CENTER FOR DRUG EVALUATION AND RESEARCH

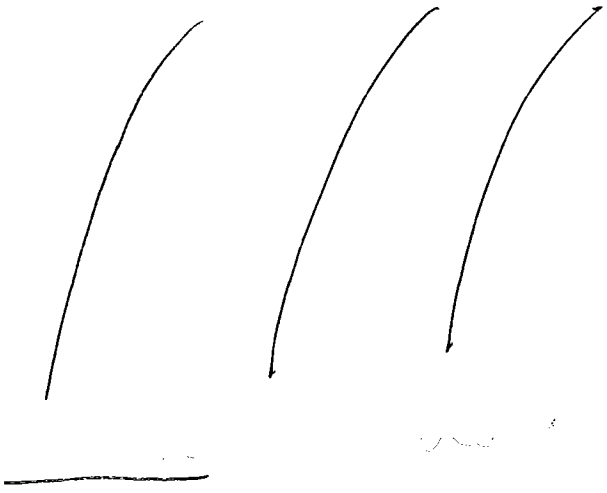
APPLICATION NUMBER:

21-486

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW(S)

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW

NDA: 21-486	Original Submission Date: 2/02/02
	Re-submission Date: 7/29/03
Submission Type; Code:	4S; 505(b)(2)
Brand/Code Name:	Lidopel Iontophoretic Drug Delivery System
Generic Name:	Lidocaine : Epinephrine
Primary Reviewer:	David Lee, Ph.D.
Secondary Reviewer	Suresh Doddapaneni, Ph.D.
OCPB Division:	DPE 2
ORM Division:	Division of Anesthetic, Critical Care and Addiction Drug Products .
Applicant:	Empi, Inc.
Relevant IND(s):	54,731
Cross References	Septodont Octocaine®ANDA #84-048 (for method validation)
	Iomed Iontocaine® NDA #20-530
Formulation; Strength(s):	Iontophoretic Delivery System
	(2% lidocaine HCl : epinephrine 1:100,000)
Proposed Indication:	
Proposed Dosage Regimen:	



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1 Executive Summary

Empi, Inc. has submitted the above NDA for approval of Lidopel topical solution (lidocaine HCl 2% and epinephrine 1:100,000 solution) for dermal iontophoresis with the Empi Dupel® Iontophoresis System and Empi Dupel® Iontophoresis Electrodes [redacted] Lidocaine and epinephrine are supplied to the tissue via Dupel® Iontophoresis Electrodes that are placed on the skin. Direct current, generated by the battery-powered Dupel® device, is applied through the drug delivery and return electrodes. The electric current facilitates the movement of the [redacted] lidocaine and epinephrine through the skin into the tissue to produce the anesthetic effect. Iontophoretic delivery of lidocaine and epinephrine and consequently produced

anesthetic effect can possibly avoid tissue deformation from injection, minimize the systemic concentrations of the drug, and may produce less pain from the drug administration by injection.

The Applicant has submitted 1 study, Study 96-08, under the Clinical Pharmacology section of the NDA. Additionally, there were one Phase II and seven Phase III studies submitted in this NDA.

Although the Applicant made a reference to data provided by Iomed, Inc. in NDA #20-530 for Iontocaine® (Lidocaine HCl 2% and Epinephrine 1:100,000 solution labeled for iontophoretic use with the Iomed Phoresor® Iontophoretic Drug Delivery System), this CPB Review mainly focused and presented data, including the proposed wording for the package insert (Section 3 of this review), from the Study 96-08 and the published information (e.g., peer-reviewed literature) on the iontophoretic delivery of lidocaine for the production of local dermal anesthesia.

In regards to Study 96-08, the healthy subjects were randomized to three electrode groups with three subjects in each group: A) 80 mA.min using the small (8.1 cm^2) delivery; B) 80 mA.min using the medium (— cm^2) delivery; and C) 80 mA.min using the large (— cm^2) delivery. The delivery current of 4 mA was applied for treatment time of approximately 20 minutes. Plasma samples contained below the limit of quantitation for lidocaine (GCMS analytical method; limit of quantitation (LOQ) was 2 ng/mL). There were three samples (—— ng/mL) with lidocaine concentrations very close to LOQ. Additionally, one sample had a lidocaine concentration of — ng/mL at 6 hour time point. The Applicant stated that blood was collected from the arm used for iontophoresis rather than from the contralateral arm, due to difficulty in blood collection procedure. Overall, minimal or no lidocaine concentrations were observed. Subsequently, no pharmacokinetic parameters were calculated. The study demonstrated that the maximum recommended iontophoretic Lidopel™ dose of 80 mA•min results in systemic plasma lidocaine concentrations far below 1.0 to 5.0 μg/mL, the reported range of systemic pharmacological activity for lidocaine. Lidocaine levels greater than 5 μg/mL are considered toxic. Epinephrine concentration was not measured in Study 96-08. However, significant addition to the endogenous epinephrine levels is not expected.

1.1 Recommendations

From Office of Clinical Pharmacology and Biopharmaceutics / Division of Pharmaceutical Evaluation II (OCPB/DPE-II) point of view, the information contained in the NDA is acceptable provided that a mutually satisfactory agreement can be reached between the Agency and Sponsor regarding the text in the package insert.

1.2 Phase IV Commitments – None

1.3 Summary of CPB Findings

In the submission, reference is made to safety and effectiveness data provided by Iomed, Inc. in NDA #20-530 for Iontocaine®, a Lidocaine HCl 2% and Epinephrine 1:100,000 solution labeled for iontophoretic use with the Iomed Phoresor® Iontophoretic Drug Delivery System. Additionally, the Applicant utilized information in the published peer-reviewed literature for the iontophoretic delivery of lidocaine for the production of local dermal anesthesia. The Applicant stated that Lidopel™ is manufactured by Novocol Pharmaceutical of Canada and is identical to Octocaine® (Septodont ANDA #84-048) in all respects except labeling. Reference to chemistry, manufacturing, and controls in ANDA #84-048 has been authorized by Septodont. The overall concept of iontophoretic delivery system is that the system can be used for the administration of lidocaine hydrochloride to provide local dermal anesthesia on normal intact skin (epinephrine supposedly increases the depth and duration of anesthesia, due to its vasoconstrictor capacity, by decreasing the rate of removal of lidocaine from the applied site). The system can be used as an alternative to hypodermic injection or topical application of lidocaine hydrochloride.

Lidopel™ Lidocaine HCl 2% and Epinephrine 1:100,000 are not marketed outside the United States. The Applicant has submitted 1 study (Study 96-08) under the Clinical Pharmacology section of the NDA.

In Study 96-08, the healthy subjects were randomized to three electrode groups with three subjects in each group:

A: 80 mA.min using the small (8.1 cm^2) delivery
B: 80 mA.min using the medium (— cm^2) delivery
C: 80 mA.min using the large (— cm^2) delivery

The delivery current of 4 mA was applied for treatment time of approximately 20 minutes. Blood samples for determination of plasma lidocaine levels were drawn from the contralateral arm. Plasma samples (a total of 72 plasma samples measure up to 6 hours post application) were below the limit of quantitation for lidocaine (GCMS analytical method; limit of quantitation (LOQ) was 2 ng/mL). However, there were three samples (— ng/mL) which had low lidocaine concentrations; lidocaine levels of theses samples were very close to LOQ. Additionally, one sample had a lidocaine concentration of — ng/mL at 6 hour time points. The Applicant stated that blood was collected from the arm used for iontophoresis rather than from the contralateral arm, due to difficulty in blood collection procedure. Overall, minimal or no lidocaine concentrations were observed. Subsequently, no pharmacokinetic parameters were calculated. The study demonstrated that the maximum recommended iontophoretic Lidopel™ dose of 80 mA•min results in systemic plasma lidocaine concentrations far below 1.0 to 5.0 μg/mL, the reported range of anti-arrhythmic activity. Lidocaine levels greater than 6 μg/mL are considered toxic. Epinephrine concentration was not measured in Study 96-08. However, significant addition to the endogenous epinephrine levels is not expected.

