CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

21-623

PHARMACOLOGY REVIEW

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

PHARMACOLOGY/TOXICOLOGY REVIEW AND EVALUATION

NDA NUMBER:	**21-623**
SERIAL NUMBER:	**N000 AZ**
DATE RECEIVED BY CENTER:	**12/27/2004**
DRUG NAME:	**7% lidocaine/7% tetracaine (S-Caine™ Patch)**
INDICATION:	[redacted]
SPONSOR:	**Zars, Inc.**
DOCUMENTS REVIEWED:	**5 of 33 volumes**
REVIEW DIVISION:	**Division of Anesthetic, Critical Care, and Addiction Drug Products (HFD-170)**
PHARM/TOX REVIEWER:	**Suzanne R. Thornton-Jones, Ph.D.**
PHARM/TOX SUPERVISOR:	**R. Daniel Mellon, Ph.D.**
DIVISION DIRECTOR:	**Bob Rappaport, M.D.**
PROJECT MANAGER:	**Allison Meyer**

Date of review submission to Division File System (DFS): 22 June 2005

EXECUTIVE SUMMARY

I. Recommendations

A. Recommendation on acceptability.
The NDA can be approved from a pharmacology/toxicology perspective.

B. Recommendation for nonclinical studies.
None.

C. Recommendations on labeling.
Note: Only the 'Impairment of Fertility' section of label was updated based on the results of the male fertility study with lidocaine.

Impairment of Fertility: Lidocaine did not affect fertility in female rats when given via continuous subcutaneous infusion via osmotic minipumps up to doses of 250 mg/kg/day (1500 mg/m^2 or 43-fold higher than the SDA). Although lidocaine treatment of male rats increased the copulatory interval and lead to a dose-related decreased homogenization resistant sperm head count, daily sperm production, and spermatogenic efficiency, the treatment did not affect overall fertility in male rats when given subcutaneous doses up to 60 mg/kg (360 mg/m^2 or 8-fold the SDA). Tetracaine did not affect fertility in male or female rats when given subcutaneous doses up to 7.5 mg/kg (45 mg/m^2 or 1-fold the SDA). Multiples of exposure are based on a single dermal administration (SDA) of 70 mg each of lidocaine and tetracaine in S-Caine Patch for 30 minutes to a 60 kg person (43 mg/m^2).

II. Summary of nonclinical findings

A. Brief overview of nonclinical findings
No affects of lidocaine base on male fertility were observed, although there was an increased copulatory interval at a dose of 60 mg/kg, and a dose-related decreased homogenization resistant sperm head count, daily sperm production, and spermatogenic efficiency, the treatment did not affect overall fertility in male rats when given subcutaneous doses up to 60 mg/kg (360 mg/m^2 or 8-fold the SDA). .

In the approvable letter for NDA 21-623 (S-Caine Patch) one of the pharmacology toxicology deficiencies dealt with the adequacy of the existing data characterizing the potential effects of lidocaine on fertility and early embryonic development. The deficiency is reproduced below:

12. The referenced reproductive toxicology literature you provided as adequate characterization of the effects of lidocaine on the fertility and early embryonic development is inadequate. For resubmission, you will need to provide data (original or public domain) that characterizes the effects of lidocaine treatment of

the male on fertility and early embryonic development. Males should be treated daily for at least 4 weeks prior to mating, through gestation until termination of the males. You should provide data that characterizes the effects of lidocaine treatment each of the following endpoints:

•Maturation of gametes
•Mating behavior
•Fertility
•Sperm counts in epididymides or testes
•Sperm viability, motility and morphology
•Histopathology of male reproductive organs (epididymis, testis, seminiferous tubules).

This deficiency was discussed during the Post-Action Meeting on 03 May 2004. At that time, the Sponsor indicated that a male fertility study on lidocaine was initiated on April 7, 2004 and included a signed protocol for the study. During that meeting, the Sponsor asked the following question: "Does the Agency concur that this study design addresses the endpoints specified in the action letter dated February 4, 2004?" As noted in the official meeting minutes, the FDA Response was as follows:

FDA Response:

• The study design for the male fertility study is acceptable.

The Sponsor submitted the final report as part of the NDA amendment. The labeling recommendations in the current review reflect the results of the study. As such, the sponsor has adequately addressed this deficiency.

B. Pharmacologic activity
Both lidocaine (amide-linked) and tetracaine (para-aminobenzoic acid ester) are local anesthetics which have similar pharmacological profiles and are about equipotent. Local anesthetics block nerve impulses by decreasing or preventing the large transient increase in the permeability of excitable membranes to Na+ that normally is produced by a slight depolarization of the membrane due to direct interaction with voltage-gated Na+ channels. Blockade of neuronal conduction prevents the action potential of sensory neurons and therefore blocks the transmission of pain signals to the CNS. Lidocaine and tetracaine blockade demonstrates both frequency and voltage-dependency. Both drugs block both open and inactivated Na+ channels.

C. Nonclinical safety issues relevant to clinical use.
None.

Reviewer Signature Suzanne R. Thornton-Jones, Ph.D.

Supervisor Signature R. Daniel Mellon, Ph.D. Concurrence Yes X No ___

TABLE OF CONTENTS

2.6 PHARMACOLOGY/TOXICOLOGY REVIEW

2.6.1 INTRODUCTION AND DRUG HISTORY

NDA NUMBER:	21-623
REVIEW NUMBER:	3
SEQUENCE NUMBER/DATE/TYPE OF SUBMISSION:	N000/17 December 2004/AZ
INFORMATION TO SPONSOR:	Yes ( ) No (X)
SPONSOR:	Zars, Inc. 1142 West 2320 South, Suite A Salt Lake City, UT 84119
MANUFACTURER FOR DRUG SUBSTANCE:	[lidocaine] [redacted] [tetracaine]
REVIEWER NAME:	Suzanne R. Thornton-Jones, Ph.D.
DIVISION NAME:	DACCADP
HFD #:	170
REVIEW COMPLETION DATE:	22 June 2005
DRUG:	
TRADE NAME:	S-Caine™ Peel
GENERIC NAME (LIST ALPHABETICALLY):	lidocaine/tetracaine
CODE NAME:	NA

CHEMICAL NAME:
[lidocaine] 2-(Diethylamino)-N-(2,6-dimethylphenyl)-acetamide
[tetracaine] 2-(Dimethylamino)ethyl p-(butylamino)benzoate

CAS REGISTRY NUMBER:	[lidocaine] 137-58-6 [tetracaine] 94-24-6
MOLE FILE NUMBER:	not specified
MOLECULAR FORMULA/MOLECULAR WEIGHT:	[lidocaine] $C_{14}H_{22}N_2O$/234.3 [tetracaine] $C_{15}H_{24}N_2O_2$/264.41

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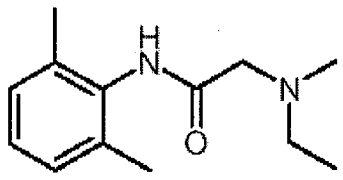
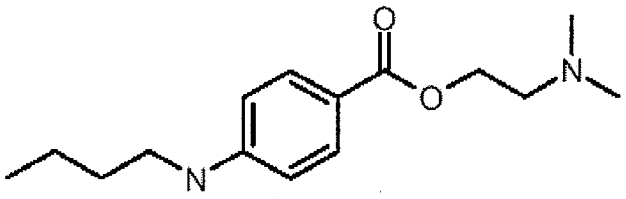


Lidocaine



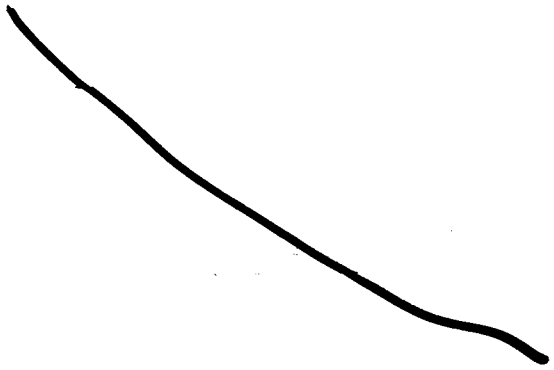
Tetracaine

RELEVANT INDS/NDAS/DMFS:	IND 59,801/NDA 21-717 (S-Caine™ Peel)
DRUG CLASS:	Local anesthetics of the amide type (lidocaine) and ester type (tetracaine).

INTENDED CLINICAL POPULATION: [redacted]

ROUTE OF ADMINISTRATION: topical

FORMULATION:



The excipients in the above formulation can be found in approved drug products at equal or greater levels and therefore do not pose any unique toxicological concerns.

BACKGROUND: The Sponsor has submitted a 505(b)(2) NDA application for S-Caine™ Patch which is a 1:1 eutectic mixture of lidocaine and tetracaine. In the current NDA the Sponsor submitted Fertility/Reproduction and Pre- and postnatal development reproductive toxicity studies for tetracaine base, and a discussion of the equivocal findings for tetracaine in the *in vitro* chromosomal aberration assay. In addition it was determined that the Sponsor submitted a male fertility and reproduction study for lidocaine base.

This review documents the study results for the male fertility and reproduction study for lidocaine base.

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

Studies reviewed within this submission: None.

Studies not reviewed within this submission (previously reviewed):

Study Title	Study no.	NDA/IND
Reproductive Toxicology		
A study to evaluate functional effects on male fertility in rats	925-019	N21-623 N000 12/27/2004

2.6.2 PHARMACOLOGY: No new studies were submitted.

2.6.3 PHARMACOLOGY TABULATED SUMMARY: No new studies were submitted.

2.6.4 PHARMACOKINETICS/TOXICOKINETICS: No new studies were submitted.

2.6.6 TOXICOLOGY

2.6.6.1 Overall toxicology summary

General toxicology: No new studies were submitted for review.

Genetic toxicology: No new studies were submitted for review.

Carcinogenicity: No new studies were submitted for review.

Reproductive toxicology: Lidocaine base did affect male fertility when administered s.c. up to a dose of 60 mg/kg/day.

Special toxicology: No new studies were submitted for review.

2.6.6.2 Single-dose toxicity: No new studies were submitted for review.
2.6.6.3 Repeat-dose toxicity: No new studies were submitted for review.
2.6.6.4 Genetic toxicology: No new studies were submitted for review.
2.6.6.5 Carcinogenicity: No new studies were submitted for review.
2.6.6.6 Reproductive and developmental toxicology:

Study Title: A study to evaluate functional effects on male fertility in rats.

Key study findings:

- Clinical observations: Treatment-related scabbing and hair loss as the injection site
- Body weight gains: Decreased in male rats at a dose of 60 mg/kg during the entire study
- Organ weights: Decrease in terminal body weight and prostate weights at a dose of 60 mg/kg
- Increased copulatory interval at a dose of 60 mg/kg, and a dose-related decreased homogenization resistant sperm head count, daily sperm production, and spermatogenic efficiency, the treatment did not affect overall fertility in male rats when given subcutaneous doses up to 60 mg/kg
- NOAEL (general) = 15 mg/kg/day for male (based on observations and body weight gains)
- NOAEL (male fertility) = 60 mg/kg/day

Study no: 925-019
Volume #, and page #: 4, pp. 5-2
Conducting laboratory and location: [redacted]
Date of study initiation: 16 March 2004
GLP compliance/QA report: Yes (X) No ( )
Drug, lot #, radiolabel, and % purity: lidocaine base/Z-02-002/purity not specified on CoA
Formulation/vehicle: sterile water containing NaH_2PO_4 or Na_2HPO_4 and hydrochloric acid for pH adjustment to 6.0

Methods:

Species/strain: Sprague Dawley rats/ [redacted] CD(SD)IGS BR, [redacted]
Doses employed: 5, 15, 60 mg/kg/day @ 1 mL/kg
Route of administration: s.c. (injections alternated between right and left scapular and lumbar regions)
Study design: only male rats were dosed, daily dosing 28 days premating, 14-21 days mating, through GD 7
Number/sex/group: 25/sex/group
Parameters and endpoints evaluated: [treated male rats] clinical observations twice daily; body weights were recorded twice weekly; food consumption was recorded weekly during premating and after mating; gross pathology, terminal body weights, testes, epididymis, seminal vesicle, and prostate organs were weighed and histopathology evaluated; sperm analysis was conducted; [untreated female rats] clinical observations twice daily; body weights and food consumption were recorded twice weekly prior to mating and GD 0, 4, 7, 10, and 13; uterine data were collected on GD 13.

Observation times and results:

Observations	**Results**
Male rats	
Mortality	One control rat was humanely euthanized on SD 43 and one rat was found dead on SD 19. No gross pathology findings were unremarkable. All other animals survived to scheduled euthanasia.
Clinical signs	Treatment-related findings associated with the s.c. administration were observed at a dose of 60 mg/kg and including abrasions, hair sparse, and scabbed area on the dorsal surface, and hair sparse and scabbed area on the lumbar region.
Body weights	Body weights were unremarkable. Body weight gains were statistically significantly decreased on SD 18-22 (premating, 28%), SD 43-46 (mating, 32%), SD 60-64 (postmating, 79%), and overall (SD 1-64, 12%) at a dose 60 mg/kg. Body weight gains were decreased in all treated groups on SD 50-53 (postmating, 44-78%).
Food consumption	Unremarkable.
Terminal/necroscopic evaluations	Scabs were observed at the injection site at doses of 15 mg/kg (11/25, 10/11 mild, 1/11 minimal) and 60 mg/kg (24/25, 5/24 mild, 19/24 moderate).
Organ weights	Terminal body weight was statistically significantly decreased (7%) and prostate weight were decreased (13%) at a dose of 60 mg/kg.
Reproductive/fertility Indices	Fertility and fecundity indices were unremarkable. The copulatory interval was statistically significantly increased by 1-2 days (4.3 days vs. 2.6 days in the control) at a dose of 60 mg/kg. The significance of the increase in the copulatory interval (number of

	days it takes the male to impregnate the female rat) is unknown and did not have an adverse effect on female fertility.
Sperm analysis	Sperm analyses showed a dose-related decrease (26%, 33%, and 36% for doses of 5, 15, and 60 mg/kg, respectively) in homogenization resistant sperm head count, daily sperm production, and spermatogenic efficiency. The significance of the sperm analysis findings is unknown because there were no affects of treatment on the testes weight which determine the number of sperm produced and female fertility was unaffected.
Female rats	
Mortality	All animals survived to scheduled euthanasia.
Clinical signs	Unremarkable.
Body weights	Unremarkable.
Food consumption	Unremarkable.
Terminal/necroscopic evaluations	Unremarkable.
Reproductive/fertility Indices	Unremarkable for fertility indices.
Cesarean section data	Uterine data revealed a decrease, although not statistically significant, in the pre-implantation loss at doses of 15 mg/kg (6.09% per animal) and 60 mg/kg (6.49% per animal) compare to the control (7.87% per animal). There were no corresponding decreases in the number of viable embryos.

[Note: GD = gestation day; SD=study day]

2.6.6.7 Local tolerance: No new studies were submitted for review.

2.6.6.8 Special toxicology studies: No new studies were submitted for review.

2.6.6.9 Discussion and Conclusions:

The sponsor conducted a standard fertility and reproductive toxicity where only the male rats were s.c. administered lidocaine base. Findings including treatment-related scabbing and hair loss as the injection site, decreased body weight gains in male rats at a dose of 60 mg/kg during the entire study, decreased terminal body weight and prostate weights at a dose of 60 mg/kg, an increased copulatory interval at a dose of 60 mg/kg, and a dose-related decreased homogenization resistant sperm head count, daily sperm production, and spermatogenic efficiency, the treatment did not affect overall fertility in male rats when given subcutaneous doses up to 60 mg/kg (360 mg/m^2 or 8-fold the SDA). and no effect on treated male or untreated female fertility when lidocaine base was given s.c.

2.6.6.10 Tables and Figures: Not applicable.

2.6.7 TOXICOLOGY TABULATED SUMMARY: Not applicable.

OVERALL CONCLUSIONS AND RECOMMENDATIONS

Lidocaine base did not affect male fertility.

Unresolved toxicology issues: None.
Recommendations: None at this time.
Suggested labeling: (Note: strike-through indicates corrections to proposed label, double underlines indicate insertions/edits to the proposed label)

Impairment of Fertility: Lidocaine did not affect fertility in female rats when given via continuous subcutaneous infusion via osmotic minipumps up to doses of 250 mg/kg/day (1500 mg/m^2 or 43-fold higher than the SDA). Although lidocaine treatment of male rats increased the copulatory interval and lead to a dose-related decreased homogenization resistant sperm head count, daily sperm production, and spermatogenic efficiency, the treatment did not affect overall fertility in male rats when given subcutaneous doses up to 60 mg/kg (360 mg/m^2 or 8-fold the SDA). Tetracaine did not affect fertility in male or female rats when given subcutaneous doses up to 7.5 mg/kg (45 mg/m^2 or 1-fold the SDA). Multiples of exposure are based on a single dermal administration (SDA) of 70 mg each of lidocaine and tetracaine in S-Caine Patch for 30 minutes to a 60 kg person (43 mg/m^2).

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/s/

Suzanne Thornton-Jones
6/22/05 11:46:18 AM
PHARMACOLOGIST

R. Daniel Mellon
6/22/05 01:37:05 PM
PHARMACOLOGIST
I concur.

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

PHARMACOLOGY/TOXICOLOGY REVIEW AND EVALUATION
Addendum

NDA NUMBER:	**21-623**
SERIAL NUMBER:	**N000 AZ**
DATE RECEIVED BY CENTER:	**12/27/2004**
DRUG NAME:	**7% lidocaine/7% tetracaine (S-Caine™**
INDICATION:	[redacted]
SPONSOR:	**Zars, Inc.**
DOCUMENTS REVIEWED:	**5 of 33 volumes**
REVIEW DIVISION:	**Division of Anesthetic, Critical Care, and Addiction Drug Products (HFD-170)**
PHARM/TOX REVIEWER:	**Suzanne R. Thornton-Jones, Ph.D.**
PHARM/TOX SUPERVISOR:	**R. Daniel Mellon, Ph.D.**
DIVISION DIRECTOR:	**Bob Rappaport, M.D.**
PROJECT MANAGER:	**Allison Meyer**

Date of review submission to Division File System (DFS): 20 June 2005

EXECUTIVE SUMMARY

I. Recommendations

A. Recommendation on acceptability.
The NDA can be approved from a pharmacology/toxicology perspective.

B. Recommendation for nonclinical studies.
None.

C. Recommendations on labeling.
See previous review.

II. Summary of nonclinical findings

A. Brief overview of nonclinical findings
No affects of tetracaine base on male or female fertility or pre- and postnatal development were observed. A discussion of the equivocal *in vitro* chromosomal aberration assay results for tetracaine was provided and reviewed. A post-NDA action meeting was held with the Sponsor on 03 May 2004 where the equivocal assay results were further discussed. It was conveyed to the Sponsor the findings would be handled in the package insert and, although not required, the assay could be repeated to clarify the equivocal finding. The Sponsor did not repeat the assay and the after review of their discussion it was decided that the assay results would remain equivocal and the patient insert was revised accordingly.

B. Pharmacologic activity
Both lidocaine (amide-linked) and tetracaine (para-aminobenzoic acid ester) are local anesthetics which have similar pharmacological profiles and are about equipotent. Local anesthetics block nerve impulses by decreasing or preventing the large transient increase in the permeability of excitable membranes to Na+ that normally is produced by a slight depolarization of the membrane due to direct interaction with voltage-gated Na+ channels. Blockade of neuronal conduction prevents the action potential of sensory neurons and therefore blocks the transmission of pain signals to the CNS. Lidocaine and tetracaine blockade demonstrates both frequency and voltage-dependency. Both drugs block both open and inactivated Na+ channels.

C. Nonclinical safety issues relevant to clinical use.
None.

Reviewer Signature Suzanne R. Thornton-Jones, Ph.D.

Supervisor Signature R. Daniel Mellon, Ph.D. Concurrence Yes X No ___

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/s/

Suzanne Thornton-Jones
6/20/05 05:35:18 PM
PHARMACOLOGIST

R. Daniel Mellon
6/20/05 05:44:31 PM
PHARMACOLOGIST
I concur.

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

PHARMACOLOGY/TOXICOLOGY REVIEW AND EVALUATION

NDA NUMBER:	**21-623**
SERIAL NUMBER:	**N000 AZ**
DATE RECEIVED BY CENTER:	**12/27/2004**
DRUG NAME:	**7% lidocaine/7% tetracaine (S-Caine™**
INDICATION:	[redacted]
SPONSOR:	**Zars, Inc.**
DOCUMENTS REVIEWED:	**5 of 33 volumes**
REVIEW DIVISION:	**Division of Anesthetic, Critical Care, and Addiction Drug Products (HFD-170)**
PHARM/TOX REVIEWER:	**Suzanne R. Thornton-Jones, Ph.D.**
PHARM/TOX SUPERVISOR:	**R. Daniel Mellon, Ph.D.**
DIVISION DIRECTOR:	**Bob Rappaport, M.D.**
PROJECT MANAGER:	**Allison Meyer**

Date of review submission to Division File System (DFS): 03 June 2005

EXECUTIVE SUMMARY

I. Recommendations

A. Recommendation on acceptability.
The NDA can be approved from a pharmacology/toxicology perspective.

B. Recommendation for nonclinical studies.
None.

C. Recommendations on labeling.
Note: The multiples of exposure that are included in the label are low because many of the doses utilized in the non-clinical studies were below or comparable the doses administered in humans. However, the low multiples of exposure do not offer a significant safety risk with S-Caine Patch because there is low or no systemic exposure of lidocaine and tetracaine after dermal application. A non-teratogenic effects section was added to the label following receipt of a consult for the Pregnancy Labeling Team (PLT) for NDA 21-717 (S-Caine Peel). The articles cited by the PLT were reviewed and the section appropriately revised to provide more details on the reported findings to assistant in future labeling of the current and future products.

Carcinogenesis, Mutagenesis, Impairment of Fertility:

Carcinogenesis: Long-term studies in animals have not been performed to evaluate the carcinogenic potential of either lidocaine or tetracaine.

Mutagenesis: The mutagenic potential of lidocaine base and tetracaine base has been determined in the *in vitro* Ames Bacterial Reverse Mutation Assay, the *in vitro* chromosomal aberration assay using Chinese hamster ovary cells, and the *in vivo* mouse micronucleus test. Lidocaine was negative in all three assays. Tetracaine was negative in the *in vitro* Ames and the *in vivo* mouse micronucleus assays. In the *in vitro* chromosomal aberration assay tetracaine was negative in the absence of metabolic activation, [redacted]

Impairment of Fertility: Lidocaine did not affect fertility in female rats when given via continuous subcutaneous infusion via osmotic minipumps up to doses of 250 mg/kg/day (1500 mg/m^2 or 43-fold higher than the SDA). Tetracaine did not affect fertility in male or female rats when given subcutaneous doses up to 7.5 mg/kg (45 mg/m^2 or 1-fold the SDA). Multiples of exposure are based on a single dermal administration (SDA) of 70 mg each of lidocaine and tetracaine in S-Caine Patch for 30 minutes to a 60 kg person (43 mg/m^2).

Use in Pregnancy:

Teratogenic Effects: Pregnancy Category B. Lidocaine was not teratogenic in rats given subcutaneous doses up to 60 mg/kg (360 mg/m^2 or 8-fold the SDA) or in rabbits up to 15 mg/kg (180 mg/m^2 or 4-fold the SDA). Tetracaine was not teratogenic in rats given subcutaneous doses up to 10 mg/kg (60 mg/m^2 or 1-fold the SDA) or in rabbits up to 5 mg/kg (60 mg/m^2 or 1-fold the SDA). S-Caine Patch components (lidocaine and tetracaine) given as a 1:1 eutectic mixture [redacted] was not teratogenic in rats [redacted] (60 mg/m^2 or 1-fold the SDA) or rabbits (120 mg/m^2 or 3- fold the SDA).

Nonteratogenic Effects. Lidocaine, contained 1:100,000 epinephrine, at a dose of 6 mg/kg (2-times the SDA) injected into the masseter muscle of the jaw or into the gum of the lower jaw of Long-Evans hooded pregnant rats on gestation day 11 lead to developmental delays in neonatal behavior among offspring. Developmental delays were observed for negative geotaxis, static righting reflex, visual discrimination response, sensitivity and response to thermal and electrical shock stimuli, and water maze acquisition. The developmental delays of the neonatal animals were transient with responses becoming comparable to untreated animals later in life. The clinical relevance of the animal data is uncertain.

Pre- and postnatal maturational, behavioral, or reproductive development was not affected by maternal subcutaneous administration of tetracaine during gestation and lactation up to doses of 7.5 mg/kg (45 mg/m^2 or 1-fold the SDA).

There are, however, no adequate and well-controlled studies in pregnant women. Because animal reproduction studies are not always predictive of human response, S-Caine Patch should be used during pregnancy only if clearly needed.

II. Summary of nonclinical findings

A. Brief overview of nonclinical findings
No affects of tetracaine base on male or female fertility or pre- and postnatal development were observed.

B. Pharmacologic activity
Both lidocaine (amide-linked) and tetracaine (para-aminobenzoic acid ester) are local anesthetics which have similar pharmacological profiles and are about equipotent. Local anesthetics block nerve impulses by decreasing or preventing the large transient increase in the permeability of excitable membranes to Na+ that normally is produced by a slight depolarization of the membrane due to direct interaction with voltage-gated Na+ channels. Blockade of neuronal conduction prevents the action potential of sensory neurons and therefore blocks the

transmission of pain signals to the CNS. Lidocaine and tetracaine blockade demonstrates both frequency and voltage-dependency. Both drugs block both open and inactivated Na+ channels.

C. Nonclinical safety issues relevant to clinical use.
None.

Reviewer Signature Suzanne R. Thornton-Jones, Ph.D.

Supervisor Signature R. Daniel Mellon, Ph.D. Concurrence Yes X No ___

TABLE OF CONTENTS

2.6 PHARMACOLOGY/TOXICOLOGY REVIEW

2.6.1 INTRODUCTION AND DRUG HISTORY

NDA NUMBER:	21-623
REVIEW NUMBER:	2
SEQUENCE NUMBER/DATE/TYPE OF SUBMISSION:	N000/17 December 2004/AZ
INFORMATION TO SPONSOR:	Yes ( ) No (X)
SPONSOR:	Zars, Inc. 1142 West 2320 South, Suite A Salt Lake City, UT 84119
MANUFACTURER FOR DRUG SUBSTANCE :	[lidocaine] [redacted] [tetracaine] [redacted]
REVIEWER NAME:	Suzanne R. Thornton-Jones, Ph.D.
DIVISION NAME:	DACCADP
HFD #:	170
REVIEW COMPLETION DATE:	25 April 2005
DRUG:	
TRADE NAME:	S-Caine™ [redacted]
GENERIC NAME (LIST ALPHABETICALLY):	lidocaine/tetracaine
CODE NAME:	NA
CHEMICAL NAME:	
[lidocaine] 2-(Diethylamino)-N-(2,6-dimethylphenyl)-acetamide	
[tetracaine] 2-(Dimethylamino)ethyl p-(butylamino)benzoate	
CAS REGISTRY NUMBER:	[lidocaine] 137-58-6 [tetracaine] 94-24-6
MOLE FILE NUMBER:	not specified
MOLECULAR FORMULA/MOLECULAR WEIGHT:	[lidocaine] $C_{14}H_{22}N_2O$/234.3 [tetracaine] $C_{15}H_{24}N_2O_2$/264.41

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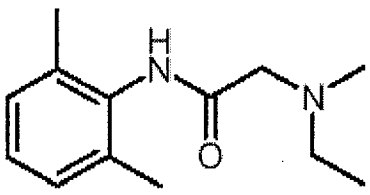
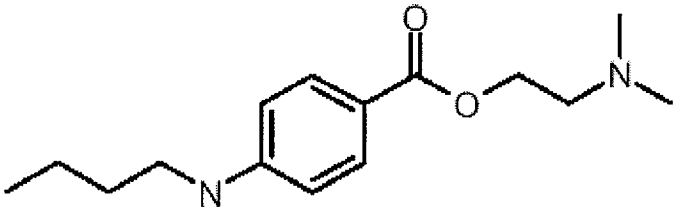


Lidocaine



Tetracaine

RELEVANT INDS/NDAS/DMFS:	IND 59,801/NDA 21-717 (S-Caine™ Peel)
DRUG CLASS:	Local anesthetics of the amide type (lidocaine) and ester type (tetracaine).

INTENDED CLINICAL POPULATION: [redacted]

ROUTE OF ADMINISTRATION: topical

FORMULATION:

[redacted]

The excipients in the above formulation can be found in approved drug products at equal or greater levels and therefore do not pose any unique toxicological concerns.

BACKGROUND: The Sponsor has submitted a 505(b)(2) NDA application for S-Caine™ Patch which is a 1:1 eutectic mixture of lidocaine and tetracaine. In the current NDA the Sponsor submitted Fertility/Reproduction and Pre- and postnatal development reproductive toxicity studies for tetracaine base, and a discussion of the equivocal findings for tetracaine in the *in vitro* chromosomal aberration assay.

Three degradation products are found in the S-Caine™ Patch, [redacted] from lidocaine, [redacted] from tetracaine. The Sponsor has established specifications of [redacted] for [redacted] respectively. [redacted] is a metabolite of lidocaine that has been found to be carcinogenic in mice and rats when administered in the diet (see Attachments). The human relevance of the types of tumors observed in the mice and rat carcinogenicity assays were found to be 'not relevant' by the CDER Executive Carcinogenicity Assessment Committee and are not included in product labels containing lidocaine. Tetracaine *in vivo* is metabolized via hydrolysis by plasma esterases to both of these degradation products. The specifications established for these degradation products are below the levels normally found in the plasma when tetracaine is administered. [redacted] It should also be noted that the specification for [redacted] in the S-Caine™ Peel NDA. There are no toxicology issues with the established specifications for these degradation products.

CHADD Heating Pod

The CHADD Heating Pod is the heat-generating component of the S-Caine™ Patch. This is an oval pouch containing a proprietary blend of iron powder, activated carbon, sodium chloride, and wood flour which generates heat when exposed to water and oxygen.

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

Studies reviewed within this submission: None.

Studies not reviewed within this submission (previously reviewed):

Study Title	Study no.	NDA/IND
Acute Toxicology/Dermal Irritation		
Modified Primary Skin Irritation (Rabbits).	X9C009G	N21-623 N000 03/31/2003
A dermal irritation study of S-Caine™ Patch in rabbits	925-002	N21-623 N000 03/31/2003
Dermal Sensitization – Buehler Method	X9C010G	I58,823
Repeat Dose Toxicology		
A 28 day dermal toxicity study of S-Caine™ Patch in rabbits	925-004	N21-623 N000 03/31/2003
Genotoxicity		
Salmonella-Escherichia coli mammalian-microsome reverse mutation assay with a confirmatory assay with lidocaine base	23840-0-409OECD	N21-623 N000 03/31/2003
Salmonella-Escherichia coli mammalian-microsome reverse mutation assay with a confirmatory assay with tetracaine base	23841-0-409OECD	N21-623 N000 03/31/2003
Chromosomal aberrations in Chinese Hamster Ovary (CHO) cells with lidocaine base	23840-0-437OECD	N21-623 N000 03/31/2003
Chromosomal aberrations in Chinese Hamster Ovary (CHO) cells with tetracaine base	23841-0-437OECD	N21-623 N000 03/31/2003
In vivo mouse micronucleus assay with lidocaine base	23840-0-455OECD	N21-623 N000 03/31/2003

Study Title	Study no.	NDA/IND
In vivo mouse micronucleus assay with tetracaine base	23841-0-455OECD	N21-623 N000 03/31/2003
Reproductive Toxicology		
Pilot Study for effects on embryo-fetal development in rats	925-012	N21-623 N000 03/31/2003
Pilot prenatal development toxicity study in New Zealand white rabbits	925-013	N21-623 N000 03/31/2003
Final toxicology report for study 925-015, Study for effects on embryo-fetal development in rats	925-015	N21-623 N000 03/31/2003
Final toxicology report for study 925-016; Study for effects on embryo-fetal development in rabbits	925-016	N21-623 N000 03/31/2003
A study to assess the effects of fertility and early embryonic development to implantation in rats	925-014	N21-717 N000 11/14/2003
Study for toxic effects on pre- and postnatal development, including maternal function, in rats	925-017	N21-717 N000 11/14/2003

2.6.2 PHARMACOLOGY: No new studies were submitted.

2.6.3 PHARMACOLOGY TABULATED SUMMARY: No new studies were submitted.

2.6.4 PHARMACOKINETICS/TOXICOKINETICS: No new studies were submitted.

2.6.6 TOXICOLOGY

2.6.6.1 Overall toxicology summary

General toxicology: No new studies were submitted for review.

Genetic toxicology: The genotoxic potential of lidocaine base and tetracaine base were determined in the *in vitro* Ames Bacterial Reverse Mutation Assay, the *in vitro* chromosome aberration assay using Chinese hamster ovary cells, and the *in vivo* mouse micronucleus assay. Lidocaine was negative in all three assays. Tetracaine was negative in the *in vitro* Ames assay and the *in vivo* mouse micronucleus assay. Tetracaine was negative in the absence of metabolic activation in the *in vitro* CHO chromosomal aberration assay, and equivocal in the presence of metabolic activation.

Carcinogenicity: No new studies were submitted for review.

Reproductive toxicology: Tetracaine base did affect male or female fertility or pre- and postnatal development in rats when administered s.c. up to a dose of 2.5 mg/kg/day.

Special toxicology: No new studies were submitted for review.

2.6.6.2 Single-dose toxicity: No new studies were submitted for review.
2.6.6.3 Repeat-dose toxicity: No new studies were submitted for review.
2.6.6.4 Genetic toxicology: No new studies were submitted for review.
2.6.6.5 Carcinogenicity: No new studies were submitted for review.
2.6.6.6 Reproductive and developmental toxicology:

A. Study Title: A study to assess the effects of fertility and early embryonic development to implantation in rats.

Key study findings: Tetracaine base administration to both the male and female rat resulted in the following key findings:

- Clinical observations: decreased activity, prostration, rapid breathing, and scabs at injection site in male and female rats at a dose of 7.5 mg/kg
- Body weight gains: decreased in male rats at a dose of 7.5 mg/kg during the entire treatment period; decreased in female rats in all treated groups during premating, and at a dose of 7.5 mg/kg during GD 0-7
- Organ weights: decrease in prostate weights and an increase in ovary weights at a dose of 7.5 mg/kg
- No effect on male or female fertility when tetracaine base was given s.c.
- NOAEL (general)= 2.5 mg/kg/day for male and female rats (based on observations and body weight gains)
- NOAEL (fertility)=7.5 mg/kg/day for male and female rats

Study no: 925-014
Volume #, and page #: 17, pp. 17-1
Conducting laboratory and location: [redacted]
Date of study initiation: 28 March 2003
GLP compliance/QA report: Yes (X) No ( )
Drug, lot #, radiolabel, and % purity: tetracaine base/Z-02-003/purity not specified on CoA
Formulation/vehicle: sterile water containing NaH_2PO_4 and Na_2HPO_4

Methods:
Species/strain: Sprague Dawley rats/ [redacted] CD(SD)IGS BR, [redacted]
Doses employed: 0.75, 2.5, 7.5 mg/kg/day @ 1 mL/kg
Route of administration: s.c. (injections alternated between right and left shoulder and lumbar regions)
Study design: daily dosing, [males] 28 days premating, 14-21 days mating, through GD7; [females] 14 days premating, 14-21 days mating, through GD7
Number/sex/group: 25/sex/group

Parameters and endpoints evaluated: [male rats] clinical observations twice daily; body weights were recorded every 3-4 days, and food consumption was recorded weekly; gross pathology, terminal body weights, testes, epididymis, seminal vesicle, and prostate organs were weighted, sperm analysis was conducted; [female rats] clinical observations twice daily, body weights and food consumption were recorded every 4 days during the pre-mating and mating periods and on GD 0, 4, 7, 10, 13; cesarean section on GD 13 with standard parameters collected, gravid uterine and ovaries/cervix were weighed

Observation times and results:

Observations	**Results**
Male rats	
Mortality	All animals survived to scheduled euthanasia.
Clinical signs	Decreased activity, ataxia, prostration, rapid breathing, hair absent or sparse and scabs at the injection sites were observed at a dose of 7.5 mg/kg during the premating, mating, and postmating periods.
Body weights	Body weights were statistically significantly decreased (5-9%) beginning on SD22 (premating period) and continuing through postmating at a dose of 7.5 mg/kg. Also at 7.5 mg/kg body weight gains were decreased for the premating, mating, and postmating periods (14%, 30%, and 17%, respectively).
Food consumption	Statistically significantly decreased at a dose of 7.5 mg/kg during the premating period (SW3-9, 9-10%), and during the postmating period (SW 9-10, 12%).
Terminal/necroscopic evaluations	Unremarkable.
Organ weights	Terminal body weight was statistically significantly decreased (9%) and prostate weight was decreased (13%) at a dose of 7.5 mg/kg.
Reproductive/fertility Indices	Unremarkable.
Sperm analysis	Unremarkable.
Female rats	
Mortality	One died at a dose of 7.5 mg/kg on SD16 30 mins after dosing. Cause of death was not determined. All other animals survived to scheduled euthanasia.
Female rats	
Clinical signs	Decreased activity, prostration, rapid breathing, and scabs at the injection sites were observed at a dose of 7.5 mg/kg during the premating, mating, and gestation periods.

Body weights	Body weights were statistically significantly decreased on SD15 (premating, 4%), and on GD 7-13 (3-6%) at a dose of 7.5 mg/kg. Body weight gains were decreased during the premating period on SD4-8 in all doses (18-31%), SD11-15 at doses ≥2.5 mg/kg (18-29%), and SD 1-15 for all doses (11-21%, statistically significant at doses ≥2.5 mg/kg. Body weight gains were decreased at a dose of 7.5 mg/kg during GD0-4 (19%, statistically significant), and GD4-7 (24%), GD0-7 (21%, statistically significant).
Food consumption	Unremarkable during premating and gestation.
Terminal/necroscopic evaluations	Unremarkable.
Organ weights	Ovary weight was increased (43%) at a dose of 7.5 mg/kg. Uterus/cervix weight was increased (16%) at a dose of 2.5 mg/kg.
Reproductive/fertility Indices	Estrous cyclicity was normal for the length and number of cycles. Unremarkable for fertility indices.
Cesarean section data	Unremarkable.

[Note: GD = gestation day; SD=study day; SW=study week]

B. Study Title: Study for toxic effects on pre- and postnatal development, including maternal function, in rats

Key study findings: Tetracaine base administration to the female rat from GD6 to LD20 resulted in the following key findings:

- Mortality: 2 dams at a dose of 2.5 mg/kg and 1 dam at a dose of 7.5 mg/kg during gestation
- Clinical observations (maternal): decreased activity, ataxia, prostration, rapid breathing, and scabs at injection site at a dose of 7.5 mg/kg
- Body weight gains: decreased at a dose of 7.5 mg/kg during gestation and in all treated groups during LD 0-4
- No developmental affects on offspring when tetracaine base was given s.c.
- NOAEL = [F_0] 2.5 mg/kg/day (based on observations and body weight gains) [F_1] 7.5 mg/kg/day

Study no: 925-017
Volume #, and page #: 22, pp. 22-1
Conducting laboratory and location: [redacted]
Date of study initiation: 28 March 2003
GLP compliance/QA report: Yes (X) No ( )
Drug, lot #, radiolabel, and % purity: tetracaine base/Z-02-003/purity not specified on CofA
Formulation/vehicle: sterile water containing NaH_2PO_4 and Na_2HPO_4

Methods:

Species/strain: timed-mated Sprague Dawley rats/ [redacted] CD(SD)IGS BR, [redacted]
Doses employed: 0.75, 2.5, 7.5 mg/kg/day @ 1 mL/kg
Route of administration: s.c. (injections alternated between right and left should and lumbar regions)
Study design: GD6-LD20
Number/sex/group: 25/group
Parameters and endpoints evaluated: Time-mated rats were used for the study. Clinical observations (twice daily), body weight, food consumption, parturition and litter observations, culling of litters to 8/sex on LD4, pup developmental indices during lactation included static righting reflex, pinna detachment, cliff aversion, eye opening, air drop righting reflex, auditory startle (end of lactation period), and during development vaginal opening, preputial separation, motor activity (PD 35) and step-through passive avoidance (PD74-77). F1 pups were allowed to mate and a cesarean section was performed on GD13 and male animals were euthanized after completion of the cesarean section.

Observation times and results:

Observations	**Results**
Mortality (maternal)	Two dams were found dead on GD 17 and 19 at a dose of 2.5 mg/kg, and 1 dam was found dead on GD17 at a dose of 7.5 mg/kg. Cause of death was not determined. All other maternal animals survived to scheduled euthanasia.
Body weights (maternal)	Body weights were unremarkable for gestation and lactation. Body weight gains were decreased on GD 6-10 (10%) and GD17-20 (12%) at a dose of 7.5 mg/kg. Body weight gains were decreased in all treated groups during LD0-4 (24-59%), and were statistically significantly decreased for the entire lactation period (LD0-21, 24%) at a dose of 0.75 mg/kg.
Food consumption (maternal)	Unremarkable during gestation and lactation.
F_0	
In-life observations	
Dams	Decreased activity, ataxia, prostration, rapid breathing, and scabs at the injection sites were observed at a dose of 7.5 mg/kg during the gestation and lactation periods. Delivery/littering data were unremarkable.
Offspring	A low incidence of desquamation (entire body) at a dose of 7.5 mg/kg, and scabbed in all dose groups were observed.

F_0
Terminal/necroscopic evaluations

Dams	Discoloration, scabs, and skin thickening were observed at a dose of 7.5 mg/kg.
Offspring	Unremarkable.

F_1
In-life observations

Male and female rats	Unremarkable for observations, developmental landmarks, and post-weaning behavioral tests. It should be noted that there were statistically significant increases in motor activity and time to achieve passive avoidance at doses $\geq$ 2.5 mg/kg. The reason for the statistical significance is that the control group animals in this study exhibited values that were outside (below) the historical control data (HCD), while the treated group values are within HCD.
Dams	Unremarkable.

Body weights

Male rats	Unremarkable.
Female rats	Unremarkable.

Terminal/necroscopic evaluations

Male rats	Unremarkable.
Dams	Unremarkable.

[Note: GD = gestation day; LD=lactation day; PD=postnatal day]

2.6.6.7 Local tolerance: No new studies were submitted for review.

2.6.6.8 Special toxicology studies: No new studies were submitted for review.

2.6.6.9 Discussion and Conclusions:

The sponsor conducted a standard fertility and reproductive toxicity and a pre- and postnatal development study in rats with tetracaine base at doses up to 7.5 mg/kg. Clinical observations in both studies were decreased activity, prostration, rapid breathing, and scabs at the injection site at a dose of 7.5 mg/kg. In the pre- and postnatal development study, 3 dams (2 dams at a dose of 2.5 mg/kg, 1 dam at a dose of 7.5 mg/kg) were found dead during gestation. The cause of death in these three animals is not known, however, due to the lack of a clear dose-relationship, these deaths do not appear to be attributable to the tetracaine. Body weight gains were decreased in the fertility study in male rats at a dose of 7.5 mg/kg during the entire treatment period, decreased in female rats in all treated groups during premating, and at a dose of 7.5 mg/kg during GD 0-7. Body weight gains were also decreased in the pre- and postnatal development study during gestation at a dose of 7.5 mg/kg and in

all treated groups during LD 0-4. There were no affects of tetracaine base on male or female fertility or pre- and postnatal development.

2.6.6.10 Tables and Figures: Not applicable.

2.6.7 TOXICOLOGY TABULATED SUMMARY: Not applicable.

OVERALL CONCLUSIONS AND RECOMMENDATIONS

Unresolved toxicology issues: None.
Recommendations: None at this time.
Suggested labeling: (Note: strike-through indicates corrections to proposed label, double underlines indicate insertions/edits to the proposed label)

Carcinogenesis, Mutagenesis, Impairment of Fertility:

Carcinogenesis: Long-term studies in animals have not been performed to evaluate the carcinogenic potential of either lidocaine or tetracaine.

Mutagenesis: The mutagenic potential of lidocaine base and tetracaine base has been determined in the *in vitro* Ames Bacterial Reverse Mutation Assay, the *in vitro* chromosomal aberration assay using Chinese hamster ovary cells, and the *in vivo* mouse micronucleus test. Lidocaine was negative in all three assays. Tetracaine was negative in the *in vitro* Ames and the *in vivo* mouse micronucleus assays.

[redacted]

In the *in vitro* chromosomal aberration assay tetracaine was negative in the absence of metabolic activation, and equivocal in the presence of metabolic activation.

Impairment of Fertility: Lidocaine did not affect fertility in female rats when given via continuous subcutaneous infusion via osmotic minipumps up to doses of 250 mg/kg/day (1500 mg/m^2 or 43-fold higher than the SDA). Tetracaine did not affect fertility in male or female rats when given subcutaneous doses up to 7.5 mg/kg (45 mg/m^2 or 1-fold the SDA). Multiples of exposure are based on a single dermal administration (SDA) of 70 mg each of lidocaine and tetracaine in S-Caine Patch for 30 minutes to a 60 kg person (43 mg/m^2).

[redacted]

Use in Pregnancy:

Teratogenic Effects: Pregnancy Category B. Lidocaine was not teratogenic in rats given subcutaneous doses [redacted] up to 60 mg/kg (360 mg/m^2 or 8-fold the SDA) ~~nor~~ in rabbits ~~at~~ [redacted] up to 15 mg/kg (180 mg/m^2 or 4-fold the SDA). Tetracaine was not teratogenic in rats given subcutaneous doses ~~at doses~~ up to 10 mg/kg (60 mg/m^2 or 1-fold the SDA) ~~nor~~ in rabbits [redacted] up to 5 mg/kg (60 mg/m^2 or 1-fold the SDA). S-Caine Patch components (lidocaine and tetracaine) given as a ~~The~~ 1:1 eutectic mixture [redacted] was not teratogenic in [redacted] rats [redacted] (60 mg/m^2 or 1-fold the SDA~~of~~) or rabbits (120 mg/m^2 or 3- fold the SDA~~of~~).

[redacted]

Nonteratogenic Effects. Lidocaine, contained 1:100,000 epinephrine, at a dose of 6 mg/kg (2- times the SDA) injected into the masseter muscle of the jaw or into the gum of the lower jaw of Long-Evans hooded pregnant rats on gestation day 11 lead to developmental delays in neonatal behavior among offspring. Developmental delays were observed for negative geotaxis, static righting reflex, visual discrimination response, sensitivity and response to thermal and electrical shock stimuli, and water maze acquisition. The developmental delays of the neonatal animals were transient with responses becoming comparable to untreated animal later in life. The clinical relevance of the animal data is uncertain.

Pre- and postnatal maturational, behavioral, or reproductive development was not affected by maternal subcutaneous administration of tetracaine during gestation and lactation up to doses of 7.5 mg/kg (45 mg/m^2 or 1-fold the SDA). [redacted]

[redacted]

There are, however, no adequate and well-controlled studies in pregnant women. Because animal reproduction studies are not always predictive of human response, S-Caine Patch should be used during pregnancy only if clearly needed.

3 Page(s) Withheld

✓ Trade Secret / Confidential

_____ Draft Labeling

_____ Deliberative Process

Withheld Track Number: Pharm/Tox- 5

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/s/

R. Daniel Mellon
2/4/04 08:42:06 PM
PHARMACOLOGIST
Supervisory Pharmacologist

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/s/

Suzanne Thornton-Jones
6/3/05 10:14:58 AM
PHARMACOLOGIST

R. Daniel Mellon
6/3/05 10:35:14 AM
PHARMACOLOGIST
I concur with Dr. Thornton-Jones. The NDA can be approved from the Pharmacology and Toxicology Perspective.

FDA Center for Drug Evaluation and Research
Division of Anesthetic, Critical Care, and Addiction Drug Products
HFD-170, Room 9B-45, 5600 Fishers Lane, Rockville, MD 20857

MEMORANDUM

Date:	February 4, 2004
To:	NDA 21-623 File
Through:	Bob Rappaport, M.D. Division Director, DACCADP
From:	R. Daniel Mellon, Ph.D. Supervisory Pharmacologist
Subject:	**PharmTox Requirement for approval of NDA 21-623 S-Caine Patch**
Date of Submission:	February 4, 2004

Background: The original pharmacology and toxicology review for NDA 21-623 provided the following recommendations for non-clinical studies:

> The following should be included in the approvable letter as recommendations to the sponsor:
>
> 1. Clarify the equivocal finding in the *in vitro* chromosomal aberrations assay for tetracaine. This clarification could take the form of a direct repeat of the assay with examination of the *in vitro* culture conditions such as pH or osmolarity changes which may contribute to a positive result. The clarification should be included in the second cycle submission.
>
> 2. As discussed during the pre-NDA meeting on December 5, 2002, submit the completed Segment I and Segment III reproduction studies on tetracaine to the S-Caine™ Patch NDA as soon as they are available. As review of this NDA will require a second cycle, these studies should be included in the resubmission package.

3. Submit all publications referenced to support the characterization of the potential reproductive toxicity of lidocaine. Provide data or references to characterize the effects of lidocaine on male fertility and provide your assessment of the adequacy of these studies according to current standards (e.g., dose selection, dose regimen).

This memo is to clarify that items 2 and 3 above are approval issues for the NDA. The second requirement has already been agreed upon by the sponsor and thus is listed here to confirm that this is now a requirement for NDA approval.

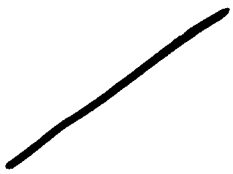
Item #3 above is also a requirement for approval. The rationale is as follows:

During the pre-NDA meeting, the sponsor was informed that "NDA submission should include the referenced reproduction toxicity studies with lidocaine along with the sponsor's assessment of the adequacy of these studies according to current standards (e.g., dose selection, dose regimen)." Although the sponsor has provided a summary of published reports, they did not provide the actual publications or any discussion of the adequacy of the studies according to current standards. Finally, there appears to be significant portions of the current standard segment I study not addressed by the literature references provided. For example, there are no data describing the effects of lidocaine treatment of the male prior to mating (generally 4 week pretreatment is recommended). As a result, there are no descriptions or discussions of the potential effect of local anesthetics on sperm morphology or mobility. The dosing rationale was not explained in the summary. The sponsor should critically review the existing study reports and provide a complete description of the potential effects of lidocaine on fertility and early embryonic development. This is particularly important in light of the summarized study reports suggesting early embryonic effects following a single dose of lidocaine. These findings were not addressed by the sponsor.

Based upon these above issues raised by the review of the submitted data, the following **approval issue** is recommended to be included in the approvable letter:

1. As discussed during the pre-NDA meeting on December 5, 2002, submit the completed Segment I and Segment III reproduction studies on tetracaine to the S-Caine™ Patch NDA as soon as they are available. These studies should be included in the resubmission package, since review of this NDA will require a second cycle.

2.



"Toxicity to Male Fertility, An Addendum to the ICH Tripartite Guideline on Detection of Toxicity to Reproduction for Medicinal Products." As described in the guidance, males should be treated with lidocaine for 4 weeks prior to mating. Treatment should be continued through mating to termination of males. These studies should provide an assessment of maturation of gametes, mating behavior and fertility. Data should also be provided to characterize the effects of lidocaine on sperm count in epididymides or testes as well as sperm viability. You may rely upon published literature, data that you have right of reference to or is otherwise within the public domain *in lieu* of animal studies.

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/s/

R. Daniel Mellon
2/4/04 05:35:30 PM
PHARMACOLOGIST
Supervisory Pharmacologist

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

PHARMACOLOGY/TOXICOLOGY REVIEW AND EVALUATION

NDA NUMBER:	21-623
SERIAL NUMBER:	N000
DATE RECEIVED BY CENTER:	April 4, 2003
DRUG NAME:	S-Caine™ Patch
INDICATION:	[redacted]
SPONSOR:	Zars, Inc.
DOCUMENTS REVIEWED:	Pharmacology and Toxicology Submissions
REVIEW DIVISION:	Anesthetic, Critical Care & Addiction Drug Products
PHARM/TOX REVIEWER:	R. Daniel Mellon, Ph.D.
PHARM/TOX SUPERVISOR:	R. Daniel Mellon, Ph.D.
PROJECT MANAGER:	Lisa Malandro

Date of review submission to Division File System (DFS): February 4, 2004

EXECUTIVE SUMMARY

1. Recommendations

1.1 Recommendation on approvability

From the non-clinical pharmacology and toxicology perspective, the NDA is approvable.

1.2 Recommendation for nonclinical studies

The following should be included in the approvable letter as recommendations to the sponsor:

1. Clarify the equivocal finding in the *in vitro* chromosomal aberrations assay for tetracaine. This clarification could take the form of a direct repeat of the assay with examination of the *in vitro* culture conditions such as pH or osmolarity changes which may contribute to a positive result. The clarification should be included in the second cycle submission.

2. As discussed during the pre-NDA meeting on December 5, 2002, submit the completed Segment I and Segment III reproduction studies on tetracaine to the S-Caine™ Patch NDA as soon as they are available. As review of this NDA will require a second cycle, these studies should be included in the resubmission package.

3. Submit all publications referenced to support the characterization of the potential reproductive toxicity of lidocaine. Provide data or references to characterize the effects of lidocaine on male fertility and provide your assessment of the adequacy of these studies according to current standards (e.g., dose selection, dose regimen).

1.3 Recommendations on labeling

The recommended labeling is provided below:

> **Carcinogenesis, Mutagenesis, Impairment of Fertility:**
>
> **Carcinogenesis**: Long-term studies in animals have not been performed to evaluate the carcinogenic potential of either lidocaine or tetracaine.
>
> **Mutagenesis**: The mutagenic potential of lidocaine base and tetracaine base has been determined in the Ames Bacterial Reverse Mutation Assay, the *in vitro* chromosome aberration assay using Chinese hamster ovary cells, and the *in vivo* mouse micronucleus assay. Lidocaine was

negative in all three assays. Tetracaine was negative in the Ames assay and the mouse micronucleus assay. [redacted] Tetracaine was negative in the absence of metabolic activation, and equivocal in the presence of metabolic activation.

Impairment of Fertility:

[redacted]

Use in Pregnancy:

Teratogenic Effects: Pregnancy Category B. Lidocaine was not teratogenic in rats at doses up to 60 mg/kg (360 mg/m^2) nor in rabbits at doses up to 15 mg/kg (180 mg/m^2). Tetracaine was not teratogenic in rats at doses up to 10 mg/kg (60 mg/m^2) nor in rabbits at doses up to 5 mg/kg (60 mg/m^2). The 1:1 eutectic mixture of the two drugs (10 mg/kg of each) was not teratogenic in either rats (60 mg/m^2) or rabbits (120 mg/m^2). There are, however, no adequate and well-controlled studies in pregnant women. Because animal reproduction studies are not always predictive of human response, S-Caine™ Patch should be used during pregnancy only if clearly needed.

2. Summary of nonclinical findings

The sponsor submitted a 505(b)(2) application for S-Caine™ Patch with the reference drug being EMLA Cream. EMLA Cream (lidocaine\prilocaine) is the referenced drug product for lidocaine. Currently there is no approved drug product containing tetracaine. As such, the application can almost be considered to be a 505(b)(1) for tetracaine and a 505(b)(2) for lidocaine. As such, the sponsor is relying upon the extensive clinical history of tetracaine and lidocaine to support the NDA.

A brief history puts these drug products into perspective. Local anesthetics were first used in 1884. In that year Koller announced the use of cocaine to anesthetize the eye. Novocaine (procaine hydrochloride) was introduced by Dr. Braun in 1905. Novocaine is comparatively weak anesthetic agent. Novocaine is not used very often today. It has been replaced by stronger anesthetics such as primacaine (4x as potent as Novocaine) and tetracaine (10x as potent as Novocaine). Tetracaine is relatively toxic in comparison to Novocaine. Lidocaine was discovered in 1943 by two Swedish chemists, Nils Lofgven and Bengt Lundquist. Although there is a long history of clinical use of tetracaine, there are currently no FDA-approved drugs containing this compound. An NDA for Neotopanol Solution (a combination of tetracaine and benzocaine) was submitted to the FDA in June of 1951 as part of the Desi Review process. On December 9, 1975, the FDA announced in the Federal Register that following review of the efficacy data during the Desi Review process, there was insufficient evidence to conclude the effectiveness of

[redacted]

2.1 Brief overview of nonclinical findings

In support of this NDA, the sponsor conducted acute local tissue irritation studies, a 28-day repeat dose toxicology study, the standard battery of genetic toxicology studies for both lidocaine and tetracaine and Segment II reproductive toxicology studies for lidocaine, tetracaine and the combination of the two in both rat and rabbit. In addition, the sponsor has agreed to complete Segment I and Segment III studies to be submitted post approval should the NDA be approved in the first cycle.

The acute local tissue reaction was characterized in two species, the rabbit and the neonatal pig. The results from the rabbit studies indicated that a 1 hour exposure to the S-Caine™ patch produced only very slight erythema and no evidence of edema and the placebo patch produced no erythema or edema. The data suggested that the S-Caine™ patch was a mild irritant. There was no clear suggesting for local tissue irritation, however, from studies conducted in the neonatal pig model, which is thought to be the best pre-clinical model for human skin. Collectively, the non-clinical studies suggest the potential for a mild local tissue reaction following acute exposure to non-abraded skin.

A 28-day repeat-dose toxicology study in rabbits was submitted to characterize the potential for the S-Caine™ patch to increase the severity of the local tissue reaction following repeated applications of the S-Caine™ patch. The study used 3 patches per animal, each applied for 2 hours once a day for a total of 28 days. This treatment regimen, which exceeded the maximum human daily exposure did not produce any evidence of systemic toxicity. The repeated exposure to the S-Caine™ patch produced increased local tissue irritation compared to the placebo patch. This local tissue irritation was characterized microscopically as epidermal surface exudates, epidermal necrosis, acute dermatitis, trace to moderate epithelial hyperplasia and fibrosis of the dermis. These changes were not evident in the skin treated with the placebo patch. Under the conditions of the assay, there were no significant differences between plasma concentrations of lidocaine or tetracaine between males and females or between abraded or non-abraded skin.

The potential for the S-Caine™ patch to produce a dermal sensitization following repeated exposure was tested via the Buehler method in the guinea pig model. Animals were treated with either with the S-Caine™ patch or control patches for 6 hours of days 0, 7 and 14. Fourteen days after the third exposure, the guinea pigs were challenged with topical application of the test article and positive control patches on the previously

unexposed flank. The application sites were scored for erythema and edema 24 and 48 hours later. The results indicated that the S-Caine™ patch induced sensitization in guinea pigs, although with less intensity than the positive control, dinitrochlorobenzene (DNCB).

The sponsor completed a standard genetic toxicology battery for both lidocaine and tetracaine. Lidocaine base tested negative in the *in vitro* bacterial reverse mutation assay (Ames assay), the *in vitro* chromosome aberrations assay in Chinese Hamster Ovary (CHO) cells and an *in vivo* mouse micronucleus assay. Tetracaine tested negative in the *in vitro* bacterial reverse mutation assay and the *in vivo* mouse micronucleus assay. Although tetracaine tested negative in the absence of metabolic activation in the *in vitro* chromosome aberrations assay, in the presence of metabolic activation, tetracaine was equivocal.

The sponsor completed Segment II studies (embryofetal development) in the rat and rabbit models. Although signs of maternal toxicity were evident, there was no indication that lidocaine or tetracaine is teratogenic under the conditions of the assays.

The sponsor is relying upon the published literature to characterize the effects of lidocaine on fertility and post-natal development. The available literature suggests that lidocaine exposure may produce subtle alterations in post-natal behavior. Smith et al. (1986) treated sperm-positive Long-Evans hooded rats with 6 mg/kg lidocaine (with epinephrine) on gestation day 11 via an inter masseter muscle of the jaw injection. There were no alterations in birth, growth or litter composition. However, offspring had longer latencies on the first day of negative geotaxis training and were more sensitive to electric footshock. Lidocaine dosed offspring responded less to the correct cue in a visual discrimination task, were slower to develop righting reflexes, made more errors in acquiring a water maze, had longer suppression times in a conditioned suppression task and had longer latencies to tail-flick. These results suggest that lidocaine (with epinephrine) exposure during mid-gestation can produce significant behavioral changes in the offspring of rats (Smith et al., 1986). This dose of lidocaine corresponds to a human equivalent dose of 58 mg dose based on a body surface are comparison.

Lidocaine administration via chronically implanted minipumps at doses of up to 250 mg/kg/day did not produce alterations in reproductive indices in the female. There do not appear to be any studies examining the effects of lidocaine on male fertility described in the NDA, not reported in the literature databases. The effects of lidocaine on peri- and post-natal development have been reported in the rat model by Smith et al. (1989). Smith treated Long-Evans hooded rats with 3, 6 or 9 mg/kg lidocaine injected into the gum on gestational day 4, 11 or 18. The offspring were evaluated via a variety of behavioral tests. The results indicate that pups treated with lidocaine on gestational day 4 showed greater sensitivity to footshock. Lidocaine administration on gestational day 11 was associated with a slight but significant alteration in sex ratios. Lidocaine administration on gestational day 18 was associated with significant alterations in behavior, including visual discrimination, shuttlebox avoidance, tail flick and water maze errors (Smith et al., 1989). The authors conclude that lidocaine may be a behavioral teratogen and that

exposure later in gestation in the rat may alter a broader range of behaviors than exposure earlier in gestation. In contrast to cocaine, neonatal exposure (birth to day 21) of rat pups to lidocaine (20 mg/kg, oral) did not significantly alter lymphocyte or total leukocyte levels or spleen weights.

2.2 Pharmacologic activity

Both lidocaine and tetracaine are local anesthetics. Local anesthetics block nerve impulses by decreasing or preventing the large transient increase in the permeability of excitable membranes to Na+ that normally is produced by a slight depolarization of the membrane due to direct interaction with voltage-gated Na+ channels. Blockade of neuronal conduction prevents the action potential of sensory neurons and therefore blocks the transmission of pain signals to the CNS. Lidocaine and tetracaine blockade demonstrates both frequency and voltage-dependency. Both drugs block both open and inactivated Na^+ channels. The frequency dependence of this blockade makes smaller unmyelinated nerve fibers more sensitive to blockade than larger heavily myelinated fibers. Therefore, Type C fibers (dorsal root and sympathetic nerves) and Type B (preganglionic autonomic nerves) are blocked at lower concentrations than heavily myelinated Type A (alpha, beta, gamma and delta) fibers. Of the type A fibers, pain and temperature sensitive neurons (delta) are more susceptible to local anesthetics than muscle spindles (gamma), touch and pressure sensitive neurons (beta) which are, in turn, more sensitive than proprioception and motor neurons (alpha). This sensitivity also correlates with the diameter of the nerve fiber, with smaller fibers being more sensitive to the local anesthetic action.

Local anesthetics can also bind to other membrane proteins such as K+ channels. However, blockade of conduction is not accompanied by any large or consistent change in resting membrane potential due to block of K+ channels since the interaction of local anesthetics with K+ channels requires higher drug concentrations. Lidocaine and tetracaine have similar pharmacological profiles and are about equipotent. Lidocaine is considered to be the faster acting of the two components, and is an amide-linked local anesthetic. Tetracaine is a para-aminobenzoic acid ester that has been used in a variety of formulations, including solutions and cream, gels, ointments, injectable, mouth spray, lozenge and even spinal block.

2.3 Nonclinical safety issues relevant to clinical use

Based upon the information available to date, there do not appear to be any specific safety issues related to the use of this product that have not already been previously described for the class of compounds. Local anesthetics, particularly the ester-linked anesthetics may cause allergic reactions which can be life-threatening. Reproductive toxicology studies indicate that lidocaine and tetracaine are not teratogenic. The Division previously agreed to allow the studies on fertility/early embryonic development and post-natal development studies for tetracaine to be submitted as a phase 4 commitment.

PHARMACOLOGY/TOXICOLOGY REVIEW

3.1 INTRODUCTION AND DRUG HISTORY

NDA number:	21-623
Review number:	1
Sequence number/date/type of submission:	N000 / April 4, 2003 / Original NDA
Information to sponsor:	Yes (X) No ( )
sponsor and/or agent:	Zars Inc. Salt Lake City, Utah 84103
Manufacturer for drug substance:	Lidocaine: [redacted] Tetracaine: [redacted]

Reviewer name:	R. Daniel Mellon
Division name:	DACCADP
HFD #:	170
Review completion date:	February 4, 2004

Drugs:

Trade name: S-Caine™ Patch

Generic names:

Lidocaine, Xylocaine, Lignocaine

Tetracaine, Amethocaine, Pontocaine

Code names: None

Chemical names:

Lidocaine: 2-(Diethylamino)-N-(2,6-dimethylphenyl)-acetamide

Tetracaine: 2-(Dimethylamino)ethyl *p*-(butylamino)benzoate

CAS registry numbers:

Lidocaine: 137-58-6

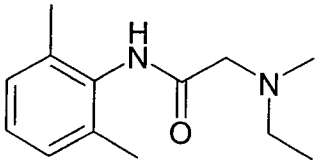
Tetracaine: 94-24-6

Molecular formula/molecular weights:

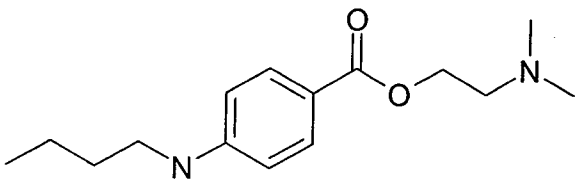
Lidocaine: $C_{14}H_{22}N_2O$ / 234.3

Tetracaine: $C_{15}H_{24}N_2O_2$ / 264.41

Structures:



Lidocaine



Tetracaine

Relevant INDs/NDAs/DMFs:

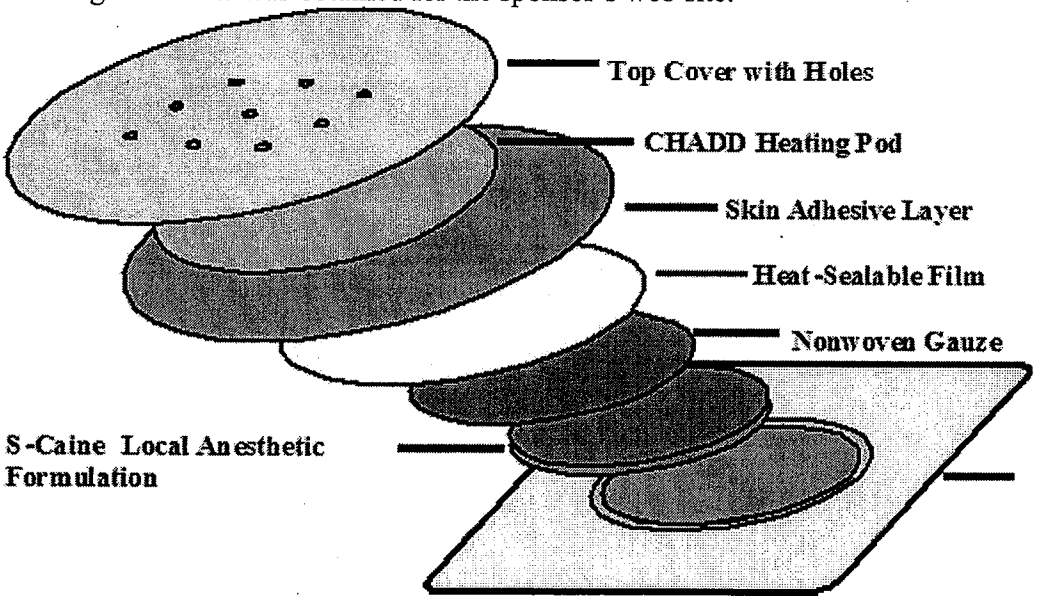
IND 58,823	Zars Inc. (S-Caine™ Patch)
IND 59,801	Zars Inc. (S-Caine™ Peel)
NDA 21-717	Zars Inc. (S-Caine™ Peel)
NDA 08-076	Neotopanol Solution (a combination of tetracaine and benzocaine) (Glenbrook) withdrawn in 1975 for lack of efficacy.

[redacted] Lidocaine
Tetracaine [redacted]

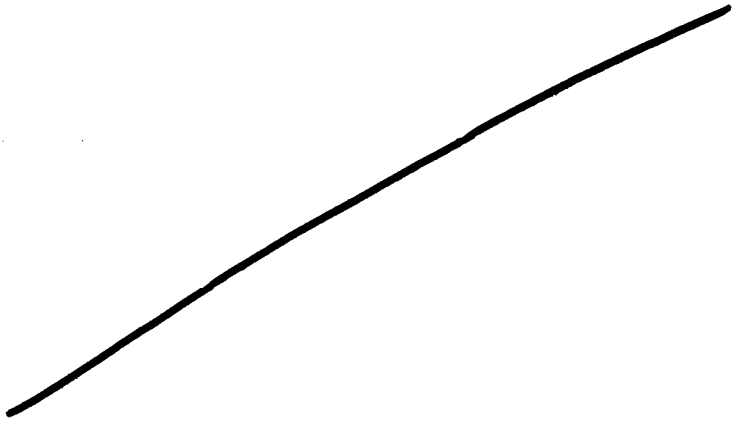
Drug class: Local anesthetics of the amide type (lidocaine) and ester type (tetracaine).

Indication: Local dermal anesthesia on intact skin.

Clinical formulation: The S-Caine™ bulk material is the active drug layer of the S-Caine™ patch. The S-Caine™ Bulk Material contains lidocaine and tetracaine (each patch contains 70 mg lidocaine and 70 mg tetracaine in a 1:1 (w:w) eutectic mixture). The diagram below was obtained for the sponsor's web site.



The components of the S-Caine™ Patch are described below:



The S-Caine™ Bulk Material contains a 1:1 eutectic mixture[1] of lidocaine base, USP and tetracaine base, USP. The components and the function of those components are presented in the sponsor's table below:

The composition of the S-Caine™ Bulk Material is listed below.

Component	Weight Percentage (%)	Weight per patch (mg)
Lidocaine Base, USP		70.00
Tetracaine Base, USP		70.00
Polyvinyl Alcohol, USP (PVA)		
Sorbitan Monopalmitate		
Water, USP		
Methylparaben, NF		
Propylparaben, NF		

The functions of the S-Caine™ Bulk Material components are listed below.

Component	Function
Lidocaine Base, USP	Active, Anesthetic
Tetracaine Base, USP	Active, Anesthetic
Polyvinyl Alcohol, USP (PVA)	
Sorbitan Monopalmitate,	
Water, USP	
Methylparaben, NF	
Propylparaben, NF	

[1] Eutectic mixture refers to a mixture whose melting point is lower than that of the individual components.

It should be noted that the clinical and preclinical studies did not all utilize the final formulation of the patch. There were a total of three different formulations of the patch as described below:

S-Caine™ Patch Investigational Formulations	Developmental A	Developmental B	Final Formulation
Amount of S-Caine™ Bulk Material in Patch			
Composition			
Lidocaine base, USP	70.00 mg	70.00 mg	70.00 mg
Tetracaine base, USP	70.00 mg	70.00 mg	70.00 mg
Polyvinylalcohol, USP			
Lecithin			
Sorbitan monopalmitate, NF			
Water			
Methylparaben, USP			
Propylparaben, USP			

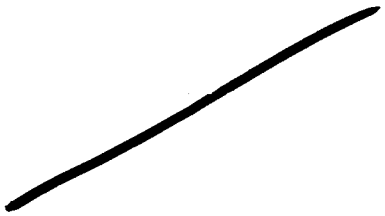
NA = not applicable, g = grams, mg = miligrams

Of the submitted preclinical studies, none of them actually used the final clinical formulation. The sponsor's table below summarizes which formulations were used in the non-clinical studies:

Study No.	Study Description	Lot No.	Formulation*
X9C009G	Modified Primary Skin Irritation Test of S-Caine™ and Placebo Using Rabbits	IP 02-24-99	A
925-002	A Dermal Irritation Study of S-Caine™ Patch in Rabbits	1262	Final
925-003	Dermal Absorption and Dermal Irritation Study of S-Caine™ Patch in Neonatal Piglets	1262	Final
X9C010G	Sensitization – Buehler Method of S-Caine™ Local Anesthetic Patch with CHADD™ (Controlled Heat)	IP 02-19-99, IP 02-20-99, IP 02-24-99, IP 04-13-99, IP 04-20-99	A
925-004	A 28 Day Dermal Toxicity Study of S-Caine™ Patch in Rabbits	1262, 1263	Final

* The components and composition of the formulations are shown in the "Investigational Formulations" Table provided in the previous section.

The following table contains the proposed regulatory specifications for the S-Caine™ Patch:



CHADD™ Heating Pod

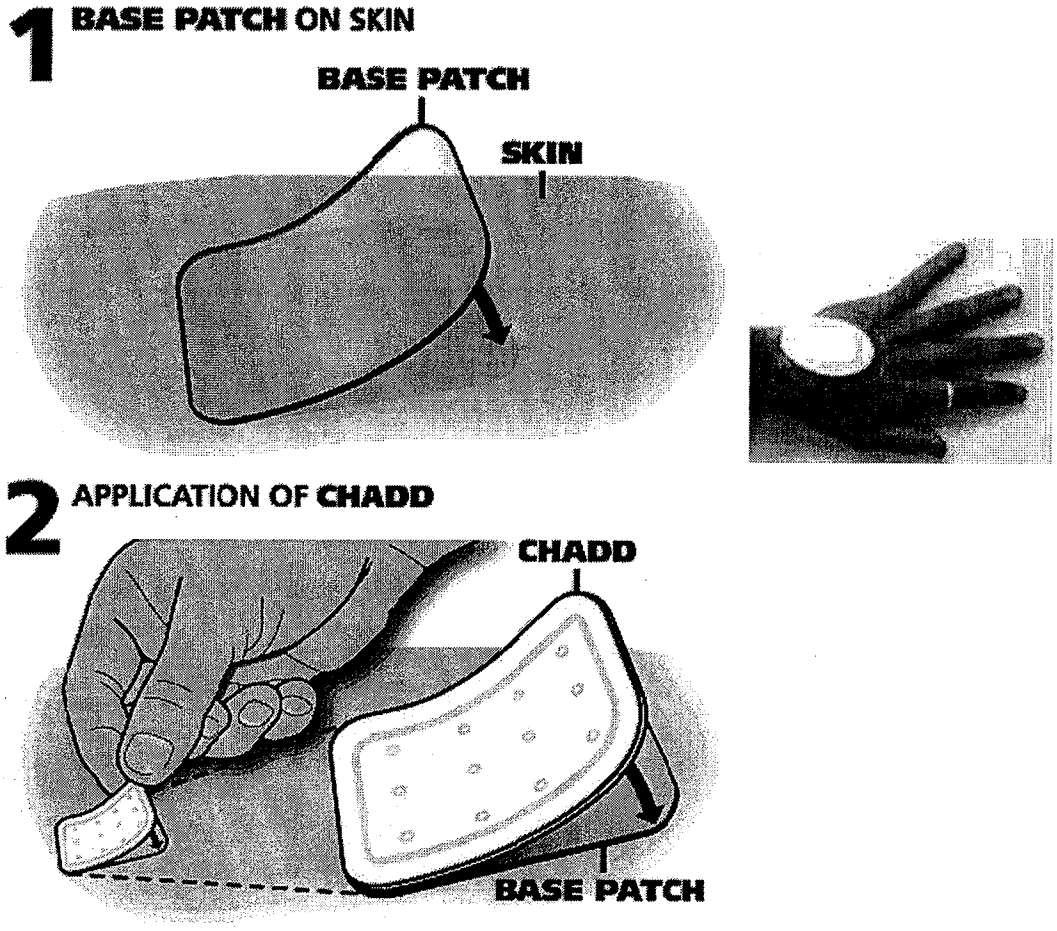
The CHADD™ Heating Pod is the heat-generating component of the S-Caine™ Patch. This is an oval pouch containing a proprietary blend of iron powder, activated carbon, sodium chloride, and wood flour which generates heat when exposed to water and oxygen. The composition and function of the components is listed in the sponsor's table below:

The composition of the CHADD™ Heating Pod is listed below.

Component	Weight Percentage (%)	Weight per patch (g)
Iron Powder		
Activated Carbon		
Sodium Chloride		
Wood Flour		
Filter Paper		

The functions of the CHADD™ Heating Pod components are listed below.

Component	Function
Iron Powder	
Activated Carbon	
Sodium Chloride	
Wood Flour	
Filter Paper	



Route of administration: Transdermal (the figures above were obtained from the sponsor's web site).

Currently, there are no approved NDAs for tetracaine. Tetracaine hydrochloride (0.5 to 1%) and tetracaine (0.5 to 1%) are listed as acceptable active ingredients for anorectal drug products for over-the-counter human use in the 21 CFR §346.1. Anorectal drug products containing this active agent are considered generally recognized as safe for human use.

Specifically, tetracaine is listed on the OTC Ingredient list (December 23, 2003) under the following indications:

OTC Ingredient List					
Ingredient Review Panel	**Report**	**Drug Category**	**ANPR**	**PR**	**FR**
Tetracaine					
---	External analgesic	Poison ivy/oak/sumac	n/a	I	Pending
Hemorrhoidal	Anorectal	Anesthetic (external)	IIIE	I	346.10(h)
Hemorrhoidal	Anorectal	Anesthetic (intrarectal)	IIIE	IIIE	55 FR 1779
Misc. external	Antifungal	Diaper rash	Defer	n/a	310.545(a)(22)(i)
Misc. external	Antimicrobial	Diaper rash	Defer	n/a	Pending
Misc. external	External analgesic	Diaper rash	Defer	IISE	310.545(a)(10)(iv)
Misc. external	External analgesic	Fever blister (topical)	Defer	I	Pending
Misc. external	Skin protectant	Diaper rash	Defer	n/a	Pending
Oral cavity	Oral health care	Analgesic/anesthetic	IIS	IIS	310.545(14)
Topical analgesic	External analgesic	Analgesic/anesthetic	I	I	Pending
Tetracaine HCl					
---	External analgesic	Poison ivy/oak/sumac	n/a	I	Pending
Antimicrobial II	Acne	Acne	IISE	IISE	310.545(l)
Hemorrhoidal	Anorectal	Anesthetic (external)	IIIE	I	346.10(i)
Hemorrhoidal	Anorectal	Anesthetic (intrarectal)	IIIE	IIIE	55 FR 1779
Misc. External	External analgesic	Fever blister (topical)	Defer	I	pending
Misc. External	Hair growth/loss	Hair grower	IIE	IIE	310.527(a)
Oral cavity	Oral health care	Analgesic/anesthetic	IIS	IIS	310.545(14)
Topical analgesic	External analgesic	Analgesic/anesthetic	I	I	Pending

ANPR = