CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

21-486

PHARMACOLOGY REVIEW(S)

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

PHARMACOLOGY/TOXICOLOGY REVIEW AND EVALUATION

NDA NUMBER:	**21-486**
SERIAL NUMBER:	**1**
DATE RECEIVED BY CENTER:	**9/26/2003**
PRODUCT:	**Lidopel™ (Lidocaine HCl 2%/Epinephrine 1:100,000)**
INTENDED CLINICAL POPULATION:	
SPONSOR:	**Empi, Inc.**
DOCUMENTS REVIEWED:	**N 000**
REVIEW DIVISION:	**Division of Anesthetic, Critical Care, and Addiction Drug Products (HFD-170)**
PHARM/TOX REVIEWER:	**Adam M. Wasserman, Ph.D.**
PHARM/TOX SUPERVISOR:	**R. Daniel Mellon, Ph.D.**
DIVISION DIRECTOR:	**Bob Rappaport, M.D.**
PROJECT MANAGER:	**Lisa Malandro**

Date of review submission to Division File System (DFS): September 23, 2004

TABLE OF CONTENTS

EXECUTIVE SUMMARY

1. Recommendations

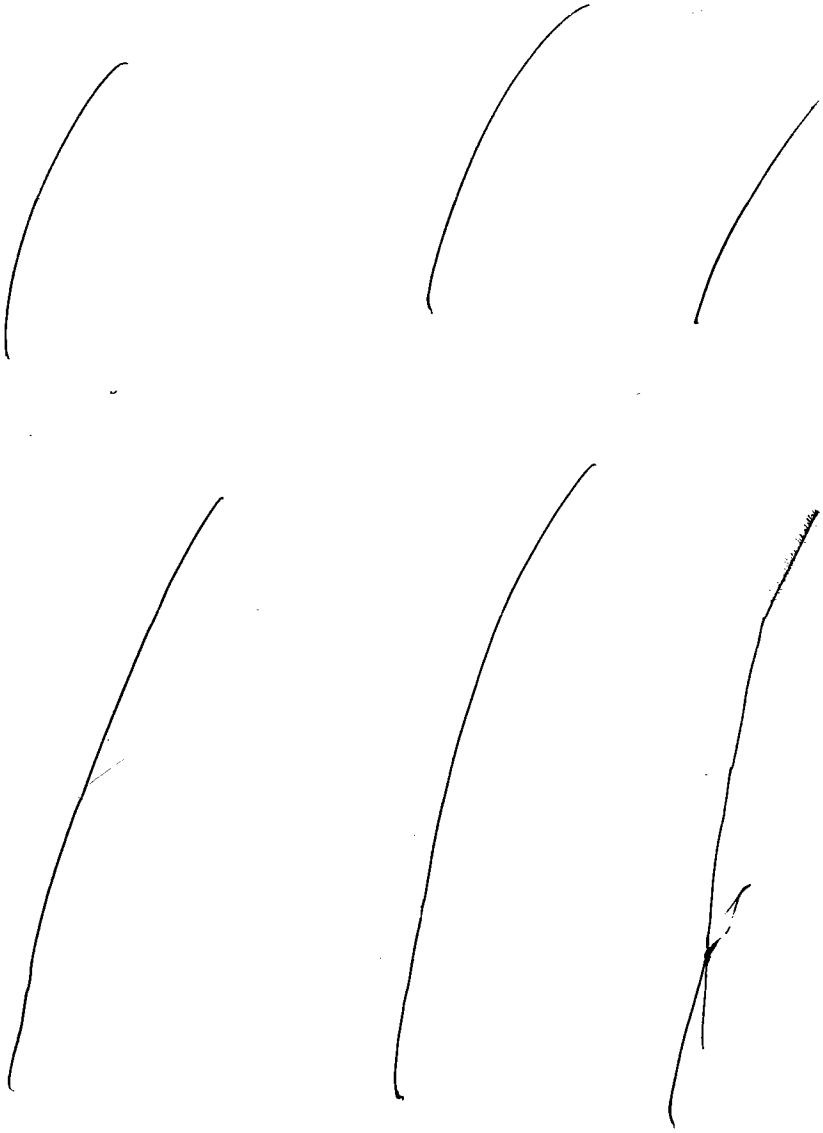
1.1 Recommendation on approvability

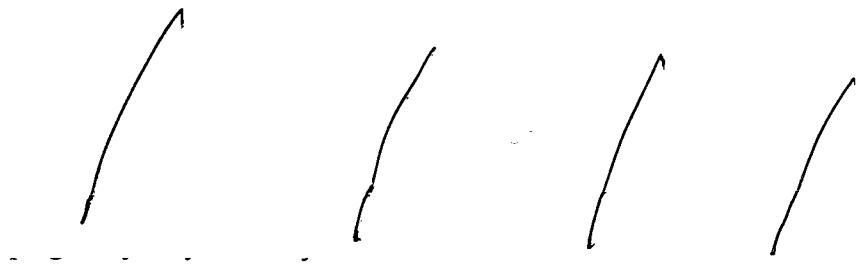
From a pharmacology/toxicology perspective, this NDA submitted by Empi, Inc. for Lidopel™ may be approved.

1.2 Recommendation for nonclinical studies

No further nonclinical studies are required at this time.

1.3 Recommendations on labeling





2. Summary of nonclinical findings

2.1 Brief overview of nonclinical findings

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) [redacted] produced significant erythema and mild 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 [redacted] methods (LLOQ = [redacted] µg/mL) in a minority of animals with all values being ≤ [redacted] 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.

2.2 Pharmacologic activity

The pharmacology of lidocaine and epinephrine are generally well understood. Lidocaine, an amide-class local anesthetic, is thought to produce its primary pharmacodynamic effect through voltage- and frequency-dependent blockade of nerve conduction which occurs by stabilization of the inactivated state of voltage-

gated Na^+ channels located primarily on Aδ and C-fiber axons of sensory neurons in the region of administration. Reduction or block of Na^+ influx across the axonal membrane reduces local membrane potential and reduces the probability of the large-scale voltage-gated Na^+ channel opening and fast depolarization required for generation of the action potential and conduction along the axonal fiber. In addition to affecting nerves underlying the sensation of pain and temperature, lidocaine used at local anesthetic concentrations can also impede the action potentials generated in autonomic fibers. Higher concentrations of lidocaine will affect voltage-gated Na^+ channels on larger diameter and more heavily myelinated sensory and motor fibers which can cause proprioceptive sensory loss and motor paralysis. Lidocaine at higher concentrations is also known to affect a number of voltage and ligand-gated ion channels and receptors including most importantly voltage-gated potassium and calcium channels which may be involved in cardiac and CNS toxicities observed at higher systemic concentrations than is normally intended or achieved with use as a local anesthetic. Lidocaine, as with other local anesthetics, can cause vasodilation in the periphery which could cause an increase in systemic exposure to the compound and reduce the levels of lidocaine at the site of administration.

Epinephrine, an endogenously produced catecholamine in the adrenal medulla, has many potential sympathomimetic effects depending on the tissues exposed. Epinephrine acts on α- and β-adrenergic receptors, each of which have several subtypes and underlie different physiologic responses. Epinephrine is used in this product to stimulate vascular α_1-adrenoreceptors which causes vasoconstriction of the local vasculature in the area of drug administration. This serves to counteract the ability of lidocaine to cause vasodilation and limit the systemic uptake and consequent exposure to lidocaine while at the same time enhancing the local tissue concentrations of the local anesthetic thereby improving both efficacy and duration of action.

2.3 Nonclinical safety issues relevant to clinical use

The principal concern with iontophoretic administration of Lidopel™ is the potential for local dermal effects. A dermal irritation study in the rabbit conducted by the sponsor demonstrated that repeated exposure to the drug product at a delivery rate (i.e. concentration instilled) [redacted] could produce significant dermal irritation including severe erythema though this did not occur until animals were exposed to several days of repeated administration. Full recovery was ultimately observed after cessation of iontophoretic drug administration. Systemic exposure to significant lidocaine concentrations which could result in cardiovascular or CNS toxicities are highly unlikely given this route of administration, the concentration of drug administered, and the use of epinephrine in the drug product. Very limited systemic exposure was observed in rabbits in the aforementioned study (≤ [redacted] μg/mL maximum, which is ~10- to 50-fold below the human therapeutic plasma concentration).

In rare cases severe allergic reactions to local anesthetics are observed but this occurs more frequently with ester-class local anesthetics than with the amide-type exemplified by lidocaine.

PHARMACOLOGY/TOXICOLOGY REVIEW

3.1 INTRODUCTION AND DRUG HISTORY

NDA number:	21-486
Review number:	1
Sequence number/date/type of submission:	N 000/Feb 12, 2002/Original N 000/Sep 26, 2003/RS
Information to sponsor:	Yes ( ) No (X)
Sponsor and/or agent:	Empi, Inc., St. Paul, MN
Manufacturer for drug substance:	Lidocaine: [redacted] Epinephrine: [redacted]
Manufacturer for drug product:	Novocol Pharmaceutical of Canada, Inc.; Cambridge, Ontario

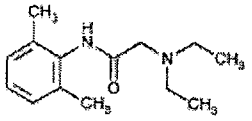
Reviewer name: Adam M. Wasserman, Ph.D.
Division name: DACCADP
HFD #: 170
Review completion date: September 23, 2004

Drug:

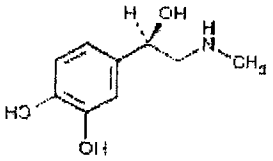
Trade name: Lidopel™
Generic name:
Lidocaine, Xylocaine, Lignocaine
Epinepherine, Adrenaline

Code name: None
Chemical name:
Lidocaine HCl: 2-Diethylamino-2',6'-acetoxylidide hydrochloride,
Epinephrine: (-)-3,4-Dihydroxy-α-[(methylamino)methyl]benzyl alcohol
CAS registry number:
Lidocaine HCl: 73-78-9
Epinephrine: 51-43-4
Molecular formula/molecular weight:
Lidocaine HCl: $C_{14}H_{22}N_2O \cdot HCl$ /270.80
Epinephrine: $C_9H_{13}NO_3$/183.21

Structure:



• HCl



Lidocaine Epinephrine

Relevant INDs/NDAs/DMFs:

IND 54,731	2% Lidocaine HCl and Epinephrine 1:100,000 (Empi)
NDA 20-530	Iontocaine® (Iomed)
ANDA 84-048	Ontocaine® (Septodont)
EMPI 510(k):	K903093, K912015, K970491, K983484 (Empi)
DMF:	
DMF:	

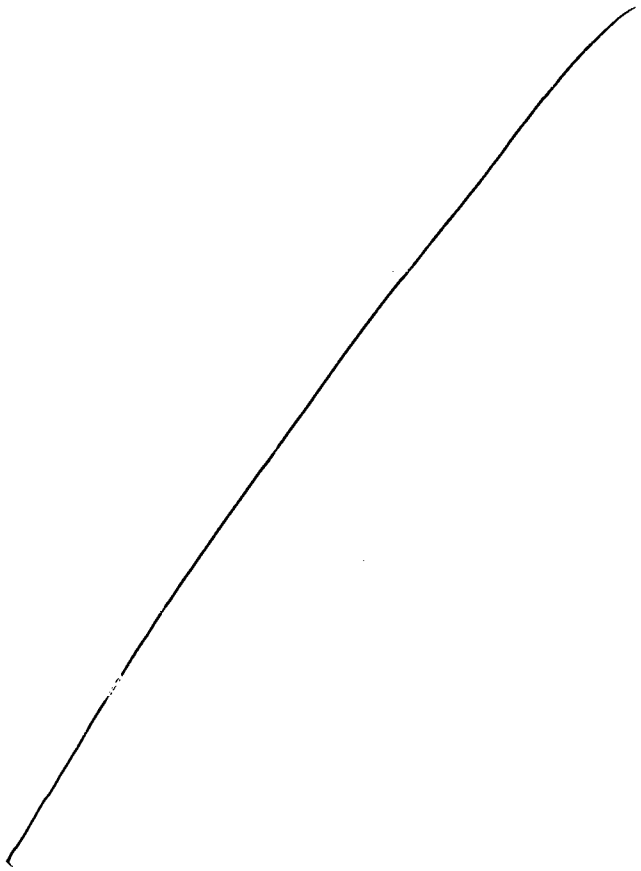
Drug class: Local anesthetic, amide-class;

Indication:

APPEARS THIS WAY
ON ORIGINAL

Clinical formulation:
Lidopel™ is comprised of the active drugs lidocaine HCl 2% (20 mg/mL) and epinephrine at 1:100,000 (10 µg/mL). Each milliliter contains lidocaine HCl 20 mg/mL, epinephrine 10 µg/mL, sodium chloride 6 mg/mL and sodium bisulfite 0.55 mg/mL in sterile water. Additionally, sodium hydroxide and/or hydrochloric acid may be added to bring the drug product to pH 3.8 – 5.5. Active drugs are consistent with the monograph for lidocaine HCl and epinephrine published in USP24/NF19, pg. 973-4. Lidopel™ will be supplied in 1.8 mL cartridges with 50 per carton. Lidopel™ is to be used with the Dupel® Iontophoresis System and Dupel® Buffered Iontophoresis Electrodes. Lidopel™ is instilled by syringe into the delivery electrode reservoir and the delivery and return electrodes are affixed to the skin and connected by lead wires to the Dupel® Iontophoresis System.