2 QBR

2.1 General Attributes of the Drug and Drug Product?

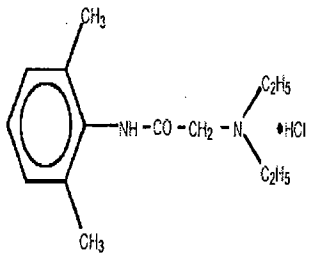
2.1.1 What is the description of the active drug?

Lidocaine is a local anesthetic agent of the amide type which works via a reversible blockade of nerve conduction. It binds to a specific receptor site within the voltage sensitive sodium (Na+) channels at the cell membrane, stabilizes the inactive state of the Na+ channel, thus preventing generation and further propagation of nerve impulses (slowing down depolarization of nerve cell membranes).

As the anesthetic action develops in a nerve, the electrical excitability increases, the duration of the action potential shortens and the impulse conduction progressively decreases. These factors decrease the probability of the propagation of the action potential and, subsequently, nerve conduction fails.

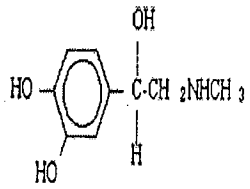
Lidocaine is rapidly de-ethylated to the active metabolite which is then hydrolyzed by amidases to various components that have reduced activity. Approximately 90% of lidocaine is excreted in the form of various metabolites and less than 10% of a dose is excreted unchanged via the kidneys.

Chemical Structure of Lidocaine HCl



2-(diethylamino)-N-(2,6-dimethylphenyl)-, monohydrochloride

Chemical Structure of Epinephrine



(-)-3,4—Dihydroxy-α-[(methylamino) methyl] benzyl alcohol

Epinephrine is a catecholamine, a naturally occurring endocrine compound secreted by the adrenal medulla into the circulatory system, essential in the neuro-humoral transmission of the sympathetic nervous system. Epinephrine acts directly on the α - and β -adrenergic receptors of tissues innervated by sympathetic nerves except for the sweat glands and arteries of the face. Parenteral administration of epinephrine is primarily used to induce cardiac stimulation, dilation of skeletal muscle vasculature, and relaxation of smooth muscle of the bronchial tree. Locally, epinephrine has been used as a vasoconstrictor by slowing the clearance of the anesthetic from the site by stimulating α - adrenergic receptors within the blood vessels, thereby prolonging the effect of the anesthetic.

Most exogenously administered or endogenously released epinephrine is very quickly inactivated by uptake into adrenergic neurons, diffusion, plasma protein binding and enzymatic degradation in the liver and body tissues.

Enzymes responsible for the inactivation of epinephrine are catechol-O-methyltransferase (COMT) and monamine oxidase (MAO). Metabolites are excreted in the urine mainly as glucuronide or sulfate ether conjugates. Epinephrine does not reach pharmacologically active concentrations in the body after oral administration because it is destroyed in the gastrointestinal tract and rapidly conjugated and oxidized in the liver.

2.1.2 What is the description and composition of the drug product?

The Lidopel drug product consists of lidocaine/epinephrine drug solution and Dupel iontophoresis System. The drug solution contains lidocaine HCl (20 mg/mL), epinephrine (10 μg/mL), sodium chloride (6 mg/mL) and sodium bisulfite (0.55 mg/mL) in water for injection. The solution is adjusted to a pH of 3.8 to 5.5 with sodium hydroxide and/or hydrochloric acid.

Lidopel™ Lidocaine HCl 2% and Epinephrine 1:100,000 Topical Solution for Dermal Iontophoresis with the Dupel® Iontophoresis System (Lidopel™) is identical to Octocaine® (ANDA #84-048), manufactured by Novocol Pharmaceutical of Canada, Inc. (Novocol), and already Agency approved for production of local anesthesia by injection and nerve block. All clinical studies presented in this NDA used the Agency-approved formulation.

