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*APPLICATION NUMBER:*

**21-504**

**PHARMACOLOGY REVIEW(S)**

## PHARMACOLOGY AND TOXICOLOGY REVIEW

**NDA #:** 21-504

**Drug Name:** To be determined

**Drug substance:** Lidocaine HCl/Epinephrine bitartrate

**Sponsor:** Vyteris, Inc.

**Indication:** Local dermal anesthesia

**Division:** Anesthetic, Critical Care and Addiction Drug Products

**Reviewer:** Timothy J. McGovern, Ph.D.

**Regulatory Recommendation:** AP

**Date:** July 24, 2003

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## ***EXECUTIVE SUMMARY***

### **1. Recommendations**

1.1 Recommendation on approvability: This drug product application is approvable from a nonclinical perspective.

1.2 Recommendation for nonclinical studies: None at this time.

1.3 Recommendations on labeling: A label review was conducted and it is detailed under Section 3.6. —

### **2. Summary of nonclinical findings**

#### **2.1 Brief overview of nonclinical findings**

The primary safety issue with this product is the potential for dermal effects at the patch treatment site. In studies submitted to IND 48,365, the sponsor performed evaluations with lidocaine alone and with epinephrine. Primary dermal irritation studies in rabbits and Guinea pigs did not produce any erythema or edema following 15 minutes exposure with iontophoresis and 4-24 hours after subcutaneous lidocaine injection. In another study, severe dermal irritation reactions at the active patch sites were observed in Guinea pigs. Evaluations determined that there was no effect due to voltage spikes or whether the animals were depilated or clipped animals. Administration of lidocaine HCl (10%) and phenylephrine (1%) produced mild to moderate irritation in rabbits following iontophoresis that recovered within 7 days in some animals. In more recent studies submitted to the NDA, application of the iontophoretic patch (pH 4.0) in a setting that mimics clinical use produced dermal irritation scores in male New Zealand white rabbits that demonstrated a lack of irritancy potential. Histopathology findings identified the presence of minimal to mild inflammation of the panniculus carnosus muscle in the hypodermis of several abraded and intact sites. Similar results were observed in a 14-day repeat dose study in New Zealand white rabbits. Observations at the patch site included small red scab like areas at the anode sites of most animals and histologic assessment of treated skin samples following 14-day treatment demonstrated an increased incidence and severity of findings in lidocaine treated animals; findings included hyperplasia, crusting, fibrosis, congestion/hemorrhage and focal degeneration of hair follicle units. An evaluation of delayed contact hypersensitivity in Hartley Guinea pigs demonstrated that the Lidocaine Iontophoretic patch was non-sensitizing. Based on the submitted studies, the potential for dermal irritation has been adequately characterized in nonclinical models.

A genetic toxicology battery of studies with lidocaine conducted by the sponsor resulted in negative findings.

The Sponsor provided a review of the available literature regarding the reproductive toxicology potential of lidocaine and epinephrine. In vitro assessments of embryonic development identified the potential for lidocaine-induced neural tube defects that was not observed in vivo. Additionally, some postnatal developmental effects have been observed in certain animal models. Studies with epinephrine have demonstrated reductions in fertility parameters, embryo-fetal development parameters (aortic arch abnormalities associated with ECG abnormalities) and a high incidence of embryonic death. Other developmental effects included cleft palate formation in mice, hemorrhagic lesions of fetal extremities followed by necrosis, and a high incidence of fetal death following direct administration of epinephrine to rat fetuses; cataracts were observed in surviving fetuses. An increased number of runts were observed in offspring of pregnant rabbits. Postnatal effects in mice included increased locomotor activity and grooming and decreased defecation while less active offspring were observed following dosing of rat. In light of the observed low levels of clinical systemic exposure to lidocaine and epinephrine and the vast previous human experience with both compounds, the above-described potential developmental effects are not considered to be of clinical significance for the proposed drug product. Additionally, the referenced product, Iontocaine, is labeled as Category B for pregnancy. The review team concluded that a Pregnancy Category of B for the proposed product would be acceptable.

## 2.2 Pharmacologic activity

When applied locally to nerve tissue in appropriate concentrations, local anesthetics such as lidocaine reversibly block the action potentials responsible for nerve conduction. A local anesthetic in contact with a nerve trunk can cause both sensory and motor paralysis in the area innervated. The action is reversible at clinically relevant concentrations. Local anesthetics block conduction by decreasing or preventing the large transient increase in the permeability of excitable membranes to  $\text{Na}^+$  that normally is produced by a slight depolarization of the membrane due to direct interaction with voltage-gated  $\text{Na}^+$  channels. Local anesthetics can also bind to other membrane proteins such as  $\text{K}^+$  channels. Epinephrine has marked effects on alpha-adrenergic and beta-adrenergic receptors. Lidocaine has demonstrated CNS stimulatory effects and modulatory effects on the cardiovascular system. Epinephrine has demonstrated vasoconstrictive properties, as well as smooth muscle relaxation in the respiratory and gastrointestinal systems. The observed effects are not of significant concern for the current product given the limited systemic exposure observed with both lidocaine and epinephrine.

## 2.3 Nonclinical safety issues relevant to clinical use

The only nonclinical safety issue relevant to clinical use is the potential for local irritation effects. Generally mild erythema and edema have been observed in animal models with some associated histopathology. The reviewing medical officer has been made aware of

these findings. Clinical assessments have identified similar types of findings including edema, erythema and blistering.

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**PHARMACOLOGY/TOXICOLOGY REVIEW****3.1 INTRODUCTION AND DRUG HISTORY****NDA number:** 21-504**Review number:** 1**Sequence number/date/type of submission:** 000/September 30, 2002/Original NDA  
000/March 31, 2003/BP  
000/June 28, 2003/BZ  
000/July 14, 2003/BP**Information to sponsor:** Yes ( ) No (X)**Sponsor and/or agent:** Vyteris, Inc., Fair Lawn, NJ**Manufacturer for drug substance:** The manufacturer of the finished iontophoretic patch is Vyteris. The manufacturer of lidocaine hydrochloride monohydrate is \_\_\_\_\_  
The manufacturer of epinephrine (+) bitartrate is \_\_\_\_\_**Reviewer name:** Timothy J. McGovern, Ph.D.**Division name:** Anesthetic, Critical Care and Addiction Drug Products**HFD #:** 170**Review completion date:** July 24, 2003**Drug:**

Trade name: To be determined

Generic name: Lidocaine HCl/Epinephrine bitartrate

Code name: NA

Chemical name:

Lidocaine: 2-(Diethylamino)-2',6'-acetoxylidide mono-hydrochloride, monohydrateEpinephrine: 1,2 Benzenediol, 4-[1-hydroxy-2-(methylamino)ethyl]-, (R)-, [R-(R\*,R\*)]-2,3-dihydroxybutanedioate (1:1) (salt)

CAS registry number:

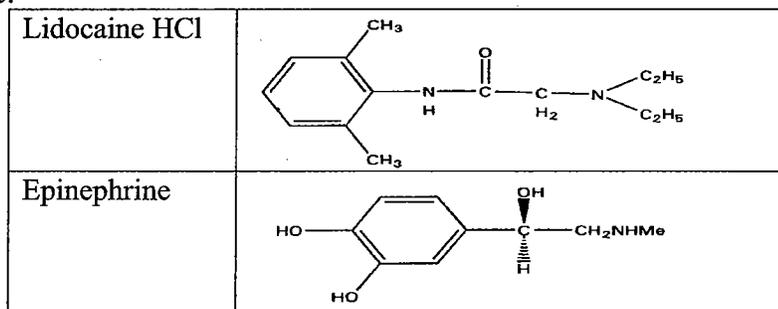
Lidocaine: 137-58-6

Epinephrine: 721-50-6

Molecular formula/molecular weight:

Lidocaine: C<sub>14</sub>H<sub>22</sub>N<sub>2</sub>O/288.81Epinephrine: C<sub>9</sub>H<sub>13</sub>NO<sub>3</sub>•C<sub>4</sub>H<sub>6</sub>O<sub>6</sub>/333.29

Structure:



Relevant INDs/NDAs/DMFs: IND 48,365 (lidocaine iontophoretic drug delivery system); DMF ————; DMF ————  
 NDA 20-530 (Iontocaine)

Drug class: amide class of local anesthetic

Indication:

Clinical formulation: The drug patch with iontophoretic device is shown below:



FIGURE 4.1 Picture of Iontophoretic Drug Delivery System

The drug reservoir contains — mg lidocaine HCl, — mg epinephrine bitartrate (equivalent to 1.0 mg of epinephrine) and excipients consisting of sodium chloride, glycerin, preservatives (2-phenoxyethanol, methyl-, ethyl-, propyl-, butyl-, and isobutyl-p-hydroxybenzoate), citric acid as a buffer and chelator, edetate disodium as a chelator, and sodium metabisulfite as an antioxidant, in a non-sterile hydrogel. The elongated return reservoir contains glycerin, sodium chloride, preservatives (2-phenoxyethanol, methyl-, ethyl-, propyl-, butyl-, and isobutyl-p-hydroxybenzoate), and monobasic sodium

phosphate as an acidulating agent. The drug and return reservoirs are made from a polyvinylpyrrolidone (PVP) hydrogel.

TABLE 4.2.4-I Quantitative Composition of Commercial Batch Size

Description	Composition by weight Aqueous solution	mg per patch	a ner	ka ner
			patches	patches
Drug Formulation, (Anode)	Lidocaine hydrochloride	100 *	/	/
	Epinephrine bitartrate	1.05 **		
	Glycerin			
	Sodium metabisulfite			
	Sodium chloride			
	Citric acid			
	Edetate disodium			
	Total			

\* Lidocaine hydrochloride on the anhydrous basis.  
 \*\* Epinephrine content as the free base

Description	Composition by weight Aqueous solution	mg per patch	a ner	ka ner
			patches	patches
Electrolyte Formulation, (Cathode)	Glycerin		/	/
	Monobasic sodium phosphate			
	Sodium chloride			
	Total			

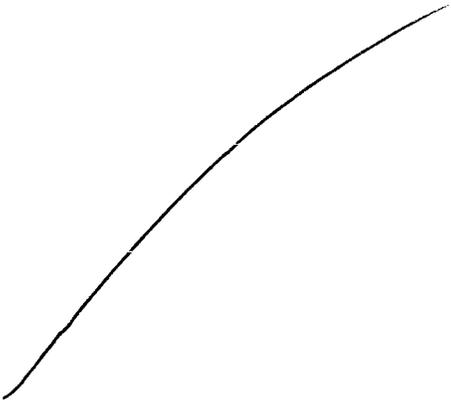
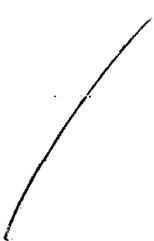
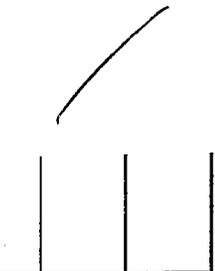
Description	Composition	mg per patch	a ner patches	ka ner patches
Cathode Hydrogel			/	/

Transfer  
Pad, Anode

Transfer  
Pad,  
Cathode

Pouch  
Container  
Closure

TABLE 4.2.4-I Quantitative Composition of Commercial Batch Size (cont.)

Description	Composition	mg per patch	4000 patches	4000 patches
Electrode Subassembly				
Anode Hydrogel				

**Route of administration:** Iontophoretic topical (dermal) patch

**Proposed use:**

The Northstar Lidocaine Iontophoretic Drug Delivery System (Northstar System) consists of the Northstar Lidocaine Iontophoretic Patch (Northstar Patch) and the Northstar Iontophoretic Controller (Northstar Controller). The Northstar System delivers lidocaine and epinephrine simultaneously through a process known as iontophoresis to achieve local dermal anesthesia. This

iontophoresis is based on the principle that a soluble salt or drug can be transported across the skin barrier as a part of an electric current induced in the skin. The quantity and distribution of delivered drug(s) is dependent on the ion charge, molecular weight, intensity of the electric current, concentration of the drug(s), and duration of current. At a nominal pH 4.5, lidocaine HCl and epinephrine are both positively charged. In most iontophoretic systems, iontophoresis is measured as total charge delivered in milliamperes-minutes (mA-min) units.

The Northstar Controller is designed with a non-replaceable battery that provides approximately 100 drug applications at 1.77 mA for 10 minutes (17.7 mA-min.). The Northstar Patch is for one use only and disposable. The patch contains drug and return reservoirs. The 5 cm<sup>2</sup> circular drug reservoir delivers lidocaine and epinephrine to the skin whereas the elongated return reservoir contains electrolytes to complete the electrical circuit. One Northstar Patch is to be used with one Northstar Controller. Northstar Patches are supplied as individually-pouched, single-use, iontophoretic patches containing 2 mg Lidocaine and 0.1 mg Epinephrine, and are to be used only in conjunction with the Northstar Iontophoretic Controller. The Northstar Controller is designed with a non-replaceable battery that provides approximately 100 drug applications at 1.77 mA for 10 minutes (17.7mA-min.). Northstar Controller can only be used with the Northstar Patch in the complete Northstar Iontophoretic Drug Delivery System.

The Northstar System has a fixed delivery profile that cannot be altered by the user. The entire delivery is accomplished in approximately 600 seconds. Delivery is initiated by pressing the ON button and the subsequent detection of skin at the patch site. Once started, the profile proceeds through three stages.

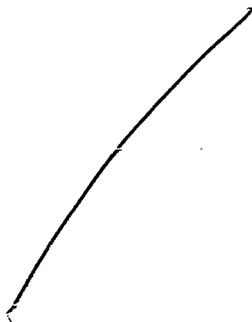
*Ramp-Up:* When the controller detects the presence of skin, it begins the delivery. To minimize patient discomfort the current is slowly ramped up from zero to 1.77 milliamperes. This ramp up requires approximately 30 seconds to complete.

*Main Delivery:* When the controller has reached the 1.77 mA current, it holds this current constant for the next 550 seconds.

*Ramp-Down:* Upon completion of the main delivery, and again for patient comfort, the current is slowly ramped down to zero. This ramp-down takes about 20 seconds.

For use in patients 5 years of age or older.

Directions for use:



1   Page(s) Withheld

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

   § 552(b)(5) Deliberative Process

   ✓ § 552(b)(4) Draft Labeling

**Studies reviewed within this submission:**

Study title	Study #
<b>Pharmacokinetics/Toxicokinetics:</b>	
Lidocaine and epinephrine skin doses from BD Northstar System	99-8402-8392-06
<b>Genetic Toxicology:</b>	
Bacterial Reverse Mutation Assay	AA48ZP.503.BTL
In Vitro Mammalian Chromosome Aberration Test	AA48ZP.331.BTL
Mammalian Erythrocyte Micronucleus Test	AA48ZP.123.BTL
<b>Special Toxicology Studies:</b>	
Modified primary dermal irritation	GLP31737
Primary Dermal Irritation (Iontophoresis)	32PD04.01
Delayed Contact Hypersensitivity -- Modified Buehler Method	GLP31738
A 14-Day Repeated Application Dermal Irritation /Toxicity Study	31736
Biological Reactivity Test – In vitro: L929 MEM elution test	860853
Biological Evaluation of Medical Devices-Part 10: Test for Irritation and Sensitivity According to ISO 10993-10, 1995(E)-(FDA Requirements, per 21CFR 58)	GLP31735
Biological Evaluation of Medical Devices-Part 10: Test for Irritation and Sensitivity According to ISO 10993-10, 1995(E)-(FDA Requirements, per 21CFR 58)	GLP31739

**Studies not reviewed within this submission:** The following reviews were previously reviewed in the original IND review for IND 48,365 (April 3, 2000) by Dr. M. Anwar Goheer and are summarized in the relevant sections of this review:

Skin Irritation in the Rabbit following Iontophoresis on BDTS T23700694 and Lidocaine HCl	BDRC Protocol/ Project No. 2930-0692, Amendment 4B
Skin Irritation in the Rabbit following Iontophoresis on BDTS Prototype Patches	BDRC Protocol/Project No. 2930-0692, Amendment 8
Guinea Pig Skin Sensitization Test - Buehler Method Using Iontophoretic Drug Delivery Patches	7300-500
Guinea Pig Skin Sensitization Test - Buehler Method Using Iontophoretic Drug Delivery Patches - Time 10 Minutes	7300-501
Guinea Pig Skin Sensitization Test - Buehler Method Using Iontophoretic Drug Delivery Patches	7300-502
Follow-up Study to Evaluate the Dermal Irritation Response Produced by the Northstar Iontophoretic System during the Sensitization	94-4400-002 and 95-4400-003
Primary Skin Irritation Study in Rabbits (With Iontophoresis)	Lab #12855

This NDA is submitted as a 505(b)(2) application with the listed drug being NDA 20-530 (Iontocaine). Two End of Phase 2 meetings were held with the sponsor on September 16, 1999 and February 17, 2000. Additionally, a Pre-NDA meeting was held on November 9, 2001. The sponsor was informed that under a 505(b)(2) submission, reproductive toxicology studies would not be needed and the sponsor could refer to available supporting data for lidocaine and epinephrine. The sponsor was also informed that no further nonclinical studies would be needed to support an NDA submission.

## 3.2 PHARMACOLOGY

### 3.2.1 Brief summary

The pharmacology of lidocaine and epinephrine is well known. When applied locally to nerve tissue in appropriate concentrations, local anesthetics such as lidocaine reversibly block the action potentials responsible for nerve conduction. A local anesthetic in contact with a nerve trunk can cause both sensory and motor paralysis in the area innervated. The action is reversible at clinically relevant concentrations. Local anesthetics block conduction by decreasing or preventing the large transient increase in the permeability of excitable membranes to  $\text{Na}^+$  that normally is produced by a slight depolarization of the membrane due to direct interaction with voltage-gated  $\text{Na}^+$  channels. Local anesthetics can also bind to other membrane proteins such as  $\text{K}^+$  channels. Lidocaine is considered to be fast acting but is more short-acting in comparison to bupivacaine. Epinephrine has marked effects on alpha-adrenergic and beta-adrenergic receptors. Lidocaine has demonstrated CNS stimulatory effects and modulatory effects on the cardiovascular system. Epinephrine has demonstrated vasoconstrictive properties, as well as smooth muscle relaxation in the respiratory and gastrointestinal systems. The observed effects are not of significant concern for the current product given the limited systemic exposure observed with both lidocaine and epinephrine.

### 3.2.2 Primary pharmacodynamics

Mechanism of action: The sponsor did not conduct any new experiments in this area. A review of the pharmacology of local anesthetics in general, and lidocaine specifically, is provided in Goodman and Gilman's The Pharmacological Basis of Therapeutics. When applied locally to nerve tissue in appropriate concentrations, local anesthetics reversibly block the action potentials responsible for nerve conduction. A local anesthetic in contact with a nerve trunk can cause both sensory and motor paralysis in the area innervated. The action is reversible at clinically relevant concentrations; complete recovery in nerve function occurs with no evidence of damage to nerve cell fibers or cells.

Epinephrine is one of three naturally occurring sympathomimetic amines and has marked effects on alpha-adrenergic and beta-adrenergic receptors.

Drug activity related to proposed indication: Local anesthetics block conduction by decreasing or preventing the large transient increase in the permeability of excitable membranes to  $\text{Na}^+$  that normally is produced by a slight depolarization of the membrane due to direct interaction with voltage-gated  $\text{Na}^+$  channels. Local anesthetics can also bind to other membrane proteins such as  $\text{K}^+$  channels. However, blockade of conduction is not accompanied by any large or consistent change in resting membrane potential due to block of  $\text{K}^+$  channels since the interaction of local anesthetics with  $\text{K}^+$  channels requires higher drug concentrations. Lidocaine is fast acting but is more short-acting in comparison to bupivacaine.

The function of epinephrine in the current product is that of a vasoconstrictor. Epinephrine's role is to decrease the rate of lidocaine absorption, thus localizing the anesthetic at the desired site and allows the rate at which it is destroyed to keep pace with the rate at which it is absorbed into the circulation, thereby reducing its systemic toxicity.

The Iontophoretic Drug Delivery System (Northstar System) provides local dermal anesthesia by using a small electric current to deliver lidocaine and epinephrine into the skin in the vicinity of pain receptors and nerve endings. Lidocaine and epinephrine are both positively charged and delivered simultaneously from the circular drug reservoir. Lidocaine stabilizes the neuronal membrane by inhibiting the ionic fluxes required for the initiation and conduction of nerve impulses, thereby effecting local anesthetic action. Epinephrine increases the depth and duration of anesthesia, presumably because of its vasoconstrictor activity, which decreases the rate of removal of lidocaine from the site of administration.

### 3.2.3 Secondary pharmacodynamics

The sponsor did not conduct any new experiments in this area.

### 3.2.4 Safety pharmacology

Formal safety pharmacology studies were not performed for this application and were not required due to the extensive human experience with both lidocaine and epinephrine.

Neurological effects: As with other local anesthetics, effects of lidocaine include stimulation of the CNS as illustrated by restlessness and tremor leading to clonic convulsions. Central stimulation is followed by depression and death is usually caused by respiratory failure.

Epinephrine is not a potent CNS stimulant due to its inability to enter the CNS. Observed effects such as restlessness, apprehension, headache, and tremor may be secondary to effects on the cardiovascular system, skeletal muscles and metabolism.

Cardiovascular effects: Lidocaine has a biphasic effect on blood flow. Lower concentrations are vasoconstrictive, while higher concentrations are vasodilating. Cardiovascular system effects of lidocaine may include decreased electrical excitability, conduction rate, force of contraction, arteriolar dilatation, and cardiac arrhythmias when plasma levels exceed ~ 10  $\mu\text{mol/L}$  (5 mg/L) for either compound. Cardiovascular effects are thought to be due to a pharmacological effect on sodium channel blockade.

Epinephrine is a potent vasoconstrictor due to direct myocardial stimulation, increased heart rate and vasoconstriction in many vascular beds. The primary vascular action is on the small arterioles and precapillary sphincters. Injected epinephrine decreases cutaneous blood flow, constricting precapillary vessels and small venules. Epinephrine is a cardiac stimulant by acting directly on the  $\beta_1$  receptors of the myocardium and of the cells of the pacemaker and conducting tissues. Cardiac arrhythmias have been seen in patients after

inadvertent IV administration and epinephrine can decrease the T wave amplitude in normal subjects.

Pulmonary effects: Pulmonary effects have not been associated with lidocaine administration. Epinephrine affects respiration primarily by relaxing bronchial muscle.

Renal effects: Renal effects have not been associated with lidocaine or epinephrine administration.

Gastrointestinal effects: Gastrointestinal effects have not been associated with lidocaine administration. Epinephrine generally relaxes GI smooth muscle due to activation of both  $\alpha$ - and  $\beta$ -adrenergic receptors. Intestinal tone and the frequency of spontaneous contractions are reduced.

Abuse liability: Neither lidocaine nor epinephrine has demonstrated any potential for abuse liability.

Other: None.

### 3.2.5 Pharmacodynamic drug interactions

Pharmacodynamic drug interactions with lidocaine or epinephrine have not been assessed.

## 3.3 PHARMACOKINETICS/TOXICOKINETICS

### 3.3.1 Brief summary

In a study submitted to IND 48,365, the sponsor performed evaluations with lidocaine alone and with epinephrine. Approximately 1% and 2% of lidocaine and epinephrine, respectively, were delivered by iontophoresis to compartments in an ex vivo porcine skin flap model indicating low levels of accumulation in the skin. The only new study conducted by the sponsor was a pharmacokinetic study in pigs. The mean recovery of epinephrine from skin sites was 0.24% of the loaded 1.05 mg base. For lidocaine the mean recovery from skin, 467  $\mu$ g, is only 0.54% of the loaded 86 mg base. Total recoveries of the actives from the used patches were 91.3% of loaded epinephrine and 91.4% of loaded lidocaine. Lidocaine absorption tends to be fairly rapid although it is reduced when administered in combination with epinephrine. Lidocaine is widely distributed into highly perfused tissue, followed by redistribution into skeletal muscle and adipose tissue. Lidocaine metabolism is qualitatively similar across species and almost completely metabolized before excretion; MEGX and 2,6-xylidine were identified as major metabolites. Epinephrine is rapidly inactivated by uptake into adrenergic neurons, diffusion, plasma protein binding and enzymatic degradation (COMT and MAO) in the liver and other tissues. Both lidocaine and epinephrine (and metabolites) are excreted primarily in urine.

### 3.3.2 Absorption

Lidocaine base is absorbed rapidly through mucous membranes, intact and damaged skin, and from the intestines and respiratory tract. The hydrochloride form is absorbed rapidly after parenteral administration, but absorption through intact skin or mucous membranes is poor.