A schematic of the Drug Delivery Electrode and Return Electrode is provided below (reproduced from the NDA submission).



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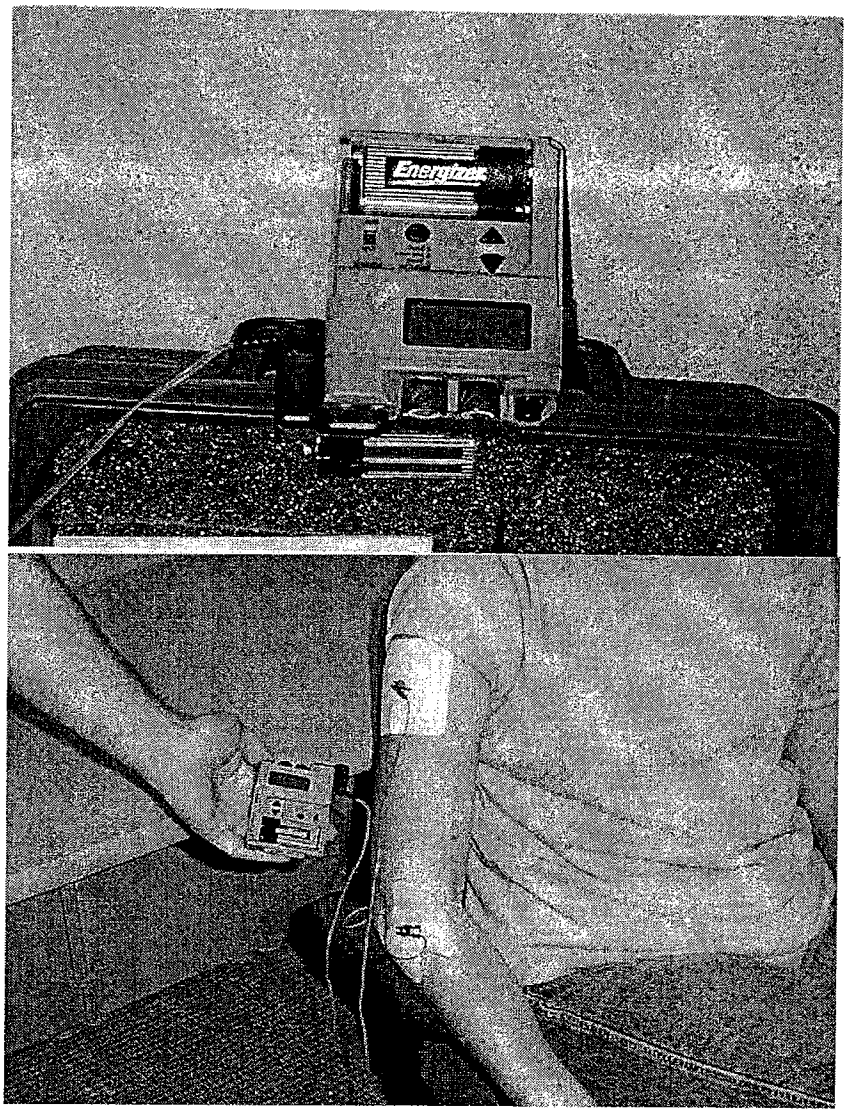
1 Trade Secret / Confidential

_____ Draft Labeling

_____ Deliberative Process

The Dupel® Iontophoresis System (premarket clearance #K903093) consists of a dual channel microprocessor-controlled battery-powered DC current generator along with lead wires and a set of Empi Iontophoresis electrodes. The Dupel® Iontophoretic System was cleared for marketing in 1990 with a 510(k) premarket notification process as a substantially equivalent Class III device. It is used with the Dupel® II Buffered Iontophoretic Electrode System described above.



Note that the single preclinical study conducted (Study #97-03) as well as early clinical studies did not use the final to-be-marketed version of the Dupel® Iontophoretic electrodes:

Differences between the electrodes used in the various studies are described in the Sponsor's table below. CDRH consult by Kevin Lee, M.D. concluded that:

> "the changes to the electrodes were not significant and thus, the new electrodes (s) and the NDA electrodes fall under the same 510(k) (#K970491)....Additionally they represent the Empi Dupel® BLUE (Bi-Layer Ultra Electrodes) Iontophoresis Electrodes which are currently on the market." (CDRH Review NDA 21-486, p.31).

No comment was made on the K983484 delivery electrode which has been designated "to be marketed" in the sponsor's table. It is unclear which sizes or how many of these electrodes will be marketed with Lidopel™.

Summary of Dupel® Iontophoresis Electrode Designs used in Empi Studies

510(k)	Electrode Size	Study Usage	Study #	Study ID
K912014	45.2 cm^2	Return Electrode	96-08.0	Phase I human PK Study
			97-03.0	***In vivo* rabbit study**
			97-07.0	Phase II pilot
			99-02.0	Phase III study
			99-07.0	Phase III study
			99-14.0	Phase III study
			00-1-03.0	Active Treatment Concurrent Control Study
K970491	8.1 cm^2 ( )	Delivery Electrode	96-08.0	Phase I human PK Study
	8.1 cm^2 ( )	Delivery Electrode	97-07.0	Phase II pilot
	10.1 cm^2	Delivery Electrode	00-1-03.0	Active Treatment Concurrent Control Study
	8.1 cm^2	Delivery Electrode	97-03.0	***In vivo* rabbit study**
			99-02.0	Phase III Study
			99-07.0	Phase III Study
			99-14.0	Phase III Study
			01-1-06.0	Uncontrolled Clinical Study
	( )	Return Electrode	01-1-06.0	Uncontrolled Clinical Study
K983484		Delivery Electrode	00-5-05.0	*In vitro* stability study

An *in vitro* study (submitted with the IND and summarized in Volume 8, Section 5, pages 8-13 of the NDA) was designed to look at the cumulative amounts of lidocaine

HCl delivered by the variously sized Dupel® Iontophoresis electrodes utilized a hairless mouse skin model system. The results of this analysis are presented in the table below:

Results:	Small 8.1 cm^2	Medium — cm^2	Large* — cm^2	Overall**
2% Lidocaine HCl and Epinephrine 1:100,000	2.5cc	—	—	N/A
Dosage(mA•min)	80	80	80	80
Mean Cumulative Amount of Lidocaine HCl Delivered (µg)	158.5	108.7	128.6	132.0
Relative Standard Deviation	38%	23%	26%	35%
95% Confidence Interval	±29.8	±12.5	±17.4	±12.8
Theoretical Plasma Lidocaine HCl Conc.	0.0031 µg/mL to 0.0045 µg/mL	0.0023 µg/mL to 0.0029 µg/mL	0.0026 µg/mL to 0.0035 µg/mL	0.0028 µg/mL to 0.0034 µg/mL

* *The large size electrode values are based on n=17, because one value was below the HPLC method's quantitation limit of 1.0 ppm in a 50 µL sample.*

** *The overall values are based on n=53.*

Although the mean cumulative drug delivery amounts differed by up to 46%, no consistent effect of patch size on drug delivery was observed. The sponsor notes that these values are lower than what was obtained at a later date (average delivery of lidocaine ~ 220 µg; data not presented in NDA) using the same procedures. Consultation with the laboratory which supplied the original mouse skin used for the assay revealed that a non-standardized approach to skin removal was used and thus the amount of adipose tissue remaining on the skin could vary depending on the individual performing the removal process. The presence of adipose tissue on the skin in the above assay was postulated to reduce the levels of drug observed through absorption of lipophilic compounds into adipose tissue which would reduce the amount of drug delivered to the receptor solution. Subsequent internal assessment with both types of skin preparation confirmed the plausibility of this explanation. Nevertheless, it appears the total amount of drug administered is largely independent of patch size though in practice the smaller electrodes would be expected to create a higher density of drug delivery and hence greater block and greater potential for local irritation or toxicity.

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1 Trade Secret / Confidential

_____ Draft Labeling

_____ Deliberative Process

Route of administration: Transdermal with use of the associated iontophoretic electrodes and system

Proposed use: The sponsor proposes the following:

Disclaimer: Tabular and graphical information are constructed by the reviewer unless cited otherwise.

Data reliance : Except as specifically identified below, all data and information discussed below and necessary for approval of NDA 21-486 are owned by Empi, Inc. or are data for which Empi, Inc. has obtained a written right of reference. Any information or data necessary for approval of NDA 21-486 that Empi, Inc. does not own or have a written right to reference constitutes one of the following: (1) published literature, or (2) a prior FDA finding of safety or effectiveness for a listed drug, as described in the drug's approved labeling. Any data or information described or referenced below from a previously approved application that Empi, Inc. does not own (or from FDA reviews or summaries of a previously approved application) is for descriptive purposes only and is not relied upon for approval of NDA 21-486.

Studies reviewed within this submission:

Study Title	Document #	Volume
Dermal Irritation Study in Rabbits Administered Lidocaine by Iontophoresis Once Daily for 14-days*	97-3.0	8; Appendix 5-2

* This study was previously reviewed by Dr. M.A. Goheer in January 1998 but was re-reviewed to conform to the subsequently released Good Review Practice guidance.

Studies not reviewed within this submission (Previously reviewed for IND and reproduced here):
N/A

Drug Product Development History

Note: This NDA is submitted as a 505(b)(2) application with the reference listed drug as Iomed Iontocaine® approved through NDA 20-530.

A Pre-IND meeting was held on July 16, 1996 during which the sponsor relayed their intention to submit a preclinical assessment of the pharmacokinetics of drug delivery

through hairless mouse skin. The Division stipulated that this should be performed as a GLP study to use for supportive information.

A second Pre-IND meeting was held May 21, 1997 at which time the preclinical requirements for subsequent clinical trials and an NDA submission were discussed. The Agency informed the sponsor of the requirement for a dermal irritation study to be conducted in the rabbit model as the Division wished to see the data regarding the effects and safety of the use of lidocaine HCl 2% with epinephrine (1:100,000) using the Dupel® Iontophoresis System and Dupel® Buffered Iontophoresis Electrodes. The Division also requested the sponsor determine the appropriate controls for the Phase II/III studies by comparison of dermal irritation produced by saline vs. saline + epinephrine in the required preclinical study. The Division agreed that mutagenicity assessment could be addressed through reference to available literature for an IND and NDA submission but specified that reference to the Anesthetic and Life Support Drugs Advisory Committee meeting of August 1993 should be made as well.

The sponsor submitted by fax the proposed protocol for the dermal irritation study in rabbit (Protocol #97-3.0) on August 5, 1997 and requested review by a pharmacology reviewer to determine adequacy. The subsequent letter from the Division (dated August 14, 1997) contained the following 5 comments: 1) Complete as a GLP study, 2) Current and duration should be at least equivalent to clinical trial, 3) Preclinical and clinical studies should be done using the same formulation, 4) At least measure body weight, food consumption, clinical signs and score dermal irritation during the study, 5) Do histopathology on all animals. The last comment is believed by this reviewer to refer to histopathologic assessment of the site of test article administration rather than a whole animal assessment.