The indication for use for the Dupel® Iontophoresis System (K903093) and Dupel® Iontophoresis Electrodes (K912015, K970491, K983484) is for administration of ionic solutions. The Dupel Iontophoresis System was cleared for marketing in 1990 by the Agency via the 510(k) premarket notification process (K903093) as a substantially equivalent Class III device. Dupel Iontophoresis Electrodes used with the Dupel Iontophoresis System have also been cleared for marketing in the United States via 510(k) premarket notification (K912015, K97049, and K983484).

The Applicant stated that there were no material changes made to any of the study products (Empi Lidopel™, the Dupel® Iontophoresis System, or Dupel® Iontophoresis Electrodes) during the clinical studies.

2.1.3 What are the Potential clinical benefits of iontophoretic delivery system?

The production of local dermal anesthesia, e.g., for venipuncture and superficial dermatological procedures such as shave removals, can be produced without the need for anesthetic injection. Iontophoretic delivery of anesthesia avoids potential tissue distortion from injection, minimizes the systemic concentrations of the drug, and produces less pain from the administration process than injection. An additional benefit of iontophoretic delivery system is the elimination of the potential for exposure to blood-borne pathogens due to accidental postinjection needle-stick injury in healthcare personnel.

2.1.4 Is there a safety concern with lidocaine exposure from Lidopel?

No, results from the Study 96-08 indicated that lidocaine concentrations were not observed in adults post administration.

2.1.5 Is there a safety concern with epinephrine exposure from Lidopel?

Epinephrine concentrations in adults were not measured. However, significant addition to the endogenous epinephrine levels is not expected.

2.1.6 What are other similar iontophoretically administered lidocaine drug products?

This Application refers to Iomed Iontocaine®, another formulation of lidocaine HCl 2% and epinephrine 1:100,000 that was approved by the Agency for the production of analgesia via iontophoresis (NDA #20-530). Iomed Iontocaine® NDA #20-530 contained a single pharmacokinetic study of Iontocaine®. The study enrolled seven healthy adults who received an iontophoretic dose of 40 mA•min. Venous blood samples for plasma lidocaine were measured (FPI; sensitivity: 1 µg/mL) immediately upon completion of delivery of an Iontocaine® dose of 40 mA•min and 30, 60, and 120 minutes post exposure. No lidocaine was detected.

2.1.7 What are the treatments and subjects used in the clinical trials?

A total of [redacted] 183 healthy adult volunteers, 156 adult patients [redacted] were studied with Lidopel.

With respect to iontophoretic doses, 20, 30, 40, 60 and 80 mA•min doses were tested in 149, 20, 71, 80, and 93 subjects, respectively.

2.2 General Clinical Pharmacology

2.2.1 Exposure-response

2.2.1.1 What are the characteristics of the exposure-response relationships (dose-response, concentration-response) for efficacy? If relevant, indicate the time to the onset and offset of the pharmacological response or clinical endpoint.

There is no concentration-exposure relationship data as no systemic lidocaine concentrations were observed. Additionally, no PD data were collected, and as such, the information on dose-response relationship is not available.

2.2.1.2 Does this drug prolong the QT or QTc interval?

QT study has not been studied. However, lidocaine and epinephrine are not known to prolong QT interval.

2.2.1.3 Is the dose and dosing regimen consistent with the known relationship between dose-concentration-response, and are there any unresolved dosing or administration issues?

The iontophoretic delivery of lidocaine / epinephrine is for the local effect. There were no systemic concentrations observed from this drug/device formulation. Thus, the relationship can not be assessed from this drug/device formulation.

2.2.2 What are the PK information from Study 96-08?

The PK characteristics of Lidopel were determined in one clinical study that enrolled nine subjects (five males and four females) who were randomized to one of three treatment groups by delivery electrode size (small: 8.1 cm^2, medium: — cm^2, large· — cm^2). This study showed that a 80 mA•min Lidopel™ dose (via iontophoresis) produces systemic lidocaine concentrations far below the range of anti-arrhythmic activity.

Systemic plasma lidocaine levels were measured using GCMS (sensitivity 2 ng/mL). Samples were drawn before and after (15 minutes, 30 minutes, one hour, two hours, four hours, and six hours) a single 80 mA•min Lidopel™ iontophoresis treatment. Lidocaine was not detected in six of nine subjects. Three subjects showed levels of approximately 2 ng/mL at four hours (n=2) and six hours (n=1). These concentrations are approximately 0.13 percent of the lowest reported therapeutic value for anti-arrhythmic activity.

One of the three subjects had a lidocaine level of — ng/mL six hours after iontophoresis due to drawing the blood sample at the iontophoresis site because of difficulty performing the phlebotomy on the contralateral arm.

Five of the nine subjects reported no adverse events over the course of the study. Four adverse events were recorded for the remaining four subjects, one event for each subject. These events were a swollen arm due to difficult phlebotomy (n=1), headache (n=1), and petechiae (n=2) at the site of the iontophoresis delivery electrode, all of which were rated as "mild."

2.2.3 What are the PK characteristics of the drug and its major metabolite?

No systemic lidocaine levels were detected from this formulation.

2.3 Intrinsic Factors

2.3.1.2 Gender, race and age

There were no PK evaluations for age and race. Study 96-08 included 5 male and 4 female subjects. Since there were no measurable systemic concentrations, gender analysis was not conducted.

2.4 Extrinsic Factors – Not applicable

2.5 General Biopharmaceutics

2.5.1 What is the in vivo relationship of the proposed to-be-marketed formulation to the pivotal clinical trial formulation in terms of comparative exposure?

See above.

2.6 Analytical Section

2.6.1 How are the active moieties identified and measured in the plasma in the clinical pharmacology and biopharmaceutics studies? For all moieties measured, is free, bound or total measured? What bioanalytical methods are used to assess concentrations?

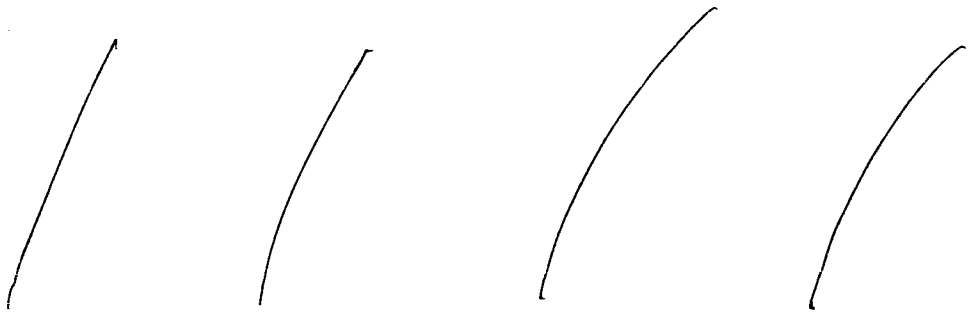
Plasma lidocaine levels were measured using GCMS (sensitivity 2 ng/mL).

2.6.1.1 What is the range of the standard curve? How does it relate to the requirements for clinical studies? What curve fitting techniques are used? What are the lower and upper limits of quantification (LLOQ/ ULOQ)? What is the accuracy, precision and selectivity at these limits? What is the sample stability under the conditions used in the study? (long-term, freeze-thaw, sample-handling, sample transport, autosampler) What is the QC sample plan?

A typical standard curve range was from 2 to 200 ng/mL. QC samples were 3.5, 22, 100, and 175 ng/mL. Within-batch standard curve data showed that % CV ranged from 0.4 to 9.5 %. Within-batch QC data showed that % CV ranged from 1.0 to 6.1%. Between-batch standard curve data showed that % CV ranged from 2.7 to 8.4 %. Between-batch QC data showed that % CV ranged from 5.2 to 8.8 %. Absolute recovery of lidocaine from plasma ranged from — Four freeze/thaw cycle data showed that % CV ranged from 1 to 2.6 %.

3 Detailed Labeling Recommendations

There are changes recommended for the Clinical Pharmacology section of the label, as below. See Appendix 4.1 for the Applicant's package insert proposal.



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_____ Trade Secret / Confidential

_____ Draft Labeling

_____ Deliberative Process

4.2 Individual Study Review

Title : Monitoring systemic lidocaine levels following iontophoretic local delivery to the skin (Pharmacokinetic Study of Lidopel™ (Empi Study #96-08.0))

Design: Single dose in healthy subjects n=9 (5 ♀ and 4 ♂); Men had mean (range) values of age, height and weight of 23.6 (20-30 yrs), 182.9 cm (175.3 to 190.5 cm), and 80.3 kgs (66.1 -90.1 kg), respectively. Women had mean (range) values of age, height and weight of 33.5 (20-39 yrs), 160.7 cm (157.5 – 165.1 cm), and 56.9 kg (52.1 – 63.4 kg), respectively. Volunteers were randomized to one of three treatment groups with three subjects in each group:

A: 80 mA.min using the small (8.1 cm^2) delivery
B: 80 mA.min using the medium (___ cm^2) delivery
C: 80 mA.min using the large (___ cm^2) delivery

Inclusion/Exclusion Criteria: Female subjects were required to be practicing medically acceptable method of birth control and have a negative serum pregnancy test at the time of screening. Subjects were excluded for abnormal clinical laboratory test results, clinically significant medical conditions or electrically sensitive implants, recent history of drug or alcohol abuse, addiction, positive urine drug abuse test, significant allergies, history of adverse reactions to electrical current devices, history of prescription drug ingestion (within 14 days of dosing), investigational drug ingestion (within 30 days of dosing), or alcohol ingestion (within 24 hours of dosing).

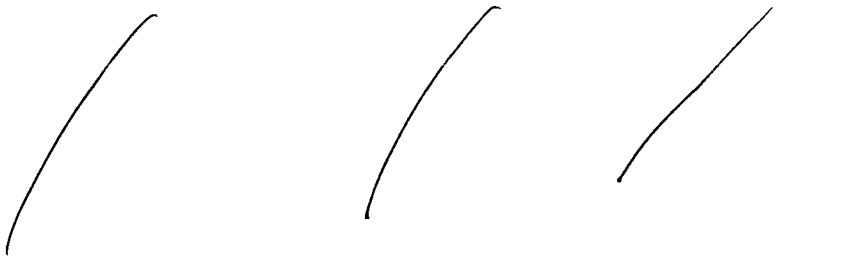
Dose administration: Dupel® Iontophoresis System to either the left or right arm. Subjects were randomly assigned to either the small (8.1 cm^2), medium (___ cm^2) or large (___ cm^2) delivery electrode. The return electrode for all three treatment groups was the same. The reservoir of the delivery electrode was saturated with a total of 2.5 ___ of the lidocaine HCl 2% and epinephrine 1:100,000 solution to fill the small, medium, or large delivery electrode, respectively. The delivery electrode was placed over the flexor muscle belly on the volar aspect of the appropriate forearm. The return electrode was moistened with room temperature water and applied to the upper protion of the same arm at least 4 inches from the delivery electrode. The electrodes were then connected to the lead wires used for the device (positive lead to the delivery and negative lead to the return electrodes). The device then was set to deliver a dose of 80 mA.min at a current of 4 mA. The treatment time was approximately 20 minutes (a constant current of 4.0 mA was applied for 20 minutes to deliver a total dose of 80 mA•min.).

Blood sample collections: Blood samples for determination of plasma lidocaine levels were drawn from the contralateral arm at eight time points: prior to, and end of iontophoresis, 0.25, 0.5, 1, 2, 4, and 6 hours post iontophoresis application.

Analysis: Plasma samples were analyzed for lidocaine by a validated GCMS method. Assay method and validation results are acceptable.

Results:

1. Lidocaine plasma concentrations (ng/mL)



1. Blood sample taken from the same arm used for iontophoresis, due difficult phlebotomy on the contralateral arm.

a. In three subjects, levels of approximately 0.002 µg/mL were found at four hours (n=2) and six hours (n=1) (sensitivity 0.002 µg/mL).

b. One of the three subjects had a lidocaine level of — µg/mL (— ng/mL) six hours after the iontophoresis treatment. This slightly higher lidocaine level was determined to have occurred because the blood sample was drawn at the iontophoresis site, due to difficulty performing the phlebotomy on the contralateral arm.

c. No PD markers were collected.

