidence of adverse events by iontophoretic dose

Drug	Iontophoretic Dose (mA·min) number of adverse events/number of treatments (%)				
	20	30	40	60	80
Placebo	8/144 (6)	0/20 (0)	11/33 (33)	3/20 (15)	27/36 (75)
Lidopel	12/110 (11)	0/20 (0)	16/27 (59)	21/24 (88)	47/89(53)
Iontocaine	6/29 (21)	N/A	N/A	N/A	N/A

N/A – not applicable as Iontocaine was only used at a 20 mA·min dose.

7.4.2.2 Explorations for time dependency for adverse findings

Adverse events that occurred either during iontophoretic treatment, e.g., stinging/tingling/burning sensations, itching, and blanching, or that developed within minutes afterwards, e.g., petechial rash and erythema would have been detected by the Investigator. Resolution of the adverse events, if immediate, e.g. burning stopped when iontophoretic treatment was complete, or prior to the dermatological procedure should have been captured by the Investigator; otherwise, determination of resolution time was based on times reported by the subjects during telephone follow up which occurred two to three days following the treatment. Most adverse events resolved fully within the course of several hours although rarely, they persisted for more than one day. These findings were consistent with those of Iontocaine and LidoSite.

7.4.2.3 Explorations for drug-demographic interactions

Table 55 on page 66 of Attachment 5 in Volume 3 of the July 29, 2003 submission provided a distribution of adverse events by study number and subject demographics. 19% of males and 22% of females had one or more adverse events. By age, the percentages of subjects experiencing one or more adverse events was [redacted], 21% of adult subjects less than 65 years of age, and 9% of geriatrics subjects. Table 56 on page 68 of the same attachment provided a distribution of adverse events by study number and event frequency. Twelve adverse events comprised more than 1% of the total reported and are discussed elsewhere but listed below for completeness.

Table 7.4-2 Adverse events comprising > 1% of all adverse event occurrences.

Adverse Event	Percentage of all adverse
Petechiae	14.3
Burning or stinging sensation during treatment	13.3
Erythema	11.6
Itching	8.0
Pain	8.0
Bruising	5.4
Congestion	4.5
Generalized aching	3.6
Lightheadedness	2.7
Slight redness	2.7
Headache	1.8
Prolonged bleeding at puncture site	1.8

7.4.2.4 Explorations for drug-disease interactions

Due to the minimal amount of systemic exposure expected for both lidocaine and epinephrine with a single application, even with repeated doses during the course of a day and/or dosing for several days, exploration for drug-disease interactions was neither required nor performed for this NDA.

7.4.2.5 Explorations for drug-drug interactions

Due to the minimal amount of systemic exposure expected for both lidocaine and epinephrine with a single application, as well as for repeated doses during the course of a

day and/or dosing for several days, exploration for drug-drug interactions was not required and was not performed for this NDA. Consistent with other iontophoretic lidocaine and epinephrine drug products, the label will warn of drug-drug interactions that occur with significant systemic exposure to epinephrine or norepinephrine.

7.4.3 Causality Determination

The skin reactions to Lidopel and placebo treatments were all considered to have a high likelihood of being caused either by the administration of electric current, application of drug(s), reaction to electrode materials, or a combination of these. Those events that appeared to be consistent with systemic exposure to epinephrine, i.e., headache and diaphoresis, would require further evaluation to determine causality. Vital sign data did not supportive, but neither did it exonerate, a drug-related etiology.

8 ADDITIONAL CLINICAL ISSUES

8.1 Dosing Regimen and Administration

The clinical trials failed to clearly identify iontophoretic doses that were appropriate for either superficial dermatological procedures or venipuncture. The data presented suggest an 80 mA·min dose may be effective for dermatological procedures and that a 20 mA·min dose may be sufficient for venipuncture in terms of providing statistically significantly better analgesia than placebo. The clinical significance appeared to be almost negligible in these trials. The lack of efficacy seen in the venipuncture trials, when iontophoretic doses greater than 20 mA·min were evaluated, raises significant concerns regarding the effects of the placebo treatment and the overall efficacy of Lidopel. In addition, the depth and duration of analgesia provided by Lidopel were not adequately characterized by the studies conducted.

Dose-toxicity and dose-response relationships have not been adequately evaluated, in part, because of the lack of a complete integrated safety database and, in part, because of what appears to be a disconnect between the dermatological procedure studies that evaluated doses of 40, 60 and 80 mA·min and the single, dose-finding, venipuncture study that evaluated 20, 30 and 40 mA·min.

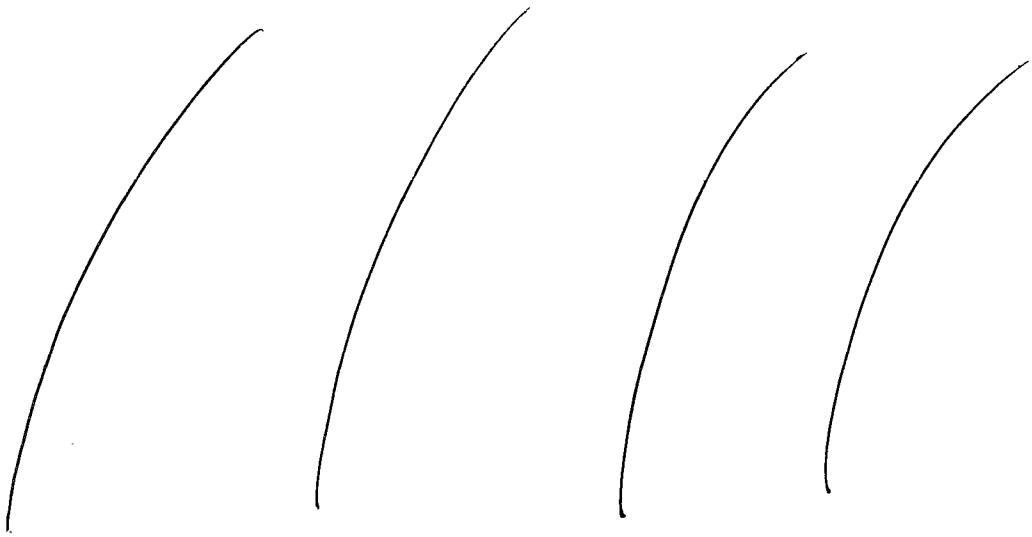
8.2 Drug-Drug Interactions

As mentioned in other sections of this review, the type of use anticipated for this product, i.e., single application with infrequent repeat dosing, and the negligible systemic exposure to lidocaine and epinephrine expected with such use have precluded the need for evaluation of drug-drug interactions. Instead, the labeling shall include language the

8.3 Special Populations

Special dosing considerations were not provided for coexisting disease states, pregnancy or lactation, and they were not specifically requested by the Division. The demographic diversity of the subject population was limited in the areas of race, age, and skin type such that special dosing considerations could not be elucidated. Specifically, the following groups were too small to make even broad comparisons: non-Caucasian races; ages greater than 65, and especially, 75 years old; and type I skin which burns easily and never tans.

8.4



8.5 Advisory Committee Meeting

Input from an Advisory Committee regarding this particular drug product or this class of drug products was neither requested nor provided.

8.6 Literature Review

Literature provided by the Sponsor in support of the NDA is discussed elsewhere. While some information supporting the efficacy of iontophoretically administered lidocaine was

provided, there was no literature submitted to address the safety of iontophoretically administered epinephrine or demonstrate a meaningful contribution of epinephrine to safety or efficacy when it is combined with lidocaine for iontophoretic administration. The issues surrounding epinephrine have not been addressed by Iontocaine, the literature (this reviewer's search provided no additional information), or the studies conducted by the Sponsor.

8.7 Postmarketing Risk Management Plan

Because there is minimal risk of abuse with local anesthetics in general and iontophoretically applied local anesthetics in particular, and the use of this product is limited to clinical settings by healthcare providers, a Postmarketing Risk Management Plan was neither required nor submitted.

8.8 Other Relevant Materials

In addition to the data and literature submitted by the Sponsor, the primary and secondary clinical reviews of the Iontocaine NDA were examined. Empi, Inc. included sections of the clinical reviews for Iontocaine with the NDA submission as well.

9 OVERALL ASSESSMENT

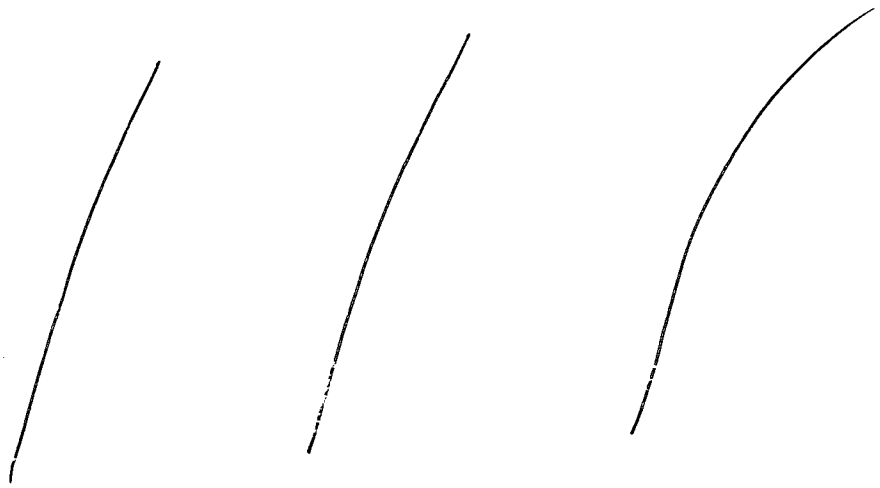
9.1 Conclusions

The clinical trials involving dermatological procedures assessed the efficacy of Lidopel compared to placebo in providing analgesia for shave removals of superficial skin lesions and punch biopsies. Study #97-07.0 was a Phase 2 study and the only study involving punch biopsies. In this study, Lidopel surpassed placebo in terms of subjects not experiencing pain with a needle-prick test; however, no placebo-treated subjects passed the needle-prick test and therefore, there was no comparator group against which Lidopel could be compared for analgesia during the punch biopsy. This same study also evaluated analgesia for shave removals and resulted in the same situation; Lidopel surpassed placebo in providing analgesia for the needle-prick test; however no placebo subjects passed the test precluding a comparison with Lidopel for analgesia during the shave removals. Study #99-02.0 compared Lidopel and placebo treatments for analgesia during shave removals. In this study, Lidopel again surpassed placebo in passing the needle-prick test, but some placebo patients also passed the test allowing for comparison of analgesia during the shave removals. At an iontophoretic dose of 60 mA·min, determined by the Sponsor to be the optimal dose for this procedure from the first part or this study, there was no significant difference between VAS scores between Lidopel and placebo in the second part of the study which was designed to confirm the findings in the first part.

The remaining three clinical trials evaluated the use of Lidopel for analgesia during venipuncture. The first part of Study 99-07.0 evaluated Lidopel versus placebo at three iontophoretic doses. The results of this part of the trial led the Sponsor to conclude that 20 mA·min was the optimal dose for this procedure, and therefore, was the dose to be used in the second part of the study. In the second part of the study, Lidopel provided statistically significant more analgesia, based on a 100 mm VAS pain score, than placebo. The mean VAS scores for Lidopel and placebo were 12.9 and 24.0 mm, respectively, among the subjects participating in part two of the study. The following findings raise concerns regarding the validity of this result and its clinical significance.

- The mean VAS scores for both treatment groups were below 30 mm suggesting minimal to no pain with the procedure.
- The protocol did not specify and the CRFs did not capture the gauge of the needles used for venipuncture. The Sponsor responded to a request for this information by calling the Investigator and reporting that he indicated that 21 gauge needles were used in the study. No written evidence supporting the Investigator's recollection was provided.

- The difference between the mean VAS scores, 11.1 mm, is relatively small and indicates there may be no clinically meaningful difference between the two treatments.
- There was no statistically significant difference between the two treatments in terms of subject global satisfaction scores for the combination of iontophoretic treatment and venipuncture procedure. The difference in these scores suggested more satisfaction with Lidopel treatment.

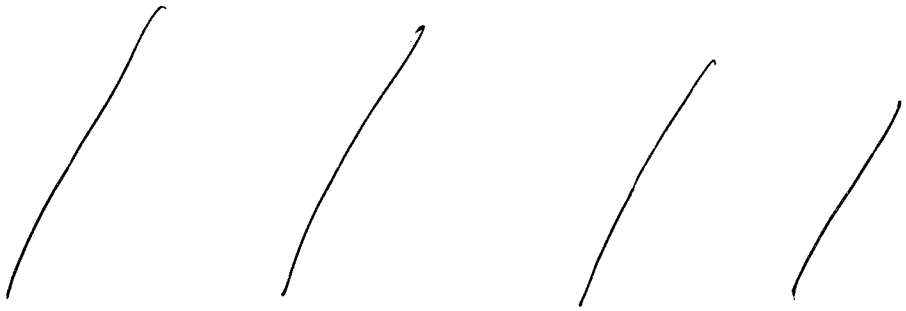


Lastly, Study #00-1-03.0 was a non-inferiority trial comparing the differences between Lidopel and placebo with those of Iontocaine and placebo. The iontophoretic dose used in the study, 20 mA·min, was half that for which Iontocaine was approved. The trial resulted in a finding of non-inferiority. Consideration of only the Lidopel and its associated placebo data indicated that Lidopel was statistically significantly better than placebo; however, the delivery electrode used was not the same as the [redacted] 8.1 cm^2 patch; it was 10.1 cm^2 in size, and the difference between the two treatments was so small as to not have significant clinical relevance.

In summary, sufficient evidence of efficacy for a single procedure was not provided for the use of Lidopel at any iontophoretic dose with its [redacted]

9.2 Recommendation on Regulatory Action

An approvable action is recommended due to the following deficiencies which the Sponsor should address to allow the adequate evaluation and labeling of this drug product for safety and dosing.



9.3 Recommendation on Postmarketing Actions

9.3.1 Risk Management Activity

None required.

9.3.2 Required Phase 4 Commitments

Safety and efficacy should be assessed for use of the drug product in the pediatric population [redacted] Such evaluation may include the use of different sized electrodes to suit the size of the patient.

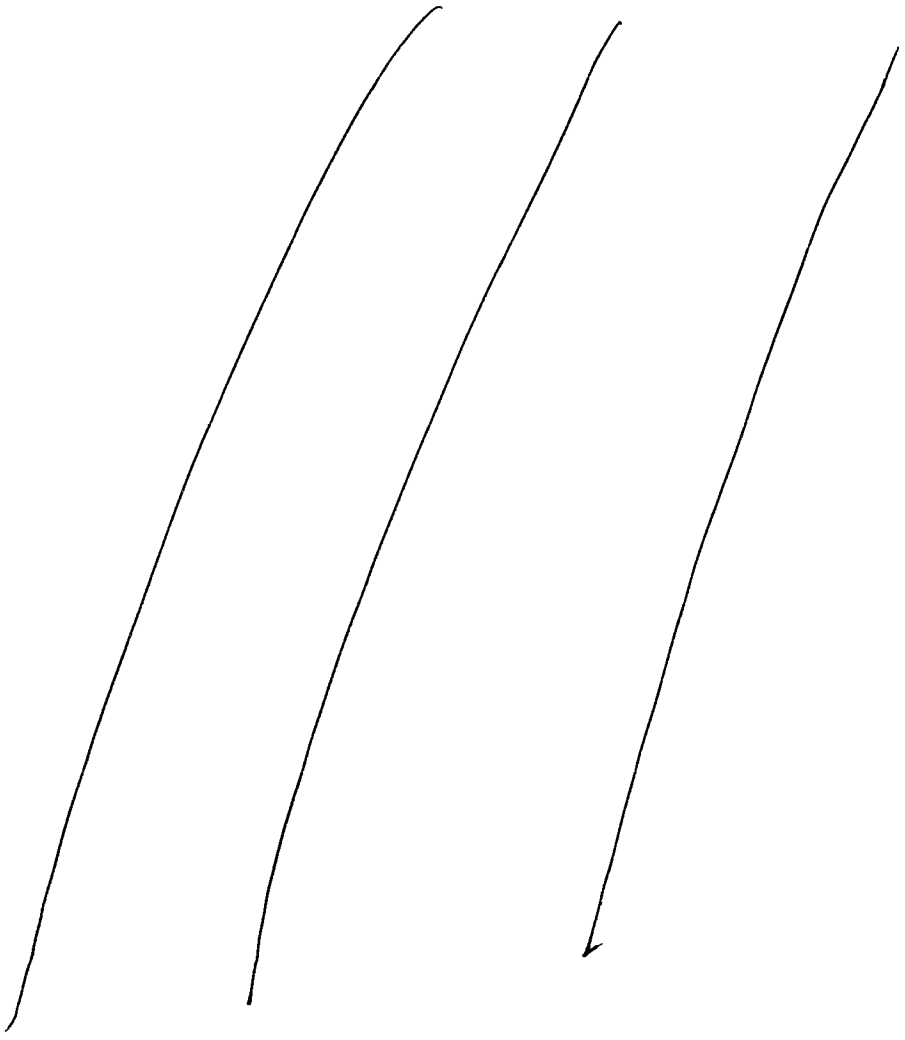
9.3.3 Other Phase 4 Requests

No requests for Phase 4 study are made at this time.

9.4 Labeling Review

The review of the product label has been deferred to interdisciplinary discussions within the division. Some comments that should be considered for inclusion based on the design of the clinical trials are listed in the Appendix, Section 10.2

9.5 Comments to Applicant



1 Page(s) Withheld

_____ Trade Secret / Confidential

_____ Draft Labeling

1 Deliberative Process

10 APPENDICES

10.1 Review of Individual Study Reports

10.1.1 Study 97-07.0: "Phase II, Placebo-Controlled, Double-Blind Trial of the Anesthetic Effect of 2% Lidocaine HCl and Epinephrine 1:100,000 Administered via Iontophoresis to Subjects Undergoing Superficial Dermatological Procedures"

10.1.1.1 Overall Summary of Findings

This study demonstrated that compared with an epinephrine-containing placebo, subjects receiving a Lidopel iontophoretic treatment with 2% lidocaine and epinephrine 1:100,000 were less likely to have pain when administered a needle-prick test, i.e., be tested for pain sensation in four quadrants of the treated area with a 30 gauge needle, and therefore, be able to undergo a dermatological procedure with some minimal level of analgesia. While the study succeeded to demonstrate a lower needle-prick test failure rate with Lidopel, it was flawed in demonstrating a clinically significant benefit, i.e., that Lidopel provided adequate analgesia for the dermatological procedure itself compared to placebo. No subjects who received placebo iontophoretic treatment "passed" the needle-prick test, and thus, there was no placebo control for comparison with Lidopel during the dermatological procedures. Additionally, Lidopel at the different iontophoretic doses failed to provide adequate analgesia in a substantial percentage of subjects for the dermatological procedure without the use of supplemental analgesia. Among the iontophoretic doses, delivery electrode sizes and procedures evaluated, the data suggested that an 8.1 cm^2 electrode delivering an 80 mA·min dose provided the most effective analgesia in subjects undergoing punch biopsies.

10.1.1.2 Study Plan

The original version of this protocol was dated May 15, 1998. There was one amendment made dated August 12, 1998. The first subject was entered on August 28, 1998 and the last subject completed the study on October 16, 1998.
Source: NDA submission, Appendix 8.2, p. 4.

10.1.1.3 Objectives

The protocol-specified objectives of the study were:

Primary Objective: Demonstrate that 2% lidocaine and epinephrine 1:100,000 administered iontophoretically produce sufficient analgesia for superficial dermatological procedures.