An End of Phase 2 meeting was held with the Sponsor on June 30, 1999 at which time the possibility of submission as a 505(b)(2) application was again discussed. The sponsor was asked to provide information on how their product differed from the referenced drug product (drug/device combination), Iomed's Iontocaine®. This information was submitted as Serial #009 to the IND. A FDA Advice Letter to the sponsor dated March 10, 2000 stated that although the Sponsor could submit a 505(b)(2) application, the sponsor was still required to provide reliable data on mutagenicity and reproductive toxicology – including information corresponding to Segment I, II and III studies – though it was not specified whether this request included only lidocaine HCl or both lidocaine HCl and epinephrine.

3.2 PHARMACOLOGY

3.2.1 Brief summary

The pharmacology of lidocaine and epinephrine are well known and a general overview can be obtained from Goodman and Gilman's The Pharmacological Basis of Therapeutics. Lidocaine is an amide-class local anesthetic which interacts with voltage-gated Na^+ channels (VGSC) along the axons of unmyelinated and myelinated fibers in a

manner that blocks conduction of this ion through the channel, reducing or effectively eliminating the entry of this cation across the axonal membrane. This impairs the generation and/or propagation of the action potential along the axon and thus functionally blocks nerve conduction. Lidocaine acts to promote the inactive state of the channel; however, the ability of lidocaine to block Na^+ channels is dependent on the channel being in an open state. Thus the drug demonstrates both voltage- and frequency-dependent blockade, with more active, smaller diameter and unmyelinated nerves being affected first. These characteristics are especially useful as pain pathways, when activated, will have higher firing frequencies and are less heavily myelinated (C-fibers) and/or are of smaller diameter (Aδ, C-fibers) than proprioceptive or motor nerve axons. Thus, selectivity for pain pathways can be achieved which can spare other pathways though at higher dosing all sensory and motor pathways can be impaired. Additionally, lidocaine has lower but non-negligible affinity for other ligand- and voltage-gated channels including: K^+ channels, L-type Ca^{2+} channels and nicotinic cholinergic receptor-linked ion channels. Higher concentrations of lidocaine are known to produce secondary effects such as disruptions in cardiac rhythm and CNS toxicity including the potential for seizures.

Epinephrine, a catecholamine, may interact with both major classes of adrenergic receptors (α, β) and their multiple subtypes which are distributed widely and underlie the response of the sympathetic nervous system. Inclusion of epinephrine in this drug product at very low concentrations serves to stimulate α1 receptors located in the smooth muscle of the local vasculature at the site of drug administration leading to vasoconstriction which both reduces local clearance of lidocaine and thus systemic exposure. This response also will increase the duration of action of the local anesthetic at the delivery site and improve the functional block due to the higher local concentrations maintained.

Significant systemic exposure to lidocaine and epinephrine is thought to be unlikely due to the transdermal mode of delivery and the limited concentrations delivered by iontophoresis, thus actions are expected to be local, specific, and limited to the primary mechanism of action of these compounds.

3.2.2 Primary pharmacodynamics

Lidopel™, a combination of lidocaine HCl 2% and epinephrine (1:100,000), represents a drug product which is based on a well described combination of drug substances designed to produce local analgesia/anesthesia during minor surgical procedures in which a more general anesthetic or regional block is unnecessary.

Mechanism of action: Lidocaine HCl is an anesthetic of the amide-class. The mechanism of action involves the ability to block both open and inactivated voltage-gated Na^+ channels along the axons of myelinated Aδ axons and unmyelinated C-fiber axons transmitting pain signals to the spinal cord and higher pain centers of the brain. Transient block of Na^+ conduction blocks the membrane depolarization necessary to generate or regenerate the action potential necessary for conducting the electrical impulse along the nerve fiber. Lidocaine is specifically thought to bind within the pore of the Na^+ channel

and gains access to its binding site only when the Na^+ channel is in an open state. Once bound, lidocaine is thought to stabilize the inactive state of the channel which prevents reactivation and therefore the channels contribution to membrane depolarization and axonal conduction. Because lidocaine requires the Na^+ channel to be activated and in an open state in order for binding and stabilization of the inactive state to occur, lidocaine demonstrates a frequency-dependence such that nerve fibers that are undergoing more frequent depolarization (i.e. are more "active") are more sensitive to blockade. This quality improves the selectivity of the anesthetic for sensory fibers made more active by noxious stimulation. Although pain fibers are preferentially affected, all nerves exhibit some sensitivity to Na^+ channel blockade (see table below) though this is determined largely by the degree of myelination and diameter of the nerve as well as the placement of the nerve within nerve bundles. The table below summarizes the differential sensitivity of nerve fiber types to the anesthetic effect of lidocaine.

Fiber Type	Function	Diameter (μM)	Myelination	Conduction Velocity (m/s)	Sensitivity to Block
Type A					
Alpha	Proprioception, motor	12-20	Heavy	70-120	+
Beta	Touch, pressure	5-12	Heavy	30-70	++
Gamma	Muscle spindles	3-6	Heavy	15-30	++
Delta	Pain, temperature	2-5	Heavy	12-30	+++
Type B					
	Preganglionic autonomic	< 3	Light	3-15	++++
Type C					
Dorsal root	Pain	0.4 – 1.2	None	0.5 – 2.3	++++
Sympathetic	Postganglionic autonomic	0.3 – 1.3	None	0.7 – 2.3	++++
Adapted from Katzung's Basic and Clinical Pharmacology, 7th edition					

For most patients treated with local anesthetics, the order of fibers affected are generally pain fibers first followed by sensations of temperature, touch, deep pressure and finally motor function (Goodman & Gilman's *The Pharmacological Basis of Therapeutics* 10th edition, 2001).

Epinephrine, a biogenic amine produced by the same biosynthetic pathway which produces dopamine and norepinephrine, binds to all known subtypes of α and β-adrenergic receptors which are located throughout the central and peripheral nervous system as well as on end organs. The administration of epinephrine results in a sympathomimetic response, the properties of which depend on the locations and subtypes of the adrenergic receptors involved.

Drug activity related to proposed indication:
Lidocaine blocks the generation and conduction of nerve impulses primarily on Aδ and C-fibers in pain pathways by binding within the pore of the Na^+ channel, stabilizing the

channel in the inactive state. Of importance, this interaction is frequency and depolarization-dependent which improves the specificity of this compound for the highly active fibers engaged in the transduction of pain sensation during surgical intervention or in the face of noxious stimuli.

The function of epinephrine in this drug product is to stimulate α1 adrenergic receptors located in the local vasculature beds surrounding the administration site which will cause vasoconstriction and markedly reduce or prevent the systemic distribution of lidocaine. This vasoconstrictive effect therefore increases the local concentration of anesthetic at the intended site and increases the duration of anesthetic action while reducing the risk of untoward systemic reactions.

3.2.3 Secondary pharmacodynamics

Local anesthetics and lidocaine in particular, have demonstrated the ability to block a number of ligand- and voltage-gated ion channels. Hirota and colleagues (1997) demonstrated that local anesthetic ability to block L-type Ca^{2+} channel current occurs at concentrations (~1 mM) that are clinically relevant and correlate with local anesthetic potency, relative conduction blocking potency, lipid solubility coefficient and cardiac output inhibition. Lidocaine and other local anesthetics also have been shown to exhibit non-competitive open channel block of muscle and neuronal nicotinic cholinergic receptors (nAChRs) with muscle nAChR and ganglionic α3β4 receptors in the periphery being more sensitive than the CNS expressed α4β2 or α4β4 (Gentry and Lukas, 2001). Lidocaine also has been shown to inhibit voltage-gated potassium currents (Xiong et al., 1999) as well as those evoked by Ca^{2+} (Benham et al., 1985; Oda et al., 1993) and ATP (Yoneda et al., 1983). Although the concentration at which I_K is inhibited is 10-fold higher than that which is required to block I_{Na}, concentrations below that required to block VGSC appear to have effects on a multitude of G-protein-linked receptors, decreasing their function through uncoupling of G-proteins from the receptor (Xiong et al., 1999). This effect has been shown to occur with TRH receptors as well as α-adrenergic receptors and effects can also be seen on mast cell release of histamine at concentrations as low as 40 μM.

Lidocaine administered systemically has a number of other noteworthy effects due to its ability to block nerve conduction as well as a number of receptor-driven responses in various end-organs. While therapeutic doses of lidocaine are used for the treatment of cardiac arrhythmia due to its ability to depress diastolic depolarization and ventricular automaticity (especially in diseased or ischemic tissue) effective serum levels are usually ~ 1-5 μg/mL; higher doses can produce asystole due to blocked cardiac conduction as well as blockade of L-type Ca^{2+} channels in the myocardium. Hypotensive episodes have been noted with intravenous administration of lidocaine; this appears to be caused primarily by block of sympathetic nerves controlling vascular tone. Epinephrine inclusion reduces this effect when lidocaine is given through topical, subcutaneous or intramuscular routes. The majority of secondary effects which are associated with lidocaine administration and are adverse occur due to CNS neurotoxicity. These include drowsiness, confusion, anxiety, tinnitus, dizziness, blurred vision and tremors at lower doses and at higher doses can include potentially fatal seizures.

3.2.4 Safety pharmacology

The Sponsor did not conduct any safety pharmacology studies for this NDA nor were any required due to the extensive human experience with lidocaine, epinephrine and these drugs used in combination. Generally, lidocaine toxicity is an extension of its pharmacologic effect, and though this is primarily due to excessive blockade of synaptic transmission through VGSC block, the many voltage- and ligand-gated receptors with which lidocaine may interact may result in unexpected toxicities. Typical therapeutic concentrations of lidocaine administered intravenously for the control of arrhythmias are associated with serum levels between 1 – 5 μg/mL (Micromedex Online, 2004). Significant toxicities may be observed when levels greater than this are achieved or at therapeutic levels when patients have conditions which reduce the production or retention of α-1-acid glycoprotein. The greatest potential safety pharmacology concerns for lidocaine are the CNS and cardiovascular systems.

Neurological effects:

Lidocaine, like other local anesthetics absorbed centrally in sufficient concentrations, may produce CNS stimulation appearing first as restlessness and tremors that may develop into clonic convulsions. This is thought to occur due to a greater sensitivity of inhibitory neurons to lower concentrations of local anesthetic activity. Higher concentrations of anesthetics will depress all neuronal types and functions and a patient may progress from CNS excitation to depression with the possibility of death caused by respiratory failure due to actions in the brainstem controlling respiratory centers and motoneurons involved in airway support. Administration of lidocaine through intraspinal routes (intrathecal, epidural, subarachnoid) not surprisingly has a greater likelihood of producing CNS neurotoxicity and has been associated with cauda equina syndrome and transient neurological syndromes (TNS).

Cardiovascular effects:

As stated before, lidocaine can be used as a treatment for ventricular tachycardia due to its ability to block Na^+ channels, in both open and inactive states. Therapeutic drug concentrations for arrhythmias are typically 1.5 – 6 μg/mL. Adverse effects on the cardiovascular system are usually only seen with systemic concentrations at which CNS effects are also obvious. Local anesthetics such as lidocaine can cause general myocardial depressant actions such as decreased contractile force and rate as well as slowing of the electrical excitability of the myocardium. Cardiac arrhythmias may occur if concentrations rise to ~ 10 μM (5 μg/mL) for either lidocaine or epinephrine. Lidocaine also has been observed to dilate arterioles which can result in a reduction in blood pressure. Occasionally low concentrations of systemically absorbed local anesthetics have been reported to produce severe myocardial depression and cardiovascular collapse. It has been suggested lidocaine may interfere with the cardiac pacemaker resulting in ventricular fibrillation though this would be expected to be uncommon as pacemaker cells in the heart are generally slightly depolarized such that Na^+ channels are in an inactive state and Ca^{2+} is the ion causing the initial depolarization resulting in the generation of the atrial contraction and the resulting heartbeat.