Epinephrine is ineffective after oral administration due to rapid conjugation and oxidation in the gastrointestinal mucosa and liver. Absorption from subcutaneous tissues occurs more slowly due to local vasoconstriction.

### 3.3.3 Distribution

Lidocaine is widely distributed into highly perfused tissue (heart, brain, kidney), followed by redistribution into skeletal muscle and adipose tissue. Lidocaine affinity for melanin has been demonstrated using labeled compound resulting in a longer elimination half-life in pigmented skin. Lidocaine readily crosses the placenta and blood brain barrier with plasma levels declining in parallel that of the mother animal. Lidocaine protein binding is approximately 66% in humans and 78% in dogs.

### 3.3.4 Metabolism

Lidocaine is almost completely metabolized before excretion with the liver as the primary site. Metabolism is qualitatively similar across species with quantitative variations. The three main types of metabolic reactions include aromatic hydroxylation, N-dealkylation and amide hydrolysis, followed by conjugation reactions. Major enzymes involved in lidocaine metabolism in human liver microsomes were CYP3A4 and CYP1A2. In a human liver slice system, MEGX and 2,6-xylydine were identified as major metabolites.

Epinephrine is rapidly inactivated by uptake into adrenergic neurons, diffusion, plasma protein binding and enzymatic degradation (COMT and MAO) in the liver and other tissues.

### 3.3.5 Excretion

Approximately 90% of lidocaine is excreted as various metabolites and less than 10% of a dose is excreted unchanged via the kidneys. Metabolites of epinephrine are excreted in the urine primarily as glucuronide or sulfate ether conjugates.

### 3.3.6 Pharmacokinetic drug interactions

Pharmacokinetic drug interactions have not been assessed.

**3.3.7 Tables and figures to include comparative TK summary**

In a study performed by the sponsor (BTD Report No. 99-8402-8392-06), Northstar gels loaded with 300 µl of a radiolabeled <sup>3</sup>H-epinephrine (375 µl) and <sup>14</sup>C-lidocaine solution (99.9 mg lidocaine HCl, 86.1 mg base; 1.91 mg epinephrine bitartrate, 1.05 mg base) were applied and run two at a time on the back of an isoflurane-anesthetized pig. Sites 1, 2 and 3 were on the left side, from head to tail, and sites 4, 5 and 6 were on the right side, from tail to head. Current (1.25-1.75 mA) was supplied by

constant current power supplies and the applied voltage (25-30 volts) and current data were recorded with a data logger. After 10 minutes, patches were removed and the anode skin sites were tape-stripped 20 times with packing tape and the sites were then excised and cut into 4 sections. Samples were then counted. Only very small percentages of the active components originally loaded in the patch were recovered from the skin by tape stripping and skin samples. For epinephrine the mean recovery from each skin site, 2.48 µg as free base, is only 0.24% of the loaded 1.05 mg base (see Table below). For lidocaine the mean recovery from skin, 467 µg, is only 0.54% of the loaded 86 mg base. Total recoveries of the actives from the used patches were 91.3% of loaded epinephrine and 91.4% of loaded lidocaine. The recoveries were only slightly lower than the values for the unused, control patches, which were 92.3% for epinephrine and 91.9 % for lidocaine. The close similarity is reasonable considering the very small skin doses.

**DOSE SUMMARY (micrograms of free base)**

RUN	<u>EPINEPHRINE</u>			<u>LIDOCAINE</u>		
	TAPES	SKINS	TOTAL	TAPES	SKINS	TOTAL
1						
2						
3						
4						
5						
6						
<b>Mean</b>	<b>1.14</b>	<b>1.35</b>	<b>2.48</b>	<b>268</b>	<b>199</b>	<b>467</b>
<b>s.d.</b>	<b>0.19</b>	<b>0.26</b>	<b>0.28</b>	<b>40</b>	<b>7</b>	<b>42</b>

## 3.4 TOXICOLOGY

### 3.4.1 Overall toxicology summary

General toxicology: No new general toxicity studies were performed by the sponsor. The primary toxicity associated with lidocaine is related to cardiac effects at greater than clinical doses; local tissue necrosis has been observed with repeated application of epinephrine. Additionally, intravenous infusion of epinephrine has resulted in the induction of ocular toxicity such as lens opacities and glaucoma in rats, mice and rabbits.

Genetic toxicology: In studies conducted by the sponsor, lidocaine HCl produced negative results in the Ames Salmonella/Mammalian Microsome Test, by analysis of structural chromosome aberrations in human lymphocytes *in vitro*, and by the mouse micronucleus test *in vivo*. No studies were conducted with epinephrine and none were identified in the literature.

A lidocaine metabolite, 2,6-xylidine, was considered weakly mutagenic (mixed results in different laboratories), and was mutagenic at the thymidine kinase locus. The compound also induced chromosome aberrations and sister chromatid exchanges in Chinese hamster ovary cell sat toxic concentrations. It was negative in an unscheduled DNA synthesis assay with rat hepatocytes, a chromosome aberration assay in polychromated erythrocytes, and a differential survival assay of DNA repair proficient versus deficient *E. coli* bacteria in mouse liver, lung, kidney, testis and blood extracts.

Carcinogenicity: Carcinogenicity studies have not been performed with lidocaine HCl. Studies are not considered necessary for this product due to the expected limited duration of use of the product. Two-year studies in rats and mice with epinephrine were conducted by NTP. Although the studies were negative, dosing was considered to be inadequate.

Reproductive toxicology: The sponsor has not conducted reproductive toxicology studies. As agreed upon during the pre-NDA meeting, the sponsor provided an assessment of the available literature concerning the potential for reproductive effects.

Fertility effects of lidocaine have not been assessed. Lidocaine treated rats demonstrated a significant delay in delivery time. *In vitro* assessments of embryo development demonstrated neural tube defects (failure to fuse the anterior neural folds) in mouse and chick embryos that were not observed in rat embryos. Other *in vitro* mouse embryo studies reported adverse effects on fertilization and early *in vitro* development in the mouse were adversely affected by lidocaine when cunnulus masses, a decreased percentage of two-cell embryos cleaving and developing to more advanced stages, or no effect. Explanted rat embryos from pregnant rats showed growth retardation, severe morphological abnormalities, reduced viability, and increased incidence of situs inversus. A single intraperitoneal injection of lidocaine (32-70 mg/kg) in pregnant mice on gestation day 9 did not affect neural tube closure but showed some potential for developmental retardation including dilatation of the 4<sup>th</sup> ventricle. A continuous

subcutaneous exposure in rats via an implanted osmotic pump (0, 100, 250 mg/kg) produced no adverse effects, while exposure to 500 mg/kg/d on gestation days 3-17 produced slight fetal weight reduction and a delay in sternal ossification. Postnatal developmental effects in rats included delayed negative geotaxis and righting reflex, enhanced footshock sensitivity, increased errors in a water maze, longer suppression times in conditioned suppression tasks and changes in operant visual discrimination responses. These responses were not reproduced across rat strains.

Subcutaneous doses of epinephrine (100 µg/day/mouse) reduced the number of pregnancies in mice. Constant infusion of epinephrine (1 µg/hr) in pregnant Wistar rats via a subcutaneously implanted osmotic mini-pump produced no maternal toxicity and had no effect on general fertility levels, pregnancy rates, survival or incidence of malformations. In pregnant Dutch-Belted female rabbits administered 600 µg/kg, bid, a decreased number of implantation sites compared to control was noted on gestation days 6-7 or 7-9. All epinephrine treated animals had a significantly lower number of normal fetuses and there was an increased incidence of fetal death. Topical application of epinephrine (single dose, 5 µg) to chick embryos produced a time-related spectrum of aortic arch abnormalities involving 3<sup>rd</sup>, 4<sup>th</sup>, and 6<sup>th</sup> pairs of aortic arches and the right 4<sup>th</sup> arch. Topical application was also associated with ECG abnormalities that were correlated with a high incidence of abnormal obliteration of the aortic arch, and a high incidence of embryonic death. Subcutaneous administration of epinephrine to pregnant mice resulted in cleft palate formation at doses of 10 µg/day and 20 µg/day on; total fetal resorption occurred at 50 µg/day. Intra-amniotic injections (5-10 µg) during gestation days 15-16 produced hemorrhagic lesions of fetal extremities followed by necrosis due to prolonged arterial vasoconstriction. Direct administration of epinephrine (8-50 µg/d, injection) to rat fetuses resulted in pale coloration and a high incidence of fetal death. Reduced fetal body weight and cataracts were observed in surviving fetuses. Subcutaneous administration of 500 µg/kg/day on gestation days 7-10 to pregnant hamsters resulted in a decrease of reproductive success and pre-implantation wastage but was not teratogenic. IM or IV injections (171 µg/day) to pregnant rabbits during gestation resulted in increased number of runts only with IV. Subcutaneous administration of epinephrine (250 µg/day) in A/Jax, BALB/Ci and C57BL/6 mice resulted in an increase, no change or decrease in spontaneous activity, respectively. Offspring of C57BL/6 mice were SC administered 0.25 µM epinephrine on gestation day 8, 10, 12 and 14 showed increased locomotor activity, increased grooming and decreased defecation. IP administration of 750 µg/kg/day during gestation in Wistar rats resulted in less active offspring in open field and water maze tests.

However, in light of the observed low levels of clinical systemic exposure to lidocaine and epinephrine and the vast previous human experience with both compounds, the potential developmental effects are not considered to be of significance for the proposed drug product and the Pregnancy Category should be listed as "B".

**Special toxicology:** In studies submitted to IND 48,365, the sponsor performed evaluations with lidocaine alone and with epinephrine. Primary dermal irritation studies in rabbits and guinea pigs did not produce any erythema or edema following 15 minutes exposure with iontophoresis and 4-24 hours after subcutaneous lidocaine injection. In another study, severe dermal irritation reactions at the active patch sites were observed in Guinea pigs. Evaluations determined that there was no effect due to voltage spikes or whether the animals were depilated or clipped animals. Administration of lidocaine HCl (10%) and phenylephrine (1%) produced mild to moderate irritation in rabbits following iontophoresis that recovered within 7 days in some animals.

The sponsor submitted two single dose and 14-day dermal irritation studies to the NDA in addition to a Guinea pig hypersensitivity study. Following application of the iontophoretic patch (pH 4.0) in a setting that mimics clinical use, dermal irritation scores were minor in male New Zealand white rabbits (0-1 for erythema and edema). Thus, the patch is considered to be a non-irritant under the test conditions. Histopathology findings identified the presence of minimal to mild inflammation of the panniculus carnosus muscle in the hypodermis of several abraded and intact sites. In a separate study, the test article #99-4400-001 was determined to be a slight irritant for the anode site and a negligible irritant for the cathode site in rabbits. In a 14-day repeat dose study in New Zealand white rabbits, the lidocaine patch produced erythema/edema scores of 0 at both the anode and cathode site on all study days. Observations at the patch site included small red scab like areas at the anode sites of most animals. Histologic assessment of treated skin samples following 14-day treatment demonstrated an increased incidence and severity of findings in lidocaine treated animals; findings included hyperplasia, crusting, fibrosis, congestion/hemorrhage and focal degeneration of hair follicle units. An evaluation of delayed contact hypersensitivity in Hartley Guinea pigs demonstrated that the Lidocaine Iontophoretic patch was non-sensitizing.

Studies were also performed to assess the irritancy potential and cytotoxicity of extracts from the top and bottom housings of the patch device. Extract solutions produced no dermal irritation in rabbits or sensitization in Guinea pigs and were not cytotoxic to L929 mouse fibroblast cells.

#### **3.4.2 Single-dose toxicity**

No single dose toxicity studies were performed.

#### **3.4.3 Repeat-dose toxicity**

No repeat dose toxicity studies were performed.

### 3.4.4 Genetic toxicology

The sponsor conducted a standard battery of genetic toxicology assays with lidocaine.

#### Study title: Bacterial Reverse Mutation Assay

#### Key findings:

- Lidocaine produced negative results in the reverse mutation assay under the conditions tested.

Study no.: AA48ZP.503.BTL

Volume #, and page #: electronic

Conducting laboratory and location: \_\_\_\_\_

Date of study initiation: September 2001

GLP compliance: Yes

QA reports: yes (X) no ( )

Drug, lot #, and % purity: Northstar (Lidocaine hydrochloride, USP), 0 1-04-0084,

#### Methods

Strains/species/cell line: Salmonella strains TA98, TA100, TA1535, and TA1537 and *E. coli* wp2 uvrA

Doses used in definitive study: 75, 200, 600, 1800 and 5000 µg per plate

Basis of dose selection: The initial toxicity-mutation assay was used to establish the dose-range over which the test article would be assayed and to provide a preliminary mutagenicity evaluation. Vehicle controls, positive controls and eight dose levels of the test article were plated, two plates per dose, with overnight cultures of TA98, TA100, TA1535, TA1537 and WP2uvrA on selective minimal agar in the presence and absence of Aroclor-induced rat liver S9.