Secondary Objective: Assess subjects' surgical pain, overall satisfaction with the treatment, and the duration of analgesia

10.1.1.4 Design

This was a single-site, randomized, placebo-controlled, double-blinded, Phase 2, pilot study that was designed to demonstrate that Lidopel produced sufficient analgesia for superficial dermatological procedures. Sixteen subjects were enrolled in each of three treatment groups:

1. 16 normal subjects receiving an iontophoretic dose of 80 mA·min with a large delivery electrode (_ cm^2) followed by a punch biopsy if analgesia was determined to be adequate.
2. 16 normal subjects receiving an iontophoretic dose of 80 mA·min with a small delivery electrode (8.1 cm^2) followed by a punch biopsy if analgesia was determined to be adequate.
3. 16 patients requiring a shave removal for seborrheic keratosis or benign nevocellular nevi receiving an iontophoretic dose of 40 mA·min with a large delivery electrode (_ cm^2) followed by shave removal procedure if analgesia was determined to be adequate.

Within each of the three groups, 8 randomly selected subjects received an active solution of lidocaine and epinephrine (Lidopel) while the remaining 8 subjects received a placebo solution consisting of Lidopel without lidocaine, i.e., an iontophoretic application of epinephrine.

10.1.1.5 Efficacy Endpoints

Primary Efficacy Endpoints:

1. Incidence of treatment failure, defined as experience of pain to a needle-prick test or request for supplementary analgesia during dermatological surgery

Secondary Efficacy Endpoints:

1. Surgical pain ratings measured by visual analog scale (VAS)
2. Subject satisfaction ratings measured on an ordered, 0-10 scale
3. Duration of analgesia by repeat of needle-prick test 30 minutes following the original test

10.1.1.6 Population

The subjects were non-institutionalized volunteers recruited from the local community surrounding the clinical center. Candidates for enrollment into the study could be of either sex presenting for shave removals of seborrheic keratosis or benign nevocellular nevi, or normal subjects willing to undergo punch biopsies on the posterior of the left upper arm.

Inclusion Criteria:

1. 18 to 70 years of age (inclusive)
2. willing to give signed, informed consent prior to admission to the study
3. females who are not post-menopausal for at least one year or surgically sterile and are willing to have a pregnancy test prior to treatment

Exclusion Criteria:

1. are experiencing significant levels of chronic pain
2. have taken long-acting analgesic medication in the last seven days or other analgesics in the last three days
3. are currently taking monoamine oxidase inhibitors, tricyclic antidepressants, phenothiazine, butyrophenones, vasopressor drugs or ergot-type oxytocic drugs
4. have broken or abraded skin at a treatment site
5. have signs of inflammation or infection at the treatment site
6. have a sensory deficit at the treatment site
7. are currently pregnant or nursing
8. have known drug sensitivities to epinephrine and/or local anesthetics such as lidocaine
9. have known allergies to sulfites
10. have reported a history of drug or alcohol abuse in the last five years
11. have consumed alcohol within 24 hours prior to the study
12. require the placement of the electrodes to be placed over the carotid sinus (neck) region
13. have a treatment site that requires the electrodes to be place over the temporal region
14. have metallic or plastic implants at or near the treatment site that might distort or in any way interfere with iontophoretic electrical current flow

15. have treatment site located on soles of feet or palms of hands
16. have known adverse reactions to the application of electrical current
17. have cardiac pacemakers or other implanted electronic device
18. have any significant health problems as documented by medical history, blood pressure and/or temperature
19. have reported a history of hypertension (BP>155/95)
20. have reported a history of myocardial infarction, angina, and/or arrhythmia requiring medication

Participants could be withdrawn from the study at any time for the following reasons.

1. adverse events
2. intracurrent illness
3. non-compliance with the study procedures
4. subject's decision
5. administrative reasons*
6. in the investigator's opinion, to protect the subject's best interest*

* Not defined in the protocol.

10.1.1.7 Methods and Procedures

Subjects were to be screened within 21 days of their treatment. Screening was to include completing the Inclusion/Exclusion checklist, demographics, vital signs, and medical and medication history. Subjects were to be instructed at that time regarding the use of analgesics and alcohol prior to treatment. All punch biopsies were to have been performed on the posterior aspect of the upper arm in volunteers without skin lesions at the biopsy site. The sites of the shave removals were not prespecified but were captured in the CRFs.

Immediately before treatment, subjects were to be reevaluated to ensure no changes in their health status and to observe the treatment site. In addition, the following were to be done at that time. An "Intact Sensation to Light Touch" test was to be performed to confirm that there was no sensory deficit at the treatment site. The test consisted of having the subject look away from the test site while the clinician lightly stroked the skin with a wisp of cotton. The subject was to indicate if and when contact was felt. Vital signs were to be recorded, including blood pressure, heart rate and respiration rate. Female subjects, who were required by inclusion criteria #3 to do so, were also to take a urine pregnancy test.

The delivery electrodes were to be filled with the appropriate test drug: 2%lidocaine HCl and epinephrine 1:100,000 for the active product, and the same formulation but without the 2% lidocaine HCl was to serve as the placebo product. 2.5 ml of study drug was to be used to fill the small delivery electrode and — ml was to be used to fill the large delivery

electrode. The delivery electrode was to be centered over the treatment site from which excessive hair was to be clipped, not shaved, to assure good contact. The return electrode was to be moistened with room temperature tap water and placed at least 4 inches from the delivery electrode on a muscle belly. The iontophoretic doses of 80 and 40 mA·min were to be achieved by applying a current of 4 mAmp for 20 or 10 minutes, respectively. Electrodes were to be removed immediately after the iontophoretic treatment, and no further touching or manipulation of the skin was to occur until the anesthetic effect was tested using the "needle-prick test" described below.

At the conclusion of the iontophoretic treatment, subjects were to comment on comfort or sensations associated with the treatment, and the Investigator was to evaluate the appearance of the skin under the two electrodes for blanching, erythema, or "other clinically significant changes" not described in the protocol. Additionally, vital signs were to again be recorded at that time.

Within 10 minutes following the completion of the iontophoretic treatment, adequacy of analgesia was to be tested by a "standard needle-prick test" in which a 30 gauge hypodermic needle was to be used to test for pain at four randomly determined points midway between the margins of the lesion or biopsy area and the border of the electrode application site. The time and response to the needle-prick test were to be recorded and anesthetic adequacy was to be inferred if the subject had no pain sensation at any of the needle-prick sites. Subjects who failed the needle-prick test were to be judged as having inadequate analgesia and were to be discontinued from the study.

Those subjects whose iontophoretically treated sites passed the "standard needle-prick test" were to undergo their dermatological procedure. If during the procedure, the subject requested supplementary analgesia due to pain, the treatment was to be considered a failure, the procedure was to be discontinued, and the subject was to be withdrawn from the study. Subjects scheduled for shave removals who were discontinued from the study due to inadequate analgesia were to be given the option to have their lesion removed by standard practices at the expense of the Sponsor. The use of additional analgesia was not applicable for subjects presenting for punch biopsy.

The investigator was to have recorded the time from the beginning to the end of the dermatological procedure. At thirty minutes following the initial needle-prick test, the sensitivity to needle-prick pain was to be repeated and vital signs again recorded. Subjects who completed the dermatological procedure were to be asked to rate their degree of discomfort experienced during the procedure on a 100 mm VAS for pain intensity. In addition, they were to be asked to rate their overall satisfaction with the iontophoretic treatment and dermatological procedure on a ten point categorical scale with "1" being not satisfied at all and "10" being completely satisfied.

At 2-3 days following the procedure, subjects were to have been contacted by phone for follow up assessment of the treatment site.

10.1.1.8 Analysis Plan

10.1.1.8.1 Analysis of Efficacy

The primary efficacy endpoint was the incidence of treatment failure in the placebo and active groups. The Fisher's exact probability test was to be used to evaluate the proportional differences between the treatment groups.

Pain ratings and subject satisfaction scores were to be compared across the surgical procedures with ANOVA or Chi-Square, as appropriate. If data was non-normally distributed, the appropriate nonparametric test was to be used. Data on duration of anesthetic effect was to be taken for descriptive purposes only.

10.1.1.8.2 Determination of Sample Size

The Sponsor expected a failure rate of no less than 95% in placebo treated subjects and no greater than 20% across all procedure and patch sizes with the Lidopel treated subjects. Thus it was determined that as few as 8 subjects per treatment group would be enough to detect the difference in failure rates with 80% power.

Sixteen subjects were to be assigned to each of three groups: patients presenting for punch biopsy who would all receive an 80 mA·min dose but with separate groups for large and small delivery electrodes, and patients presenting for shave removals of lesions all of whom would receive a 40 mA·min dose using only the large electrode.

If an adequate treatment effect for shave removals at the 40 mA·min dose was obtained using the large electrode, an additional treatment group of 16 patients could be added to assess the same dose but using the small electrode. If an adequate treatment effect for these patients was not obtained, two additional groups could be added to assess shave removals using an 80 mA·min dose and each of the two electrode sizes.

10.1.1.9 Protocol Amendments

The protocol was amended once on August 12, 1998 prior to the enrollment of the first subject. The following are summaries of the eight changes made.

1. Subjects unable to tolerate the iontophoretic treatment were originally to be registered as a treatment failure. That was changed so that they would be removed from the study and replaced. The argument was made by the Sponsor that the current used, 4 mAmp, is the maximum for the device and subjects who cannot

tolerate this in clinical practice may tolerate a lower current (presumably for a longer period of time to deliver the same dose of drug). Thus, replacing subjects who failed to tolerate the iontophoretic treatment would also ensure adequate numbers for statistical analysis of the iontophoretic dose. However, no evidence was provided to indicate that iontophoretic doses achieved by different current-time combinations were equivalent in terms of safety and efficacy. The data were to be analyzed in two ways in the amended protocol: on an intent-to-treat (ITT) basis with those unable to tolerate the treatment treated as failures and excluding subjects from the analysis who do not complete the iontophoretic treatment.

2. The ten point categorical scale was changed to eleven points so that "0" would represent no satisfaction at all and "10" would still represent complete satisfaction. This, according to the Sponsor, is more consistent with scales sited in the literature.
3. The requirement for the potential participant and a witness signing the consent documents was changed to the potential participant and the person explaining the informed consent must sign the consent documents. The Sponsor states this was done to be consistent with the requirements of the IRB and ICH Guidelines for Good Clinical Practice.
4. Case Report Form numbers were changed to be consistent with the order of activities for the study.
5. The filling of the delivery electrode by someone other than the Investigator doing the needle prick tests and dermatologic procedure, and the recording of the appearance of the delivery electrode site by the Investigator were changed to Investigator or Subinvestigator as the Sponsor believed either would be able to fulfill these responsibilities. Additionally, recording of the time at the beginning and end of the dermatologic procedure was no longer specified as the responsibility of the Investigator. No individual was specified to perform this task in the amended protocol.
6. In the original protocol, safety was to be addressed by vital signs, and by the collection of adverse events during the office procedure and for 48 hours following the procedure, and all subjects were to be required to be available approximately 48 hours later to receive a follow-up phone call questioning them on the treatment site. These were changed so that safety assessments would continue for approximately one week following the procedure and that subjects needed to be available at both 48 to 72 hours and 6 to 9 days after their procedure for follow-up phone calls questioning them on the treatment /procedure site. This was done to obtain additional safety data capturing possible procedure site infection.
7. The distinction between long-acting analgesics, banned for seven days before treatment, and short-acting analgesics was not possible as the Sponsor was unable to find a comprehensive listing of the two. Therefore, prescription analgesics were banned for seven days prior to the procedure instead.
8. The number of a section sited in the Sample Size section was corrected.

As the amendment was made before patients were enrolled it was unlikely that items 2 – 8 would have a significant effect on the final results of the trial or the conclusions drawn from them. With regards to the first item, the rationale of replacing subjects who are unable to tolerate the iontophoretic treatment to assure adequate numbers of subjects for analysis is reasonable provided the ITT analysis is conducted as planned. The use of lower iontophoretic currents in the clinical setting would require evidence not only of tolerability with lower currents but that equivalent analgesia/anesthesia can be provided when a lower current is applied for longer duration to achieve the same iontophoretic dose.

10.1.1.10 Study Conduct

The study was conducted as planned with the exception of the protocol violations noted below. The Sponsor noted that Institutional Review Board approval was required before test articles were shipped to the study site. The final study report did not indicate that the study was conducted in accordance with the Good Clinical Practice Guidelines and the Ethical Principles for Medical Research Involving Human Subjects promulgated at the 18th World Medical Association General Assembly in Helsinki and later amended, but the Sponsor attested to this in an amendment to the NDA.

The final study report gives no indication as to how the study was monitored or how quality assurance of the data was provided. There also was no indication that the recorded data were verified for accuracy compared with the CRFs, or that upon closeout of the study a full audit was performed. How the database was prepared, secured and verified was not stated.

The final report for the study stated that there were 43 deviations from the protocol for 36 subjects. This was later amended to 44 deviations for 29 subjects. The table below lists these deviations.

Table 10.1-1 Protocol Deviations (Table from App. 8-2, p. 30)

Description of Protocol Deviation	No. of Subjects
Missing height, weight, temperature, and/or respiration rate	17
The 48 to 72 hour or the 6 to9 day follow-up was not completed	10
Completed follow-up not within the specified timeframe	5
Thirty minute needle prick test not completed during the appropriate timeframe	3
Patient did not complete the pain and/or satisfaction scales	2
Baseline blood pressure reading high, however patient enrolled since had no history of high blood pressure	1
Patient did not meet inclusion/exclusion criteria since consumed alcohol	1

Description of Protocol Deviation	No. of Subjects
within 24 hours of treatment	
Second needle prick test not conducted	1
Large electrode used in error instead of small electrode	1
Initial screening conducted >21 days prior to enrollment	1
Subject withdrew from the study and was not replaced as required by the protocol	1
Physician recorded results to 30 minute needle prick test incorrectly	1
TOTAL	44

It was not specified which treatment groups were affected by these deviations. Because of the small numbers of subjects in each of the treatment groups, it is possible that the deviations could significantly impact the results of the study. The Sponsor was asked to provide patient ID and treatment category for each of the deviations. The types of deviations that occurred, failure to complete pain or satisfaction scales, use of wrong electrode, incorrectly recording results, raise serious concerns regarding the validity and usefulness of the study results.

10.1.1.10.1 Patient Disposition

The following table is constructed from statements in the NDA referencing subject disposition and from the SAS listings of the CRF data.

Table 10.1-2 Subject Disposition

Subject State	Lidopel[1]			Placebo[1]		
	P/lg/80	P/sm/80	S/lg/40	P/lg/80	P/sm/80	S/lg/40
Enrolled	9	7	8	8	8	8
Randomized	9	7	8	8	8	8
Safety Population	9	7	8	8	8	8
Intent-to-Treat (ITT) Population	9	7	8	8	8	8
Discontinued Study	3	0	7	8	8	8
Failed pinprick test	3	0	5	8	8	8
Required supplemental Analgesia[2]	N/A	N/A	2	N/A	N/A	0
Completed Study	6	7	1	0	0	0

[1]Subcategories are defined as follow:
P/lg/80 = punch biopsy with large delivery electrode (~ cm^2) and 80 mA·min dose
P/sm/80 = punch biopsy with small delivery electrode (8.1 cm^2) and 80 mA·min dose
S/lg/40 = shave biopsy with large delivery electrode (~ cm^2) and 40 mA·min dose
[2]Due to the nature of the procedures, only those subjects undergoing shave removals of lesions were eligible for supplemental analgesia.

10.1.1.11 Demographics/Group Comparability

Two thirds of the subjects were female. The ages of the subjects ranged from 19 to 70 years old. There was no significant difference between treatment groups based on composition by gender or age. The racial distribution included 79% Caucasian, 2% black, 2% American Indian, and 17% Hispanic. Among the treatment groups, there was no significant difference between the number of Caucasians and non-Caucasians enrolled. Additionally, there was no significant difference in the distribution of skin types among the treatment groups.

10.1.1.12 Treatment Compliance

Study treatment was administered under direct supervision of the study staff; therefore, treatment compliance was assured.

10.1.1.13 Unplanned Analyses

There were no unplanned analyses substituted for the planned efficacy analyses

10.1.1.14 Sponsor's Efficacy Results

10.1.1.14.1 Primary Efficacy Variables

The primary endpoint was assessment of treatment failure by use of the needle-prick test and the need for supplemental analgesia during the dermatological procedure.

The adequacy of analgesia for the dermatological procedure was determined by the needle-prick test. To "pass" the test, none of the four pinpricks could elicit a painful sensation. Based on this criterion, none of the subjects who received placebo treatment passed the needle-prick test. Among those who received the Lidopel treatments, six of nine passed who had a large electrode and received an 80 mA·min iontophoretic dose, all seven who had the small electrode and received an 80 mA·min iontophoretic dose passed the test, and only three of the eight subjects who had the large electrode and received a 40 mA·min iontophoretic dose passed. The subject who did not complete the iontophoretic treatment was given placebo, and was counted as a failure in the ITT evaluation.

Among the 16 subjects who passed the needle-prick test, only the three subjects undergoing shave removals would be able to request additional analgesia for their

procedure. The punch biopsy was not amenable to the administration of supplemental analgesia. Of the three subjects having the shave removals, two requested supplementary analgesia before or during the procedure.

10.1.1.14.2 Secondary Efficacy Variables

The secondary efficacy variables included VAS scores, subject satisfaction and duration of analgesia.

The table below presents the VAS scores and subject satisfaction ratings for those subjects who underwent their dermatological procedures. Two subjects did not complete these assessments, one who had a shave biopsy and one who had a punch biopsy following treatment with the large electrode. There was no significant difference between the treatment groups for either mean VAS or mean satisfaction scores.

Table 10.1-3 Summary of Surgical Pain Ratings and Subject Satisfaction

Treatment Group[A]	N	Mean VAS	SD of VAS	Mean Satisfaction Score	SD of Satisfaction Score
Punch/lg/80	5	43.8	45.6	4.8	4.4
Punch/sm/80	7	26.2	35.9	6.9	2.5
Shave/lg/40	2	33.0	14.1	8.0	1.4

[A]Treatment groups are defined as follow:

- Punch/lg/80 = punch biopsy with large electrode and 80 mA·min iontophoretic dose
- Punch/sm/80 = punch biopsy with small electrode and 80 mA·min iontophoretic dose
- Shave/lg/40 = shave biopsy with large electrode and 40 mA·min iontophoretic dose

There was found to be no significant difference in pain rating or subject satisfaction by treatment group or by gender.

10.1.1.15 Discussion of Efficacy Findings in Study

The only portion of this study that qualifies as controlled is the needle-prick test. For this test, more subjects receiving Lidopel treatments (16/24) passed the test then did those receiving placebo treatments. Although 100% (23/23) of subjects receiving placebo failed this test, significant percentages of those receiving Lidopel failed as well: 33% (3/9) of those with the large patch and 80 mA·min dose, and 63% (5/8) of those with the large patch and 40 mA·min dose. Of the subjects receiving the small patch and the 80 mA·min dose, 100% (7/7) passed the test. Because only those subjects who passed the needle-prick test qualified to have their dermatological procedure performed, the second

part of the study, i.e., the testing of the adequacy of the Lidopel system for dermatological surgery, was not placebo controlled. A comparison of the different iontophoretic doses of Lidopel would be inappropriate as the test groups were no longer randomized.

The primary efficacy endpoint was to include the needle-prick test and the need for more local analgesia during the procedure, however, only those subjects who underwent shave removals would be able to request additional analgesia as the nature of a punch biopsy precluded such therapy. Thus, only three of those subjects who passed the pinprick test could be assessed for the need for additional analgesia, i.e., only three subjects underwent shave removals. Two of these three subjects required supplemental analgesia. Therefore, in all, at least 42% of subjects (10/24) receiving Lidopel treatments experienced treatment failures.

As for the VAS and subject satisfaction data, some comparison between the electrode size and iontophoretic dose may be made, but the enrichment of the test population and missing evaluations of two patients limits the usefulness of this type of analysis. For VAS scores, it is possible to group scores such that values from 0 to 30 mm represent little to no pain while values from 70 to 100 mm represent severe pain. Similarly, for the subject satisfaction scores, values from 0 to 3 can represent minimal to no satisfaction and values from 7 to 10 can be used to represent high to full satisfaction. With these groupings, the tables below were constructed for review purposes.

Table 10.1-4 VAS Scores by Electrode Size & Iontophoretic Dose

Electrode/Dose	Procedure	Number of subjects		
		VAS ≤ 3	3 > VAS > 7	VAS ≥ 7
Large/80 mA·min	Punch biopsy	3	0	2
Large/40 mA·min	Shave removal	1	1	0
Small/80 mA·min	Punch biopsy	7	0	0

Table 10.1-5 Satisfaction Scores by Electrode Size & Iontophoretic Dose

Electrode/Dose	Procedure	Number of subjects		
		Satisfaction ≤ 3	3 > Satisfaction > 7	Satisfaction ≥ 7
Large/80 mA·min	Punch biopsy	3	0	2
Large/40 mA·min	Shave removal	0*	0	2
Small/80 mA·min	Punch biopsy	0	4	3

* One value recorded as "-7" was not defined in the Data Dictionary, but in other studies denoted a subject who required supplemental analgesia.

This trial was used to assess duration of analgesia. One half hour after the iontophoretic treatment, those subjects who passed the first needle-prick test and required no supplemental analgesia were retested with the needle-prick test. Thirteen of the 14 subjects who should have been evaluated were, and of those, 69% (9/13) passed the repeat test. No assessment of whether analgesia was suitable for dermatological procedures was made, and no other characterizations of the duration of analgesia were made.

In summary, there were significant shortcomings with the protocol design in this study. It could be hypothesized that the pain of a shave removal or punch biopsy exceeds that of the needle-prick test, then Lidopel failed less often than placebo to provide adequate analgesia for these procedures, however the Sponsor made no such hypothesis and no evidence was offered to support such a hypothesis. Of the iontophoretic doses and patch sizes evaluated, the 8.1 cm^2 delivery electrode used with an 80 mA·min iontophoretic dose might have provided better analgesia than did the same dose delivered through the larger, — cm^2 patch.

10.1.2 **Study #99-02.0: "Anesthetic Effect of 2% Lidocaine HCl and Epinephrine 1:100,000 Delivered via the Dupel® Iontophoresis System to Subjects Undergoing Shave Removals"**

10.1.2.1 Overall Design and Summary of Findings

This Phase 3 study was conducted in two parts. The first part consisted of a double-blinded, randomized, placebo-controlled comparison of three iontophoretic doses of Lidopel used to provide dermal analgesia for shave removals of skin lesions. The three iontophoretic doses of Lidopel included 40, 60 and 80 mA·min; placebo was administered only at an 80 mA·min iontophoretic dose. Following iontophoretic treatment, analgesia was assessed with needle-prick testing. Those patients who passed the needle-prick test underwent their procedure. Patients who failed the needle-prick test or who required supplemental analgesia were considered treatment failures. A comparison of treatment failure rates among the different dose groups constituted the primary endpoint. Those who had their procedures assessed their pain levels and global satisfaction with treatment as secondary endpoints. The iontophoretic dose shown to be most effective and safe was to be used in the second part of the study.

The second part consisted of comparing Lidopel with placebo, administered at the same iontophoretic dose, for providing analgesia during shave removals of skin lesions. The protocol and endpoints were otherwise the same as in the first part of the study.

In part one of the study, all of the Lidopel treatments fared significantly better than the placebo when it came to passing the needle-prick test, and none of the Lidopel treatments, in this context, did significantly better than the others. When the success rate combining both the results for the needle-prick test and the need for extra analgesia was considered, only that of the 40mAmin dose Lidopel treatment diminished. Based on the success rates and numbers of adverse events for each Lidopel dose, it was determined that 60 mA·min was the optimal dose for the dermatological procedure, and that this dose should be further studied in part two.

In the second part of the study, the success rate was better with Lidopel than placebo both for passing the needle-prick test and the need for additional analgesia. In this part of the study, there was no significant difference in the VAS scores between Lidopel and placebo treatments although there was a significant difference in global satisfaction scores which favored Lidopel.

In addition to the above, the following points were noted.

1. Mean VAS scores were less than 30 mm for all groups in both parts of the study suggesting only mild procedural discomfort even with placebo treatment.
2. In part one where the greatest VAS differences occurred between Lidopel and placebo treatments, there was no significant difference in global satisfaction scores between the two groups. This was the reverse of the findings in the second part of the study.
3. Evidence of the validity of an 80 mA·min dose of epinephrine as a placebo treatment has not been provided.

10.1.2.2 Study Plan

The original version of this protocol was dated January 17, 2000. The protocol was amended four times. The amendments dated March 2, 2000, March 10, 2000, March 17, 2000 and June 6, 2000 were included with the NDA. Protocol amendment #2 was not included in the original NDA and was requested from the Sponsor. Subjects underwent their dermatological procedures between March 3 and July 21, 2000.
Source: NDA submission, Clinical Study Report for Protocol #99-02.0 p. 4 and addenda (Appendix 8-3 of the NDA Submission)

10.1.2.3 Objectives

Primary objectives: "to confirm the optimal dose for iontophoretic administration of 2% lidocaine HCl and epinephrine 1:100,000 as a local anesthetic, and

demonstrate that the iontophoretic administration of the drug is safe and produces sufficient analgesia for superficial dermatological procedures such as shave removals."

Secondary objectives: "demonstration of pain ratings and satisfactory subject global evaluations."

10.1.2.4 Design

This study was a Phase II, randomized, placebo-controlled, double-blinded, single-center trial conducted in two phases. There were a total of 140 patients evaluated.

Eighty patients were enrolled in the first phase and randomized in an equal allocation to one of four study arms:

Group 1: 20 subjects receiving an iontophoretic dose of 40 mA·min with a lidocaine-epinephrine drug combination.
Group 2: 20 subjects receiving an iontophoretic dose of 60 mA·min with a lidocaine-epinephrine drug combination.
Group 3: 20 subjects receiving an iontophoretic dose of 80 mA·min with a lidocaine-epinephrine drug combination.
Group 4: 20 subjects receiving an iontophoretic dose of 80 mA·min with a placebo drug.

The effectiveness of the delivered analgesia was evaluated at three time points. Patients unable to tolerate the iontophoretic treatment were classified as treatment failures. Those completing the treatment were given a needle-prick test at four locations within the drug delivery site. Patients with positive pain sensation at any site were also classified as treatment failures. In addition, any patients requesting supplemental analgesia during the dermatological procedure were identified as treatment failures.

The patients who underwent the dermatological procedures rated the discomfort of the procedure using a visual analog scale (VAS) and their overall satisfaction with the treatment and procedure using an 11 point ordered scale.

The second phase of the study was considered a "confirmatory phase" in which an additional 60 patients were enrolled to undergo the same dermatological procedures utilizing the iontophoretic dose from the first phase of the study deemed to be most safe and efficacious, 60 mA·min. In this phase, 40 patients received the active drug solution and 20 patients received the placebo product. The assessments of anesthetic effect of the iontophoretic treatment, discomfort of the procedure and global satisfaction with the procedure were the same as in the first phase of the study. Similarly, patients were identified as treatment failures using the same criteria as in the first phase of the study.

10.1.2.5 Primary Efficacy Variable

Incidence of treatment failure – defined as a subject who is unable to tolerate iontophoretic treatment, experiences pain during the needle-prick test or requests supplementary analgesia during the dermatological procedure

10.1.2.6 Secondary Efficacy Variables

Pain ratings for the dermatological procedure
Subject overall satisfaction ratings (global)

10.1.2.7 Population

Subjects of either sex undergoing shave removals for seborrheic keratosis or benign nevocellular nevi and normal subjects of either sex willing to undergo punch biopsies on the posterior aspect of their upper arm were considered for participation in the study. The following criteria were applied for the final determination of eligibility [quoted from the original protocol p. 11 (Appendix 8-2 p.43 of the NDA)].

Inclusion Criteria:

1. They are 18 to 70 years of age (inclusive).
2. They are willing to give signed, informed consent prior to admission to the study.
3. They are females that are post-menopausal for at least 1 year or surgically sterile. If they are females of childbearing potential, they must be willing to have a pregnancy test, which must be negative, prior to treatment.
4. They have seborrheic keratosis or benign nevocellular nevus lesions within 0.3 to 1.0 cm (inclusive) in size.

Exclusion Criteria:

1. They are experiencing significant levels of pain from any source.
2. They are currently taking monoamine oxidase inhibitors, tricyclic antidepressants, phenothiazine, butyrophenones, vasopressor drugs or ergot-type oxytocic drugs.
3. They have taken any prescription analgesics within three days prior to study participation.
4. They have broken or abraded skin at a treatment site.
5. They have signs of inflammation or infection at the treatment site.
6. They have a sensory deficit at the treatment site.
7. They are currently pregnant or nursing.
8. They have known drug sensitivities to epinephrine and/or local anesthetics such as lidocaine.

9. They have known allergies to sulfites.
10. They have reported a history of drug or alcohol abuse in the last five years.
11. They have a treatment site that requires the placement of the electrodes over the carotid sinus (neck) region.
12. They have a treatment site that requires the electrodes to be place over the temporal region.
13. They have a treatment site that requires the electrodes to be place over or near the orbital region.
14. They have metallic or plastic implants at or near the treatment site that might distort or in any way interfere with iontophoretic electrical current flow.
15. They have treatment site located on soles of feet or palms of hands.
16. They have known adverse reactions to the application of electrical current.
17. They have cardiac pacemakers or other implanted electronic device.
18. They have any significant health problems as documented by medical history, blood pressure and/or temperature, in the opinion of the Investigator/Subinvestigator.
19. They have reported a history of myocardial infarction, angina, and/or arrhythmia requiring medication.

10.1.2.8 Methods and Procedures

Phase I

Subjects were to be screened within 21 days of their treatment. Screening was to include completing the Inclusion/Exclusion checklist, demographics, vital signs, and medical and medication history.

Immediately before treatment, subjects were to be reevaluated to ensure no changes in their health status and to observe the treatment site. An "Intact Sensation to Light Touch" test (previously described in Study 97-07.0) was to be performed to confirm that there was no sensory deficit at the treatment site. Vital signs were to be recorded, including blood pressure, heart rate and respiration rate. Female subjects, who were required by inclusion criteria #3 to do so, were also to take a urine pregnancy test.

The delivery electrodes (8.1 cm^2) were to be filled with the appropriate test drug: 2%lidocaine HCl and epinephrine 1:100,000 for the active product, and the same formulation but without the 2% lidocaine HCl to serve as the placebo product. Two ml of study drug was to be used to fill the delivery electrode. The delivery electrode, connected to the anode, was to be centered over the treatment site from which excessive hair was to be clipped, not shaved, to assure good contact. The return electrode, connected to the cathode, was to be moistened with room temperature tap water and placed at least 4 inches from the delivery electrode on a muscle belly. The iontophoretic

dose of 80, 60 or 40 mA·min was to be achieved by applying a current of 4 mAmp for 20, 15 or 10 minutes, respectively. Electrodes were to be removed immediately after the iontophoretic treatment, and no further touching or manipulation of the skin was to occur until the anesthetic effect was tested using the "needle-prick test."

At the conclusion of the iontophoretic treatment, the Investigator was to evaluate the appearance of the skin under the two electrodes for blanching, erythema, or "other clinically significant changes." Additionally, vital signs were to again be recorded at that time.

Within 10 minutes following the completion of the iontophoretic treatment, adequacy of analgesia was to be tested by a "standard needle-prick test" in which a 30 gauge hypodermic needle was to be used to test for pain at four randomly determined points midway between the margins of the lesion or biopsy area and the border of the electrode application site. The time and response of the needle prick test was to be recorded and anesthetic adequacy was to be inferred if the subject had no pain sensation at any of the pin prick sites. Subjects who failed the needle prick test were to be judged as having inadequate analgesia and were to be discontinued from the study. Subjects scheduled for shave removals who were discontinued from the study due to inadequate analgesia were to be given the option to have their lesion removed by standard practices.

Those subjects whose iontophoretically treated sites passed the needle-prick test were to undergo their dermatological procedure within 15 minutes of the completion of their iontophoretic treatment. If during the procedure, the subject requested supplementary analgesia due to pain, the treatment was to be considered a failure and the subject was to be withdrawn from the study. Those subjects discontinued from the study prior to completion of the procedure were to be given the option of having their lesion removed following satisfactory analgesia from injection of a commercially available lidocaine solution.

The investigator was to have recorded the time from the beginning to the end of the dermatological procedure. Subjects who completed the dermatological procedure were to be asked to rate their degree of discomfort experienced during the procedure on a 100 mm VAS for pain intensity. In addition, they were to be asked to rate their overall satisfaction with the iontophoretic treatment and dermatological procedure on an eleven-point categorical scale with "0" being not satisfied at all and "10" being completely satisfied.

Subjects undergoing their dermatological procedure were to have applied polysporin ointment to the surgical site in the morning and at night until a scab formed over the wound. They were also to have been available for telephone follow up at 48-72 hours and 6-9 days following their procedure.

Phase II

The second phase of the study was to evaluate 60 subjects treated with the "optimal dose" as determined from an interim data analysis of the results from the first phase of the study. The subjects were to have received either the active or placebo solution based on a 2:1 randomization schedule, i.e., 40 subjects would receive active drug, 20 subjects would be given placebo. Aside from the above, all other aspects of the phase I portion of the protocol were to have been followed in the second phase.

10.1.2.9 Analysis Plan

10.1.2.9.1 Analysis of Efficacy

The primary efficacy end point, the incidence of treatment failure in the placebo and active groups, were to be evaluated using the Fisher's exact probability test to compare proportional differences. Reasons for treatment failure were to be examined across treatment groups.

Pain ratings and subject satisfaction ratings were to be compared across treatment groups with the Student's t, ANOVA or Chi-Square tests, as appropriate, or by nonparametric tests if the data were non-normally distributed.

10.1.2.9.2 Determination of Sample Size

The Sponsor expected that placebo-treated subjects would exhibit no less than a 95% treatment failure rate and that active-treated subjects would experience a failure rate of no greater than 20%. Because the success/failure rates for the two treatment groups were expected to be so extreme, as few as 8 subjects per treatment group would have been sufficient to detect the difference in failure rates with 80% power.

10.1.2.10 Protocol Amendments and Changes in the Planned Analysis

There were four amendments to the protocols however, only three were included with the NDA; the missing amendment, #2, was submitted as an amendment to the NDA.

Amendment #1 was dated March 2, 2000 and included the following changes to the protocol.

- A change in Institutional Review Board (IRB) secondary to a site change.
- Adverse reactions associated with iontophoresis, lidocaine, epinephrine and shave removals were modified in the Protocol section to include muscle twitch, loss of hearing, hypertension and inflammation, respectively, to be consistent with the listings in the Investigator's Brochure.
- The following statement was added to the Statistical Analysis section to provide additional information on how study data were to be analyzed. "Study data retrieved on Case Report Forms will be entered into a database created in Access utilizing double data entry to ensure accuracy. Once the database is complete, it will be downloaded into Excel so that it may then be transferred into SPSS for statistical analysis."

Amendment #2 was dated March 10, 2000 and included the following change to the protocol.

- All subjects were to be available to return to the clinic for a follow-up visit 48-72 hours post-operatively so that the iontophoretic treatment sites could be visually inspected by the study staff. This change was made at the request of the FDA to ensure that all adverse events were captured including delayed hypersensitivity.

Amendment #3 was dated March 17, 2000 and included the following changes to the protocol.

- The Inclusion Criteria were modified to include ages 18 years or greater instead of the original "18 to 70 years of age (inclusive)." This was done in response to a letter from the Division that studies "include an adequate number of patients over the age of 75."

Amendment #4 was dated June 6, 2000 and included the following changes to the protocol.

- The Synopsis and Treatment sections were modified so that the follow-up evaluation of the treatment sites would occur at 2-3 days following the procedure instead of 48-72 hours.
- Sample Size was changed from "approximately equal numbers of subjects requiring the removal of a seborrheic keratosis and benign nevocellular nevus will be recruited as part of the study for a total of 140 subjects" to "approximately the same ratio of subjects requiring the removal of a seborrheic keratosis and benign nevocellular nevus as in phase one of this study will be recruited for phase two of the study for a total of 140 subjects." The reason given was that the ratio of subjects presenting with the two types of lesions would be representative of the ratio of people in the general population presenting for removal of these lesions.

- Study Duration was extended from four to five months from the receipt of supplies to completion. The change was made due to administrative delays and the need for more time for subject enrollment.
- Medical Monitor and Adverse Events sections were changed such that all serious and unanticipated adverse events and any adverse events that are serious and unexpected would be reported within 24 hours of discovery. Originally, the sections required that adverse events that were serious and/or unanticipated or serious and/or unexpected be reported within 24 hours of discovery. The change was made so that only the serious unexpected adverse events would be reported to the Medical Monitor and the Sponsor within 24 hours of discovery. All other adverse events would be subject to periodical review by the same parties.

10.1.2.11 Study Conduct

The study was conducted as planned with the exception of the protocol violations noted below. A total of 68 deviations involving 59 patients occurred in Phase I of the study, and 5 protocol deviations involving 5 patients occurred in Phase II.

The Sponsor noted that Institutional Review Board approval was required before test articles were shipped to the study site. The final study report did not indicate that the study was conducted in accordance with the Good Clinical Practice Guidelines and the Ethical Principles for Medical Research Involving Human Subjects promulgated at the 18th World Medical Association General Assembly in Helsinki and later amended, although the Sponsor asserted this in an amendment to the NDA.

The final study report gives no indication as to how the study was monitored or how quality assurance of the data was provided. There also was no indication that the recorded data were verified for accuracy compared with the CRFs, or that upon closeout of the study, a full audit was performed. How the database was prepared, secured and verified was not stated.

The final report for the study stated that there were 68 deviations involving 59 patients from the Phase I protocol, and 5 deviations involving 5 patients from the Phase II protocol. The tables below list these deviations.

Table 10.1-6 Protocol Deviations for Phase I of Study

Description of Protocol Deviation	No. of Subjects
Did not initial the last page of the Informed Consent form	2
Completed the first follow-up visit earlier than the scheduled 48-72 hour window post-procedure	45
Missed the first follow-up visit	2

Description of Protocol Deviation	No. of Subjects
Completed the second follow-up visit earlier or later than the scheduled 6-9 days post-procedure	4
Missed the second follow-up visit scheduled 6-9 days post-procedure	1
Site failed to notify Medical Monitor and Sponsor of unexpected, but not serious, adverse event within 24 hours of occurrence	8
Missed readings	4
Subject use of prescription analgesic drug for unrelated knee pain	1
Incorrect recording of Iontophoresis stop time	1
TOTAL	68

Table 10.1-7 Protocol Deviations for Phase II of Study

Description of Protocol Deviation	No. of Subjects
Did not initial the last page of the Informed Consent form	2
Subject use of prescription medication for prevention of migraines	1
Completed the second follow-up visit later than the scheduled 6-9 days post-procedure	2
TOTAL	5

It was believed that none of the deviations had a significant impact on the study results.

10.1.2.11.1 Patient Disposition

The following tables are constructed from statements in the NDA referencing subject disposition and from the SAS listings of the CRF data.

Table 10.1-8 Subject Disposition for Phase I of the Study (from data in the CRFs)

Subject State	Number of Subjects
Enrolled	80
Randomized	80
Safety Population	80
ITT Population	80
Discontinued Study	29
Completed Study	51

Table 10.1-9 Subject Disposition for Phase II of the Study (from data in the CRFs)

Subject State	Number of Subjects
Enrolled	60
Randomized	60
Safety Population	60
ITT Population	60
Discontinued Study	20
Completed Study	40

10.1.2.12 Demographics/Group Comparability

In the first phase of the study, most of the subjects, were female, 58/80 (73%), and Caucasian, 72/80 (90%). Non-Caucasian subjects included 2 black, 2 Asian and 4 Hispanic subjects. While the distribution of subjects by gender was not significantly different between treatment groups, it was by race. Most of the non-Caucasians, 6/8 (75%) were enrolled in one treatment group: 80 mA·min dose; active treatment. The distribution of skin types and complexions across treatment groups was not significantly different; however, these data were not captured until the protocol was amended, which was after the first 18 subjects had enrolled. The average age of all subjects was 41.8 years (range: 18 to 89), and the average age of subjects by treatment group ranged from 38.4 to 44.1. Distribution by age across treatment groups was not significantly different.

In the second phase of the study, again most of the subjects were female, 45/60 (75%) and Caucasian, 56/60 (93%). Four Hispanic subjects comprised the entire non-Caucasian subject population. The average age was 42.8 years (range: 18 – 70) for the active treatment group and 46.0 years (range: 23- 42) for the placebo group. Distribution across treatment groups did not differ significantly for gender, race, age, or skin type and complexion.

The objectives indicated that "superficial dermatological procedures" would be studied, but only shave removals were performed, as indicated by the protocol title. The sites of the lesions were not prescribed but were captured in the CRFs.

10.1.2.13 Treatment Compliance

Study treatment was administered under direct supervision of the study staff; therefore, treatment compliance was assured.

10.1.2.14 Unplanned Analyses

No unplanned analyses were conducted.

10.1.2.15 Sponsor's Efficacy Results

Based on the following results in the Phase I portion of the study (quoted from NDA Appendix 8-3 pp. 17 and 18), the Sponsor concluded that "the 60 mA·min dose achieved the desired combination of safety and effectiveness." Thus, this dose was chosen for use in the Phase II portion of the study.

1. There were the fewest adverse events associated with the 40 mA·min/active treatment group (only one "minor" observation) followed by the 80 mA·min/placebo treatment group (six events).
2. The range of treatment success in achieving the anesthetic effect was from 70% to 90% with the use of the active drug, while only 10% in patients receiving the placebo drug. The highest success was achieved with the 60 mA·min/active treatment, although the differences between the three groups receiving the active drug were not significant.
3. The VAS discomfort readings were significantly higher with the placebo than the active drug treatment groups. The lowest VAS score was again associated the 60 mA·min/active treatment, but the differences between active groups did not reach statistical significance.
4. The overall ratings of satisfaction with the iontophoresis treatment and shave removal procedures were not different between the four treatment groups. However, only two subjects from the 80 mA·min/placebo group had the procedure conducted and went on to rate their overall satisfaction.

The Sponsor drew the following efficacy conclusions from the results of the second phase of the study (quoted from NDA Appendix 8-3 p. 37).

1. The Treatment Success in creating an anesthetic effect with use of the Active drug (87.5%) was significantly higher ($p<0.001$) than that with the Placebo drug (25.0%). The observed Treatment Success rate of 87.5% for the 60 mA·min/active drug combination in Phase II was similar to the rate of 90.0% observed in Phase I of the study.
2. The mean VAS discomfort readings in patients, who went on to have the scheduled dermatological procedure, were higher in patients receiving the Placebo drug than the Active drug, but the difference between treatment groups did not reach statistical significance ($p = 0.177$). The small number of Placebo patients

undergoing the dermatological procedure (n = 5) limited the assessment of this difference.

3. The patients' overall ratings of satisfaction with the iontophoresis and shave removal procedures were significantly higher (p = 0.025) in the Active than the Placebo drug group.

10.1.2.15.1 Primary Efficacy Variables

In the first phase of the study, 90% (18/20) of subjects receiving placebo treatment failed the needle-prick test compared with 25% (5/20), 10% (2/20) and 15% (3/20) of subjects receiving Lidopel treatments with doses of 40, 60 and 80 mA·min, respectively. The Sponsor indicated the level of significance for the difference between the active and placebo treatments was $p < 0.001$ by the Fisher's Exact test. The differences between the three active treatments were not significant, $p = 0.421$ by the Kruskal-Wallis test, and the Pass/Fail percentages between the three active groups was also not significant, $p = 0.574$ by the Fisher's Exact test.

Of the 52 subjects who passed the needle-prick test, only one patient (who received a 40 mA·min Lidopel treatment) requested additional analgesia during the dermatological procedure reducing the success rate in that group to 70% (14/20).

In Phase II, where a 60 mA·min iontophoretic dose was used in both the Lidopel (n=40) and placebo (n=20) treatment groups, there was a significant difference in the percentage of patients who passed the needle-prick test. In the active group, 37/40 (92.5%) passed compared to placebo where 5/20 (25%) passed ($p<0.001$, Fisher's Exact test). Of the 42 patients who passed the needle-prick test and went on to have their dermatological procedure, two patients in the active group required supplemental analgesia. This resulted in an overall success rate of 87.5% for the active group compare to the unchanged 25% for the placebo group which was still significantly different ($p < 0.001$).

There was no significant effect on these success rates due to gender ($p = 0.347$, Fisher's Exact test), race ($p = 0.306$, Fisher's Exact test) or skin type ($p = 0.812$, Fisher's Exact test).

10.1.2.15.2 Secondary Efficacy Variables

The 51 subjects in Phase I of the study who had their dermatological procedure performed without supplemental analgesia were evaluated for their discomfort during the procedure and overall satisfaction with the iontophoretic treatment and dermatological procedure.

VAS scores were recorded in millimeters and could range from "0" for no pain to "100" for extreme pain. Summary statistics were computed by the Sponsor and are presented in the table below.

Table 10.1-10 VAS Scores by Treatment Group (App. 8-3, p. 13, Table 13)

Treatment	Mean (mm)	Std. Dev.	Min.	Max.
40 mA·min/Active (n=14)	11.9	17.4	0	50
60 mA·min/Active (n=18)	3.6	11.5	0	49
80 mA·min/Active (n=17)	7.1	14.1	0	46
80 mA·min/Placebo (n=2)	28.5	0.7	28	29

The differences between the four treatment groups were significant (p = 0.039, Kruskal-Wallis test) as was the difference between the active and placebo groups (p = 0.041, Mann-Whitney U test). Although the mean for the 40 mA·min active group was higher than the other two active groups, the differences among the three were not significant (p = 0.106). It was noted that one subject in the 40 mA·min active group reported taking analgesic medications (aspirin and lodine) the day of the procedure. The Sponsor indicated that exclusion of this patient's VAS score of 8.0 resulted in a "borderline nonsignificant finding" for differences between the four treatment groups (p = 0.053), but had little impact on active versus placebo differences (p = 0.040). The differences between the three active drug groups remained not significant (p = 0.160)

The Sponsor reported no significant differences in VAS scores due to gender (p = 0.260, Mann-Whitney U), race (p = 0.430, Mann-Whitney U) or skin type (p = 0.938, Kruskal-Wallis test).

Overall satisfaction with the iontophoretic treatment and dermatological procedure was assessed on a 0-10 scale where "0" indicated "not at all satisfied" and "10" indicated "completely satisfied." Summary statistics for the 51 subjects who participated in Phase I of the study are presented in the table below.

Table 10.1-11 Satisfaction Ratings by Treatment Group (App. 8-3, p. 14, Table 14)

Treatment	Mean	Std. Dev.	Min.	Max.
40 mA·min/Active (n=14)	8.9	2.3	2	10
60 mA·min/Active (n=18)	9.0	2.1	2	10
80 mA·min/Active (n=17)	9.5	1.4	5	10
80 mA·min/Placebo (n=2)	8.5	0.7	8	9

The differences between the four treatment groups were not significant (p = 0.213, Kruskal-Wallis test) and neither was the difference between active and placebo (p = 0.072, Mann-Whitney U test). The mean scores for all groups fell in a narrow range. For

the active groups alone, the associated p-value for a test of differences was equal to 0.631.

Exclusion of the Satisfaction rating of 10 given by the subject who had taken aspirin and Iodine on the day of the study resulted in no change in the finding for differences between the four treatment groups and in minimal change in the active versus placebo difference ($p = 0.077$). The differences between the three active groups also remained non-significant ($p = 0.592$).

No differences were reported in Satisfaction ratings due to gender ($p = 0.287$, Mann-Whitney U test), race ($p = 0.595$, Man-Whitney U test) or skin type ($p = 0.539$, Kruskal-Wallis test).

In Phase II of the study, 42 subjects passed the needle-prick test and thereby qualified to undergo their dermatological procedures. As in Part 1 of the study, significantly more placebo-treated subjects failed the needle-prick test than did Lidopel-treated subjects. Of those patients who passed the needle-prick test, two required additional analgesia to complete the procedure and were included in the treatment failure group. The 40 remaining patients rated their pain and overall satisfaction with the iontophoresis treatment and dermatological procedure. The tables below summarize these results.

Table 10.1-12 VAS Ratings by Treatment Group (App. 8-3, p. 32, Table 13)

Treatment	Mean (mm)	Median	Std. Dev.	Min.	Max.
60 mA·min/Active (n=35)	4.9	0.0	9.4	0	37
60 mA·min/Placebo (n=5)	12.4	4.0	20.2	0	48

Table 10.1-13 Satisfaction Ratings by Treatment Group (App. 8-3, p. 33, Table 14)

Treatment	Mean	Median	Std. Dev.	Min.	Max.
60 mA·min/Active (n=35)	9.6	10.0	0.9	6	10
60 mA·min/Placebo (n=5)	7.0	7.0	3.7	1	10

Although the mean VAS score for Lidopel treatment was less than that of placebo treatment, it did not reach significance ($p=0.177$; Mann Whitney U test). However, the differences in mean global satisfaction scores was significant ($p=0.025$; Mann Whitney U test).

10.1.2.16 Discussion of Efficacy Findings in the Study

The primary outcome measure of efficacy for both phases of this study was comparison of percentages of Lidopel treatments and placebo treatments that succeeded in passing an

initial needle-prick test and then providing sufficient analgesia for a dermatological procedure to be performed without need for supplemental local analgesic.

In phase I of the study, three iontophoretic doses of Lidopel, 40, 60 and 80 mA·min, were compared to an epinephrine-containing placebo with an applied iontophoretic dose of 80 mA·min. Of these different treatments, only 10% of the placebo-patch patients passed the needle-prick test whereas 75, 90 and 85% of subjects receiving the 40, 60 and 80 mA·min doses, respectively, of Lidopel treatments passed. All of the Lidopel treatments significantly outperformed the placebo treatment on the needle-prick test which qualified patients to proceed with their dermatological procedure. Of those patients who underwent their dermatological procedure, only one in the Lidopel treatment group, receiving a dose of 40 mA·min, required supplemental local analgesia whereas, no patient in the placebo group required additional analgesia. Despite the additional treatment failure for the use of supplemental local anesthetic, significantly more Lidopel-treated patients succeeded in undergoing their dermatological procedure without supplemental analgesia than did placebo-treated patients.

The placebo used in the first phase of the study poses two problems. First, there is a concern that the placebo, epinephrine 1:100,000 applied with an 80 mA·min iontophoretic dose, may not be a valid placebo. In the only approved product for iontophoretic delivery of 2% lidocaine with epinephrine 1:100,000, Iontocaine, studies conducted for the NDA utilized a placebo containing epinephrine alone which was administered with a 40 mA·min iontophoretic dose. There is no evidence that this placebo at an 80 mA·min dose does not cause untoward effects related either to prolonged exposure to the iontophoretic current or the exposure to additional epinephrine. The second problem with this phase of the study is that the design does not adequately address the clinical issue which is whether or not the product effectively provides sufficient analgesia for dermatological procedures. Although Lidopel was shown to provide better analgesia for a needle-prick test than a questionable placebo treatment, whether it is sufficient for the dermatological procedure in question was not assessed in a blinded, randomized fashion using a validated comparator.

Even if success with needle-prick testing is an appropriate way to assess efficacy for providing analgesia for a dermatological procedure, the clinical significance of the results must be considered. In this study, the placebo-treated subjects had a mean VAS score less than 30mm suggesting only a mild level of discomfort with the procedure. In addition, none of the placebo-treated subjects had requested supplemental local anesthetic for their procedure. Statistically, the Lidopel-treated patients had significantly lower mean VAS scores, but the clinical difference is questionable for such a small difference in the means, 16.6-24.9 mm for part one of the study. The significance of the difference is further confounded when consideration is given to the fact that the Lidopel-treated patients were not significantly more satisfied than placebo-treated patients in this part of the study. The difference in mean VAS scores, 7.5 mm for part two of the study, was not

statistically significant although the subject satisfaction scores were with Lidopel use associated with greater patient satisfaction.

The most frequent site of the lesions removed in this study was the upper back, however a significant number of lesions were removed from the chest, and abdomen as well. Relatively few lesions were removed from the extremities: nine from the upper extremities and five from the lower extremities.

10.1.3 **Study #99-07.0: "Anesthetic Effect of 2% Lidocaine HCl and Epinephrine 1:100,000 Delivered via the Dupel® Iontophoresis System to Subjects Undergoing Venipuncture**

10.1.3.1 Overall Design and Summary of Findings

This study was a single-center, randomized, double-blinded, placebo-controlled, Phase 3 trial which evaluated the analgesic effects of Lidopel compared to placebo in adult volunteers undergoing blood draws by venipuncture. Each subject received both a placebo and Lidopel treatment simultaneously, one on each arm. The placebo consisted of iontophoretic treatment with the same formulation as the Lidopel treatment excluding the lidocaine HCl. The study was conducted in two phases. The first phase was to assess which of three iontophoretic doses, 20, 30 or 40 mA·min, provided the best analgesia, and the second was to expand on the first phase findings by repeating the protocol with additional subjects using only the optimal iontophoretic dose as found in phase one. Sixty subjects participated in the first phase of the study; forty more participated in the second phase.

Based on a 100-mm visual analog scale (VAS) scores for pain, the combined iontophoretic doses of Lidopel provided significantly more analgesia than the combined placebo treatments. There were no significant differences in pain levels among the iontophoretic doses when VAS scores for Lidopel treatments were subtracted from those of the corresponding placebo treatments. These findings, in conjunction with the lack of adverse events occurring in the 20 mA·min, led the Sponsor to conclude that the 20 mA·min provided the optimal treatment and to use this dose in the second phase of the study. The data from the second phase were combined with the equivalent data from the first phase, i.e., all subjects who received an iontophoretic dose of 20 mA·min, and were analyzed *en masse*. The combining of data from the two parts of the study was not included in the protocol. The results of the second phase indicated a significant difference in analgesia between the Lidopel and placebo treatments. The magnitude of the difference in the second phase was similar to that in the first.

Since the clinical significance of the mean of differences in VAS scores was questionable due to the small magnitude of the differences, the global satisfaction scores were used to gain perspective. In the first phase of the study, there was a difference favoring Lidopel treatment when the data from all three iontophoretic dose groups were combined. Although there was no comparison of satisfaction scores performed within each iontophoretic dose group, the greatest difference occurred in the 20 mA·min dose group, 1.2 (out of a possible 10), which was 12 and 4 times that observed in the 30 and 40 mA·min dose groups, respectively. The second phase of the study however, indicated there was no significant difference in subject satisfaction between Lidopel and placebo at this iontophoretic dose. The data suggest that, in the setting of venipuncture, Lidopel does not provide clinically more meaningful analgesia, based on VAS and global satisfaction scores, than placebo treatment at iontophoretic doses of 20, 30 and 40 mA·min.

The Division analysis of the Lidopel and placebo VAS scores for each iontophoretic dose revealed that there was a statistically significant difference between the two treatments only at the 20 mA·min dose. This finding conflicts with what is known from Iontocaine, i.e., 40 mA·min doses of 2%lidocaine and epinephrine 1:100,000 provide better analgesia than placebo, and with what is generally understood regarding local anesthetics, i.e., higher doses result in greater analgesia up to the point of complete anesthetic effect.

A possible explanation for these findings is that iontophoretically applied epinephrine is actually an active comparator with either increasing analgesic properties with increasing doses or increasing hyper-sensitization properties with decreasing doses, or possibly, both. This is supported by the decreases in mean VAS scores observed with placebo treatments as iontophoretic dose increased.

10.1.3.2 Study Plan

The original version of this protocol was dated January 17, 2000. The protocol was amended three times. The amendments dated March 14, 2000, March 20, 2000 and June 7, 2000 were included with the NDA. Subjects underwent venipuncture procedures at a single study center between March 24 and June 22, 2000.
Source: NDA submission, Clinical Study Report for Protocol #99-07.0 p. 5 and addenda (Appendix 8-4 of the NDA Submission).

10.1.3.3 Objectives

Primary objectives: "to confirm the optimal dose for iontophoretic administration of 2% lidocaine HCl and epinephrine 1:100,000 as a local anesthetic for

venipuncture, and demonstrate that the iontophoretic administration of the drug is safe and reduces or eliminates the pain associated with venipuncture."

Secondary objective: "determine subject global satisfaction."

10.1.3.4 Design

This study was a Phase 3, randomized, placebo-controlled, double-blinded, single-center trial conducted in two phases. Placebo consisted of iontophoretic administration of the same formulation of the active solution without the lidocaine HCl. There were a total of 100 patients evaluated.

Sixty subjects were enrolled in the first phase and randomized in an equal allocation to one of three iontophoretic dosage arms:

Group 1: 20 subjects receiving an iontophoretic dose of 20 mA·min.

Group 2: 20 subjects receiving an iontophoretic dose of 30 mA·min.

Group 3: 20 subjects receiving an iontophoretic dose of 40 mA·min.

All subjects received an active and a placebo treatment, randomized to each arm. Additionally, the order of the venipunctures was randomized by arm. Up to two attempts at venipuncture could be made at each treatment site. Regardless of the success of the venipuncture, pain and satisfaction were to be assessed for each treatment site. Subjects rated the discomfort of the venipuncture using a 100 mm visual analog scale (VAS) and their overall satisfaction with the treatment and procedure using an 11-point ordered scale.

The second phase of the study was considered a "confirmatory phase" in which an additional 40 subjects were enrolled to undergo venipuncture utilizing the iontophoretic dose from the first phase of the study deemed to be most safe and efficacious, i.e., 20 mA·min. In this phase, as in the first, all subjects received one treatment, active or placebo, on each arm. The assessment of discomfort of the procedure and global satisfaction with the procedure were the same as in the first phase of the study.

10.1.3.5 Primary Efficacy Variable

Pain ratings during blood draws using a 100 mm VAS scale.

10.1.3.6 Secondary Efficacy Variable

Overall satisfaction ratings (global) using an 11-point categorical scale.

10.1.3.7 Population

Subjects of either sex from the community at large willing to undergo the withdrawal of blood from both arms were considered for participation in the study. The following criteria were applied for the final determination of eligibility [quoted from the original protocol p. 40-41 (Appendix 8-4 of the NDA)].

Inclusion Criteria:

1. They are 18 to 70 years of age (inclusive).
2. They are willing to give signed, informed consent prior to admission to the study.
3. They are females that are post-menopausal for at least 1 year or surgically sterile. If they are females of childbearing potential, they must be willing to have a pregnancy test, which must be negative, prior to treatment.

Exclusion Criteria:

1. They are experiencing significant levels of pain from any source.
2. They are currently taking monoamine oxidase inhibitors, tricyclic antidepressants, phenothiazine, butyrophenones, vasopressor drugs or ergot-type oxytocic drugs.
3. They have taken any prescription analgesics within three days prior to study participation.
4. They have broken or abraded skin at a treatment site.
5. They have signs of inflammation or infection at the treatment site.
6. They are currently pregnant or nursing.
7. They have known drug sensitivities to epinephrine and/or local anesthetics such as lidocaine.
8. They have known allergies to sulfites.
9. They have reported a history of drug or alcohol abuse in the last five years.
10. They have metallic or plastic implants at or near the treatment site that might distort or in any way interfere with iontophoretic electrical current flow.
11. They have known adverse reactions to the application of electrical current.
12. They have cardiac pacemakers or other implanted electronic device.
13. They have any significant health problems as documented by medical history, blood pressure and/or temperature, in the opinion of the Investigator/Subinvestigator.

14. They have reported a history of myocardial infarction, angina, and/or arrhythmia requiring medication.

10.1.3.8 Methods and Procedures

Phase I

Subjects were to be screened within 21 days of their treatment. Screening was to include completing the Inclusion/Exclusion checklist, demographics, vital signs, and medical and medication history.

Immediately before treatment, subjects were to be reevaluated to ensure no changes in their health status occurred and to observe the treatment sites. An "Intact Sensation to Light Touch" test (previously described) was to be performed to confirm that there was no sensory deficit at the treatment sites. Vital signs were to be recorded, including blood pressure, heart rate and respiration rate. Female subjects, who were required by inclusion criteria #3 to do so, were also to take a urine pregnancy test.

The delivery electrodes (8.1 cm^2) were to be filled with the appropriate test drug: 2% lidocaine HCl and epinephrine 1:100,000 for the active product, or the same formulation but without the 2% lidocaine HCl which was to serve as the placebo product. The delivery electrode, connected to the anode, was to be centered over the treatment site from which excessive hair was to be clipped, not shaved, to assure good contact. The return electrode, connected to the cathode, was to be moistened with room temperature tap water and placed at least 4 inches from the delivery electrode on a muscle belly. The iontophoretic doses of 20, 30 and 40 mA·min were to be achieved by applying a current of 4 mAmp for 5, 7.5 or 10 minutes, respectively. Electrodes were to be removed immediately after the iontophoretic treatment, and no further touching or manipulation of the skin was to occur until after the blood draws had been completed.

At the conclusion of the iontophoretic treatment, the Investigator was to evaluate the appearance of the skin under the two electrodes for blanching, erythema, or "other clinically significant changes." Additionally, vital signs were to be recorded at that time.

Within 10 minutes following the completion of the iontophoretic treatment, a blood draw of 5 ml was to have been done on the arm randomly selected to undergo venipuncture first. Immediately following the first blood draw, or two failed attempts to do so, venipuncture was to have been performed on the opposite arm, again to withdraw 5 ml of blood within two attempts. The investigator was to have recorded the time of each blood draw, the number of attempts on each arm, and whether or not the blood draw was successful. The protocol did not specify the size needle to be used for the venipuncture, and there was no requirement or provision for documenting such information. Subjects

were to be asked to rate their degree of discomfort experienced during the procedure on a 100-mm VAS for pain intensity. In addition, they were to be asked to rate their overall satisfaction with the iontophoretic treatment and dermatological procedure on a eleven-point categorical scale with "0" being not satisfied at all and "10" being completely satisfied.

All subjects were to have been required to be available 48 to 72 hours after the procedure to receive a follow-up phone call questioning them on the iontophoretic treatment site. Subjects might have been required to return to the clinic for further evaluation if it was deemed appropriate by the Investigator or Subinvestigator.

Phase II

The second phase of the study was to have evaluated 40 subjects treated with the "optimal dose" as determined from an interim data analysis of the results from the first phase of the study. All other aspects of the phase I portion of the protocol were to have been followed in the second phase. The 20 mA·min dose was selected for this phase based on the lack of a significant difference in mean VAS scores between dose groups and the absence of adverse events in this, the lowest dose group.

10.1.3.9 Analysis Plan

10.1.3.9.1 Analysis of Efficacy

While all subjects receiving an iontophoretic treatment were to be included in the safety analyses, only those who had successfully completed blood draws were to be included in the efficacy analysis.

Pain ratings and subject satisfaction ratings were to be compared across treatment groups with the Student's t or Chi-Square tests, as appropriate, or by nonparametric tests if the data were non-normally distributed.

10.1.3.9.2 Determination of Sample Size

A sample size of ten subjects was determined to be sufficient to detect an effect size of 1.0, mean difference/standard deviation of difference, for paired pain readings within subjects at a two-sided significance level of 0.05 with 80% power. This effect size was reported to have been observed in previous studies.

10.1.3.10 Protocol Amendments and Changes in the Planned Analysis

Amendment #1 was dated March 14, 2000 and included the following changes to the protocol.

A. The treatment section was modified to require subjects to return to the clinic for a follow-up visit and visual inspection of the treatment site.
B. The lists of adverse reactions associated with iontophoresis, lidocaine, epinephrine, and venipuncture were modified to include muscle twitch, loss of hearing, hypertension and inflammation, respectively, making the clinical protocol consistent with the Investigator's Brochure.
C. The statistical analysis section was modified with the addition of the comment that study data retrieved on Case Report Forms will be entered into an MS Access database utilizing double data entry. Once the data have been verified, they will be downloaded into MS Excel for transfer into SPSS for statistical analysis.

Amendment #2 was dated March 20, 2000 and included the following change to the protocol.

A. Inclusion criteria were modified for age to include subjects 18 years of age or greater instead of the original 18 to 70 years of age inclusive.

Amendment #3 was dated June 7, 2000 and included the following changes to the protocol.

A. The Synopsis and Treatment sections were modified so that follow-up evaluation could occur from 2 to 3 days following treatment instead of 48 to 72 hours. This change allowed greater flexibility in scheduling.
B. The completion time of the study was changed to specify only that subject enrollment would be expected to be complete within four months of receipt of supplies.

Only the last amendment was made during the conduct of the study. None of the amendments were expected to have significant impact on the outcomes of the study.

10.1.3.11 Study Conduct

The study was conducted as planned with the exception of the protocol violations noted below. A total of 30 deviations involving 60 patients occurred in Phase I of the study, and 13 protocol deviations involving 40 patients occurred in Phase II.

Institutional Review Board approval was provided for each of the amendments. The final study reports, one for Phase I results and one for both phase I and II results, did not indicate that the study was conducted in accordance with the Good Clinical Practice Guidelines and the Ethical Principles for Medical Research Involving Human Subjects promulgated at the 18th World Medical Association General Assembly in Helsinki and later amended, but the Sponsor attested to this in an amendment to the NDA.

The final study reports give no indication as to how the study was monitored or how quality assurance of the data was provided. There also was no indication that the recorded data were verified for accuracy compared with the CRFs, or that upon closeout of the study a full audit was performed. How the database was prepared, secured and verified was not stated.

The final reports for the study stated that there were 30 deviations involving patients from the Phase I protocol, and 17 deviations involving patients from the Phase II protocol. All the deviations from the first phase of the study and 13 of the deviations from the second phase were related to the timing of the follow-up visits that were originally to occur within 48 to 72 hours of treatment. For the second phase of the study, the Sponsor indicated that all of the 13 follow-up visits in question occurred within 2 to 3 days of treatment although not within the exact time frame specified by the original protocol. No comment was made as to how far outside the specified time frame the follow-up visits occurred for the phase I subjects.

The remaining protocol deviations for the second phase of the study included 3 instances where the Investigator or Subinvestigator did not address "slightly higher than normal" blood pressures measured at baseline, and one instance where the Medical Monitor was not informed within 24 hours of an unexpected patient complaint as required by the protocol. The Sponsor did not specify what the complaint was, but did state it was unrelated to the study.

It was believed that none of the deviations had a significant impact on the efficacy results of the study.

10.1.3.11.1 Patient Disposition

The following tables are constructed from statements in the NDA referencing subject disposition and from the SAS listings of the CRF data.

Table 10.1-14 Subject Disposition for Phase I and II of the Study (derived from CRFs)

Subject Status	Phase I	Phase II
Enrolled	60	40
Randomized	60	40
Safety Population	60	40
Intent-to-Treat (ITT) Population	60	40
Completed Study	60	40

10.1.3.12 Demographics/Group Comparability

The Sponsor indicated that there was no significant difference between dose groups in phase I of the study for the distribution of gender, race, age, skin complexion and skin type. Overall in this phase of the study, 62% of the subjects were female, 93% were Caucasian, the average age was 43.8 years (range: 19-70 years), and 67% had "normal" skin.

In the second phase of the study, the distribution of gender, race, age, skin complexion and skin type did not significantly differ from that for the 20 mA·min group in phase I. In this phase, 60% of subjects were female, 90% were Caucasian, the average age was 39.9 years (range: 18-76 years), and 57% had "normal" skin.

10.1.3.13 Treatment Compliance

Study treatment was administered under direct supervision of the study staff; therefore, treatment compliance was assured.

10.1.3.14 Unplanned Analyses

No unplanned analyses were conducted; however, the data from the second part of the study were combined with the corresponding, previously-analyzed, data from the first part of the study.

10.1.3.15 Sponsor's Efficacy Results

There was no significant difference between venipuncture success rates based on order or treatment. Blood draws were to be initiated within 10 minutes of treatment. In the first phase of the study, 56/60 (93%) of the first blood draws required only one attempt at venipuncture. Of the four first attempts that failed, two were associated with placebo and two were associated with Lidopel treatments. Blood draws were unsuccessful in three of the four subjects who required a second venipuncture. Two of these incidents were associated with placebo; the other was with Lidopel treatment. In the second blood draw, i.e., on the opposite arm, 52/60 (87%) required only one attempt at venipuncture. Of those 8 subjects who required a second attempt, 3 had received a placebo treatment and 5 had been given Lidopel treatments. On the second attempt, only one subject in each treatment group had a successful blood draw.

In the second phase of the study, 38/40 (95%) of the first blood draws succeeded with the first venipuncture. The second attempted venipuncture failed in both subjects who had unsuccessful first attempts. In the second blood draw, 36/40 (90%) of the first blood draws succeeded on the first attempt. None of the second attempts were successful at completing the blood draws. Two of the subjects failed to have a successful blood draw in either arm.

10.1.3.15.1 Primary Efficacy Variables

In the first phase of the study, equal numbers of left and right arms were selected for the first blood draw and equal numbers of placebo and Lidopel treatments were assigned to the left and right arms at each draw. The mean VAS score for the first and second blood draws including all iontophoretic doses were not significantly different, 11.3 (SD = 12.0; range: 0-55.0) and 14.5 (SD = 20.6; range: 0-90.0), respectively. The mean VAS score for placebo treatments of all three iontophoretic doses was 17.6 (SD = 20.1; range: 0-90.0) which was significantly higher than that of the Lidopel treatments for all three iontophoretic doses combined, 8.2 (SD = 11.2; range: 0-51.0)

The Sponsor compared the effect of iontophoretic dose by evaluating the differences between VAS scores with placebo treatment and VAS scores with Lidopel treatment (placebo score – Lidopel score) for each subject. Summary statistics were provided and are shown in the table below taken from the NDA.

Table 10.1-15 Difference in VAS scores by Dose (App. 8-4, p. 12, Table 11)

Dose Group	Mean Difference	Median Difference	Std. Dev.	Range (min, max
20 mA·min (n=20)	17.1	9.5	21.5	(-8, 66)
30 mA·min (n=20)	4.7	1.5	15.8	(-29, 40)
40 mA·min (n=20)	6.4	6.5	18.4	(-50, 43)

The greatest difference between placebo and Lidopel occurred in the 20 mA·min dose, however, there was no statistical significance between mean differences of the three dose groups. The Sponsor indicated that the differences between the mean and median values suggest skewed responses among subjects.

The Sponsor combined the results of the 40 subjects involved in the second phase of the study with those who received the same iontophoretic dose in phase I. Among the total of 60 subjects exposed to 20 mA·min doses, equal numbers had left and right arms selected for the first blood draw and equal numbers of placebo and Lidopel treatments were assigned to each arm. There was no significant difference between the mean VAS scores for the first and second blood draws, 17.2 (SD = 19.2) and 17.0 (SD = 21.3), respectively. The mean VAS score for placebo treatments was 23.7 (SD = 23.5) which was significantly greater than the mean VAS for Lidopel treatments, 10.6 (SD = 13.5).

The Sponsor compared the mean differences in VAS scores between males (n = 24) and females (n = 36) and noted a greater average difference in males, 19.2, than in females, 9.1, although the difference was not significant (p = 0.152, Mann Whitney U Test).

10.1.3.15.2 Secondary Efficacy Variables

The secondary efficacy variable for both phases of this study was the eleven-point global satisfaction score where "0" indicated being "not satisfied at all," and "10" indicated being "completely satisfied." For both phases, there was no significant difference in the mean scores of the first and second blood draws. In phase I, the mean satisfaction score was significantly greater in the Lidopel-treated group (all iontophoretic doses combined) than in the combined, placebo-treated group, 8.8 (SD = 2.2; range: 1 – 10) and 8.3 (SD = 2.2; range: 2 – 10), respectively. The difference between Lidopel and placebo treatment scores for each iontophoretic dose group was analyzed for the first phase of the study. The table below is taken from the NDA and summarizes these results.

Table 10.1-16 Differences in Satisfaction Scores by Dose (App. 8-4, p.13, Table 12)

Dose Group	Mean Difference	Median Difference	Std. Dev.	Range (min, max
20 mA·min (n=20)	1.2	0.0	2.4	(-3, 9)
30 mA·min (n=20)	0.1	0.0	1.4	(-4, 3)
40 mA·min (n=20)	0.3	0.0	2.5	(-8, 5)

The greatest difference was observed in the lowest iontophoretic dose group, although overall, the differences between dose groups were not significant.

The satisfaction results from the second phase of the study indicated no significant difference between placebo and Lidopel treatment ($p = 0.052$, Wilcoxon Signed Ranks Test).

10.1.3.16 Discussion of Efficacy Findings in Study

Based on the 100-mm visual analog scale (VAS) scores for pain, the combined data for all three iontophoretic doses evaluated in the first part of the study showed that Lidopel treatment provided significantly more analgesia than the placebo treatments. The mean of the differences in VAS scores (placebo – Lidopel) for each of the iontophoretic doses were compared and found not to be significantly different. The greatest mean of the difference in VAS scores occurred at the 20 mA·min dose. This was the only statistically significant mean difference in VAS scores and was more than 2.5 times that observed for the other two doses.

Based on the above findings, in conjunction with the lack of adverse events occurring in the 20 mA·min treatment, the Sponsor concluded that the 20 mA-min was the optimal treatment and opted to use this dose in the second phase of the study.

Although the combined Lidopel treatments produced VAS scores that were significantly less than those of the placebo treatments, the differences in mean VAS scores for individual doses were so small as to be of questionable clinical significance even if they could be found to be statistically significant. The mean differences in VAS scores between placebo and Lidopel treatments were 17.1, 4.7 and 6.4 mm (out of a possible 100 mm) for the 20, 30 and 40 mA·min iontophoretic doses, respectively. The global satisfaction score results were similar in that very small differences existed between treatment groups and the mean difference was greatest for the 20 mA·min iontophoretic dose group, 1.2 (out of a possible 10) versus 0.1 and 0.3 for the 30 and 40 mA·min groups, respectively. While the differences in satisfaction scores for all iontophoretic doses combined were significantly greater for Lidopel treatments, significance was not evaluated within each dose group. In each case, the mean difference favored Lidopel treatment. It should also be noted that in each iontophoretic dose group, there were subjects who were much more satisfied with the placebo treatment than with the Lidopel treatment.

Drs. Kammerman and Permutt of the Office of Biostatistics analyzed the differences in VAS scores between Lidopel and placebo for each of the iontophoretic doses. They determined that there was a statistically significant reduction in VAS scores only at the 20 mA·min dose.

The data from the second phase of the study were combined with the corresponding data from the first phase, i.e. all subjects who received an iontophoretic dose of 20 mA·min, and analyzed *en masse*. This combining of data after that obtained in the first part of the study had already been analyzed, was not described in the protocol. The combined results of the two phases indicated a significant difference in analgesia between the Lidopel and placebo treatments. The mean of the differences in VAS scores was similar to that in the first part of the study, and was found to be statistically significant, but the magnitude of the difference, 13.1 (out of a possible 100) was so small as to be of questionable clinical significance. In this phase, the global satisfaction scores were not significantly different between the treatment groups. As this was the dose group whose satisfaction scores most influenced the analysis in the first phase of the study, the second phase findings confound the issue. The mean global satisfaction scores for the two treatments in this phase of the study were 8.1 for placebo treatment and 8.6 for Lidopel treatment.

When the data that were obtained from the second part of the study were analyzed alone, i.e., the corresponding data from the first part were removed, there was still a significant difference between Lidopel and placebo treatments; mean VAS scores and (standard deviations) were 12.9 (15.2) and 24.0 (22.2) for the two treatments, respectively. In a paired Student's t test of the data, a significant difference was noted, i.e., p=0.011. Confirmation of the finding of a significant difference was provided by the statistics reviewer. Although the difference is statistically significant, the clinical significance remains questionable as the magnitudes of both values were relatively small on the scale of 0-100. Additionally, the size of the needle to be used for venipuncture was neither specified by the protocol nor recorded on the CRFs thus limiting further assessment of the clinical meaning of these results.

Lastly, review of the raw data suggested that the placebo may provide analgesia in a dose dependent fashion. The table below was derived from the data tables and demonstrates the decreasing VAS scores for increasing iontophoretic doses with placebo, which indicates decreasing discomfort with increasing iontophoretic dose. The magnitude of the changes in VAS for placebo treatments is such that it could confound the significance of the Lidopel VAS values and perhaps erroneously suggest that the 20 mA·min dose is most effective when in actuality, the higher doses may be. Additionally, the differences observed in mean VAS scores for the placebo treatment are of the same order of magnitude as that observed for the differences between Lidopel and placebo treatments at each iontophoretic dose. This raises the concern that either lidocaine does not contribute significantly to the efficacy of the treatments or that what is actually being observed is background noise in the measurements and clinically meaningful analgesia was not achieved.

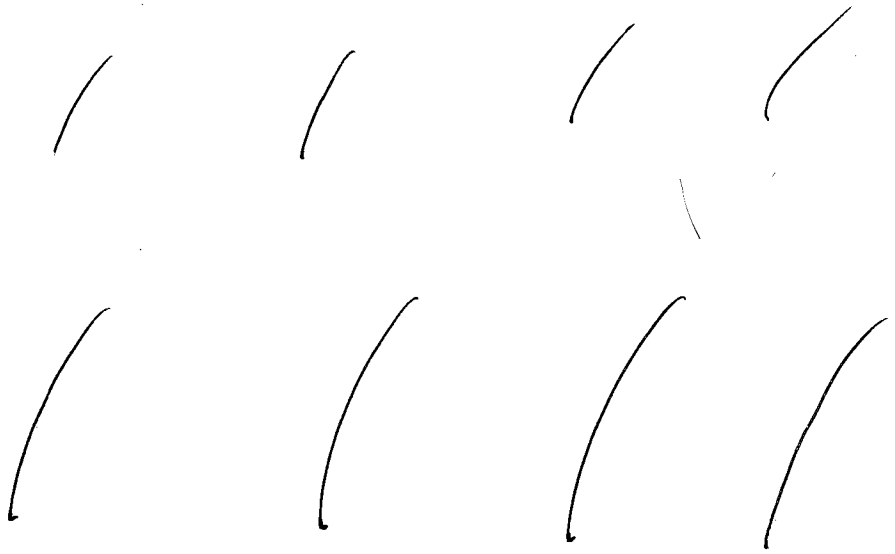
Table 10.1-17 Mean VAS scores for each treatment and iontophoretic dose

	Mean VAS (SD) by Treatment/Calculation		
Iontophoretic Dose	Placebo	Lidopel	Lidopel – Placebo
20 mA·min (n=60)	23.7 (23.5)	10.8 (13.5)	-12.9 (24.8)
30 mA·min (n=20)	16.0 (16.8)	11.3 (12.9)	-4.7 (15.8)
40 mA·min (n=20)	13.9 (14.8)	7.4 (12.2)	-6.5 (18.4)

Drs. Kammerman and Permutt analyzed the decreases in VAS scores observed with increasing iontophoretic doses of placebo. They found that the p value for a difference among the placebo responses was 0.07, suggesting there is a difference. Without adjusting for multiple comparisons, the difference between placebo VAS scores at the 40 mA·min dose was significantly lower than at the 20 mA·min dose. Differences between 20 and 30 mA·min doses, and between 30 and 40 mA·min doses were not significant.

In summary, there is concern that Lidopel treatment at two of three iontophoretic doses tested, 30 and 40 mA·min, failed to significantly differ, statistically and clinically, from placebo treatment in providing analgesia for venipuncture as measured by VAS scores. At 20 mA·min iontophoretic dosing, Lidopel treatment provided statistically significant more analgesia than placebo treatment, but the clinical significance of this difference is questionable based on the magnitude of the mean difference in VAS scores and the lack of significant difference in global satisfaction scores. Additionally, there is evidence that the placebo has analgesic properties which possibly confounds the efficacy results

10.1.4



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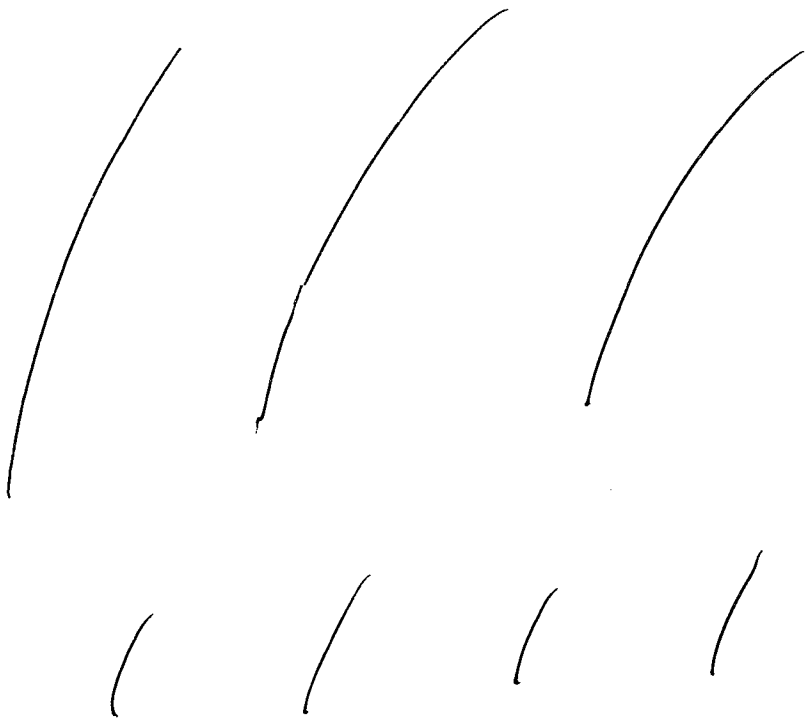


10.1.5 **Study #00-1-03.0: "Comparative Study of Two Iontophoretically Delivered 2% Lidocaine HCl and Epinephrine 1:100,000 Formulations in Subjects undergoing Venipuncture"**

10.1.5.1 Overall Design and Summary of Findings

This non-inferiority study compared the pain perceived by healthy adult subjects undergoing bilateral blood draws from the antecubital fossae following iontophoretic treatment on one arm with one of two active treatments (Lidopel or Iontocaine) and placebo (epinephrine delivered through the same type of iontophoretic device as used for the active treatment) on the opposite arm. Subjects presented for two treatment sessions so as to be exposed to both active treatments and two placebo treatments. VAS scores were used to assess pain and an 11-point global satisfaction score was used to assess overall satisfaction with the treatment and blood draw.

The results of the study led to the rejection of the null hypothesis, i.e., that the drug-device combinations differed in analgesia provided. This result, however, is confounded by the iontophoretic dose used in the study, 20 mA·min. This is the iontophoretic dose deemed optimal for Lidopel, but only half the dose for which Iontocaine is labeled. An additional concern with this study is related to the size of the delivery patch electrode utilized. A 10.1 cm^2 electrode patch was used for the two active treatments; however, the Lidopel patch —— evaluated in the other Phase 3 trials is 8.1 cm^2 in area. The difference in surface area when using the same iontophoretic dose could result in a less effective block for the treatment with the larger patch due to the less concentrated application of local anesthetic to the skin.

10.1.5.2 Study Plan

The original version of this protocol was dated October 4, 2000. The protocol was amended once on October 19, 2000. The amendment was included with the NDA. Subjects underwent venipuncture procedures at a single study center between October 3, (one day before the date of the original protocol) and November 20 2000.

Source: NDA submission, Clinical Study Report for Protocol #00-1-03.0 p. 5 and addenda (Appendix 8-6 of the NDA Submission).

10.1.5.3 Objectives

Primary objectives: "to demonstrate that Empi's 2% lidocaine HCl and epinephrine 1:100,000 administered via the Empi Dupel® Iontophoresis System has a similar anesthetic effect to that of Iontocaine® administered via the Iomed Phoresor® II Auto Iontophoretic Drug Delivery System in subjects undergoing venipuncture."

Secondary objectives: to demonstrate "similar safety and satisfaction profiles between the two different products."

10.1.5.4 Design

This study was a Phase III, single-center, randomized, double-blinded, placebo-controlled, cross-over trial. Thirty volunteer subjects presented for two treatment visits separated by 7 to 14 days. At each visit, the subject received an active (either Iomed or Lidopel) treatment on one, randomly-assigned arm and a placebo treatment on the other.

The placebo treatment consisted of iontophoretically delivered Lidopel solution without the lidocaine HCl. After the treatment, 5 ml of blood was drawn from each arm starting with the right arm in all cases. On the second visit, the alternative active treatment was administered to the same arm that previously received active treatment, and a placebo treatment was again applied to the opposite arm. Following treatment, 5 ml of blood was again withdrawn from both arms starting with the right arm in all cases. The active treatments consisted of Lidopel and Iomed 2% lidocaine and epinephrine 1:100,000 delivered in a 20 mA·min iontophoretic dose; the placebo consisted of a 20 mA·min iontophoretic treatment using the same formulation as that utilized in the Lidopel system but without the lidocaine HCl.

Following venipuncture, subjects rated the discomfort of the venipuncture using a 100 mm visual analog scale (VAS) and their overall satisfaction with the treatment and procedure using an 11-point ordered scale.

10.1.5.5 Primary Efficacy Variable

Pain ratings during blood draws using a 100 mm VAS scale

10.1.5.6 Secondary Efficacy Variables

Overall satisfaction ratings (global) using an eleven-point satisfaction scale

10.1.5.7 Population

Subjects of either sex from the community at large willing to undergo the withdrawal of blood from both arms, during two separate treatment visits, were considered for participation in the study. The following criteria were applied for the final determination of eligibility [quoted from the original protocol p. 29-30 (Appendix 8-6 of the NDA)].

Inclusion Criteria:

1. They are 18 or older.
2. They are willing to give signed, informed consent prior to study admission.
3. They are females that are post-menopausal for at least 1 year or surgically sterile. If they are females of childbearing potential, they must be willing to have a pregnancy test, which must be negative, prior to treatment.

Exclusion Criteria:

1. They are experiencing significant levels of pain from any source.
2. They have taken any prescription analgesics within three days prior to treatment as part of the study.
3. They are currently taking monoamine oxidase inhibitors, tricyclic antidepressants, phenothiazine, butyrophenones, vasopressor drugs or ergot-type oxytocic drugs.
4. They have broken, abraded, damaged, or denuded skin or other recent scar tissue at a treatment site.
5. They have signs of inflammation or infection at a treatment site.
6. They have a sensory deficit at a treatment site.
7. They are currently pregnant or nursing.
8. They have known drug sensitivities to epinephrine and/or local anesthetics such as lidocaine.
9. They have known allergies to sulfites.
10. They have reported a history of drug or alcohol abuse in the last five years.
11. They have metallic or plastic implants at or near the treatment site that might distort or in any way interfere with iontophoretic electrical current flow.
12. They have known adverse reactions to the application of electrical current.
13. They have cardiac pacemakers or other implanted electronic device.
14. They have any significant health problems as documented by medical history, blood pressure and/or temperature, in the opinion of the Investigator/Subinvestigator.
15. They have reported a history of myocardial infarction, angina, and/or arrhythmia requiring medication, and/or any unusual problems associated with venipuncture procedures.

10.1.5.8 Methods and Procedures

Subjects were to be selected from non-institutionalized volunteers from the community at large. They were to have been screened on the day of their first treatment. Screening was to include completing the Informed Consent, the Inclusion/Exclusion checklist, demographics, vital signs, and medical and medication history.

Immediately before treatment, the electrode placement sites were to be evaluated. An "Intact Sensation to Light Touch" test (previously described) was to be performed to confirm that there was no sensory deficit at the treatment site. Vital signs were to be recorded, including blood pressure, heart rate and respiration rate. Female subjects, who were required by inclusion criteria #3 to do so, were also to take a urine pregnancy test. Prior to the second treatment, subjects were to be evaluated again to ensure that their health status had not changed since screening.

Subjects were to be treated via iontophoresis simultaneously on both arms with the active treatment and the arm for its placement randomly determined prior to study initiation. The delivery electrodes (10.1 cm^2 for both Lidopel and Iomed) were to be filled with the appropriate test drug: 2%lidocaine HCl and epinephrine 1:100,000 for the active product, and the Empi formulation but without the 2% lidocaine HCl for the placebo product. The electrode sites were to be prepped with alcohol and dried prior to electrode application. The delivery electrode, connected to the anode, was to be centered over the treatment site from which excessive hair was to be clipped, not shaved, to assure good contact. The Empi return electrode, connected to the cathode, was to be moistened with room temperature tap water and placed at least 4 inches from the delivery electrode on a muscle belly. The Iomed return electrode was not to be moistened and was to have been placed at least six inches away from the treatment site over a major muscle on the same side of the body. The iontophoretic doses of 20 mA·min were to be achieved by applying a current of 4 mAmp for 5 minutes. Electrodes were to be removed immediately after the iontophoretic treatment, and no further touching or manipulation of the skin was to occur until after the blood draws had been completed. Those subjects who could not tolerate the iontophoretic treatment were to have their treatment stopped, but they were to have continued with the blood draws and evaluations.

At the conclusion of the iontophoretic treatment, the Investigator was to evaluate the appearance of the skin under the two electrodes for blanching, erythema, or "other clinically significant changes."

Within 10 minutes following the completion of the iontophoretic treatment, a blood draw of 5 ml was to have been done on each arm with the right arm done first. Immediately following the first blood draw, or two failed attempts to do so, venipuncture was to have been performed on the left arm, again to withdraw 5 ml of blood. The investigator was to have recorded the time of each blood draw, the number of attempts on each arm, and whether or not the blood draw was successful. Subjects were to be asked to rate their degree of discomfort experienced during the procedure on a 100 mm VAS for pain intensity. In addition, they were to be asked to rate their overall satisfaction with the iontophoretic treatment and dermatological procedure on an eleven-point categorical scale with "0" being not satisfied at all and "10" being completely satisfied. Additionally, vital signs were to again be recorded.

All subjects were to have been required to be available two to three days after the procedure to receive a follow-up phone call questioning them on the iontophoretic treatment site. Subjects might have been required to return to the clinic for further evaluation if it was deemed appropriate by the Investigator or Subinvestigator. One week following the first treatment visit, subjects were to have returned to the clinic and, provided no irritation was present at the treatment sites, been treated with the other drug-device combination followed by bilateral blood draws. If irritation was present, the subject was to have returned to the clinic in six to eight days to be re-evaluated and have the second treatments/blood draws performed provided the irritation had resolved. If the

irritation persisted two weeks following the initial treatment, the subject was to have been removed from the study. Following the second treatment, all subjects were required to return to the clinic for follow-up evaluation of the treatment sites. Additional clinic visits may have been required for further evaluation if it was deemed appropriate by the Investigator or Subinvestigators.

10.1.5.9 Analysis Plan

10.1.5.9.1 Analysis of Efficacy

Summary statistical measures were to be calculated for all continuous and categorical study variables, including both subject and outcome data, as appropriate.

The differences in VAS pain intensity ratings and overall satisfaction scores between active and placebo drugs were to be compared between the two study devices using both parametric (Student's t test) and nonparametric (Wilcoxon)methods.

10.1.5.9.2 Determination of Sample Size

The sample size for the evaluation of the primary study hypothesis was based on a paired Student's t test of the equivalence of VAS pain scores [ΔVAS_{Iomed} versus $\Delta VAS_{Lidopel}$ within subjects]. Using a one-sided Type I error of 0.05, a statistical power of 80%, and an estimate of 20.0 points for the within-patient standard deviation of the differences, it was estimated that a total of 27 evaluable subjects would be required to establish equivalence within 10 points on the 100 point VAS scale. The estimate of 20.0 points for the within-patient standard deviation of the difference between ΔVAS values was based on study 99-07.0, which also served as the basis for selecting the iontophoretic dose for this study. In study 99-07.0, the between-patient standard deviation of active versus placebo differences in VAS scores was estimated to be 24.8 points which was thought to exceed the within-patient variability that would be observed in this study. Thus, a "study enrollment of 30 subjects was chosen to account for a 10% loss of subject data due to missing data." (p. 48, Appendix 8-6 of the NDA)

10.1.5.10 Protocol Amendments and Changes in the Planned Analysis

The single amendment to the protocol was dated October 19, 2000. It added the following instruction to the methods.

"Secondary to the 'stickiness' associated with Iomed delivery electrode, following iontophoresis the delivery electrode site will be gently wiped with a damp cloth prior to venipuncture. In order to maintain the same comparison, the delivery electrode sit will also be gently wiped with a damp cloth following iontophoresis with the Empi Dupel® iontophoresis System."

It was not expected that this amendment would alter the outcome or results of this study.

10.1.5.11 Study Conduct

The final study report did not indicate that the study was conducted in accordance with the Good Clinical Practice Guidelines and the Ethical Principles for Medical Research Involving Human Subjects promulgated at the 18th World Medical Association General Assembly in Helsinki and later amended, although the Sponsor asserted this in an amendment to the NDA.

The final study report gives no indication as to how the study was monitored or how quality assurance of the data was provided. There also was no indication that the recorded data were verified for accuracy compared with the CRFs, or that upon closeout of the study a full audit was performed. How the database was prepared, secured and verified was not stated.

The final study report indicated only three protocol deviations occurred. In all three cases, the follow-up contact after the first treatment visit occurred one day later than the protocol-specified interval of two to three days.

10.1.5.11.1 Patient Disposition

The following table was generated by information provided in the Study Report.

Table 10.1-25 Subject Disposition (based on data reported in final study report)

Subject Status	Number	
Enrolled	30	
Randomized	30	
Withdrawn Prior to 1st Treatment	0	
Treated - 1st Session	15 (Empi)	15 (Iomed)
Withdrawn Prior to 2nd Treatment	1	0
Treated - 2nd Session	15 (Empi)	14 (Iomed)
Completed 2nd Session	15 (Empi)	14 (Iomed)

One subject was withdrawn between treatments due to "pain, muscle aches, and numbness of right forearm and hand, reported as unrelated to the drug or the device." This subject had received Lidopel at the first treatment, but the affected side was treated with placebo.

10.1.5.12 Demographics/Group Comparability

Eleven subjects (37%) were male and 19 (63%) were female; all were identified as Caucasian. Ages ranged from 19-73 years with a mean of 35.1 years. Among the male subjects, none had Type I skin, i.e., always burns easily, never tans, and the majority, 64%, had Type IV skin which burns minimally, always tans. Among the female subjects, 53% had Type III skin which burns moderately, tans gradually; 10% had Type I skin. Most subjects of each gender had normal complexions, 91% of males and 63% of females.

10.1.5.13 Treatment Compliance

Study treatment was administered under direct supervision of the study staff; therefore, treatment compliance was assured.

10.1.5.14 Unplanned Analyses

No unplanned analysis was conducted.

10.1.5.15 Sponsor's Efficacy Results

The distribution between the two active treatments was nearly evenly divided between right and left arms. One subject who initially received Lidopel treatment on the left arm was withdrawn from the study prior to the second treatment due to an adverse event, "shoulder ache/numbness secondary to arthritis." All subjects received 5-6 minutes of iontophoretic treatment corresponding to 20-24 mA·min doses.

The table below summarizes the blood draw results from the two treatment visits combined.

Table 10.1-26 Needle stick requirements for successful blood draws (based on data in final study report)

Treatment N	Success on 1st attempt n (%)	Success on 2nd attempt n (%)	Unsuccessful blood draws n (%)
Lidopel (30)	24 (80%)	2 (7%)	4 (13%)
Iontocaine (29)	25 (86%)	1 (3%)	3 (10%)
Placebo (59)	54 (92%)	2 (3%)	3 (5%)

10.1.5.15.1 Primary Efficacy Variables

The table below summarizes the VAS scores measured in millimeters on a scale from "0" for no pain to "100" for severe pain. The one that follows shows reductions in VAS scores ($VAS_{placebo}$–VAS_{active}) combined across left and right arms associated with the use of the iontophoretic devices.

Table 10.1-27 VAS scores by device at treatment visits (App. 8-6, p. 11, Table 9)

Visit	Empi Dupel® mean (SD)/n		Iomed Phoresor® mean (SD)/n	
	Active	Placebo	Active	Placebo
1st Tx right arm	7.5 (9.4)/8	15.7 (18.3)/7	15.1 (22.6)/7	16.8 (12.4)/8
1st Tx left arm	4.6 (3.9)/7	11.2 (9.1)/8	3.6 (4.4)/8	14.7 (17.5)/7
2nd Tx right arm	14.0 (15.4)/7	14.6 (25.5)/8	11.0 (19.4)/8	16.7 (15.5)/6
2nd Tx left arm	8.4 (9.8)/8	30.6 (25.4)/7	17.5 (17.8)/6	16.9 (29.4)/8

Table 10.1-28 Reductions in VAS scores by device and visits (App. 8-6, p. 11, Table 10)

Visit	Empi Dupel® Mean (SD)/n	Iomed Phoresor® Mean (SD)/n	P-Value Student's t/Mann Whitney
1st	7.2 (14.1)/15	6.8(24.1)/15	0.956/0.486
2nd	11.1 (27.0)/15	3.0 (15.5)/14	0.337/0.847

The Sponsor indicated that although the reductions in VAS scores associated with the Empi Dupel® were greater than those with the Iomed Phoresor®, the two independent-group comparisons of differences did not reach statistical significance at either treatment visit. Because the subjects used both devices, a within-subject comparison was made of the VAS reductions due to therapy ($VAS_{placebo}$–VAS_{active}) between the two devices. That is, the Sponsor evaluated the results of (Empi first treatment–Iomed second treatment) combined with (Empi second treatment–Iomed first treatment). The statistics from this comparison included a mean difference of VAS reductions of 4.6 mm, favoring the Empi product, a median value of 0.0 mm, standard deviation of 20.2 mm, a range of -32.0 to

56.0 mm, and a 95% confidence interval of -3.1 to 12.3 mm. The mean difference was not found to be significantly different from zero. Males showed a larger mean difference than females, 12.1 versus 0.0, respectively, but this difference did not reach statistical significance.

As the lower end of the 95% confidence interval of the mean within-subject difference between the VAS reductions observed for the Empi Dupel® and Iomed Phoresor® devices was within the critical difference of 10 points specified in the study protocol for demonstrating equivalence, the null hypothesis was rejected in favor of the alternative hypothesis of equivalence of the two iontophoresis systems.

10.1.5.15.2 Secondary Efficacy Variables

The global satisfaction score (GSS) was used to evaluate overall satisfaction with the iontophoretic treatment and blood draw on an eleven-point scale with a "0" indicating "not satisfied at all" and a "10" indicating "completely satisfied." The table below is taken from the NDA and summarizes the satisfaction scores by device and treatment visit.

Table 10.1-29 Satisfaction scores by device and visit (App. 8-6, p. 12, Table 12)

Visit	Empi Dupel® mean (SD)/n		Iomed Phoresor® mean (SD)/n	
	Active	Placebo	Active	Placebo
1st Tx right arm	9.9 (0.4)/8	9.0 (2.2)/7	8.6 (1.8)/7	8.5 (2.4)/8
1st Tx left arm	8.9 (2.2)/7	9.9 (0.4)/8	8.8 (2.4)/8	8.9 (1.5)/7
2nd Tx right arm	9.3 (0.8)/7	9.0 (2.8)/8	9.2 (1.0)/8	8.5 (2.3)/6
2nd Tx left arm	9.0 (2.8)/8	8.9 (1.1)/7	8.5 (3.2)/6	9.6 (0.7)/8

Similar to what was done for the VAS scores, improvements in satisfaction scores (GSS_{active}–$GSS_{placebo}$) combined across left and right arms, associated with the use of the iontophoretic devices were determined and summarized in the table below.

Table 10.1-30 Improvements in satisfaction scores by device and treatment visit (App. 8-6, p. 13, Table 13)

Visit	Empi Dupel® Mean (SD)/n	Iomed Phoresor® Mean (SD)/n	P-Value Student's t/Mann Whitney
1st	-0.1 (0.3)/15	0.1 (1.3)/15	0.707 /0.412
2nd	0.2 (0.6)/15	-0.2 (0.9)/14	0.143 /0.172

The mean improvements in satisfaction scores associated with either the Empi Dupel® or the Iomed Phoresor® were of small magnitude. The two independent-group comparisons of differences between devices were not significant at either treatment visit.

As with the VAS scores, a within-subject comparison of the improvements in satisfaction scores due to therapy (GSS_{active}–$GSS_{placebo}$) between the two devices was performed. As before, the two sequences of treatment, Empi first and Empi second as well as Iomed first and Iomed second were combined. The mean difference was 0.2, the median was 0.0, the standard deviation was 1.1, and the range of differences was from -2.0 to 4.0. The mean difference was not statistically different from 0 (p=0.421; Student's t test). Males showed a larger mean difference favoring Empi than females, but the difference did not reach statistical significance.

10.1.5.16 Discussion of Efficacy Findings in Study

There are two aspects to the efficacy evaluations of this study. The first is the comparison of Lidopel treatment with that of Iomed. The Sponsor was successful in providing evidence that, for venipuncture, the Lidopel system was indistinguishable from an approved iontophoretic system with the indication of local dermal analgesia; however, the dose of Iontocaine used was only half of that for which it is labeled. This raises the issue of whether or not at a 40 mA·min iontophoretic dose (for which Iontocaine was approved), the two systems would provide equivalent analgesia. In other studies submitted to this NDA, there is evidence to suggest that at the 40 mA·min dose, Lidopel provides no better analgesia than placebo, although this evidence was confounded by the changes in pain levels perceived with varying iontophoretic doses of the epinephrine placebo. In addition, the levels of pain perceived in this trial were relatively mild from a clinical perspective, i.e., VAS $\leq$ 30 mm. Only the mean VAS for the placebo group who had their blood drawn first from the arm treated with Lidopel exceeded 30 mm. It was observed that differences in VAS scores tended to be greatest when blood was drawn first from an arm treated with placebo especially on the initial visit. In all, 17 of the 118 (14%) VAS scores were greater than 30 mm. Of the VAS scores $\geq$ 30 mm, 11 were associated with the use of placebo treatment, 5 with Iontocaine, and 1 with Lidopel.

Another aspect of the study, not further evaluated by the Sponsor, is the difference in delivery electrode size evaluated in the trial compared with [redacted]. The electrode used for this trial was 25% larger than [redacted], 10.1 versus 8.1 cm^2, respectively. If the iontophoretic doses were the same for both electrodes, 20 mA·min, the amount of lidocaine and epinephrine delivered to the skin should have been equal for both. With the larger patch, the local anesthetic would have been delivered over a greater surface area compared to the [redacted] version, and therefore, it would be expected to produce a weaker block.

In an ad hoc analysis comparing only the Lidopel treatment with its corresponding placebo treatment, the mean VAS scores and their (standard deviations) for all treatments without regard to treatment session or order of blood draw were 8.6 (10.4) and 17.7 (20.8), respectively. Using a two-tailed, paired Student's t test, the p value for the difference between the two groups is 0.025. Confirmation of this finding from the statistics reviewer is pending. The significance of this finding is questionable in the context of the delivery electrode size used and the relatively small differences in VAS scores from both each other and zero.

10.1.6 An Evaluation of dermal Irritation Following the Administration of Two Consecutive 80 mA·min Iontophoretic Doses of Lidocaine to the Same Skin Site

This study was an open-label, single-center, observational, clinical study that evaluated the skin reactions to two consecutive iontophoretic treatments of Lidopel administered simultaneously on an arm and the thigh of the contralateral leg. The second treatments were administered within 15 minutes of the completion of the first treatment, and the iontophoretic delivery electrodes for the second treatments were positioned on the same sites as the electrodes for the first treatment. There were no restrictions on the placement of the return electrodes as long as they were at least 4 inches from the treatment site on a major muscle on the same side of the body.

10.1.6.1 Objectives

Primary Endpoints:

- incidence and seriousness of adverse experiences due to repeat treatments
- dermal irritation scores

Secondary Endpoint

- incidence and seriousness of adverse experiences due to simultaneous treatments

10.1.6.2 Population

Subjects were adult volunteers of both sexes in good health with no implantable electronic devices, no sensitivities or allergies to sulfites, local anesthetics or epinephrine, and normal, intact unabraded, undamaged skin at the planned treatment sites.

10.1.6.3 Protocol

Subjects having moderate to severe erythema and/or significant irritation or skin changes at the delivery electrode sites following the first treatments ere not to have undergone the second treatments. Should only one of the two delivery electrode sites have had moderate to severe erythema and/or significant irritation or skin changes, only the delivery electrode placement site not having the changes was to have undergone the second treatment.

Following the two treatments, subjects were to have remained in the clinic for at least one hour for a post-treatment evaluation. Additionally, subjects were to been required to be available for a telephone follow up the next day and to return to the clinic in 2-3 days after the treatments for follow up.

Following each treatment, the appearance of the skin under the delivery and return electrode sites were to have been observed. The presence of blanching and/or mild erythema was to be recorded by not counted as adverse events. Any other clinically significant changes in the appearance of the skin occurring from the treatments were to be recorded as an adverse event. Following the second treatment, blood pressure, heart rate and respiratory rate were to have been recorded. One hour after the second treatment, repeat site observations and vital sign assessments were to be performed. The same was to be done at the return-to-clinic visit 2 to 3 days following the treatments.

10.1.6.4 Results

1. All of the subjects had blanching at only the delivery electrode following the first treatment and persisted after the second treatment.
2. No occurrence of erythema at any site was rated as worse than mild.
3. Erythema occurred at both electrode sites in all of the subjects' arms by the end of the second treatment. There was some indication of an accumulative effect. No erythema was evaluated as worse than mild.
4. Erythema in the legs was similar to that in the arms but milder in appearance. After the second treatment, 33% of subjects had no erythema at the delivery electrode site, but only 8% had no erythema at the return electrode site.
5. Among the 3 males and 9 female enrolled in the study, all of whom were Caucasian, there was no significant effect of skin type on erythema at either electrode site or of gender at the delivery electrode site.
6. A higher proportion of female subjects had erythema at the return electrodes than male subjects. The proportion was significant at the leg sites.
7. Vital sign changes that were significant included a decrease in mean systolic blood pressure by 16 and 12 mmHg at immediate and one-hour post-treatment assessment, respectively, and a decrease in mean heart rate by 9 and 10 bpm at the same time points, respectively.

8. Only one subject had erythema, at the arm delivery electrode site, which persisted beyond the 2-3 day follow up. For this subject, resolution occurred one week following the treatment.

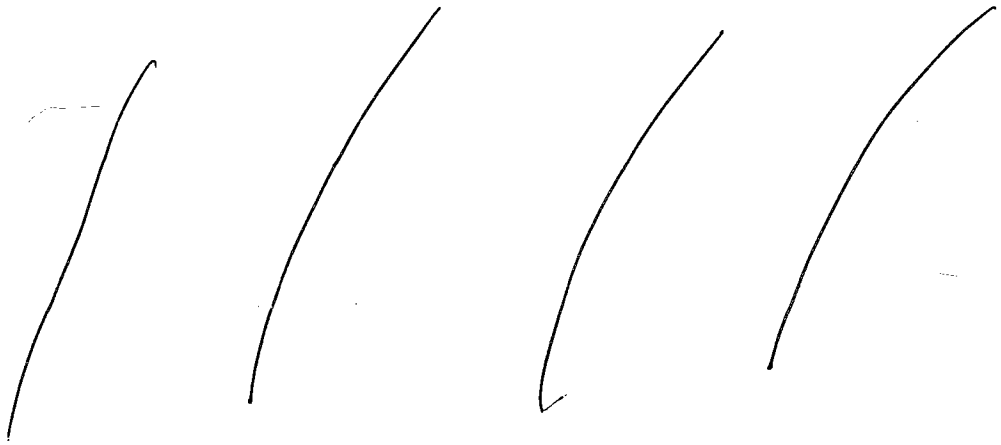
10.1.6.5 Discussion of findings

The findings of this study were reassuring in that they suggest repeat and simultaneous dosing to not incur significant risk to underlying skin at the delivery electrode site. The study was deficient or could have been made more meaningful in the following ways.

1. Placement of return electrodes at the same site for both treatments would have better established the safety profile, especially as a greater proportion of subjects had erythema at the return electrodes in the leg sites than at the arm sites.
2. Assessment of the degree of analgesia that resulted from the second treatment could have resolved concerns over whether repeat dosing to one site would increase analgesia or the sensitivity of the area to painful stimuli.
3. Assessment of serum levels of lidocaine and epinephrine could have resolved some concerns from the PK study regarding sporadic elevated levels of lidocaine, and perhaps address the unexplored issue of whether clinically relevant systemic exposure to epinephrine could occur with iontophoresis.

10.2 Line-by-Line Labeling Review

Line-by-line review is deferred to interdisciplinary discussions within the division. The following points will be considered for inclusion in the label.



APPEARS THIS WAY
ON ORIGINAL

REFERENCES

Ashburn MA, Gauthier M, Love G, Basta S, Gaylord B, Kessler K. Iontophoretic administration of 2% lidocaine HCl and 1:100,000 epinephrine in humans. Clin J Pain. 1997; Mar;13(1):22-6.

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

/s/

Arthur Simone
10/4/04 06:01:43 PM
MEDICAL OFFICER

Nancy Chang
10/5/04 11:57:02 AM
MEDICAL OFFICER

Medical Team Leader Memo

Application Type:	New Drug Application
Submission Number:	021-486
Submission Code:	N-000
Letter Date:	February 8, 2002
Stamp Date:	February 11, 2002
(Extended) PDUFA Goal Date:	October 26, 2004
Primary Reviewer:	Arthur Simone, MD, PhD
Secondary Review:	Nancy Chang, MD
Review Completion Date:	August 20, 2004
Established Name:	iontophoretic lidocaine 2% with epinephrine 1:100,000
(Proposed) Trade Name:	Lidopel
Therapeutic Class:	Local anesthetic
Applicant:	Empi, Incorporated
Priority Designation:	standard
Formulation:	iontophoretic transdermal system
Dosing Regimen:	single dose
Indication:	
Intended Population:	adults

Background

Refer also to the primary clinical review by Dr. Arthur Simone, upon which much of this review is based.

Lidopel is a topical solution of 2% Lidocaine HCl with 1:100,000 Epinephrine intended for iontophoretic cutaneous delivery using the Dupel Iontophoresis System that was 510(k) cleared in 1999 as a general use iontophoretic drug delivery system. Lidopel will be identical to the approved generic product Octocaine with the exception of labeling.

Lidopel has been the subject of a complicated and contentious regulatory history. Lidopel is very similar to the approved product Iontocaine (N20530), which also utilizes 2% lidocaine with 1:100K epinephrine for topical iontophoretic delivery but with the Phoresor Iontophoretic Drug Delivery System and TransQ electrodes. The application was originally submitted as a 505(b)(2) application referencing Iontocaine but without submission of a user fee. Regulatory review determined that the application did require a fee because the requested "indication" for Lidopel differed from the Iontocaine product in 2 respects: 1) Lidopel specified a higher dose compared to Iontocaine (up to 80 mA-min vs. 40 mA-min, respectively) and 2) [redacted]. Following this determination, in order to avoid payment of a user fee, Empi agreed to alter the originally submitted language [redacted] However, a "refuse to file" action was issued in December 2002 due to problems related to the interpretability, completeness and legibility of the dataset. An incomplete response to the "refuse to file" letter was submitted July 2003, and the application was filed in December 2003.

It is documented that the division reviewed and accepted the designs of the major Phase III studies and also agreed that a total safety database of 300 could be appropriate; fewer than 300 could be accepted if the sponsor could document minimal differences from the referenced product.

Overview of Clinical Development

Table 1: Clinical Studies Overview

Type of Study	Study Number	Phase	Dose(s) mA·min	Deliv Electrode Size(s) Cm^2	Number of Treatments L=Lidopel P=Placebo I=Iontocaine
PK	96-08.0	1	80	—	3 L
			80	10.1	3 L
			80	8.1	3 L
Shave Removal Punch Biopsy Analg Duration	97-07.0	2	40	—	7 L; 8 P
			80	8.1	9 L; 8 P
			80	—	8 L; 8 P
Shave Removal	99-02.0	3	40	8.1	20 L
			60		60 L; 20 P
			80		20 L; 20 P
Venipuncture Adult	99-07.0	3	20	8.1	60 L/P
			30		20 L/P
			40		20 L/P
Venipuncture Adult	00-1-03.0	3	20	10.1	30 L/P
					29 I/P
Dermal Irritation	01-1-06.0	1	80	8.1	48 L

— Placebo treatments were identical to the lidopel treatments in the electrode size and iontophoretic doses administered and differed only in that lidocaine was not present in the drug solution. Epinephrine was present in placebo drug.

Note that in referring to specific studies throughout this review, the leading and trailing 0's are omitted from the study numbers as listed in Table 1.

Pharmacokinetics

Nine healthy adult subjects were studied for systemic lidocaine levels following a single 80 mA·min iontophoretic application of Lidopel (3 each using the 8.1, — and — cm^2 delivery electrodes). Detectable (>2 ng/mL) plasma levels were found in only 3 of 9

subjects. The Tmax appeared to be at approximately 4-6 hours; however, samples were only collected out to 6 hours after treatment, and 2 subjects had their highest plasma levels at that time point. The highest plasma level recorded in this study, [redacted] ng/mL, was drawn at 6 hours.

The systemic absorption of epinephrine was not assessed in PK studies; however, vital signs data from the clinical studies suggest that clinically meaningful systemic epinephrine exposures probably do not occur at the doses studied.

No PK data for special populations, including pediatrics, are available.

Summary of Efficacy

Five single-site clinical efficacy studies were conducted.

Study 97-07

This was a phase 2, placebo controlled, double blind study enrolling 2 groups of patients:

1) Normal subjects who volunteered to undergo a punch biopsy of the posterior left arm (randomized to [redacted] or 8.1 cm^2 delivery electrode with iontophoretic dose of 80 mA·min)

2) Patients presenting for shave removal of seborrheic keratosis or benign nevocellular nevi (all treated with [redacted] cm^2 delivery electrode with iontophoretic dose of 40 mA·min)

Within each group, subjects were randomized 1:1 to receive placebo or Lidopel.

Within 10 minutes of iontophoretic treatment, subjects would undergo needle prick testing using a 30-gauge needle at 4 points within the application site. If the subject reported pain at any needle-prick site, they were considered treatment failures and did not undergo further efficacy evaluations. Subjects who requested supplemental analgesia during shave removals were also considered treatment failures. Due to the nature of the procedure, punch biopsy subjects could not request supplemental analgesia. The primary efficacy endpoint was to be a comparison of treatment failure rates.

Table 2: Subject Disposition, Study 97-07

Subject State	Lidopel[1]			Placebo[1]		
	P/lg/80	P/sm/80	S/lg/40	P/lg/80	P/sm/80	S/lg/40
Enrolled	9	7	8	8	8	8
Randomized	9	7	8	8	8	8
Discontinued Study	3	0	7	8	8	8
Failed pinprick test	3	0	5	8	8	8
Required supplemental anesthesia[2]	N/A	N/A	2	N/A	N/A	0
Completed Study	6	7	1	0	0	0

[1]Subcategories are defined as follow:
P/lg/80 = punch biopsy with large delivery electrode (— cm^2) and 80 mA·min dose
P/sm/80 = punch biopsy with small delivery electrode (8.1 cm^2) and 80 mA·min dose
S/lg/40 = shave biopsy with large delivery electrode (— cm^2) and 40 mA·min dose
[2]Due to the nature of the procedures, only those subjects undergoing shave removals of lesions were eligible for supplemental anesthesia.

The Lidopel groups were notable for a substantial number (8/24) of subjects who failed the pinprick test. In addition, 2 of 3 subjects who were eligible to request supplemental anesthesia did so. Thus, the total treatment failure rate for Lidopel was 42%, although this figure might have been higher had the punch biopsy subjects been able to request supplemental analgesia if desired.

As seen in Table 2, none of the placebo subjects passed the pinprick test and underwent a dermatological procedure. Therefore, although Lidopel was found to be significantly different from placebo in the prespecified primary endpoint, the proposed indicated use of Lidopel was tested in an uncontrolled and essentially unblinded manner. Thus, a determination cannot be made regarding the comparative efficacy of Lidopel versus placebo in providing analgesia for the dermatological procedures tested.

Pinprick testing and secondary efficacy endpoints (VAS and satisfaction scores performed after dermatological procedure) suggest an efficacy advantage of small over large electrodes, and of greater over smaller iontophoretic dose. However, the differences in secondary endpoints did not consistently support this trend; nor were they statistically significantly different among the active arms.

Study 99-02

This study was performed in 2 phases, both of which utilized the — 8.1 cm^2 delivery electrode in adult patients undergoing shave removal of seborrheic keratosis or benign nevocellular nevi. Efficacy endpoints were the same as for study 97-07.

Phase I

The first phase of the study was intended as a pilot to identify an optimal dose for "confirmatory" study in phase 2. 20 subjects were enrolled in each of 4 arms:

1. Lidopel 40 mA·min
2. Lidopel 60 mA·min
3. Lidopel 80 mA·min
4. Placebo 80 mA·min (placebo testing was not done at 40 or 60 mA·min)

90% of placebo subjects failed the pinprick test, compared to 25%, 10% and 15% in the 40, 60, and 80 mA·min Lidopel groups, respectively. The difference between placebo and active groups was significant. Among subjects who underwent shave removal, VAS scores (but not satisfaction scores) were also significantly different between the placebo and the active groups. One subject, from the 40 mA·min Lidopel group, requested additional analgesia, and neither of the placebo subjects requested additional analgesia. The active groups were not significantly different from one another with respect to pinprick testing, VAS or satisfaction scores; nor was there a clear dose-response relationship among the active treatments in any of these measures.

Phase II

The 60 mA·min dose was associated with the highest success rate and the lowest VAS score in phase I (though not significantly different from the other doses), so this dose was selected for confirmatory study in phase II. 60 subjects were randomized 2:1 to receive Lidopel or placebo (also at 60 mA·min), respectively.

37/40 (92.5%) of Lidopel subjects passed the needle prick test compared to 5/20 (25%) of placebo subjects ($p<0.001$). Of the 42 patients who passed the needle-prick test and went on to have their dermatological procedure, two patients in the active group (and none in the placebo group) required supplemental anesthesia. This resulted in an overall success rate of 87.5% for Lidopel, which was still significantly different from placebo. The mean VAS score for Lidopel treatment was less than that of placebo treatment (4.9 mm vs. 12.4 mm), and the difference in mean global satisfaction scores also supported efficacy for Lidopel, though only the latter achieved statistical significance.

Study 99-07

Like study 99-02, this study was also divided into 2 phases. Subjects were healthy adult volunteers who received randomized simultaneous treatments with Lidopel and placebo, one on each arm, prior to venipuncture in each arm. All treatments were with the to-be-marketed 8.1 cm^2 electrode, and the primary efficacy variable was the pain rating on a 100-mm VAS scale. Global satisfaction was also rated on an 11-point categorical scale.

Phase I

In Phase I, 20 subjects were randomized to each of 3 iontophoretic doses: 20, 30, and 40 mA·min.

A statistically significant difference between Lidopel and placebo VAS scores was found only at the 20 mA·min dose. The 3 active treatment groups were not significantly different from one another and did not exhibit a clear dose relationship. The mean VAS scores combined across dosage groups were also significantly different between Lidopel and placebo, at 8.2 mm and 17.6 mm, respectively. However, the median difference in satisfaction scores between placebo and active treatments was 0 in each dosing group. In addition, a decrease in mean VAS scores was observed with placebo treatments as iontophoretic dose increased (p=0.07).

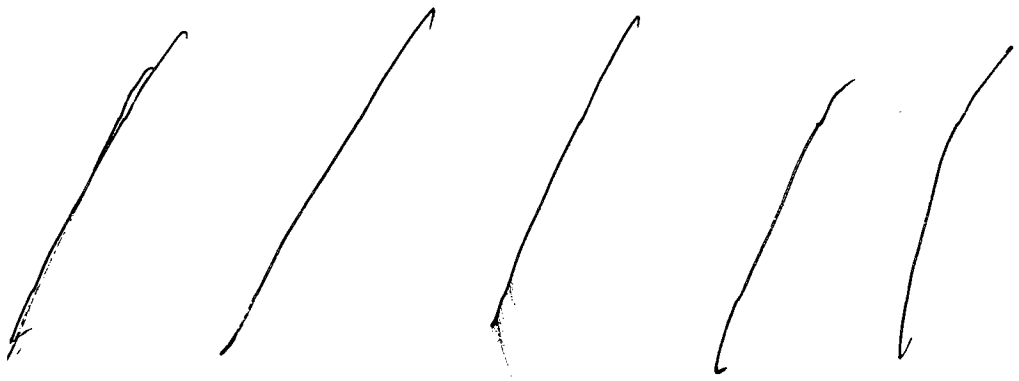
Table 3: Mean VAS scores for each treatment and iontophoretic dose

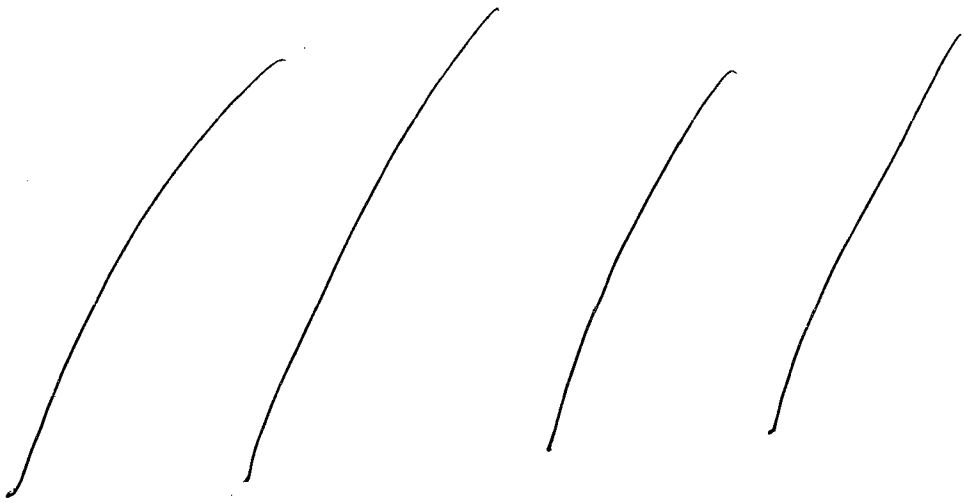
	Mean VAS (SD) by Treatment/Calculation		
Iontophoretic Dose	Placebo	Lidopel	Lidopel – Placebo
20 mA·min (n=60)*	23.7 (23.5)	10.8 (13.5)	-12.9 (24.8)
30 mA·min (n=20)	16.0 (16.8)	11.3 (12.9)	-4.7 (15.8)
40 mA·min (n=20)	13.9 (14.8)	7.4 (12.2)	-6.5 (18.4)

* The 20 mA·min dose combines data from phase I and II. Separate analyses of phase I and II data at this dose gives substantially similar results as the combined analysis.

Phase II

The 20 mA·min dose was selected for study of 40 additional subjects in phase II because the greatest difference between Lidopel and placebo VAS scores was found at this dose in phase I and because this dose was not associated with any adverse events. Whether data from phase II are analyzed on their own or in combination with data from phase I, there is a statistically significant difference between placebo and Lidopel VAS scores at this dose.





Study 1-03

This was a crossover study of adult volunteers who were treated during two separate visits 7-14 days apart prior to bilateral peripheral venipuncture. At the first visit, each subject was randomized to receive a 20 mA·min dose of either Iontocaine administered using the Iomed Phoresor II system or Lidopel using the Empi Dupel system on a randomly-assigned arm. Placebo treatment at 20 mA·min was administered simultaneously to the other arm, and at the second visit, the subject received the remaining active treatment and corresponding placebo.

This study utilized 10.1 cm^2 delivery electrodes for all groups, different from the 8.1 cm^2 electrode for Lidopel. The tested iontophoretic dose, 20 mA·min was half of the approved dose for Iontocaine. The primary efficacy variable was the subject VAS pain score following venipuncture, and a global satisfaction rating on an 11-point categorical scale was also captured.

Table 4: VAS scores by device at treatment visits

Visit	Empi Dupel® mean (SD)/n		Iomed Phoresor® mean (SD)/n	
	Active	Placebo	Active	Placebo
1st Tx right arm	7.5 (9.4)/8	15.7 (18.3)/7	15.1 (22.6)/7	16.8 (12.4)/8
1st Tx left arm	4.6 (3.9)/7	11.2 (9.1)/8	3.6 (4.4)/8	14.7 (17.5)/7
2nd Tx right arm	14.0 (15.4)/7	14.6 (25.5)/8	11.0 (19.4)/8	16.7 (15.5)/6
2nd Tx left arm	8.4 (9.8)/8	30.6 (25.4)/7	17.5 (17.8)/6	16.9 (29.4)/8

As seen in Table 4, VAS scores associated with active treatments were generally lower than those associated with placebo. An analysis of statistical significance between active and placebo groups was not presented by the sponsor, perhaps because the study was intended to be a non-inferiority study between Lidopel and Iontocaine. Lidopel and

Iontocaine were found to be equivalent, based on a pre-specified "delta" of 10 mm on the 100-mm VAS scale. However, it should be noted that the differences in mean VAS scores between active and placebo groups were less than 10 mm for both treatment modalities. It is also notable that the global satisfaction scores did not support a benefit associated with either treatment modality (Table 5).

Table 5: Improvements in satisfaction scores* by device and treatment visit

Visit	Empi Dupel® Mean (SD)/n	Iomed Phoresor® Mean (SD)/n	P-Value Student's t/Mann Whitney
1st	-0.1 (0.3)/15	0.1 (1.3)/15	0.707 /0.412
2nd	0.2 (0.6)/15	-0.2 (0.9)/14	0.143 /0.172

* Satisfaction scores were graded on an 11-point scale ranging from 0 to 10.

Efficacy Conclusions

The 5 clinical efficacy studies offer supportive evidence of efficacy, but are insufficient to make a conclusive determination of efficacy at any setting or dose.

Study 97-07 (40, 80 mA·min;— 8.1 cm^2 electrode): Lidopel was significantly different from placebo in the predetermined primary endpoint (treatment failures). However, no placebo subjects passed the pinprick test. Thus, there was no blinded randomized comparison of Lidopel to placebo in providing analgesia for a dermatological procedure, which is the intended indication for this drug. Only 7 subjects were studied using the — 8.1 cm^2 electrode, and these were punch biopsy subjects for whom the primary efficacy measure was inappropriate because they could not request supplemental analgesia.

Study 99-02 (40, 60, 80 mA·min (phase I); 60 mA·min (phase 2); 8.1 cm^2 electrode): This study also found a significant difference between Lidopel and placebo in the incidence of treatment failures, but like 97-07, it utilized the pinprick test and eliminated most of the placebo subjects prior to undergoing shave removal. Among subjects who underwent shave removal, VAS scores (secondary endpoint) were significantly different between Lidopel and placebo in phase I (though not in phase 2). Among those same subjects who underwent shave removal, there was a higher failure rate (request for supplemental analgesia) in the Lidopel groups compared to placebo, which is more pertinent to the pre-specified primary endpoint than the VAS. The use of an 80 mA·min placebo dose against which to compare several different Lidopel doses in phase I is also of questionable validity.

Study 99-07 (venipuncture; 20, 30, 40 mA·min (phase I); 20 mA·min (phase 2);; 8.1 cm^2 electrode): Statistically significant difference in VAS scores between Lidopel and placebo at 20 mA·min only.

Study 1-03 (Iontocaine crossover; 20 mA·min, 10.1 cm^2 electrode): Lidopel was found non-inferior to Iontocaine at an Iontocaine dose lower than approved. The sponsor did not provide treatment effect analysis.

For the studies in which placebo and Lidopel were administered simultaneously (99-07, 1-03), VAS scores should be interpreted cautiously. Because subjects were aware that they were receiving simultaneous active and placebo treatments, the magnitude of difference in VAS scores is likely to have been magnified. This is supported by data from study 1-03, which suggest that the order of testing influenced VAS scores.

The following considerations also limit our ability to make a determination of efficacy:

1. All studies were single center studies.
2. The following considerations raise doubts about conclusions based on a difference between Lidopel and epinephrine "placebo":
   a. The placebo contains an active drug, and the effect of the epinephrine placebo in this setting has not been defined. Indeed, studies that included more than one dose of placebo (99-07, 99-14) suggest that the placebo effect appears to change in a dose-related manner.
   b. There were no studies conducted to satisfy the combination rule and elucidate the respective roles of epinephrine, lidocaine and current in this product.
   c. The epinephrine doses delivered in the placebo groups would be predicted to be greater than in the Lidopel groups when the same current is applied because all of the current in the placebo group would carry epinephrine and not lidocaine. Therefore, the placebo differs from Lidopel in 2 aspects, the independent effects of which are poorly characterized: epinephrine dose (higher than active) and lidocaine dose (lower than active).
3. Contrary to expectation based on the scientific principals of iontophoretic drug delivery, there does not appear to be a clear dose-response relationship that relates efficacy to iontophoretic dose. Indeed, in studies 99-07 and 99-14, the lowest dose appeared to be most efficacious.
4. The degree of stimulus (and therefore the degree of pain) may not have been well controlled in the venipuncture studies. The needle gauge(s) or type(s) used were not specified or documented. The local effects of the iontophoretic treatment may have systematically differed between treatment and placebo arms. Therefore, if investigators were free to choose a needle depending on the appearance of the vein, there may have been a systematic difference in the needle types and sizes used between placebo and Lidopel groups.

Safety

Adverse events data as submitted were generally tabulated uni-dimensionally, without a comprehensive listing of AE's by treatment (Lidopel vs. placebo vs. Iontocaine), site of occurrence (e.g. return vs. delivery electrode), iontophoretic dose, onset, duration, disposition and subject demographics. Therefore, Dr. Simone's analyses of AE's by more than one factor (e.g. by demographic and treatment group, or by treatment group and dose) were conducted by manually constructing an ISS based on data entries from all of the individual study CRT's. Because this is a paper NDA, this manual data reconstruction may be prone to error. At the time of this review, the sponsor has not responded to a request to conduct these analyses.

A total of 414 subjects were enrolled in clinical studies. 325 subjects received a total of 361 applications of Lidopel, and 247 placebo applications were administered. [redacted], and 23 subjects older than 65 years of age participated in the clinical trials, two of which were older than 75 years of age.

In all cases, placebo treatment consisted of Lidopel without lidocaine, though the iontophoretic dose varied within and across studies. No deaths or serious adverse events were reported. All AE's were reported as mild (85%) or moderate (15%) severity, and all AE's resolved, with the exception of 1 mild case of petechiae that was reported to have insufficient follow-up. However, 14% of AE's required medical or therapeutic intervention, and an additional 7% required discontinuation of iontophoretic therapy.

The timing and nature (i.e. telephone versus clinic visit) of follow-up for adverse events varied from study to study. The studies generally incorporated a telephone or clinic follow-up at 2-3 days after treatment, and some also included a second telephone follow-up at 6-9 days after treatment.

Adverse events were predominantly local dermal events, including blanching, burning sensation, bruising, erythema, itching, pain and rash. The incidence and nature of events was similar to those reported for Iontocaine and for LidoSite, another lidocaine/epinephrine product approved for topical iontophoretic delivery. Non-dermal AE's were uncommon, and the nature of these events and the temporal relationship to treatment were not suggestive of events related to systemic drug exposure. Adverse events occurred with a similar incidence in Lidopel and placebo groups, with a somewhat higher incidence reported in Lidopel groups for pain (2.5% vs. 1.2% for placebo) and for rash (5.5% vs 0.4% for placebo). The incidence of adverse events was not clearly dose-related; however, the database was not large enough to make a meaningful examination of dose dependency.

The only attempt at determining the time course of Lidopel effect was in study 97-07, in which 13 of 14 subjects who passed an initial needle prick test were re-tested by needle prick one-half hour after iontophoretic treatment. 9/13 subjects (69%) were assessed as "passing" (i.e., experienced persistent diminished sensation to pinprick) upon re-testing. No further evaluations to characterize the anesthetic effect or time course of anesthesia or analgesia with Lidopel were made.

Study 01-1-06.0 was the only study that evaluated repeat or simultaneous applications of Lidopel. Adult volunteers received simultaneous 80 mA·min applications of Lidopel to an arm and contralateral thigh. The treatment was repeated once 15 minutes after completion of the first treatment. Application sites were evaluated immediately, one hour and 2-3 days after each treatment. In addition, vital signs were recorded immediately after and 1 hour after the second treatment.

Most subjects experienced blanching and erythema, and there was some evidence of increased effect on repeat treatment. Erythema was noted at both delivery and return electrodes, but no case of erythema was rated worse than "mild". All erythema resolved by 2-3 days except for one case, which resolved in 1 week. There was no increase in heart rate or blood pressure consistent with a systemic epinephrine effect.

Safety Conclusions

1. The safety database is limited and scattered among many different treatment doses and patch sizes, but there were no adverse events of major concern and the safety profile of Lidopel appears to be similar to that of Iontocaine and LidoSite.
2. Patch application sites in clinical studies were limited to exposures on the trunk and limbs.
3. The geriatric safety database is particularly limited, although existing data do not indicate that the elderly are more susceptible to adverse events.
4. [redacted]
5. Data on multiple applications are limited to a single repeat application. Formal skin sensitization and irritation stud(ies) were not conducted.
6. Duration and extent of anesthetic effect are poorly characterized.
7. Limitations in the sponsor's presentation of the safety database limit our ability to review this database and may possibly impact the accuracy of review.

Summary and Conclusions

Major variables that might impact on safety and efficacy for this product include the iontophoretic dose (mA·min), electrode size, patient population, nature of the procedure/stimulus, and dose delivery profile (e.g. ramp-up profile, variations in time versus current). As seen in table 6 below, the database is scattered and limited in its ability to distinguish the effects of variations in these parameters. Variation of some

parameters, such as dose delivery profile, were not systematically studied or characterized.

Table 6: Lidopel treatments by dose, procedure and delivery electrode size

	Delivery Electrode Patch Size (cm^2)							
	8.1					10.1		
Iontophoretic Dose (mA·min)	20	30	40	60	80	20	40	80
Shave removal			20	60	20		8	
Punch biopsy					7			9
Venipuncture – adult	60	20	20			30		
Column Totals	**100**	**20**	**50**	**60**	**27**	**30**	**8**	**9**

Within the limitations of interpreting this database, Lidopel appears to be reasonably safe. However, serious flaws in the design of the efficacy studies limit our ability to interpret these studies and make a determination of efficacy. General concerns relate to the activity and poor characterization of the placebo, absence of predicted dose response, the possibility that the degree of stimulus may not have been adequately controlled and that all studies were single center. Even if it were possible to put aside all of these concerns, only one study, 99-07, could be seen as demonstrating efficacy, for the limited indication for use in adults prior to venipuncture at 20 mA·min.

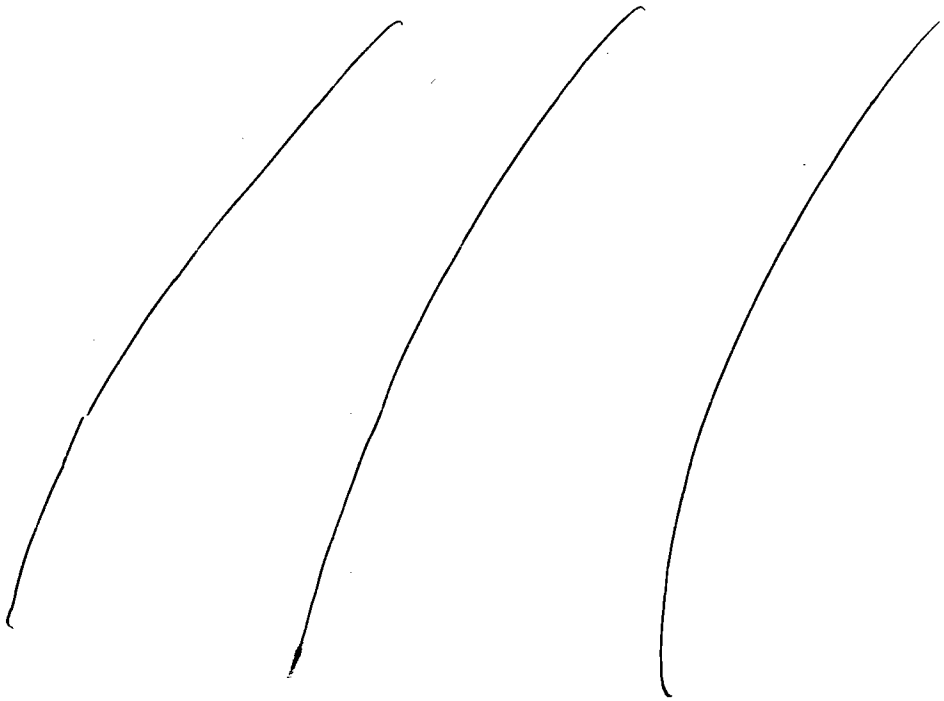
Another possible approach would be to reason that the data are generally supportive, if not demonstrative, of efficacy and that the determination of safety and effectiveness could be based largely on the previous finding for Iontocaine. While this may be an acceptable approach from a regulatory standpoint, it is scientifically problematical. The Iontocaine application was subject to the same flaws as the current application. Indeed, all of the clinical efficacy studies, including venipuncture studies, were performed by first eliminating subjects who responded to pinprick testing. As with the current application, the FDA clinical reviewer for Iontocaine questioned the validity of the substantively unblinded and uncontrolled studies.

Iontocaine was approved and tested only at 40 mA·min, whereas the strongest evidence of efficacy in this Lidopel application is at 20 mA·min and data supporting efficacy at 40 mA·min are weak. Furthermore, evidence of efficacy for Iontocaine, such as it was, was primarily for superficial dermal procedures. Efficacy of Iontocaine for peripheral venous access was borderline insignificant. Therefore, the indications, settings and doses for which the scientific evidence of efficacy for Iontocaine are strongest do not closely

mirror the indications, settings and doses which are most scientifically appropriate for Lidopel. The delivery electrode sizes for Iontocaine (5.71 and 11.1 cm^2) differ somewhat from — Lidopel —, and might account for some differences in the safety and efficacy profiles for these products.

Another alternate approach might be to judge studies 97-07 and 99-02 to be "wins" based on the pre-specified primary endpoint, treatment failure rate, particularly as the general clinical trial designs were agreed to by the division in 2001. While this might be a pragmatic regulatory approach, again, this would be scientifically flawed. Because all or nearly all of the placebo subjects were eliminated prior to the procedure based on the needle-prick test, to place reliance on the "win" would presume that the placebo effect is well known and that the needle prick itself predicts the analgesic effect of the drug. As discussed, the placebo is poorly characterized and understood, and while needle prick testing is certainly indicative of a drug effect, it has not been demonstrated to be predictive of analgesic effect in the range of populations and settings for which an indication is sought. Indeed, among subjects who did go on to undergo a painful procedure, examination of the endpoint most relevant to the sponsor's pre-specified primary endpoint found that all requests for supplemental analgesia were among Lidopel subjects. There were no requests for supplemental analgesia in the placebo groups. Furthermore, the reported failure rates for Lidopel in the settings tested were high.

In conclusion, I recommend an "approvable" action for this NDA with the following deficiencies:



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/s/

Nancy Chang
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