Epinephrine has a multitude of stimulatory effects on the cardiovascular system due to actions on alpha and beta-adrenergic receptors on coronary arteries, pacemaker cells, conducting pathways and myocardial cells involved in the generation of contractile force. This would only be a concern with accidental intravascular administration of the present lidocaine/epinephrine combination drug product but it remains a potential source of cardiotoxicity. The iontophoretic method of administration of this drug combination greatly reduces any concern over potential systemic exposure to and toxicity resulting from the epinephrine contained in the drug product.

Pulmonary effects:
The safety concerns relating to pulmonary effects of local anesthetics are relatively minor in non-allergic individuals. Lidocaine at low doses may cause smooth muscle contraction but instead local anesthetics typically produce a vascular and bronchiolar smooth muscle relaxation.

Epinephrine effects on the pulmonary system are primarily a relaxation of the bronchiolar smooth muscle through interaction with β2 receptors.

Renal effects:
Although rare, urethritis has been associated with the topical administration of lidocaine. The local tissue reactions include burning, tenderness, swelling, tissue irritation and in some patients sloughing and tissue necrosis have been reported.

Gastrointestinal effects:
Lidocaine administration is not associated with adverse gastrointestinal effects although *in vitro* systems have detected an inhibitory potential for lidocaine on GI musculature. Epinephrine causes smooth muscle relaxation in the gut due to interaction with α and β adrenergic receptors with consequent reduction in GI motility.

Abuse liability:
There is no evidence with the extensive clinical experience with these compounds that either lidocaine or epinephrine is an abusable compound. *In vitro* as well as *in vivo* animal studies support the absence of abuse potential for either of these drugs.

Other: **Hypersensitivity:** Local anesthetics can rarely cause a hypersensitivity reaction manifested as allergic dermatitis or an asthma attack. This is almost exclusively linked to anesthetics containing an ester linkage. As lidocaine contains an amide linkage, hypersensitivity and allergic reactions are rare, although have been reported. These reactions may be characterized by cutaneous lesions, urticaria, bronchospasm, edema, shock or anaphylaxis depending on the route of exposure.

3.2.5 Pharmacodynamic drug interactions

Concomitant use of epinephrine-containing products with monoamine oxidase inhibitors or tricyclic antidepressants has been associated with the production of severe or prolonged hypertension. Phenothiazines and butyrophenones have been demonstrated to reverse the pressor effect of epinephrine or short its duration of action.

3.3 PHARMACOKINETICS/TOXICOKINETICS

3.3.1 Brief summary

Lidopel™ contains lidocaine HCl 2% and epinephrine at 1:100,000. This solution is loaded into the Dupel® Buffered Iontophoresis Electrodes and connected to the Dupel® Iontophoretic System for transdermal delivery at a rate which is proportional to the current intensity and duration applied. Absorption of the reference listed drug Iontocaine with identical charge and duration demonstrated a lack of systemic absorption (i.e. below the limit of detection). Distribution of lidocaine is extensive when given systemically though this is reduced and slowed greatly when given by transdermal route. The inclusion of epinephrine 1:100,000 promotes vasoconstriction of the local vasculature which helps maintain the local lidocaine concentration, both potentiating the anesthetic effect and reducing the degree of systemic absorption. Protein binding occurs with systemic absorption of lidocaine though as stated previously, the level of lidocaine circulating in the blood is likely below detection limits of 0.1 μg/mL. Metabolism of lidocaine occurs predominantly by liver cytochrome P450 isozymes (DrugDex Online, 2004) and occurs through hydrolysis of the amide linkage and deethylation (Elvin et al., 1981, Zito & Reid 1981). Metabolites of lidocaine are active and show similar pharmacology to lidocaine; one metabolite, 2,6-xylidine, has been determined to be a rat carcinogen but has been dismissed as a high risk carcinogen in humans by an FDA advisory panel (Anesthetic and Life Support Drugs Advisory Committee; August 23, 1993) and the Executive Carcinogenicity Assessment Committee (Exec CAC). Although ~ 90% of lidocaine is metabolized by the liver, approximately 10% is excreted unchanged by the kidneys.

Epinephrine is subject to rapid reuptake into noradrenergic neurons where it is catabolized by COMT and MAO into inactive metabolites. Circulating epinephrine is metabolized by these enzymes which are also present in the liver.

Elimination of lidocaine and epinephrine proceeds through the renal mechanisms, both overwhelmingly eliminated as metabolites. Lidocaine can be excreted into breast milk but is considered reasonably safe for breast feeding due to the negligible plasma levels and short duration of exposure for the current indication.

3.3.3 Absorption

Absorption of lidocaine through the transdermal route of administration is related to surface area exposed to lidocaine and the duration of exposure when applied as a cream or non-iontophoretic patch. Topical absorption has been described as poor (Micromedex's DRUGDEX® Online, 2004). Absorption through the skin occurs with

the compound in an uncharged (unprotonated) state though activity requires the protonated and thus charged form. Absorption of lidocaine and epinephrine by transdermal iontophoretic application is directly proportional to charge applied (i.e. current) and duration of current. Empi references two studies conducted by Iomed under NDA 20-530 for Iontocaine® in which in one study (BT-93-07) lidocaine HCl 2%/epinephrine 1:100,000 was delivered iontophoretically using their Phoressor system to hairless mouse skin and in the other study (BT-93-09) delivered through mouse skin or human cadaver skin using a range of iontophoretic doses (20, 40, 60 and 80 mA•min). Mouse skin showed similar results in both studies with iontophoresis efficiencies (amount of drug delivered/theoretical amount of drug delivered with applied current charge and duration x 100) between 3.5 – 4.9% and efficiency of delivery through human cadaver skin being nearly twice as efficient, ~ 7%. Iontophoresis efficiencies were not altered over the range of iontophoretic driving forces tested. Note that iontophoretic efficiency is not the same as the % drug utilization which is the amount of drug delivered as a percentage of the total drug added to the electrode.

Nonclinical studies conducted by Empi (#97-03.0) utilizing iontophoretic application of Lidopel® at 80 mA•min to the skin of rabbits in a dermal irritation study detected little to no systemic absorption of lidocaine, in most cases being below the level of quantitation (LOQ = ⁓ μg/mL) but occasionally rising slightly above the lower limits of quantitation (maximum ≤ ⁓ μg/mL) in rabbit serum. See study in Special Toxicology section of this report for details of this study.

3.3.4 Distribution

The distribution of lidocaine is extensive when absorbed systemically. Tissues receiving the highest concentrations of drug are the kidney, lungs, liver and heart while skeletal muscle and fat also take up drug. Passive diffusion of lidocaine occurs through both the blood-brain-barrier and placental barrier and thus, lidocaine has been detected in both CSF and fetal tissue. Protein binding is reportedly 33 – 80% (DrugDex Online, 2004), primarily to α-1-acid glycoprotein, thus protein binding is altered in patients with pathologic and nonpathologic conditions which affect the production of α-1-acid glycoprotein. Conditions known to increase α-1-acid glycoprotein synthesis include such diverse disease states as acute illness, infection, various cancer types, and cardiovascular disease such as MI, CNS disorders such as epilepsy, uremic patients and those who have undergone renal transplantation. Synthesis of α-1-acid glycoprotein is decreased and volume of distribution may therefore be affected in individuals with decreased levels as occurs with hepatitis, cirrhosis, hyperthyroidism, nephrotic syndrome, malnutrition and cachexia as well as other conditions (Israili and Dayton, 2001). The volume of distribution in humans is generally 1 – 1.7 L/kg with the lower V_d seen primarily with patients in heart failure. Lidocaine has also been demonstrated to bind to melanin which can prolong the elimination half-life in individuals with pigmented skin.

3.3.5 Metabolism

Lidocaine is highly metabolized by the liver and the rate of metabolism with systemic exposure is dependent primarily on hepatic blood flow, though other sites of metabolism such as intestines, lungs and kidney may play a minor role. The liver cytochrome P450

isoenzymes 3A4 and 1A2 appear to be the principal enzymes involved in lidocaine metabolism. Aromatic hydroxylation, N-dealkylation and amide hydrolysis followed by conjugation reactions are the main metabolic pathways followed. The primary metabolites of lidocaine are monoethylglycinexylidide (MEGX) and glycinexylidide (GX) both of which are active and show similar pharmacology and toxicology, though less potency, than the parent compound. MEGX is further metabolized into N-ethylglycine and xylidine. The major excreted human metabolite is 4-hydroxy – 2, 6-dimethylaniline, representing approximately 75% of the detected metabolites in urine. A minor metabolite in humans, 2, 6-xylidine, has been shown to be carcinogenic in the rat but is not considered to present a high risk in the human. Lidocaine metabolism within the skin has not been demonstrated.

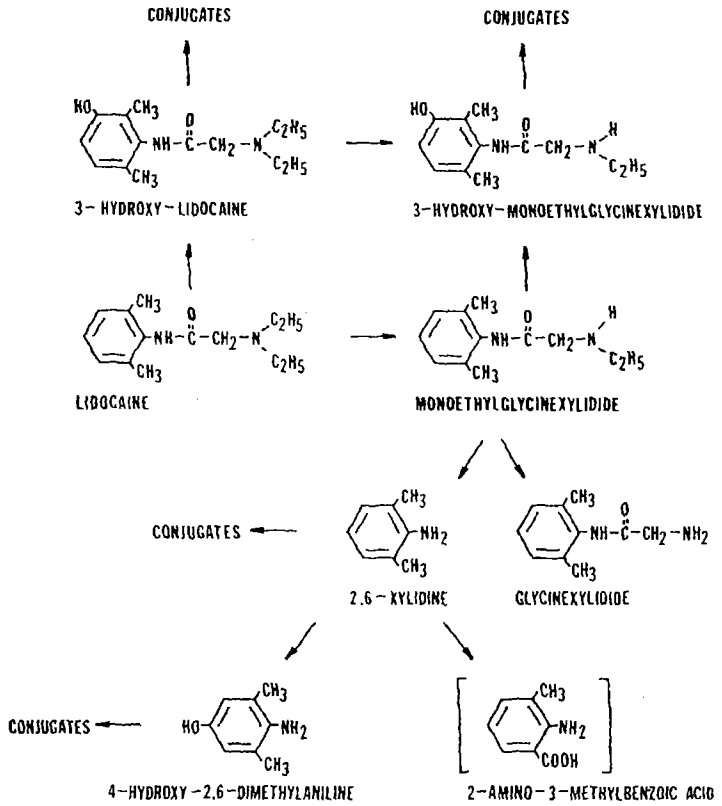


FIG. 1. Chemical structures of lidocaine and its major metabolites. The arrows indicate the probable pathways of lidocaine metabolism in rats, guinea pigs, dogs and man. Absolute identification of 2-amino-3-methylbenzoic acid (*in brackets*) was not possible.

Epinephrine when present in systemic circulation is taken up by adrenergic neurons as well as liver and other tissues with subsequent degradation by COMT and MAO to 3-Methoxy-4-hydroxymandelic acid (VMA).

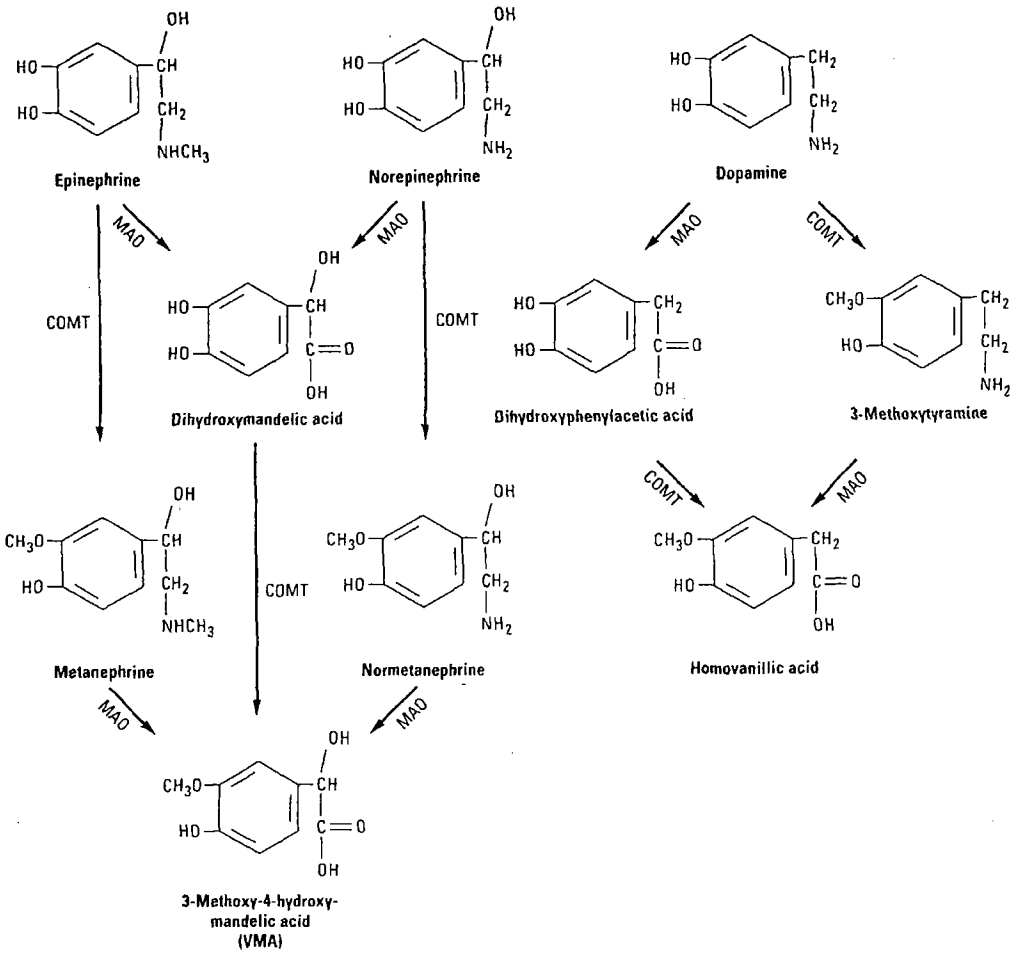


Figure 6–6. Metabolism of catecholamines by catechol-*O*-methyltransferase *(COMT)* and monoamine oxidase *(MAO)*. (Modified and reproduced, with permission, from Greenspan FS, Strewler GJ: *Basic and Clinical Endocrinology*. 5th ed. Appleton & Lange, 1996.)

3.3.6 Excretion

Lidocaine is eliminated through renal mechanisms primarily as metabolites (90%) with only ~ 10% unchanged drug detectable in the urine. Elimination half-life of lidocaine is generally 1.5 – 2 hours (Thomson et al., 1973, Rowland et al., 1971). Acidic urine conditions can increase the excretion rates of lidocaine, thus elimination is partly affected by urinary pH. Lidocaine is excreted in breast milk (milk:plasma ratio 0.4) but is considered safe for breastfeeding by the American Association of Pediatricians.

Metabolites of epinephrine are excreted in the urine primarily as glucuronide or sulfonated ether conjugates.

3.3.7 Pharmacokinetic drug interactions

The sponsor did not provide drug interaction information though this information for lidocaine and epinephrine is well known and available in the public literature. Lidocaine

is affected by drugs that alter CYP3A4 metabolism (ex: atazanavir, amprenavir, cimetidine, phenytoin, tobacco), displace lidocaine from protein binding sites (ex: bupivacaine), alter local blood flow (epinephrine, clonidine) or hepatic blood flow (ex: propranolol).

The interaction between epinephrine and lidocaine is through vasoconstriction and reduction in lidocaine local clearance and systemic exposure with consequent increase in lidocaine efficacy and duration of action. The ratio of epinephrine (1:100,000) included with lidocaine HCl in this product is consistent with that of numerous other products and is not expected to have any additional effects.

3.3.10 Tables and figures to include comparative TK summary

N/A

3.4 TOXICOLOGY

3.4.1 Overall toxicology summary

General toxicology:
The general toxicology of lidocaine and epinephrine are well known and are extensions of their pharmacologic effects. Systemic exposure to lidocaine at concentrations above the therapeutic window of approximately 1-5 μg/mL, can produce cardiotoxic effects such as arrhythmias and myocardial depression as well as CNS toxicity consisting of restlessness and tremor which can progress to seizures. Higher doses of intravenous lidocaine will produce a general CNS depression which can cause death due to depression of medullary respiratory centers and motorneurons controlling airway support.

Epinephrine toxicity consists mainly of alterations in cardiac function manifesting as the development of excessive chronotropic and inotropic stimulation with the potential for subendocardial necrosis and life-threatening ventricular arrhythmias. Other toxicities noted with epinephrine are the potential for degenerative changes in the retina, the production of lens defects and corneal opacity as well as increases in intraocular pressure. Administration of epinephrine to sensitive sites with poor collateral blood supply can result in tissue necrosis due to excessive vasoconstriction.

Genetic toxicology:
No genetic toxicology studies were submitted in support of this NDA, however lidocaine has been evaluated in a bacterial reverse mutation assays (Ames assay), an *in vitro* chromosomal aberration study and an *in vivo* mouse micronucleus assay. These assays determine the potential for the compound, in this case lidocaine, to cause point mutations, chromosomal damage or structural rearrangements and were reportedly negative.

Carcinogenicity:
The sponsor was not required to conduct carcinogenicity assessments for lidocaine or epinephrine as according to ICH M3 guidance; only products to be used continuously for >6 months require carcinogenicity studies be conducted.

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 though evaluation of this risk by the Anesthetics and Life Support Drugs Advisory Committee determined that in consideration of the differences in metabolism between rat and human as well as the typical use of these products (i.e. acute use) that this compound presents a low carcinogenic risk for human use.

Reproductive toxicology:
The sponsor did not conduct any reproductive toxicology studies in support of their NDA application but instead provided an assessment of the potential reproductive effects of the drug product through a review of the available published literature as well as a summary of studies conducted in support of marketed lidocaine products. Lidocaine has been reported to have little effect on female rat fertility and early embryonic development as reported in a published study (Fujinaga & Mazze, 1986) in which lidocaine was administered by osmotic pump for two weeks prior to mating and during pregnancy and showed little evidence of maternal toxicity or fetal effects below 250 mg/kg/day though 500 mg/kg/day given during gestation days 3-17 produced a slight reduction in rat fetal weight that was attributed to a slight delay in development. Male fertility has not been assessed in any published study but would require lidocaine exposure in males during the 4 week period prior to mating according to current guidelines. Potential teratogenic effects of lidocaine administration have been reported in the study described previously of Fujinaga and Mazze (1986). Examination of fetuses on Day 21 after removal by cesarean section demonstrated no external, visceral or skeletal abnormalities in any of the fetuses of the lidocaine-treated dams other than a slight and non-significant increase in incomplete ossification of the sternebrae at the 500 mg/kg/day dose group. The sponsor submitted the labeling claims of other lidocaine containing products which have completed Segment II reproductive toxicology studies and not documented any teratogenic effects of lidocaine. Postnatal developmental studies in the literature have conflicting view on the potential for lidocaine to produce alterations in behavior or development in the juvenile rat with reports suggestive of no effects while other reports describe alterations in nociception, task learning and visual discrimination. Strain differences, timing of drug administration and/or the inclusion of epinephrine in the tested article may contribute to the different findings though this is not entirely clear.

Special toxicology:
A local tolerance study consisting of a 14-day primary dermal irritation assay (study #97-3.0) was conducted by the sponsor to evaluate the potential for dermatologic toxicity of the drug product as delivered by the iontophoretic delivery system indicated. Administration of Lidopel™ using the Dupel® Iontophoretic System at a delivery rate (80 mA•min with one version of the Dupel® Iontophoretic Electrodes was associated with little observable dermal irritation with the first several days of exposure. Mild irritation

consisting primarily of erythema was observed beginning on days 3-5 depending on the animal. Dermal irritation was scored as being mild to moderate throughout the remainder of the study days without a notable increase in severity beyond that observed in the first week. Recovery animals demonstrated that recovery was related to the severity of the dermal irritation, in some cases recovering within a day after cessation of dosing but generally within 3-7 days. All animals demonstrated complete recovery within 9 days after cessation of drug administration. No other overt toxicities were observed and toxicokinetic analysis demonstrated that systemic exposure to lidocaine was detected in a minority of samples taken almost exclusively from the earliest time-point assessed (10 min) and was maximally only slightly above the lower limits of quantitation of — µg/mL (maximum = — µg/mL) indicating that significant exposure to systemic lidocaine did not occur with this method of administration.

3.4.2 Single-dose toxicity

The sponsor did not conduct any single-dose toxicity studies to support this NDA nor were any required.

Review of the Registry of Toxic Effects of Chemical Substances (RTECS) database revealed the following information relating to acute toxicity of lidocaine through various routes and in several species.

TDLo/TCLo – Lowest Published Toxic Dose or Concentration			
Species	**Route**	**Dose**	**Effects observed**
Rat	i.p.	2 mg/kg	*Blood* – other changes
	i.v.	5 mg/kg	*Vascular* – BP lowering not characterized
Mouse	s.c.	50 mg/kg	*Peripheral Nerve and Sensation* – Local anesthetic
Rabbit	intradermal	0.024 mg/kg	
	i.t.	5 mg/kg	*Peripheral Nerve and Sensation* – Local anesthetic
Dog	i.v.	2 mg/kg	*Cardiac* – change in rate
	i.v.	5 mg/kg	*Vascular* – Measurement of regional blood flow
LDLo/LClo – Lowest Published Lethal Dose or Concentration			
Rabbit	i.v.	41 mg/kg	
Guinea pig	i.v.	65 mg/kg	

LD50/LC50 – Dose or Concentration Producing 50% Lethality			
Species	**Route**	**Dose**	**HED* (mg per 60 kg individual)**
Rat	i.v.	18 mg/kg	174
	i.p.	133 mg/kg	1,287
	p.o.	317 mg/kg	3,068
	s.c.	335 mg/kg	3,242
Mouse	i.v.	20 mg/kg	98
	i.p.	102 mg/kg	498
	p.o.	220 mg/kg	1,073
	s.c.	238 mg/kg	1,161

Guinea pig	s.c.	120 mg/kg	1,565

* HED = Human Equivalent Dose (based on body surface area conversion)

3.4.3 Repeat-dose toxicity

The sponsor did not conduct any repeat-dose toxicity studies to support this NDA nor were any required.

3.4.4. Genetic toxicology

The sponsor did not conduct any genetic toxicology studies to support this NDA nor were any required through prior agreement with the Agency. Mutagenicity risk assessment for lidocaine, epinephrine and lidocaine/epinephrine products was supplied by reference to Iomed Iontocaine® NDA 20-530 as well as the available published literature in the public domain.

Iomed Inc. cited three genetic toxicology studies in support of approval for Iontocaine® in which 2% lidocaine/1:100,000 epinephrine was tested in the following assays:

1. Bacterial Mutation Assay (Ames assay) with *Salmonella* and *E. coli* Reverse Mutation in the Presence and Absence of S9
2. Chromosomal aberration assay in human lymphocytes
3. *In vivo* mouse micronucleus assay

All assays were judged to be valid and negative for mutagenicity.

Additional data from other approved and marked lidocaine products were provided by the sponsor and are reproduced in the table below (Note: Lidoderm® Patch is under patent protection, therefore the information provided below for this product by the sponsor is informative but is not relied upon for support of NDA 21-486 approval.):

Product	Contents	Tests Conducted	Results	Reference
Lidoderm® Patch	5% Lidocaine HCl	1) Ames assay 2) Chromosomal aberration w/human lymphocytes 3) *In vivo* mouse micronucleus assay	Negative for all 3 assays	Lidoderm® Package Insert 1999
EMLA® Anesthetic Topical Adhesive System (Disc and Cream)	2.5% Lidocaine/ 2.5% Prilocaine	1) Ames assay 2) Chromosomal aberration w/human lymphocytes 3) *In vivo* mouse micronucleus assay	Negative for all 3 assays	EMLA® Package Insert 1998
ELA-Max® Topical Cream and	4% Lidocaine	1) Ames assay 2) Chromosomal aberration assay w/human	Negative in all assays	ELA-Max® Topical Cream and ELA-Max®5 Anorectal Cream

ELA-Max®5 Anorectal Cream	5% Lidocaine	lymphocytes 3)*In vivo* mouse micronucleus assay		Package Inserts 2000

No marketed products with the combination lidocaine/epinephrine were listed as having genetic toxicology studies conducted in support of their approval. Literature references containing studies in which epinephrine or lidocaine were assessed for mutagenic potential include the following three provided studies (table reproduced from sponsor):

Compound	Dose Tested	Tests Conducted	Results	Citation
Epinephrine	100 – 10,000 µg/plate	Ames assay	Negative	Zeiger et al., 1987
Epinephrine	0.05 – 500 µg/plate	1) Ames Assay 2) *In vitro* mouse micronucleus assay 3) Sperm abnormality assay	Negative in all 3 studies	Bruce and Heddle, 1979
Lidocaine	8,000 µg/plate	Ames assay	Negative	Waskell, 1978

Additional mutagenicity information on the lidocaine metabolite 2,6-xylidine was provided by the sponsor. This metabolite has been examined by the Agency during the review of both EMLA® Cream and Iomed Iontocaine®. The National Toxicology Program completed a series of genetic toxicology studies and carcinogenicity study in Charles River CD Rats (NTP Technical Report Series No. 278) 2,6-xylidine has been found to be mutagenic in the Ames assay with metabolic activation, mutagenic in forward mutation assays such as the Mouse Lymphoma assay (thymidine kinase locus) both with and without metabolic activation, and has been associated with chromosomal aberrations and sister chromatid exchanges. The sponsor notes that these effects occurred at concentrations high enough to cause precipitate to form (1.2 mg/mL). All *in vivo* assays of mutagenicity with 2,6-xylidine have been reportedly negative including in UDS in rat hepatocytes, *in vivo* mouse micronucleus assays and studies of preferential killing of DNA repair-deficient bacteria in liver, lung, kidney, testes and blood extracts of mice. The sponsor notes that the positive *in vitro* mutagenicity results with the metabolite are at a concentration which is not theoretically or practicably obtainable following iontophoretic administration of lidocaine. Studies by Ashburn and colleagues (1997) were unable to detect lidocaine in the plasma of human subjects after iontophoresis of 2% lidocaine HCl/1:100,000 epinephrine (using the Iomed Iontocaine® drug product with Phoressor Iontophoretic Device) at a delivery current of 40 mA•min and with sensitivity reported as 0.1 µg/mL. EMPI submitted a study in 9 subjects by [redacted] (Study 96-08.0) in which the highest level of systemic lidocaine detected using the Lidopel™ drug product with the Dupel® Iontophoretic System and a delivery current of 80 mA•min was [redacted] µg/mL while the majority (6 of 9) had undetectable plasma levels of lidocaine. The sponsor notes that the Iomed Iontocaine® NDA suggested the theoretical limit of lidocaine available systemically after iontophoretic administration at the currents/duration

used (40 mA•min) was 0.008 μg/mL. Thus, the sponsor argues that the potential exposure to systemic lidocaine is 150,000 – 600,000-fold below the level of 2,6-xylidine associated with a positive mutagenic response.

3.4.5. Carcinogenicity

The sponsor did not conduct any carcinogenicity studies to support this NDA nor were any required as communicated to the sponsor in Agency Advice Letter dated 3/10/00.

3.4.6. Reproductive and developmental toxicology

The sponsor did not conduct reproductive and developmental toxicology studies on lidocaine or epinephrine (as agreed to in Pre-IND meeting of 5/21/97 and confirmed in Advice letter from the Agency dated 3/10/00) instead relying on:

1) The demonstration 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.

The following sections are summaries and evaluations of the sponsor's assessment.

Currently, approximately 100 products are marketed containing lidocaine, of which 27 contain the combination of lidocaine HCl and epinephrine and 10 have the same concentrations (2% Lidocaine HCl and epinephrine 10 μg/mL) of these drugs within the drug product (FDA Orange Book, 2004). The sponsor notes that the majorities of these products were approved under ANDA guidelines and therefore were exempt from providing reproductive toxicology studies in their applications for approval. The elimination of this requirement appears to be due to both the widespread availability of information on the reproductive and developmental effects of lidocaine and epinephrine as well as human clinical experience with these products.

Effects on fertility and early embryonic development

Published studies supporting the safety of lidocaine in regards to reproductive fertility (i.e. Segment I studies) include data from Fujinaga and Mazze (1986) in which lidocaine was infused via osmotic mini-pump in female rats in doses of 100 or 250 mg/kg/day for two weeks prior to mating and then continuing through pregnancy. No evidence of maternal toxicity was observed during the study and no differences from control were observed in the following parameters: copulatory rate, pregnancy rate, number of corpora lutea, implantations or indices of fetal wastage. A separate group of female rats treated with a higher dose of lidocaine (500 mg/kg/day) for gestation days 3-17 demonstrated fetuses with reduced weight at Day 21 compared with controls, a finding which was revealed as an effect of marginally delayed development (lidocaine 500 mg/kg/day pups delivered spontaneously an average of 7.2 hr later than control pups).

There are no reports from the literature that were cited by the sponsor nor found by this reviewer which assessed male fertility after repeated lidocaine exposure.

Effects on embryo-fetal development

The sponsor's teratogenicity assessment relies in part on the approval of Iomed Iontocaine® NDA 20-530. This NDA contained reproductive toxicity data supportive of approval that was derived from a Segment II teratogenicity study conducted in support of ELA-Max® topical cream and ELA-Max® anorectal cream in which the administration of lidocaine/epinephrine in the same concentration as found in Lidopel® in rats at doses up to 6.6-fold the human dose found "no harm" to the fetus. Other lidocaine/epinephrine products currently marketed with embryo-fetal reproductive toxicity studies described in their package inserts include the following (from sponsor's table):

Reproductive Toxicity Studies			
Product Name	**Company**	**Doses Studied**	**Results**
EMLA® Cream and Anesthetic Disk (lidocaine 2.5%/prilocaine 2.5%)	AstraZenica LP	Cited 30 mg/kg s.c. lidocaine studies; 40 mg/kg s.c. lidocaine/prilocaine study conducted	No teratogenic, embryotoxic or fetotoxic effects (Package insert 2000)
Lidoderm® Patch (lidocaine 5%)	Endo Laboratories	Cite 30 mg/kg s.c. (lidocaine); patch not studied	No observable harm to fetus (Package insert 1999)
Xylocaine w/Epinephrine Injection (lidocaine 2%/epinephrine 1:100,000)	AstraZenica LP	Cite 6.6-fold human dose exposure in rat studies	No harm to the rat fetus observed (Package insert 2000; PDR 54th ed.)

Preclinical studies with data supporting the lack of teratogenicity of lidocaine in include the study by Fujinaga and Mazze (1986) conducted in rats previously described in which female rats received implantable osmotic mini-pumps which delivered 100 or 250 mg/kg/day for two weeks prior to mating and continuing throughout pregnancy or 500 mg/kg/day for gestation days 3-17. Examination of fetuses on Day 21 after removal by cesarean section demonstrated no external, visceral or skeletal abnormalities in any lidocaine group other than evidence of incomplete ossification of the sternebrae in the 500 mg/kg/day group. This finding, though elevated, was not statistically significant compared with controls. Assessment of lidocaine levels in the fetal plasma relative to maternal plasma indicated comparable levels of exposure. Ramazzotto and colleagues (1985) assessed potential teratogenicity of lidocaine hydrochloride administered as 56 mg/kg/day intraperitoneally to female rats for three days during different gestational periods (Days 5-7, 9-11, 12-14, or 15-17). No animals received this dose of lidocaine for the gestational period recommended by current Segment II guidelines. Fetuses were removed by caesarean section on Day 21 and assessed for gross morphologic abnormalities, histologic alterations in selected organs (liver, spleen, heart and lungs) and enzymological (succinic dehydrogenase activity in liver). No differences between exposed fetuses and controls were observed for any parameter of the study.

Effects on pre- and post-natal development

Though published studies provided by the sponsor do not meet the current regulatory requirements of Segment III reproductive toxicology studies, the sponsor cites several preclinical studies, all conducted in rats, in which lidocaine (Teiling et al., 1987, Mullenix and Moore, 1988) or the combination of lidocaine and epinephrine (Smith et al., 1986; Smith et al., 1989) have been administered to pregnant rats and resulting effects on pre- and post-natal behavior and development have been assessed.

Smith and colleagues (1986) administered a single dose of lidocaine 6 mg/kg with epinephrine 1:100,000, mepivacaine 6 mg/kg or saline i.m. to the masseter jaw of female Long-Evans rats on Day 11 of gestation. Maternal toxicity was not noted and the resulting offspring of this group was not different from control (saline-treated) on birth, growth and litter parameters. Resulting litters were culled to 3 animals/sex/group. Pups exposed to lidocaine evidenced poorer performance in a visual discrimination task compared with controls and were different from controls in a variety of learning and behavior assessments including slower performance on righting reflex, water maze acquisition, longer suppression times in a conditioned suppression task and had evidence of reduced nociception as measured by tail-flick but not footshock assays.

Teiling and colleagues (1987) administered 6 mg/kg i.m. to female rats over Days 10 and 11 of gestation and compared the resulting offspring to those of rats administered saline over the same days. No maternal toxicity was evident with this dose of lidocaine as mortality did not occur and clinical signs, body weight and food consumption were no different than dams given saline. Litters were culled to 4 animals/sex/group. Offspring of treated and control animals were assessed for spontaneous activity, learning ability, nociception and physical development. In contrast to the findings of Smith et al. (1986) no significant differences were observed between lidocaine-exposed and control offspring in any monitored test including a test in discrimination learning ability which was previously suggested as being sensitive to this treatment. The authors suggest that the smaller sample size in the study by Smith and colleagues may have contributed to the observed differences, presumably by being more sensitive to outliers within the culled litter. Other differences between the studies relate to the frequency of lidocaine administration (single vs. over two-days) and the presence of epinephrine in the former study as well as the strain used (Sprague-Dawley vs. Long-Evans hooded rats).

Smith and colleagues (1989) attempted to resolve the differences in findings between the two studies by performing a more comprehensive study in Long-Evans rats which would include several dose levels (3, 6 or 9 mg/kg in a single dose) of lidocaine 2%/epinephrine 1:100,000 covering the gestational period, as well as having sham and vehicle (epinephrine 1:100,000) dosed rats. Animals were dosed through injection into the gum within the oral cavity on gestational days 4, 11 or 18. Results obtained refuted their previous findings of alterations with GD11 dosing and both GD4 and GD11-treated offspring were no different from sham (uninjected) controls. Interestingly, epinephrine-treated vehicle controls appeared behaviorally different from uninjected controls with footshock sensitivity being enhanced in the vehicle-treated animals and barbiturate-induced sleep time being significantly reduced. Pups whose were exposed at GD18

demonstrated a number of altered behavioral findings (nociception, task learning and visual discrimination). Of some interest, these findings were not dose-dependent as higher dose groups in several cases failed to demonstrate the alterations observed in the lower dose groups. Alterations in footshock responsiveness and barbiturate-induced sleep time were also observed in GD18 epinephrine-exposed pups as well.

Using a protocol of s.c. administration of lidocaine 20 mg/kg/day for GD15-17, exposed offspring were compared with saline (i.e. vehicle)-exposed pups at 5 months of age on behavioral responses involving motor activity and exploratory behavior in a novel environment and were found to be not significantly different (Mullenix and Moore, 1988). These authors concluded that lidocaine exposure at this stage of development did not appear to be a behavioral teratogen.

3.4.7 Local tolerance

The following Dermal Irritation Study in Rabbits was required by of the sponsor as described in the Pre-IND meeting minutes of May 17, 1997. The report was originally reviewed by M. Anwar Goheer, Ph.D. I have re-reviewed the study to conform to Good Review Practice guidance but am in agreement with the conclusions made.

Study title: Dermal Irritation Study in Rabbits Administered Lidocaine by Iontophoresis Once Daily for Fourteen Days

Key study findings:

- Iontophoresis of 2% lidocaine/1:100,000 epinephrine (i.e. test article) at a dose of 80 mA•min for 14 consecutive days to rabbits resulted in mild to moderate dermal irritation, primarily consisting of erythema which occasionally was scored as being severe. Edema was notably less common and rated less severe in all instances.
- Recovery from dermal irritation appeared to be complete 7 days after cessation of iontophoretic drug administration though the most severe dermal irritation scores were found in the recovery group several days after cessation of dosing.
- Use of electrodes containing the test article but without a current applied did not result in dermal irritation.
- Histopathologic assessment of test article delivery electrode sites revealed evidence of inflammation, hypertrophy and necrosis of the epidermis and edema of the dermis in rabbits which correlated with in-life findings. Recovery animals lacked these findings with the exception of a single animal having evidence of edema of the dermal layer.
- Toxicokinetic analysis of rabbit serum obtained between 10 minutes and 6 hrs after dosing on Days 0, 6 and 13 indicated that in the vast majority of samples (~ 90%), lidocaine was not detectable (LLOQ = — µg/mL), though in 8 samples (~ 10%) obtained 10 min to 1 hr after iontophoretic administration of drug, lidocaine levels were detectable but in all cases were ≤ —. µg/mL.

Study no.: 97-3.0
Volume 8, Appendix 5-2

Conducting laboratory and location:

Date of study initiation: 8/18/1997
GLP compliance: Yes
QA report: yes (X) no ( )
Drug, lot #, and % purity: Lidocaine HCl 2%/Epinephrine 1:100,000, Lot # 7218, purity undefined but certificate of analysis indicates drug meets USP standards for quality.

Control article #1: Saline 0.9%; Lot #270113; Source Vedco (St Joseph, MO)

Control article #2: Epinephrine, sodium chloride, sodium bisulfite; Lot #7257; Purity undefined but certificate of analysis indicates drug meets USP standards for quality.

Methods

Doses: 80 mA•min (4 mA for 20 min) or 0 mA•min (0 mA for 20 min).
Species/strain: New Zealand White Rabbit (*Oryctolagus cuniculus*)
Number/sex/group or time point (main study): See tables below:

Group	Number of Animals	Electrode Set	Solution	Current (mA)	Duration (min/day)	Dose (mA•min)	Number of Days
Primary Dermal Irritation Study Design							
T1-A	6	A	Lidocaine with Epinephrine	4	20	80	14
		B	Saline				
T1-B	6	A	Lidocaine with Epinephrine	4	20	80	14 treatment days + 6 days recovery
		B	Saline				
T2	3	A	Lidocaine with Epinephrine	0	20	0	14
Study Design to Select Control for Adequate Blinding							
T3-A	1	A	Lidocaine with Epinephrine	4	20	80	1
		B	Saline				
T3-B	1	A	Saline with Epinephrine	4	20	80	1
		B	Saline				

T3-C	1	A	Lidocaine with Epinephrine	4	20	80	1
		B	Saline with Epinephrine				
* Electrode set "A" and "B" refer to placement of the electrodes to the left or right of the midline of the animal, respectively.							

Route, formulation, volume, and infusion rate: Iontophoretic transdermal administration of solutions in the dose and rate described in the table above.
Satellite groups used for toxicokinetics or recovery: 6 animals (3/sex) used for recovery (6 days). See table above.
Age: Approximately 3 months at time of initial test article administration.
Weight (nonrodents only): 2.0 – 2.5 kg at time of initial test article administration.
Unique study design or methodology (if any):

Test article administration: 24 hr prior to first treatment, fur was removed from the back of the animal by clipping (not shaving) and was maintained in this way throughout treatment as deemed necessary to allow for adequate electrode contact. Animals were sedated with acepromazine prior to and during the iontophoretic application of test or control articles. Electrode set "A" and "B" were positioned to the left and right (respectively) of the midline of the animal with the delivery electrode of the set being positioned as caudal as possible and the return electrode of the set being positioned approximately 4 inches rostral to the delivery electrode. Electrodes were connected to the Dupel® iontophoresis device for subsequent delivery of the test and control articles.

Electrode size: Not specified in study but from table in CMC section of NDA submission, the delivery electrode appears to be 8.1 cm^2 and the return electrode 45.2 cm^2 and correspond to the electrodes classified by premarket clearance as K970491 and K912015, respectively.

Establishment of appropriate controls: Per FDA request (see Drug History) control group (T3 A, B & C) animals were added for the purpose of determining whether saline or saline + epinephrine (1:100,000) would be the appropriate control for Phase II/III clinical studies.

Observations Methodology and Results

Mortality: No mortality observed.

Clinical signs: Observations taken prior to and immediately after iontophoresis and at 4 hr following iontophoresis (except on Day 4 when the 4 hr time-point was not taken). Animals in group T1-B were assessed once daily during the recovery phase.

Discoloration of feces which was observed to occur in several animals occasionally throughout the study was the only clinical observation reported and did not appear to be

treatment-related as discoloration was observed in one animal prior to onset of dosing and is a considered a frequent treatment-unrelated clinical observation in this species.

Body weights: Body weights were recorded upon receipt of the animal, prior to study initiation, on Days 6 and at termination on Day 13.

Small decreases in body weight were noted after the first week in T1-A and T2 animals while a slight increase in weight was seen in T1-B animals. By Day 13, all groups gained weight compared to Day 0 measurements but early effects on body weight were reflected in the slightly reduced, but not significantly different, terminal body weights of T1-A and T2 animals compared with T1-B animals. Effects on body weight would not be due to administration of test article as T2 (control) animals showed a similar body weight response as T1-A (test article) animals.

Body Weight (kg)					
Treatment Group	**Day 0**	**Day 6**	**Day 13**	**Recovery Period (Day 20)**	**% Change (Day 0 – Day 13)**
T1-A (Lido/Epi)	2.29 ± .08	2.28 ± .12	2.41 ± .11	N/A	+ 5%
T2 (Lido/Epi w/o current)	2.26 ± .15	2.23 ± .07	2.41 ± .05	N/A	+ 7%
T1-B Lido/Epi + recovery)	2.25 ± .14	2.31 ± .08	2.48 ± .10	2.74 ± .52	+ 10%

Food consumption: Food consumption was recorded daily for animals in Groups T1-A, T1-B, T2 and T3 using a scale of 0 (no food consumed) – 4 (all food consumed). Scale scoring corresponded to the following: 0 = 0% food consumed; 1 = 1 – 25% food consumed; 2 = 26 – 50% food consumed; 3 = 51 – 75% food consumed; 4 = 76 – 100% food consumed. Food consumption was not reported on a grams/day basis.

No effects on food consumption were observed in any group during the course of the study although occasional and isolated instances of decreased food intake were noted in individual animals. However, the relative lack of sensitivity in the scale used to report food consumption conceivably may have obscured subtle but significant changes in this parameter. The absence of reduced food consumption scores in T1-A and T2 animals relative to T1-B animals during the first 7 days of the study during which the former animals exhibited a slight reduction in weight while the latter animals gained weight during this period may reflect the insensitivity of this scale.

Ophthalmoscopy: Not done
EKG: Not done
Hematology: Not done

Clinical chemistry: Not done
Urinalysis: Not done
Gross pathology: Not done
Organ weights: Not done

Dermal Irritation:
Dermal irritation was evaluated and scored for T1-A, T1-B and T2 animals prior to the first exposure on Day 0 and immediately after each treatment, approximately 1 hr after dosing and at approximately 23 hr post treatment. With the exception of the three animals in group T1-B who were eventually replaced, all animals had skin samples obtained from all treatment sites for histopathologic analysis at the conclusion of the experiment.

Animals in treatment group T3 (used to select the appropriate control solution for future clinical studies) were observed visually following iontophoresis for blanching immediately after exposure and at 1 hr following administration of test vehicles.

The scale for scoring skin reactions is based on the "Draize" scale (Draze, 1959) in which scores for erythema and eschar, as well as edema are given a value of 0 – 4 depending on severity. Scores for erythema and eschar formation (E) for each animal in each group were scored at each interval, summed and divided by the number of animals in the group to arrive at an average score. Average scores were summed to arrive at a subtotal score for erythema and eschar formation. Scores for edema (D) formation were similarly determined to arrive at a subtotal score for this index. The two scores were added together to arrive at a total irritation score which was divided by the number of observation intervals to obtain the primary dermal irritation index (PDII) for that specific study day. The interpretation of the PDII was as described below:

Primary Dermal Irritation Index (PDII) Scale		
From	**To**	**Interpretation**
0.00		Non-irritant
0.04	0.99	Irritation barely perceptible
1.00	1.99	Slight irritation
2.00	2.99	Mild irritation
3.00	5.99	Moderate irritation
6.00	8.00	Severe irritation

Note: Dermal irritation scores were noted but not reported for Group T3 animals and were used for determining the appropriate vehicle controls for later clinical studies.

Table 1: Primary Dermal Irritation Index, Group T1-A (Treated animals)

Site	Study Day													
	0	1	2	3	4	5	6	7	8	9	10	11	12	13
1	0	0	0.06	0.06	0.28	0	0	0	0.11	0	0	0.06	0	0.06
2	0	0	0.17	0.06	0.11	0	0.44	0	0	0	0.06	0	0.06	0
3	0.06	0.45	0.11	0.44	1.73	3.11	1.94	2.44	3.05	2.72	2.50	2.55	2.94	2.45
4	0.61	0.22	0.17	0.72	0.78	1.11	1.22	0.67	0.72	0.61	0.78	0.94	0.55	0.22

Site 1 = Test article return electrode
Site 2 = Control article return electrode
Site 3 = Test article delivery electrode
Site 4 = Control article delivery electrode

Table 2: Primary Dermal Irritation Index (T1-B)

Treatment period:

Site	Study Day													
	0	1	2	3	4	5	6	7	8	9	10	11	12	13
1	0	0.11	0	0	0	0	0	0	0	0	0	0	0	0
2	0	0	0.06	0.06	0.11	0	0	0	0	0	0	0	0	0
3	0.22	0.67	0.61	2.34	3.16	3.22	3.67	3.11	3.06	3.89	3.50	3.61	3.61	4.11
4	0.06	0.11	0.11	0.17	0.84	1.39	1.33	0.67	0.39	0.50	1.00	1.06	0.89	0.61

Recovery period:

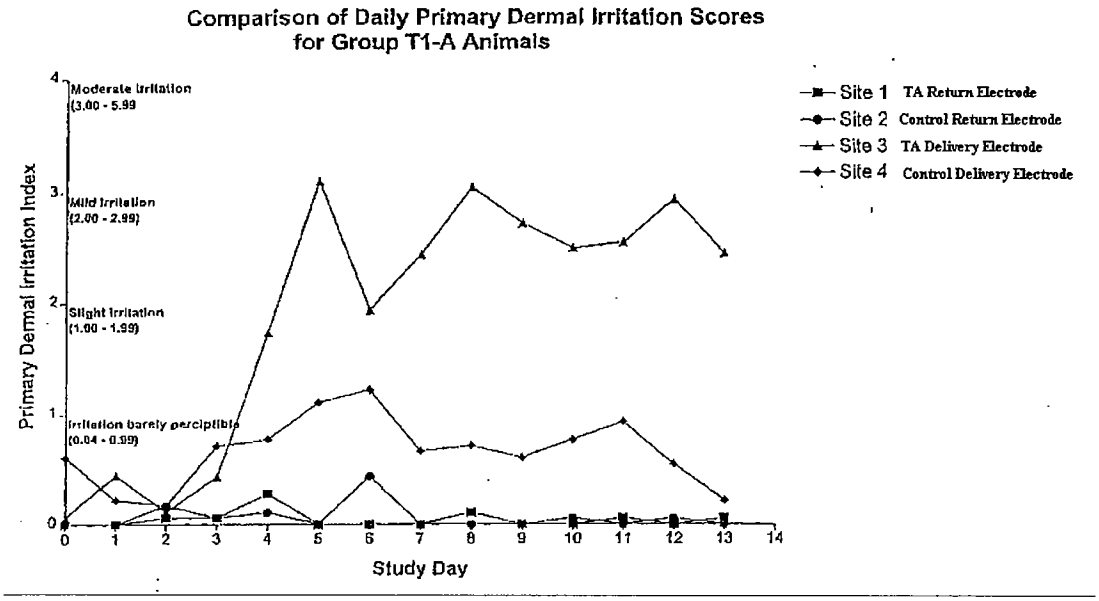
Site	Study Day					
	15	16	17	18	19	20
1	0	0	0	0	0	0
2	0	0	0	0	0	0
3	3.34	5.00	5.00	3.66	3.66	0
4	0	0	0	0	0	0

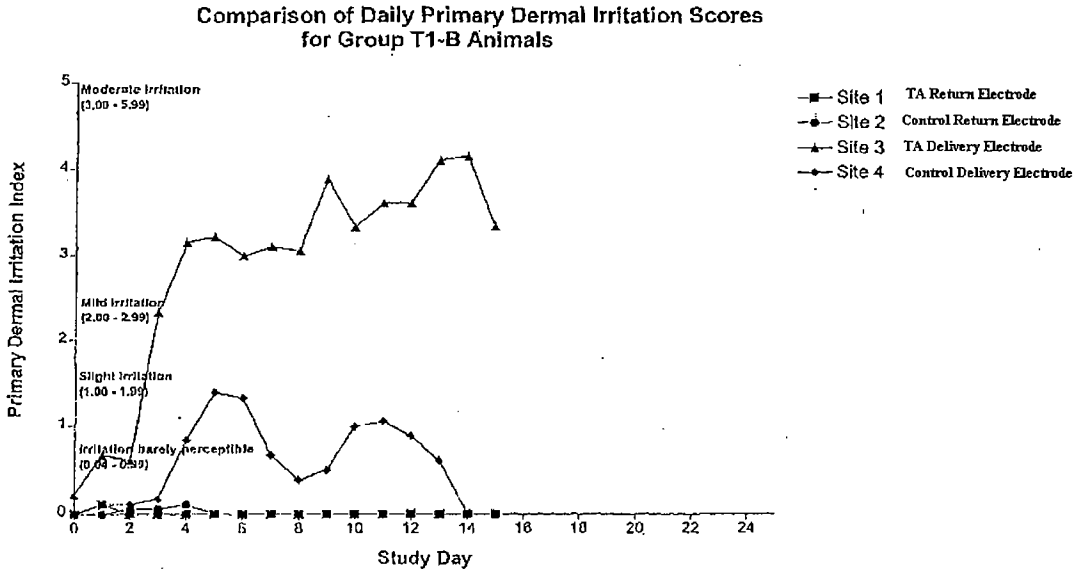
Site 1 = Test article return electrode
Site 2 = Control article return electrode
Site 3 = Test article delivery electrode
Site 4 = Control article delivery electrode

Table 3: Primary Dermal Irritation Index, Group T2 (Control animals, no current)

Site	Study Day													
	0	1	2	3	4	5	6	7	8	9	10	11	12	13
1	0	0	0	0	0	0	0	0	0	0	0	0	0	0
3	0	0	0	0	0	0	0	0	0	0	0	0	0	0

Site 1 = Test article return electrode
Site 2 = Control article return electrode
Site 3 = Test article delivery electrode
Site 4 = Control article delivery electrode





Barely perceptible irritation was observed associated with return electrodes in T1-A animals (PDII max = 0.44) within the first week of the study and were not apparent during the second week of observation. In contrast, dermal irritation was rated as being mild to moderate in severity in association with the lidocaine/epinephrine delivery electrode in both T1-A and T1-B groups (PDII max = 3.11 in T1-A, Day 5; 4.11 in T1-B, Day 13). The mild to moderate dermal irritation observed developed during the first 3 -5 days of the study and were maintained throughout the treatment period without evidence of tolerance or significant increase in response. Although overall dermal

irritation was considered to be moderate at maximal effect, tabular data (not shown) indicate that the principal component of this irritation was erythema which was rated as severe in 3/6 T1-A animals with milder evidence of edema reported. Similar though slightly higher PDII responses were observed in T1-B animals. As can be seen in the table provided for Group T1-B animals, however, the severity of dermal irritation appeared to be maximal on Days 16 and 17 (Day 3 and 4 of recovery; PDII = 5.00) but reportedly resolved by the final day of recovery (Day 20). An animal which was one of three replacement animals used in this group (three animals were replaced in this group after skin samples were not taken for histopathologic analysis) demonstrated moderate irritation through Day 21 with resolution on Day 22 was not included in the recovery data as the other two replacement animals were terminated on Day 15 due to a PDII score of 0 (i.e. no irritation). Therefore, recovery data scores are derived from a sample size of 3 original animals in this treatment group. The recovery data are not captured by the plot of PDII in T1-B animals provided by sponsor as this plot ends on Day 15 (Recovery Day 2).

T2 animals which received the lidocaine/epinephrine delivery electrode in the absence of a current (0 mA•min) did not demonstrate any evidence of dermal irritation at any time during the course of the study.

Histopathology: Adequate Battery: yes (X), no ( ) — Full histopathology of all tissues and organs was not conducted though all treatment sites from animals in group T1-A, T2 and treatment sites from 3 animals added to group T1-B as replacements were evaluated microscopically by an external veterinary pathologist ( ), as recommended by the Division after review of the study protocol (comments faxed to the sponsor on August 14, 1997). No other organs or tissues were evaluated microscopically.

Peer review: yes ( ), no (X)

Examination of T1-A animals revealed evidence of microscopic changes at site 3 (Test article delivery electrode) which varied between treated animals (see table below). Two animals (#805 and 806) had two findings each: hyperplasia and inflammation of the epidermis (#805) and inflammation and necrosis of the epidermis (#806). No evidence of dermal changes was observed at the return electrode sites (1 and 2) or at the site of delivery of control article (site 4) in any animal.

Dermal Findings: Incidence and severity*	**T1-A** Lido/Epi + current	**T2** Lido/Epi – current	**T1-B** Lido/Epi + current +recovery
Dermis			
Edema	1/6	0/3	1/6
Epidermis			
Hyperplasia	1/6	0/3	0/6
Inflammation	2/6	0/3	0/6
Necrosis	2/6	0/3	0/6
* All findings were judged to be minimal to mild in severity and correlated with ante-			

mortem observations.

All sites in T2 (control) group animals were considered within normal limits by microscopic evaluation. Evaluation of T1-B (recovery) animals indicated that dermal findings largely resolved after 7 days although mild edema of the dermis was noted in one animal at the conclusion of the recovery period.

Toxicokinetics: Blood (2 mL) was collected by jugular venipuncture of T1-A animals on Day 0 just prior to iontophoresis and at 10 minutes, 1, 2, 4 and 6 hr following iontophoresis. Blood collected on Days 6 and 13 collected similarly though the 4 hr time-point was not taken. Serum was sent for analysis to [redacted] for analysis of lidocaine concentrations using the [redacted] method.

84 samples were analyzed, of these only 8 had levels of lidocaine equal to or above the lower limit of quantitation (LLOQ) of [redacted] µg/mL. Maximal lidocaine concentration detected from the serum of any animal at any time-point was [redacted] µg/mL. Seven of the eight samples that were above the LLOQ were from 10 min post-iontophoresis collection time-points. The only other sample with detectible lidocaine levels in serum was from a 1 hr time-point from the animal with the highest systemic lidocaine exposure ([redacted] µg/mL at 10 min; [redacted] µg/mL at 1 hr).

3.4.8 Special toxicology studies

N/A

3.6 OVERALL CONCLUSIONS AND RECOMMENDATIONS

Conclusions:

The sponsor, Empi, Inc., is submitting a 505(b)(2) NDA for the drug product Lidopel™. Lidopel™ is a combination solution containing 2% lidocaine HCl/1:100,000 epinephrine to be topically administered for the production of local dermal analgesia using the Dupel® Iontophoresis System and Dupel® Iontophoresis Electrodes. The reference drug used to support this 505(b)(2) application is Iomed Iontocaine® (NDA# 20-530) which is an iontophoretically administered 2% lidocaine/1:100,000 epinephrine product and was approved in 1995.

Lidocaine and epinephrine have been used widely in clinical practice and the pharmacology of these compounds is well known. Several lidocaine/epinephrine-containing products are currently marketed for use as a topically applied local anesthetic. As described above, Iomed Iontocaine® is an identical drug combination differing only in the proprietary iontophoretic delivery system used. As such the principal safety concern for the present NDA was the potential for dermal irritation with this product. To address this issue, the sponsor conducted a 14-day dermal irritation study in the rabbit which included toxicokinetic measurements to determine potential systemic exposure to lidocaine and a recovery group. Results from this study revealed that the drug administered at a delivery dose (80 mA•min) [redacted]

—— , produced only slight dermal irritation during the first few days of the study and only after the 5th day of exposure did mild to moderate irritation develop. This irritation consisted principally of erythema which was generally scored as moderate but in several animals was rated as being severe. Edema was less pronounced in all cases. Full recovery was observed within 7 days after cessation of dosing. Lidocaine concentrations in rabbit plasma was barely above the limits of quantitation (LLOQ = — µg/mL) when detected in a minority of samples, all obtained at 10 min or 1 hr post drug administration and was maximally — µg/mL. This plasma concentration is roughly 10 to 50-fold below the therapeutic window for intravenously administered lidocaine given for control of arrhythmia (plasma concentrations typically 1 – 5 µg/mL).

The sponsor did not conduct genetic toxicology studies with Lidopel™ and instead referred to mutagenicity studies conducted in support of the reference drug Iontocaine®. These studies included a bacterial reverse mutation assay, a chromosomal aberration study in human lymphocytes and an *in vivo* mouse micronucleus assay (studies to assess the potential for induction of point mutations as well as *in vitro* and *in vivo* assessments of the potential generation of abnormalities in chromosomal structure). All genetic toxicology studies conducted for Iontocaine® were judged to be negative. Additional support for Lidopel™ safety was the inclusion of reports of negative mutagenicity found for other approved lidocaine drug products currently marketed as well negative data from mutagenicity assays conducted with either lidocaine or epinephrine found in a review of the published literature.

The sponsor did not conduct reproductive toxicology studies with Lidopel™ noting the number of approved lidocaine or epinephrine products approved under ANDA guidelines which required no reproductive toxicology studies be conducted. Further support was derived from the literature for the effects of lidocaine on fertility and early embryonic development as well as for the potential for developmental deficits corresponding to Segment I and Segment III studies. Although published studies appear to support the absence of an effect of lidocaine on female fertility and early embryonic development, information regarding the effects of lidocaine exposure on male fertility, however was notably absent. Information regarding lidocaine and potential teratogenicity, corresponding to Segment II reproductive toxicology studies, was provided by referencing currently marketed lidocaine products which have reported embryo-fetal developmental studies which were judged negative as well as published studies which have arrived at the same conclusion. Published pre- and post-natal developmental studies offer conflicting views of the potential for prenatal exposure to lidocaine to affect later development and produce behavioral deficits. Nevertheless the use of the product as described would provide reasonable assurance that fetal exposure to lidocaine would be exceedingly low and the risk from a developmental toxicity standpoint to be negligible.

Carcinogenicity studies were not required of this drug product and were not conducted.

Unresolved toxicology issues (if any):

1. It is not clear from the sponsor's submission which electrodes are to be marketed with Lidopel™. The table reproduced on page 9 indicates that

the electrode with the surface area of —

2. The sponsor was unable to adequately assess the potential for lidocaine to affect male fertility as the published literature lacks information corresponding to Segment I reproductive toxicology studies in male animals.

Recommendations: The sponsor has addressed the preclinical issue of concern identified in meetings with the Agency which was the potential for dermal irritation with use of Lidopel™ with the associated Dupel® Iontophoresis System and Electrodes. From a pharmacology/toxicology perspective, this NDA may be **approved**.

Suggested labeling: Please see labeling suggestions in the Executive Summary.

Signatures (optional):

Reviewer Signature ___Adam M. Wasserman, Ph.D._____

Supervisor Signature__R. Daniel Mellon, Ph.D._____ Concurrence Yes _X_ No ___

3.7. APPENDIX/ATTACHMENTS

N/A

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/s/

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I concur.