2. Adverse Events

a. Five of the nine subjects (56 percent) reported no adverse events over the course of the study. A total of four adverse events were recorded for the remaining four subjects, each for a single subject. None of the events were reported as being related to the device and three events were reported as probably related (n=2) or possibly related (n=1). All events were reported as mild. The swollen arm was believed to be due to difficult venipuncture and the petechiae were at the site of the delivery electrode (n=2).

b. No individual case report forms are provided.

4.3

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_____ Draft Labeling

_____ Deliberative Process

Office of Clinical Pharmacology and Biopharmaceutics
New Drug Application Filing and Review Form

General Information About the Submission

	Information		Information
NDA Number	**21-486**	**Brand Name**	**Lidopel**
OCPB Division (I, II, III)	**II**	**Generic Name**	**Lidocaine/epinephrine**
Medical Division	**HFD-170**	**Drug Class**	**Anesthetic**
OCPB Reviewer	**David Lee**	**Indication(s)**	[redacted]
OCPB Team Leader	**Suresh Doddapaneni**	**Dosage Form**	**Iontophoretic delivery**
		Dosing Regimen	**Single dose**
Date of Submission	**2/02/02**	**Route of Administration**	**Topical**
Estimated Due Date of OCPB Review	**-**	**Sponsor**	**Empi, Inc.**
Medical Division Due Date	**6/11/04**	**Priority Classification**	**4S**
PDUFA Due Date			

Clin. Pharm. and Biopharm. Information

	"X" if included at filing	Number of studies submitted	Number of studies reviewed	Critical Comments If any
STUDY TYPE				
Table of Contents present and sufficient to locate reports, tables, data, etc.	**X**			
Tabular Listing of All Human Studies	**X**			
HPK Summary	**X**			
Labeling	**X**			
Reference Bioanalytical and Analytical Methods	**X**			
I. Clinical Pharmacology				
Mass balance:				
Isozyme characterization:				
Blood/plasma ratio:				
Plasma protein binding:				
Pharmacokinetics (e.g., Phase I) -				
Healthy Volunteers-				
single dose:	*x*	*x*	*x*	*Iontophoretic delivery*
multiple dose:				
Patients-				
single dose:				
multiple dose:				
Dose proportionality -				
fasting / non-fasting single dose:				
fasting / non-fasting multiple dose:				
Drug-drug interaction studies -				
In-vivo effects on primary drug:				
In-vivo effects of primary drug:				
In-vitro:				
Subpopulation studies -				
ethnicity:				
gender:				
pediatrics:				
geriatrics:				
renal impairment:				
hepatic impairment:				
PD:				
Phase 2:				
Phase 3:				
PK/PD:				
Phase 1 and/or 2, proof of concept:				

Phase 3 clinical trial:				
Population Analyses -				
Data rich:				
Data sparse:				
II. Biopharmaceutics				
Absolute bioavailability:				
Relative bioavailability -				
solution as reference:				
alternate formulation as reference:				
Bioequivalence studies -				
traditional design; single / multi dose:				
replicate design; single / multi dose:				
Food-drug interaction studies:				
Dissolution:				
(IVIVC):				
Bio-wavier request based on BCS				
BCS class				
III. Other CPB Studies				
Genotype/phenotype studies:				
Chronopharmacokinetics				
Pediatric development plan				
Literature References				
Total Number of Studies		1	1	

Filability and QBR comments		
	"X" if yes	Comments
Application filable ?	**X**	Reasons if the application is not filable (or an attachment if applicable) For example, is clinical formulation the same as the to-be-marketed one?
Comments sent to firm ?		Comments have been sent to firm (or attachment included). FDA letter date if applicable.
QBR questions (key issues to be considered)		
Other comments or information not included above		
Primary reviewer Signature and Date		
Secondary reviewer Signature and Date		

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/s/

David Lee
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Suresh Doddapaneni
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