Negative controls: Water

Positive controls: All salmonella strains and the E.coli used 2-aminoanthracene (1 and 10 µg/plate, respectively). Controls for TA 98 were 2-nitrofluorene (1 µg/plate), TA 100 and TA 1535 was sodium azide (1 µg/plate), TA 1537 was 9-aminoacridine (75 µg/plate), WP2uvrA was methyl methanesulfonate (1000 µg/plate). All positive controls were diluted in dimethyl sulfoxide (DMSO) except for sodium azide, which was diluted in water.

**Incubation and sampling times:** The test system was exposed to the test article via the plate incorporation methodology. On the day of its use, minimal top agar was melted and supplemented with G-histidine, D-biotin and L-tryptophan solution to a final concentration of 50  $\mu\text{M}$  each. Top agar not used with S9 or Sham mix was supplemented with 25 mL of water for each 100 mL of minimal top agar. Bottom agar was Vogel-Bonner minimal medium E (Vogel and Bonner, 1956) containing 1.5 % (W/V) agar. Nutrient bottom agar was Vogel-Bonner minimal medium E containing 1.5 % (W/V) agar and supplemented with 2.5% (W/V) Oxoid Nutrient Broth No. 2 (dry powder). Nutrient Broth was Vogel-Bonner salt solution supplemented with 2.5% (W/V) Oxoid Nutrient Broth No. 2 (dry powder). One-half (0.5) milliliter of S9 or Sham mix, 100  $\mu\text{L}$  of tester strain and 50  $\mu\text{L}$  of vehicle or test article dilution were added to 2.0 mL of molten selective top agar at 45 degrees C. After vortexing, the mixture was overlaid onto the surface of 25 mL of minimal bottom agar. When plating the positive controls, the test article aliquot was replaced by a 50  $\mu\text{L}$  aliquot of appropriate positive control. After the overlay had solidified, the plates were inverted and incubated for approximately 48 to 72 hours at 37°C. Plates that were not counted immediately following the incubation period were stored at 2-8°C until colony counting could be conducted.

## Results

**Study validity:** The test was performed in triplicate. The criteria for the test article to be evaluated positive were acceptable (Must cause a dose-related increase in the mean revertants per plate of at least one tester strain over a minimum of two increasing concentrations of test article. Data sets for tester strains TA1535 and TA1537 were judged positive if the increase in mean revertants at the peak of the dose response is equal to or greater than three times the mean vehicle control value. Data sets for tester strains TA98, TA100 and WP2 *uvrA* were judged positive if the increase in mean revertants at the peak of the dose response is equal to or greater than two times the mean vehicle control value. The counting method was appropriate and the positive controls produced the expected results.

**Study outcome:** Initial dose levels tested were 2.5, 7.5, 25, 75, 200, 600, 1800 and 5000  $\mu\text{g}$  per plate. In the initial toxicity-mutation assay, no positive mutagenic response was observed in the presence and absence of Aroclor-induced rat liver S9 (10% fraction). Concentrations from 0.050 to 100mg/mL were soluble and clear solutions. Neither precipitate nor appreciable toxicity was observed. Based on the findings of the initial toxicity-mutation assay, the maximum dose plated in the confirmatory mutagenicity assay was 5000  $\mu\text{g}$  per plate. In the confirmatory mutagenicity assay, no positive mutagenic response was observed. Dose levels tested were 75, 200, 600, 1800 and 5000  $\mu\text{g}$  per plate. Neither precipitate nor appreciable toxicity was observed.

In conclusion, lidocaine produced negative results in the reverse mutation assay under the conditions tested. This conclusion is in concurrence with that of the sponsor.

**Study title:** In vitro mammalian chromosome aberration test

**Key findings:**

- In conclusion, lidocaine was negative in the in vitro chromosome aberration assay with CHO cells under the conditions tested. This conclusion is in agreement with that of the sponsor.

**Study no.:** AA48ZP.331.BTL

**Volume #, and page #:** electronic

**Conducting laboratory and location:** \_\_\_\_\_

**Date of study initiation:** September 2001

**GLP compliance:** Yes

**QA reports:** yes (X) no ( )

**Drug, lot #, and % purity:** Northstar (Lidocaine hydrochloride, USP), 01-04-0084,  
\_\_\_\_\_

**Methods**

Strains/species/cell line: Chinese hamster ovary (CHO-K,) cells (repository number CCL 61)

Doses used in definitive study: 250, 500, 1000, 000, 2200, 2400, 2600, and 2800 µg/ml under all test conditions

Basis of dose selection: Dose levels for the chromosome aberration assay were selected following a preliminary toxicity test and were based upon a reduction of cell growth (cell growth inhibition) relative to the solvent control.

Negative controls: sterile water

Positive controls: Mitomycin C and was dissolved and diluted in sterile distilled water to stock concentrations of 1 and 2 µg/d for use as the positive control in the non-activated test system. Cyclophosphamide was dissolved and diluted in sterile distilled water to stock concentrations of 100 and 200 µg/d for use as the positive control in the S9 activated test system.

Incubation and sampling times:

The chromosome aberration assay was performed using standard procedures (Evans, 1976), by exposing duplicate cultures of CHO cells to the test article as well as positive and solvent controls. For the chromosome aberration assay, CHO cells were seeded at approximately  $5 \times 10^5$  cell/25 cm<sup>2</sup> flask and were incubated at 37°C in a humidified atmosphere for 16-24 hours. Treatment was carried out by refeeding duplicate flasks with 4.5 mL complete medium for the non-activated study or 4.5 mL S9 reaction mixture for the S9 activated study, to which was added 500 µL of dosing solution of test or control article in solvent or solvent alone. The osmolality of the highest concentration of dosing

solution in the treatment medium was measured. The pH of the highest concentration of dosing solution in the treatment medium was measured using test tape.

In the non-activated study, the cells were exposed to the test article for 4 hours or continuously for 20 hours up to the cell harvest at 37°C in a humidified atmosphere. In the 4 hour exposure group, after the exposure period, the treatment medium was removed, the cells washed with CMF-PBS, refed with complete medium and returned to the incubator. Two hours prior to the scheduled cell harvest, Colcemid was added to duplicate flasks for each treatment condition at a final concentration of 0.1 µg/mL and the flasks returned to the incubator until cell collection.

In the S9 activated study, the cells were exposed for 4 hours at 37°C in a humidified atmosphere in air. After the exposure period, the treatment medium was removed, the cells washed with CMF-PBS, refed with complete medium and returned to the incubator. Two hours prior to the scheduled cell harvest, Colcemid was added to duplicate flasks for each treatment condition at a final concentration of 0.1 µg/ml and the flasks were returned to the incubator until cell collection. A concurrent toxicity test was conducted in both the non-activated and the S9 activated test systems. After cell harvest an aliquot of the cell suspension was removed from each culture and counted using a Coulter counter. The presence of test article precipitate was assessed using the unaided eye. Cell viability was determined by trypan blue dye exclusion. The cell counts and percent viability were used to determine cell growth inhibition relative to the solvent control.

Two hours after the addition of Colcemid, metaphase cells were harvested for both the non-activated and S9 activated studies by trypsinization. Cells were collected approximately 20 hours after initiation of treatment. The cells were collected by centrifugation at approximately 800 rpm for 5 minutes. The cell pellet was resuspended in 2-4 mL 0.075 M potassium chloride (KCl) and allowed to stand at room temperature for 4-8 minutes. The cells were collected by centrifugation, the supernatant aspirated and the cells fixed with two washes of approximately 2 mL Carnoy's fixative. The cells were stored overnight or longer in fixative at approximately 24°C. To prepare slides, the fixed cells were centrifuged at approximately 800 rpm for 5 minutes, the supernatant was aspirated, and 1 mL fresh fixative was added. After additional centrifugation (at approximately 800 rpm for 5 minutes) the supernatant fluid was decanted and the cells resuspended to opalescence in fresh fixative. A sufficient amount of cell suspension was dropped onto the center of a glass slide and allowed to air dry.

Metaphase cells with 20 centromeres were examined under oil immersion without prior knowledge of treatment groups. Initially, the non-activated and S9 activated 4 hour exposure groups were evaluated for chromosome aberrations and when a negative result was obtained in the non-activated 4 hour exposure group, the non-activated 20 hour continuous exposure group was then evaluated for chromosome aberrations. A minimum of 200 metaphase spreads (100 per duplicate flask) were examined and scored for chromatid-type and chromosome-type aberrations.

Fragments (chromatid or acentric) observed in the absence of any exchange figure were scored as a break (chromatid or chromosome). Fragments observed with an exchange figure were not scored as an aberration but instead were considered part of the incomplete exchange. Pulverized chromosome(s), pulverized cells and severely damaged cells e l 0

aberrations) were also recorded. Chromatid gaps and isochromatid gaps were recorded but not included in the analysis. The XY coordinates for each cell with chromosomal aberrations were recorded using a calibrated microscope stage. Polyploid and endoreduplicated cells were evaluated from each treatment flask per 100 metaphase cells scored.

## Results

Study validity: The test was performed in duplicate. The criteria for the test article to be evaluated positive were acceptable (when the percentage of cells with aberrations is increased in a dose-responsive manner with one or more concentrations being statistically significant). The assay and counting method was appropriate and the positive controls produced the expected results. Dose selection for analysis was also acceptable.

### Study outcome:

In the preliminary toxicity test, CHO cells were exposed to solvent alone and to nine concentrations of test article ranging from 0.5 µg/ml to 5000 µg/mL in the absence and presence of an S9 reaction mixture. The test article was soluble in treatment medium at all dose levels tested. The osmolality in treatment medium of the highest concentration tested, 5000 µg/mL, was 279 mmol/kg. The osmolality of the solvent (water) in treatment medium was 258 mmol/kg. The pH of the highest concentration of test article in treatment medium was approximately 7.0. Substantial toxicity (i.e., at least 50% cell growth inhibition, relative to the solvent control) was observed at dose level 5000 µg/mL in the non-activated 4 and 20 hour exposure groups and in the S9 activated 4 hour exposure group. Based on these findings, the doses chosen for the chromosome aberration assay ranged from 125 to 4000 µg/mL for all three treatment groups.

In the chromosome aberration assay, the test article was soluble in treatment medium at all dose levels tested. The osmolality in treatment medium of the highest concentration tested, 2800 µg/mL, was 270 mmol/kg. The osmolality of the solvent (water) in treatment medium was 274 mmol/kg. The pH of the highest concentration of test article in treatment medium was approximately 7.0. Toxicity of Northstar (Lidocaine hydrochloride, USP) (cell growth inhibition relative to the solvent control) in CHO cells when treated for 4 hours in the absence of S9 activation was 10% at 2400 µg/ml, the highest test concentration evaluated for chromosome aberrations. The mitotic index at the highest dose level evaluated for chromosome aberrations, 2400 µg/ml, was 52% reduced relative to the solvent control. The dose levels selected for microscopic analysis were 500, 1000, and 2400 µg/mL. The percentage of cells with structural and numerical aberrations in the test article-treated groups was not significantly increased above that of the solvent control, regardless of dose level. The percentage of structurally damaged cells in the MMC (positive control) treatment group (13.5%) was statistically significant.

Toxicity in CHO cells when treated for 4 hours in the presence of S9 activation was 42% at 2600 µg/mL, the highest test concentration evaluated for chromosome aberrations. The mitotic index at the highest dose level evaluated for chromosome aberrations, 2600 µg/mL, was 56% reduced relative to the solvent control. The dose levels selected for

microscopic analysis were 1000, 2000, and 2600 µg/mL. The percentage of cells with structural aberrations in the test article-treated groups was statistically increased above that of the solvent control at dose level 2600 µg/mL. However, the percent aberrant cells in the test article-treated group (2.5%) was within the historical solvent control range of 0.0% to 6.5%. Therefore it is not considered to be biologically significant. The percentage of cells with numerical aberrations in the test article-treated groups was not statistically increased above that of the solvent control, regardless of dose level. The percentage of structurally damaged cells in the CP (positive control) treatment group (21%) was statistically significant.

In the absence of a positive response in the non-activated 4 hour exposure group, slides from the non-activated 20 hour exposure group were evaluated for chromosome aberrations. Toxicity was 15% at 1000 µg/mL, the highest test concentration evaluated for chromosome aberrations in the non-activated 20 hour continuous exposure group. The mitotic index at the highest dose level evaluated for chromosome aberrations, 1000 µg/ml, was 57% reduced relative to the solvent control. The dose levels selected for microscopic analysis were 250,500, and 1000 µg/ml. The percentage of cells with structural and numerical aberrations in the test article-treated groups was not significantly increased above that of the solvent control, regardless of dose level. The percentage of structurally damaged cells in the MMC (positive control) treatment group (14.5%) was statistically significant.

In conclusion, lidocaine was negative in the in vitro chromosome aberration assay with CHO cells under the conditions tested. This conclusion is in agreement with that of the sponsor.

**Study title:** Mammalian Erythrocyte Micronucleus Test (in vivo)

**Key findings:**

- Lidocaine produced negative results in the in vivo mouse micronucleus assay at IP doses up to 80 mg/kg under the conditions tested.

**Study no.:** AA48ZP.123.BTL

**Volume #, and page #:** electronic

**Conducting laboratory and location:** —

**Date of study initiation:** September 2001

**GLP compliance:** Yes

**QA reports:** yes (X) no ( )

**Drug, lot #, and % purity:** Northstar (Lidocaine hydrochloride, USP), 01-04-0084, —

## Methods

Strains/species/cell line: ICR mice; at the initiation of the study, the mice were 6 to 8 weeks old. Five animals per sex at all doses at 24 hours; 5/sex for vehicle control and high dose at 48 hours. Animal body weights recorded at randomization were within the following ranges:

Pilot Toxicity Study: Male: 29.2 - 33.1 g; Female: 25.1 - 27.9 g

Toxicity Study: Male: 28.9 - 33.1 g; Female: 25.2 - 29.6 g

Micronucleus Assay: Male: 28.6 - 33.3 g; Female: 24.8 - 27.7 g

Doses used in definitive study: 0 (water), 20, 40, 80 mg/kg. The test article-vehicle mixture, the vehicle alone, or the positive control was administered by a single intraperitoneal injection at a constant volume of 20 ml/kg body

Basis of dose selection: In the pilot study, mice were randomly assigned to one group of five males and five females (dosed with 2000 mg test article/kg body weight) and to four groups of two males each (dosed with 1000, 100, 10 or 1 mg/kg).

In a toxicity study, mice were randomly assigned to four groups of five males and five females each. The animals were dosed with 40, 60, 80 or 100 mg test article/kg body weight.

Negative controls: water

Positive controls: cyclophosphamide, 50 mg/kg,

Incubation and sampling times:

At the scheduled sacrifice times (24 and 48 hours), five mice per sex per treatment were sacrificed by CO<sub>2</sub> asphyxiation. Immediately following sacrifice, the femurs were exposed, cut just above the knee, and the bone marrow was aspirated into a syringe containing fetal bovine serum. The bone marrow cells were transferred to a capped centrifuge tube containing approximately 1 mL fetal bovine serum. The bone marrow cells were pelleted by centrifugation at approximately 100 x g for five minutes and the supernatant was drawn off, leaving a small amount of serum with the remaining cell pellet. The cells were resuspended by aspiration with a capillary pipet and a small drop of bone marrow suspension was spread onto a clean glass slide. Two slides were prepared from each mouse. The slides were fixed in methanol, stained with May-Gruenwald-Giemsa and permanently mounted.

Slides were coded using a random number table by an individual not involved with the scoring process. Using medium magnification, an area of acceptable quality was selected such that the cells were well spread and stained. Using oil immersion, 2000 polychromatic erythrocytes per animal were scored for the presence of micronuclei which are defined as round, darkly staining nuclear fragments, with sharp contour with diameters usually from 1/20 to 1/15 of the erythrocyte. The number of micronucleated normochromatic erythrocytes in the field of 2000 polychromatic erythrocytes was

enumerated for each animal. The proportion of polychromatic erythrocytes to total erythrocytes was also recorded per 1000 erythrocytes.

The incidence of micronucleated polychromatic erythrocytes per 2000 polychromatic erythrocytes was determined for each mouse and treatment group. Statistical significance was determined using the Kastenbaum-Bowman tables. All analyses were performed separately for each sex and sampling time. In order to quantify the proliferation state of the bone marrow as an indicator of bone marrow toxicity, the proportion of polychromatic erythrocytes to total erythrocytes was determined for each animal and treatment group.

## Results

Study validity: The criteria for the test article to be evaluated positive were acceptable (the test article was considered to induce a positive response if a dose-responsive increase in micronucleated polychromatic erythrocytes was observed and one or more doses were statistically elevated relative to the vehicle control ( $p > 0.05$ ), at any sampling time. The dose selection and counting method were appropriate and the positive control produced the expected results.

### Study outcome:

In the pilot study, dosing formulations were administered in a total volume of 20 mL test article-vehicle mixture/kg body weight by a single IP injection. Mortality occurred after dose administration as follows: 0/2 males at 10 mg/kg, 1/2 males at 100 mg/kg, 2/2 males at 1000 mg/kg and 5/5 males and 5/5 females at 2000 mg/kg. Due to mortality after dose administration, clinical signs in males and females at 1000 and 2000 mg/kg were not observed. One surviving male mouse at 100 mg/kg on the day of dosing exhibited convulsions, lethargy and piloerection and had crusty eyes.

In the toxicity study (40, 60, 80 and 100 mg/kg, IP), mortality was observed only after dose administration in 1/5 males at 100 mg/kg. Clinical signs observed immediately following dose administration included: ataxia and lethargy in males and females at 80 and 100 mg/kg in addition to convulsions in males and females at 100 mg/kg. Piloerection was also seen approximately four hours after dose administration in males at 100 mg/kg. The MTD appears to be 80 mg/kg.

In the micronucleus test (20, 40 or 80 mg/kg as well as with the negative or positive control article, IP) no mortality occurred at any dose level during the course of the micronucleus study. Clinical signs, which were noted after dose administration included: ataxia in males and females at 80 mg/kg and lethargy in males at 80 mg/kg. All other mice treated with the test or control articles appeared normal during the study.

Reductions of 1% to 2% in the ratio of polychromatic erythrocytes to total erythrocytes were observed in some of the test article-treated groups relative to the respective vehicle controls suggesting that the test article did not inhibit erythropoiesis. The number of micronucleated polychromatic erythrocytes per 2000 polychromatic erythrocytes in test

article-treated groups was not statistically increased in either male or female mice, regardless of dose level or bone marrow collection time relative to the respective vehicle controls. CP induced a significant increase in micronucleated polychromatic erythrocytes in both male and female mice.

Lidocaine produced negative results in the in vivo mouse micronucleus assay at IP doses up to 80 mg/kg under the conditions tested. This conclusion is in concurrence with that of the sponsor.

### 3.4.5 Carcinogenicity

Carcinogenicity studies with lidocaine, epinephrine or their combination have not been conducted and are not deemed necessary due to the limited duration of exposure expected and the endogenous nature of epinephrine. The lidocaine metabolite 2,6-xylidine was carcinogenic in mice and/or rats (see the reviews for NDA 19-941 dated June 19, 1992 and September 28, 1992 by Dr. Dou Lucy Jean for details). 2,6-xylidine produced carcinomas and adenomas in the nasal cavity and a rhabdomyosarcoma (rare) in rats at an oral dose of 150 mg/kg. An increased incidence of subcutaneous fibromas and/or fibrosarcomas was also noted in males while neoplastic nodule of the liver were observed in females. In May 1996, the relevancy of the rat tumor findings to humans was discussed by CDER's Executive Carcinogenicity Assessment Committee (see minutes dated May 14, 1996 under NDA 19-941). The committee concluded that the tumor findings are not relevant to humans and should not be included in the labeling nor should the labeling of other anesthetic products containing lidocaine be revised.

Assessment of the carcinogenic potential of epinephrine (aerosol inhalation) in rats and mice was performed by NTP in 1990. Rats were administered 0, 1.5 or 5 mg/m<sup>3</sup> epinephrine HCl, 5 days/week for 103 weeks. Mice were administered 0, 1.5 or 3 mg/m<sup>3</sup>, 5 days/week for 104 weeks. Although dose levels exceeded maximum human therapeutic levels, they were less than one-half the MTD. No carcinogenic effects were observed but the studies were considered to be inadequate, as doses were too low for the animals to have received an adequate systemic challenge from the compound.

### 3.4.6 Reproductive and developmental toxicology

The sponsor did not perform formal reproductive and developmental toxicology studies with lidocaine or epinephrine. As agreed to during the pre-NDA meeting, the sponsor submitted a review of the available information in the literature. The following is a review of the sponsor's submission (dated March 31, 2003) regarding the potential reproductive effects.

The sponsor's assessment was performed following an expanded search of the MEDLINE and TOXNET databases of the National Library of Medicine.

#### Effects on fertility and early embryonic development:

##### Lidocaine:

Female Sprague-Dawley rats were continuously administered lidocaine HCl via an implanted osmotic pump at doses of 0, 100 or 250 mg/kg/day for 2 weeks prior to mating<sup>1</sup>. Separate groups were exposed to 500 mg/kg/day lidocaine or saline only after pregnancy was established. No maternal toxicity was observed and there were no significant differences in terms of reproductive parameters. Fetal body weight in the high-dose lidocaine group (500 mg/kg) was reduced by 24% when compared to its control group. No treatment related effects on the number or external, visceral or skeletal abnormalities. An increased incidence of incomplete ossification of the sternbrae was noted in the high-dose group compared to the control group (12.8% vs 0%).

To further assess the observed body weight effects on fetal weight, timed-pregnant rats were continuously exposed to sterile water or lidocaine on gestation day 3 to natural delivery. Lidocaine treated rats demonstrated a significant delay in delivery time compared to the control group. There were, however, no significant effects on neonatal body weight.

Plasma levels in these animals are summarized in the table below. Plasma levels increased in dams in a generally proportional manner and the concentration in fetuses was similar to that of the dams.

Group	Dose (mg/kg/day)	Plasma concentration (µg/ml)
Pregnant rats	100	2.8
	250	6.5
	500	11.9
Fetus (gestation day 21)	500	8

##### Epinephrine:

Subcutaneous doses (100 µg/day/mouse) administered for 1-6 days pre-implantation or 7-10 days post-implantation reduced the number of pregnancies in mice<sup>2</sup>. The effect was reversed by treatment with progesterone or prolactin. Epinephrine inhibited prolactin

<sup>1</sup> Fujinaga and Mazze, 1986.

<sup>2</sup> Robson et al, 1969.

release centrally and did not inhibit progesterone effects on the uterus or vaginal mucification.

Constant infusion of epinephrine (1 µg/hr) in pregnant Wistar rats via a subcutaneously implanted osmotic mini-pump on gestation days 1-8, 8-15 and 15-22 produced no maternal toxicity and had no effect on general fertility levels, pregnancy rates, survival or incidence of malformations<sup>3</sup>.

In pregnant Dutch-Belted female rabbits administered 600 µg/kg, bid, on gestation days 3-5, 6-7, or 7-9, a decreased number of implantation sites compared to control was noted on gestation days 6-7 or 7-9. All epinephrine treated animals had a significantly lower number of normal fetuses and there was an increased incidence of fetal death.

#### **Effects on embryo-fetal development:**

##### **Lidocaine:**

Explanted mouse embryos (somite stage 1-2) obtained from pregnant female C57BL/6 mice (gestation day 9) demonstrated neural tube defects (failure to fuse the anterior neural folds) after a 36 hour incubation in a serum containing lidocaine (0.24 µg/ml)<sup>4</sup>. This finding was not repeated in rat embryos at concentrations up to 500 µM<sup>5</sup>. Mouse embryos cultured with lidocaine for 30 hours followed by 6 hours of control serum appeared morphologically and ultrastructurally normal. SEM examination showed that neuroepithelium cells were partially elevated and there was a loss of microfilament bundles microtubules. Other in vitro mouse embryo studies reported adverse effects on fertilization and early in vitro development in the mouse were adversely affected by lidocaine when cumulus masses are exposed to lidocaine for 30 minutes prior to fertilization<sup>6</sup>, a decreased percentage of two-cell embryos cleaving and developing to more advanced stages<sup>7</sup>, or no effect on development following a 30 minute exposure<sup>8</sup>. Explanted rat embryos from pregnant rats showed growth retardation at 375 µM, severe morphological abnormalities at 500 µM, reduced viability (16%) at 500 µM and 100 µM (100%), and increased incidence of situs inversus at 10 and 250 µM (8-34%)<sup>9</sup>. Chick embryos exhibited a dose-related inhibition of neural tube closure following 6 hours of exposure to 100-400 µg/ml lidocaine with higher doses inducing embryo lethality<sup>10</sup>. A relaxation of the neural fold was observed following 3-6 hours of incubation with 200 µg/ml lidocaine<sup>11</sup>; recuperation of the effect was noted 7-24 hours later.

A single intraperitoneal injection of lidocaine (32-70 mg/kg) in pregnant JB/T/Jd mice on gestation day 9 did not affect neural tube closure but showed some potential for developmental retardation including dilatation of the 4<sup>th</sup> ventricle<sup>12</sup>. Intraperitoneal

<sup>3</sup> Trend and Bruce, 1989.

<sup>4</sup> O'Shea and Kaufman, 1980).

<sup>5</sup> Fujinaga and Baden, 1993.

<sup>6</sup> Schnell et al, 1992.

<sup>7</sup> Del Valle and Orihuela, 1996.

<sup>8</sup> McFarland et al, 1989.

<sup>9</sup> Fujinaga, 1998.

<sup>10</sup> Lee and Nagle, 1985.

<sup>11</sup> Lee et al, 1988.

<sup>12</sup> Martin and Jurand, 1992.

injections of 56 mg/kg/day in Sprague-Dawley rats on gestation days 5-7, 9-11, 12-14 or 15-17 resulted in no effects on embryo-fetal development<sup>13</sup>. A continuous subcutaneous exposure via an implanted osmotic pump (0, 100, 250) for 2 weeks prior to mating through gestation day 21 produced no adverse effects, while exposure to 500 mg/kg/d on gestation days 3-17 produced slight fetal weight reduction and a delay in ossification in sternbrae<sup>1</sup>.

#### Epinephrine:

Topical application of epinephrine (single dose, 5 µg) to chick embryos at 4 hour intervals for 22-190 hours produced a time-related spectrum of aortic arch abnormalities involving 3<sup>rd</sup>, 4<sup>th</sup>, and 6<sup>th</sup> pairs of aortic arches and the right 4<sup>th</sup> arch between 60-148 hours (peak response 108-112 hours)<sup>14</sup>. In another study, topical application was associated with ECG abnormalities that were correlated with a high incidence of abnormal obliteration of the aortic arch, and a high incidence of embryonic death<sup>15</sup>. Subcutaneous administration of epinephrine to pregnant mice resulted in cleft palate formation at doses of 10 µg/day on gestation days 11-14 or 20 µg/day on gestation days 12 or 13; total fetal resorption occurred at 50 µg/day. Intra-amniotic injections (5-10 µg) during gestation days 15-16 produced hemorrhagic lesions of fetal extremities followed by necrosis due to prolonged arterial vasoconstriction<sup>16</sup>. No effects were observed in a study in which 10 µg epinephrine/day was administered by IP, IM or SC routes on gestation days 11-14<sup>17</sup>.

Direct administration of epinephrine (8-50 µg/d, injection) to fetuses of White pregnant rats resulted in paleness and a high incidence of fetal death. Reduced fetal body weight and cataracts were observed in surviving fetuses<sup>18</sup>.

Subcutaneous administration of 500 µg/kg/day on gestation days 7-10 to pregnant hamsters resulted in a decrease of reproductive success and pre-implantation wastage but was not teratogenic<sup>19</sup>. IM or IV injections (171 µg/day) to pregnant rabbits during gestation days 15-17, 16, 16-18, 20, 21-23 or 22-24 resulted in increased number of runts only with IV administration during the latter two periods tested<sup>20</sup>.

#### Effects on prenatal and postnatal development:

##### Lidocaine:

Injection of 6 mg/kg lidocaine on gestation day 11 in pregnant Long-Evans hooded rats resulted in offspring exhibiting delayed negative geotaxis and righting reflex, enhanced footshock sensitivity, increased errors in a water maze, longer suppression times in conditioned suppression tasks and changes in operant visual discrimination responses<sup>21</sup>. Injection of the same dose into the masseter muscle of Sprague-Dawley rats on gestation

<sup>13</sup> Ramazzotto et al, 1985.

<sup>14</sup> Hodach et al, 1974.

<sup>15</sup> Kolesari and Schnitzler, 1986.

<sup>16</sup> Davis and Robson, 1970.

<sup>17</sup> Blaustein et al, 1971.

<sup>18</sup> Pitel and Lerman, 1962.

<sup>19</sup> Hirsch and Fritz, 1981.

<sup>20</sup> Cliff and Reynolds, 1959.

<sup>21</sup> Smith et al, 1985.

day 10 and 11 did not have significant effects on developmental parameters<sup>22</sup>. A similar lack of effect was reported following SC injection of 20 mg/kg/d on gestation days 15-17<sup>23</sup>. Injection of lidocaine (with 1:100,000 epinephrine) at doses of 3, 6, or 9 mg/kg into the gum of the lower jaw of pregnant female Long-Evans rats on gestation days 4, 11 or 18 resulted only in non-dose-related changes in footshock sensitivity and avoidance, visual discrimination, and water maze errors<sup>24</sup>.

#### Epinephrine:

Subcutaneous administration of epinephrine (250 µg/day) on each successive day during the first 2 days of pregnancy in A/Jax, BALB/Ci and C57BL/6 mice resulted in an increase, no change or decrease in spontaneous activity, respectively.<sup>25</sup> Offspring of C57BL/6 mice were SC administered 0.25 µM epinephrine on gestation day 8, 10, 12 and 14 showed increased locomotor activity, increased grooming and decreased defecation.<sup>26</sup> IP administration of 750 µg/kg/day during gestation days 7-14 in Wistar rats resulted in less active offspring in open field and water maze tests, effects were greater at postnatal day 30 compared to day 60.<sup>27</sup>

#### 3.4.7 Local tolerance

No studies on local tolerance were performed by the sponsor.

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<sup>22</sup> Teiling et al, 1987.

<sup>23</sup> Mullenix and Moore, 1988.

<sup>24</sup> Smith et al, 1989.

<sup>25</sup> Thompson and Olian, 1961.

<sup>26</sup> Liberman, 1963.

<sup>27</sup> Young, 1964.

### 3.4.8 Special toxicology studies

**Study title:** Modified primary dermal irritation – (FDA Requirements, per 21 CFR 58)

**Key study findings:**

- Following application of the iontophoretic patch (pH 4.0) in a setting that mimics clinical use, dermal irritation scores were minor; 0-1 for erythema and edema in male New Zealand white rabbits.
- The Primary Irritation Index was 0.25 for the anode site and 0 for the cathode site. Thus, the patch is considered to be a non-irritant under the test conditions.
- Histopathology findings identified the presence of minimal to mild inflammation of the panniculus carnosus muscle in the hypodermis of several abraded and intact sites.

**Study no.:** GLP31737

**Volume #, and page #:** electronic

**Conducting laboratory and location:**

**Date of study initiation:** October 2001

**GLP compliance:** Yes

**QA reports:** yes (X) no ( )

**Drug, lot #, and % purity:** Lidocaine/epinephrine patches, lots 0171001, 0172002, 0173003, Lidocaine (lot LDD9B26X-C) and epinephrine (lot 433), lidocaine, epinephrine

**Formulation/vehicle:** Iontophoretic patch with pH 4.0 Adjusted Cathode, part # AR301267, adhesive patch with an anode and a cathode

Anode patch: lidocaine (100.3 mg, ), epinephrine (1.9 mg, ), NaCl, EDTA, citric acid, glycerin, sodium metabisulfite

Cathode patch: NaCl, monobasic sodium phosphate monohydrate, glycerin

#### Methods

Male New Zealand White rabbits (n=6, "young", 14-15 weeks old, 2-3 kg)

**Doses:** Test patches contained 100.3 mg lidocaine (30%) and 1.9 mg epinephrine bitartrate (0.57%); 491-547 µg lidocaine upon full transfer; 5.6-6.2 µg epinephrine upon full transfer

**Study design:** Each rabbit had two test areas; sites were 1.5 x 2.5 square inches and located lateral to the midline of the back. The center area of the test site on the left side of the midline was abraded by making minor incisions through the stratum corneum (3 abrasions ~ 4-6 cm; not deep enough to disturb the derma) while the right side site remained intact. Each test article (one for each site) was placed on the sites for 5 minutes prior to beginning iontophoresis. The skin was exposed to the test article through iontophoresis for 10 minutes. After iontophoresis the patch remained in place for 20 minutes to simulate clinical usage.

Once patches were removed the cathode and anode areas were marked and covered with a 2 inch square gauze patch and then the entire trunk of the animal was placed in impermeable occlusive wrapping. Following 24 hours of residual exposure, the patches were removed and the skin around the test site was washed with warm tap water to remove any unabsorbed test article. Each test site was individually examined at 24 and 72 hours post application for erythema and edema and was scored using the Draize method. Following the final dermal observation, animals were euthanized and necropsied. Tissues collected and preserved included heart, lungs, liver, kidneys, testes, spleen and normal skin. Both abraded and intact treatment sites were collected and preserved.

**Results:**

All animals registered a score of 0 (none) for erythema and eschar formation at the anode test site at both time points. Three of six animals registered a score of 1 (very slight) at the abraded site at 24 hours; one had a score of 1 at 72 hours. Two of six registered a score of 1 at the intact site at 24 hours. One animal exhibited a 1 x 1 cm<sup>2</sup> bruise on the abraded and intact site. All scores for erythema and edema at the cathode were 0. Gross necropsy observations were unremarkable. The Primary Irritation Index was 0.25 for the anode site and 0 for the cathode site. Thus, the patch is considered to be a non-irritant under the test conditions.

Histopathology findings identified the presence of minimal to mild inflammation of the panniculus carnosus muscle in the hypodermis of several abraded and intact sites.

**Study title:** Primary dermal irritation following iontophoresis with BDTS Northstar patches

**Key study findings:**

- The test article #99-4400-001 was determined to be a slight irritant for the anode site and a negligible irritant for the cathode site in rabbits. The control patch was non-irritating.

**Study no.:** 32PD04.01

**Volume #, and page #:** electronic

**Conducting laboratory and location:** Worldwide Medical Toxicology, Becton Dickinson and Co., RTP, NC

**Date of study initiation:** October 1998

**GLP compliance:** Yes

**QA reports:** yes (X) no ( )

**Drug, lot #, and % purity:** No information provided in the study report other than the test article was 99-4400-001; unclear that this article contained lidocaine and/or epinephrine; sponsor's NDA summary indicates that the test article patch was a 10% lidocaine and 0.1% epinephrine formulation; Lidocaine (lot LDD9B26X-C) and epinephrine (lot 433), — lidocaine; — epinephrine

**Formulation/vehicle:** Iontophoretic patch: Anode patch: lidocaine (100.3 mg, epinephrine (1.9 mg, , NaCl, EDTA, citric acid, glycerin, sodium metabisulfite  
Cathode patch: , NaCl, glycerin  
Control patches with saline, water, glycerin, and monobasic sodium phosphate monohydrate

### Methods

Healthy naïve female New Zealand White rabbits (n=6, approximately 3 month of age; 2-3 kg)

Doses: Test patches contained 100.3 mg lidocaine (30%) and 1.9 mg epinephrine bitartrate (0.57%)

Study design: Prior to application of test patch, rabbits' backs were clipped free of fur. Six animals (gender not specified) were selected. Each rabbit had two test areas; one for test patch and one for the control (saline) patch. The sites of 3 rabbits were abraded and the other 3 were left intact. Patches were applied directly to animals and remained on the sites for 5 minutes prior to beginning iontophoresis. The skin was exposed to the test article through iontophoresis (1.8 mA) for 10 minutes. After iontophoresis the patch remained in place for 15 minutes for an approximate total patch contact time of 30 minutes. Evaluations for dermal reactions of anode and cathode sites were conducted immediately following patch removal, with subsequent evaluations at 24, 48, and 72 hours following patch removal. Each test site was individually examined for erythema and edema and was scored using the Draize method. The sum of the scores was divided by the total number of observations, giving a Primary Dermal Irritation Index.

**Results:** One animal with abraded sites demonstrated erythema and edema scores of 1 (slight) following administration of the test patch at the anode site at the 24, 48 and 72 hour timepoints. All other animals in this group were scored with a 0. Two animals with intact sites demonstrated effects due to the test patch: at the anode site one was scored a 1 (slight) for erythema at all timepoints and 1 for edema at 72 hours only; the other was scored 1-2 for erythema (slight to well-defined) at the anode site for all timepoints and 1 for erythema at the cathode site at 48 and 72 hours. Control patches produced no adverse findings. Primary Dermal Indices of 0.8 and 0.1 for the anode and cathode sites, respectively, were identified for the test article #99-4400-001. Thus, the test article is considered to be a slight irritant for the anode site and a negligible irritant for the cathode site in rabbits.

**Study title:** A 14-Day Repeated Application Dermal Irritation /Toxicity Study**Key study findings:**

- New Zealand white rabbits administered the lidocaine patch demonstrated scores of erythema/edema scores of 0 at both the anode and cathode site on all study days. Observations at the patch site included small red scab like areas at the anode sites of most animals.
- Histologic assessment of treated skin samples following 14-day treatment demonstrated an increased incidence and severity of findings in lidocaine treated animals; findings included hyperplasia, crusting, fibrosis, congestion/hemorrhage and focal degeneration of hair follicle units.

**Study no.:** GLP31736**Volume #, and page #:** electronic**Conducting laboratory and location:****Date of study initiation:** October 2001**GLP compliance:** Yes**QA report:** yes (X) no ( )**Drug, lot #, and % purity:** Lidocaine (lot LDD9B26X-C) and epinephrine (lot 433),  
— lidocaine; — % epinephrine**Formulation/vehicle:** Iontophoretic patch: Anode patch: lidocaine (100.3 mg, epinephrine (1.9 mg, — , — NaCl, EDTA, citric acid, glycerin, sodium metabisulfite

Cathode patch: — NaCl, glycerin and monobasic sodium phosphate monohydrate

Control patches: anode: epinephrine (1.9 mg, — , — NaCl, EDTA, citric acid, glycerin, sodium metabisulfite; cathode: — NaCl, glycerin and monobasic sodium phosphate monohydrate

**Methods**

Doses: 99.8-102.3 mg/patch lidocaine, 491 µg – 547 µg lidocaine upon full transfer; 1.02-1.06 mg/patch epinephrine, 5.6-6.2 µg epinephrine upon full transfer

Species/strain: Rabbit/New Zealand white

Number/sex/group or time point (main study): 10

Route, formulation, volume, and infusion rate: dermal, Lidocaine (lots 0171001, 0172002, 0173003) or placebo (lot 0236004) iontophoretic patch (hydrogel on an adhesive patch, NA, NA

Satellite groups used for toxicokinetics or recovery: none

Age: according to protocol young adult or adult

Weight: according to protocol 2-3 kg

Unique study design or methodology (if any): Approximately 24 hours before the initial test article application, each test rabbit had the dorsal area of the trunk clipped free of hair. Two test sites were selected per rabbit. The sites were lateral to the mid-line of the back as well as parallel and on opposite sides of the midline of the dorsal region of the back. The sites were used in an alternating pattern. Daily, the test article or control

were applied and left in place for five minutes. The skin was exposed through iontophoresis with "low level current" for 10 minutes. Once completed, the patch remained in place for 20 minutes. Once removed, the areas of the anode and cathode were marked. Patches were applied every day to alternating sites for 14 days.

### Results:

Two control animals were sacrificed due to "non-product related injury". The animals were not replaced. Animals administered the placebo patch were examined at both the anode and cathode sites. All scores for erythema and eschar and edema were 0 (none) except for 2 animals, which exhibited very slight edema (1) on days 1 and 6, respectively, at the anode site. The scores returned to 0 on the next day. Other observations included small bruise like areas, and scabbing. Animals administered the lidocaine iontophoretic patch demonstrated scores of 0 at both the anode and cathode site on all study days. Observations included small red scab like areas at the anode sites of most animals.

Blood samples were drawn on Day 0 and 19. Serum, whole blood and plasma were retrieved for analysis. The following parameters were assessed: WBC, RBC, hemoglobin, hematocrit, platelets, albumin, ALT, AST, bilirubin, BUN, Ca, Cl, creatinine, glucose, GGT, LDH, magnesium, Phosphorous, Potassium, sodium, uric acid, and total protein. Overall, no significant differences were observed between placebo patch treated animals and lidocaine treated animals although there was a large amount of variability in the data and not all parameters were assessed in all animals.

At study termination, samples from untreated and treated areas were obtained and preserved in 10% buffered formalin. Additionally, the lungs, heart, kidneys, normal skin, spleen, liver and testes/ovaries were preserved for possible future assessment.

performed histopathology assessment and four representative skin sections from each animal were trimmed, paraffin-embedded, and sectioned.

Reactive changes in treated skin samples following 14-day treatment were slightly more severe in lidocaine treated animals. Average (composite) severity scores were 3 and 5.6 in control males and females, respectively, and 19.4 and 23.2 in lidocaine treated males and females, respectively. Microscopic changes included hyperplasia, crusting, fibrosis, congestion/hemorrhage and focal degeneration of hair follicle units. Reversibility of these findings was not assessed.

Microscopic findings at patch treatment sites: Incidence (severity)

Specimen site	Males		Females	
	Placebo (n=4)	Lidocaine (n=5)	Placebo (n=4)	Lidocaine (n=5)
<b>Epidermis</b>				
Hyperplasia (acanthosis)	1 (1)	5 (1-3)	2 (1-2)	5 (1-3)
Seroellular crust	3 (1)	5 (1-3)	4 (1)	5 (1-3)
Hyperkeratosis	0	0	1 (1)	2 (1-2)
Erosion/Ulcer	0	1 (1)	0	1 (1)
<b>Dermis</b>				
Infiltrates, lymphocytic	1 (1)	3 (1-2)	2 (1)	3 (1-2)
Fibroplasia, fibrosis	2 (1)	5 (1-3)	4 (1-2)	5 (1-3)
Congestion/hemorrhage	0	3 (1)	0	3 (1)
Degeneration hair follicle	0	5 (2-3)	0	5 (2-3)
<b>Hypodermis</b>				
Inflammation, NOS	1 (1)	0	0	0

Severity score: 1 (minimal); 2 (mild); 3 (moderate)

**Study title:** Delayed contact hypersensitivity – Buehler Method

**Key study findings:**

- The evaluated lots of Lidocaine Iontophoretic patch were non-sensitizing under the conditions tested in Hartley Guinea pigs.

**Study no.:** GLP 31738

**Volume #, and page #:** electronic

**Conducting laboratory and location:**

**Date of study initiation:** October 2001

**GLP compliance:** Yes

**QA reports:** yes (X) no ( )

**Drug, lot #, and % purity:** Lidocaine iontophoretic patch, lots 0171001, 0172002, 0173003, Lidocaine (lot LDD9B26X-C) and epinephrine (lot 433), lidocaine; % epinephrine

**Formulation/vehicle:** Iontophoretic patch: Anode patch: lidocaine (100.3 mg epinephrine (1.9 mg, NaCl, EDTA, citric acid, glycerin, sodium metabisulfite

Cathode patch: NaCl, glycerin and monobasic sodium phosphate monohydrate

Control patches: anode: epinephrine (1.9 mg, 0.57%), NaCl, EDTA, citric acid, glycerin, sodium metabisulfite; cathode: NaCl, glycerin and monobasic sodium phosphate monohydrate

**Methods**

**Doses:** 99.9 mg lidocaine; 1.06 mg epinephrine: 491-547 µg lidocaine upon full transfer; 5.6-6.2 µg upon full transfer

**Study design:** Guinea pig, Hartley derived (53-75 days old; 300-500 g; 15/sex for test article, 5 /sex for control; Placebo iontophoretic patch). Each of 20 test group Guinea pigs (10 per sex) had a shaved site selected for the induction phases. For each of 3 induction phases, the test article was placed on this site with a piece of elastikon tape placed over the patch to aid in keeping it in place. The patch was on the test site for 5 minutes prior to initiating iontophoresis with low level current. Iontophoresis occurred for 10 minutes and once completed the patch remained on the site for 20 minutes. The adhesive patch was removed and the anode and cathode sites were marked and each site then covered with a square gauze patch. Each of 10 control animals was also dosed for 3 induction phases with the control vehicle. The patches for test and control groups were removed after 6 hours and warm water was used to remove any residue. Scoring of both sites then occurred at the 6 hour, 24 hour and 48 hour post-test article application. The induction phase was repeated 2 more times (weekly) on the same test site. Following a 2-week rest period, animals were dosed and wrapped as in the induction phase on a naïve test site for the challenge phase. The patches for test and control groups were removed after 6 hours and warm water was used to remove any residue. Scoring of both sites then occurred at the 6 hour, 24 hour, 48 hour and 72 hours post-test article application. A positive control group (DNCB, 0.5%) is validated every 6 months.

**Results:** At the cathode site, all animals were unremarkable at the 6, 24 and 48 hour time periods for all 3 induction phases. At the 6 hour time point for the challenge phase, all animals appeared normal. Two animals had very faint, non-confluent erythema (0.5) at the 24, 48 and 72 hour time points.

At the anode site, 7 animals (3 males, 4 females) were scored a 0.5 at various time points and various induction dosing periods. Findings in males were observed primarily at 24 hours after the first induction; findings in females occurred in all induction phases but findings in individual animals occurred only in single phases. A response to the challenge occurred in only 2 females at 48 and 72 hours after challenge, respectively. One of the females had exhibited no response during the induction phase.

Vehicle control animals were unremarkable except for 1 male, which demonstrated a score of 0.5 at the anode site at 24 and 48 hours after the first induction dose.

Based on the results, the evaluated lots of Lidocaine Iontophoretic patch are determined to be a non-sensitizer.

**Study title:** Biological evaluation of medical devices – Part 10: Tests for irritation and sensitivity according to ISO 10993-10, 1995 (E)

**Key study findings:**

- An extract of Top and Bottom Housings Lots 00-09-0154 and 00-09-0155 was a non-sensitizer in Guinea pigs under the conditions tested.

**Study no.:** GLP 31739

**Volume #, and page #:** electronic

**Conducting laboratory and location:**

**Date of study initiation:** October 2001

**GLP compliance:** Yes

**QA reports:** yes (X) no ( )

**Drug, lot #, and % purity:** Top and Bottom housings, Lots 00-09-0154 and 00-09-0155, NA

**Formulation/vehicle:** NA

**Methods**

The objective of the study is to evaluate the potential of an extract of Top and Bottom Housings, in a 50% EtOH and 50% WFI solution, to induce a systemic hypersensitivity response by a modified Buehler method.

Doses: 0.5 ml of an extract of the test article

Study design: Guinea pig, Hartley derived (300-500 g; 15/sex for test article, 5 /sex for control; Placebo iontophoretic patch). Each of 20 test group Guinea pigs (10 per sex) had a shaved site selected for the induction phases. For each induction phase for the test group, a mass of ~ 3.5 g (half top housing and half bottom housing) was weighed out and subdivided into small pieces. The test material was then rinsed with 70 ml of WFI and agitated for ~ 30 seconds and the WFI was then decanted. The rinsing method was repeated and the test material was dried prior to execution. The test material was then placed in an extraction vessel and 20 ml of 50% EtOH and 50% WFI solution was added; the sample was agitated. The test material was extracted for 1 hour at 121 degrees C. For the challenge phase, 2 extractions were performed and combined. The vehicle control was 20 ml 50% EtOH /50% WFI solution.

For each of 3 induction phases, 0.5 ml of an extract of the test article was placed on the test site. Each site was covered with a square gauze patch secured with non-irritating tape, overwrapped with plastic film and secured with additional non-irritating tape. Each of 10 control animals was also dosed for 3 induction phases with 0.5 ml of control extract for the vehicle control. The patches for test and control groups were removed after 6 hours and warm water was used to remove any residue. Scoring of the sites occurred at the 6 hour, 24 hour and 48 hour post-test article application. The induction phase was repeated 2 more times (weekly) on the same test site. Following a 2-week rest period, animals were dosed and wrapped as in the induction phase on a naïve test site for the challenge phase. Additionally, the naïve control group were dosed the same. The patches

for test and control groups were removed after 6 hours and warm water was used to remove any residue. Scoring of both sites then occurred at the 6 hour, 24 hour, 48 hour and 72 hours post-test article application. A positive control group (DNFB, 0.5%) is validated every 6 months.

**Results:** All animals were unremarkable at the 6, 24 and 48 hour time periods for all 3 induction phases except for two animals which were scored a 1 (slight erythema) at the 6 hour time point at induction 1 and the 6 hour time point at induction 2, respectively. All scores during the challenge phase were 0. The vehicle control group and naïve control group were score as 0 at all time points.

Based on the results, an extract of Top and Bottom Housings Lots 00-09-0154 and 00-09-0155 are determined to be a non-sensitizer under the conditions tested.

**Study title:** Biological evaluation of medical devices – Part 10: Tests for irritation and sensitivity according to ISO 10993-10, 1995 (E)

**Key study findings:**

- An extract of Top and Bottom Housings Lots 00-09-0154 and 00-09-0155 was a non-dermal irritant in male New Zealand white rabbits under the conditions tested.

**Study no.:** GLP 31735

**Volume #, and page #:** electronic

**Conducting laboratory and location:**

**Date of study initiation:** October 2001

**GLP compliance:** Yes

**QA reports:** yes (X) no ( )

**Drug, lot #, and % purity:** Top (SB300229) and Bottom housings (SB300230), Lots 00-09-0154 and 00-09-0155, NA

**Formulation/vehicle:** NA

**Methods**

The objective of the study is to evaluate the potential of devices and their constituent materials to produce irritation from the exposure of rabbit skin to an extract of Top and Bottom housings

Doses: 0.5 ml of an extract of the test article or vehicle control.

Study design: New Zealand White rabbit; 6 males; ~ 2 kg. A mass of ~ 3.6 g composed of both top and bottom housing) was weighed out and subdivided into small pieces. The test material was then rinsed with 70 ml of WFI and agitated for ~ 30 seconds and the WFI was then decanted. The rinsing method was repeated and the test material was dried prior to extraction. The test material was then placed in an extraction vessel and 20 ml of 50% EtOH and 50% WFI solution was added; the sample was agitated. The test material

was extracted for 1 hour at 121 degrees C. The extraction was decanted and used within 24 hours.

Each rabbit had 4 shaved test sites selected. Two were selected per side and were located on opposite sides lateral to the midline of the back. The two front sites were for test article and the two back sites were for control article. The center area of the test sites on the left side was abraded with a sterile 18 gauge needle. The abraded test sites consisted of four abrasions; ~ 2 cm in length. The sites on the right side remained intact. A single application of 5 ml extract or 0.5 ml of control (extractant alone) was applied to each designated site and then covered with a square gauze patch. After all sites were treated, the entire trunk was encased in a semi-occlusive wrapping held in place with Elastikon tape. Following 4 hours of exposure, the patch was removed and any residual test or control article was wiped away using warm water. Each site was examined at 1 hour post patch removal and at 24, 48 and 72 hours.

**Results:** All test sites on all animals were graded 0 for edema and erythema at all time points. The Primary Irritation Index was 0 (negligible).

Based on the results, an extract of Top and Bottom Housings Lots 00-09-0154 and 00-09-0155 was not found to be a primary skin irritant under the conditions tested.

**Study title:** Biological reactivity test – In vitro: L929 MEM elution test

**Key study findings:**

- Thus, the extracts from the Top and Bottom housings were non-cytotoxic to L929 mouse fibroblast cells after 48 hours of exposure under the conditions of the test.

**Study no.:** 860853

**Volume #, and page #:** electronic

**Conducting laboratory and location:** \_\_\_\_\_

**Date of study initiation:** September 2001

**GLP compliance:** Yes

**QA reports:** yes (X) no ( )

**Drug, lot #, and % purity:** Top (SB300229) and Bottom housings (SB300230), Lots 00-09-0154 and 00-09-0155; NA

**Formulation/vehicle:** NA

**Methods**

The objective of the study is to determine whether samples elicit a cytotoxic effect on a monolayer of mouse fibroblast cells (ATCC CCL-1, NCTC Clone 929)

Doses: 2 ml of top and bottom housing extract

**Study design:** Use of mouse fibroblasts, strain ATCC CCL-1, NCTC Clone 929 subcutaneous connective tissue, areolar and adipose. Cells were cultured in MEM with 10% FBS, penicillin and streptomycin. Test sample was prepared as 0.2 g of sample/ml combining both top and bottom housing which comprise one unit and are both made from the same material. Samples were extracted in 20 ml of MEM supplemented with fetal bovine serum and penicillin and streptomycin for 24 hours at 37 degrees C. A positive control (natural latex rubber) and negative control (silicone tubing) were prepared (both sides combined) 60 cm<sup>2</sup> total surface area, cut to 50 x 3 mm strips and extracted. Extracts were sterilized by passing through a 0.22 μ filter. The medium from the cell culture was aspirated and replaced with 2 ml of extract and samples were incubated at 37 degrees C for up to 48 hours. Cells were removed for observations of change in morphology at 24 and 48 hours. Extracts were tested in triplicate.

**Results:** No signs of cellular reactivity (Grade 0) were observed for test article and no signs of cellular activity were observed for the negative control article. Moderate reactivity (Grade 3) was noted for the positive control article at 24 and 48 hours.

Thus, the extracts from the Top and Bottom housings were noncytotoxic to L929 mouse fibroblast cells after 48 hours of exposure under the conditions of the test.

### 3.6 OVERALL CONCLUSIONS AND RECOMMENDATIONS

**Conclusions:** The proposed lidocaine iontophoretic patch is intended to deliver a locally anesthetizing dose to a dermal area. The addition of epinephrine to the product formulation is intended to prolong the duration of action of the anesthetic. This NDA refers to the previously approved Iontocaine NDA.

The pharmacology of lidocaine and epinephrine are well characterized and there is extensive clinical experience with both compounds. Clinical trials have demonstrated limited potential for systemic exposure, thus limiting concern for systemic toxicity.

The primary safety issue with this product is the potential for dermal effects at the patch treatment site. In studies submitted to IND 48,365, the sponsor performed evaluations with lidocaine alone and with epinephrine. Primary dermal irritation studies in rabbits and Guinea pigs did not produce any erythema or edema following 15 minutes exposure with iontophoresis and 4-24 hours after subcutaneous lidocaine injection. In another study, severe dermal irritation reactions at the active patch sites were observed in Guinea pigs. Evaluations determined that there was no effect due to voltage spikes or whether the animals were depilated or clipped animals. Administration of lidocaine HCl (10%) and phenylephrine (1%) produced mild to moderate irritation in rabbits following iontophoresis that recovered within 7 days in some animals. In more recent studies submitted to the NDA, application of the iontophoretic patch (pH 4.0) in a setting that mimics clinical use produced dermal irritation scores in male New Zealand white rabbits that demonstrated a lack of irritancy potential. Histopathology findings identified the

presence of minimal to mild inflammation of the panniculus carnosus muscle in the hypodermis of several abraded and intact sites. Similar results were observed in a 14-day repeat dose study in New Zealand white rabbits. Observations at the patch site included small red scab like areas at the anode sites of most animals and histologic assessment of treated skin samples following 14-day treatment demonstrated an increased incidence and severity of findings in lidocaine treated animals; findings included hyperplasia, crusting, fibrosis, congestion/hemorrhage and focal degeneration of hair follicle units. An evaluation of delayed contact hypersensitivity in Hartley Guinea pigs demonstrated that the Lidocaine Iontophoretic patch was non-sensitizing. Based on the submitted studies, the potential for dermal irritation has been adequately characterized in nonclinical models.

A genetic toxicology battery of studies with lidocaine was conducted by the sponsor and resulted in negative findings. Carcinogenicity studies have not been conducted with lidocaine and are not considered to be necessary for this product. Epinephrine was negative in 2-year studies in rats and mice conducted by NTP although the dosing was considered to be inadequate.

The Sponsor provided a review of the available literature regarding the reproductive toxicology potential of lidocaine and epinephrine. In vitro assessments of embryonic development identified the potential for lidocaine-induced neural tube defects that was not observed in vivo. Additionally, some postnatal developmental effects have been observed in certain animal models. Studies with epinephrine have demonstrated reduced pregnancies in mice and decreased implantation sites in rabbits. Topical application to chick embryos produced a time-related spectrum of aortic arch abnormalities and was also associated with ECG abnormalities that were correlated with a high incidence of abnormal obliteration of the aortic arch and a high incidence of embryonic death. Developmental effects included cleft palate formation and total fetal resorption following subcutaneous administration in mice, hemorrhagic lesions of fetal extremities followed by necrosis following intra-amniotic injections, and a high incidence of fetal death following direct administration of epinephrine to rat fetuses; cataracts were observed in surviving fetuses. Intravenous injections to pregnant rabbits resulted in increased number of runts. Offspring of mice showed increased locomotor activity, increased grooming and decreased defecation following direct SC administration while IP dosing of rat dams resulted in less active offspring in open field and water maze tests. In light of the observed low levels of clinical systemic exposure to lidocaine and epinephrine and the vast previous human experience with both compounds, the above-described potential developmental effects are not considered to be of clinical significance for the proposed drug product. Additionally, the referenced product, Iontocaine, is labeled as Category B for pregnancy. The review team concluded that a Pregnancy Category of B for the proposed product would be acceptable.

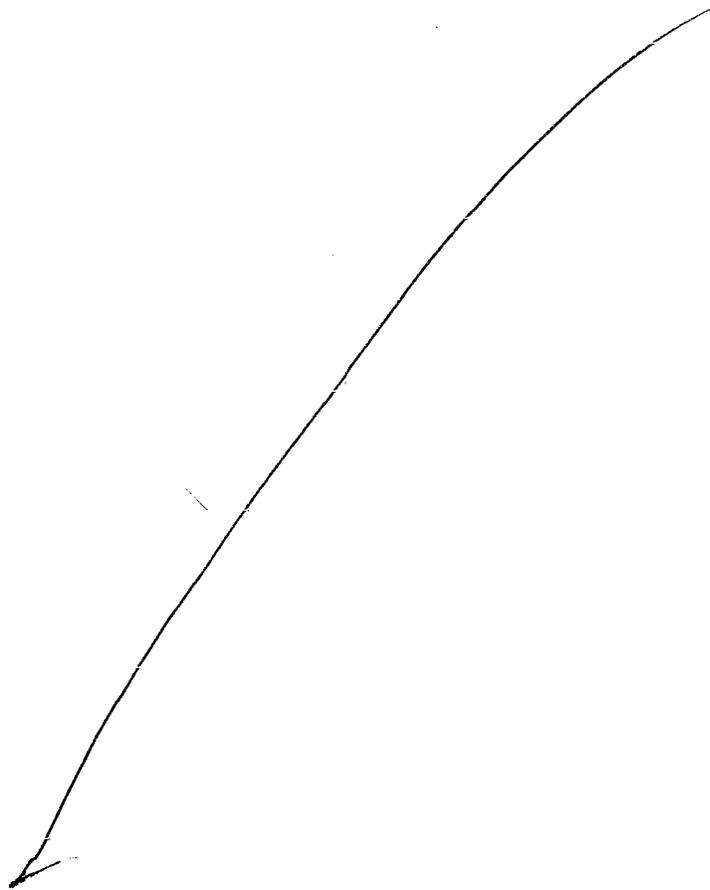
Studies performed to assess the irritancy potential and cytotoxicity of extracts from the top and bottom housings of the patch device demonstrated that extract solutions produced no dermal irritation in rabbits or sensitization in Guinea pigs and were not cytotoxic to L929 mouse fibroblast cells.

Unresolved toxicology issues (if any): None at this time.

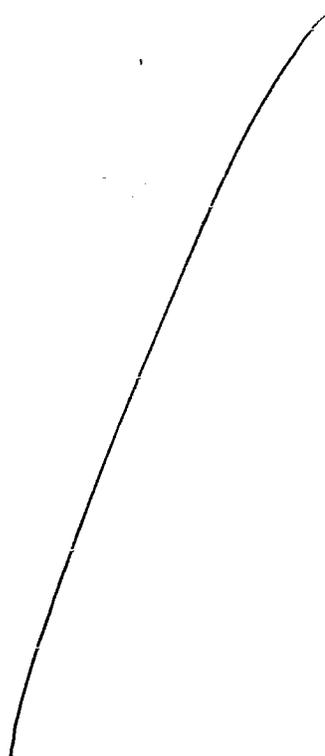
Recommendations: This NDA application is approvable from a non-clinical perspective.

Suggested labeling:

The sponsor proposed the following wording for the label regarding nonclinical data:



The following sections of the proposed label should be revised as follows:



Signatures (optional):

Reviewer Signature Timothy J. McGovern, Ph.D.  
Supervisory Pharmacologist

**3.7. APPENDIX/ATTACHMENTS**

None.

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

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Timothy McGovern  
7/24/03 08:50:45 AM  
PHARMACOLOGIST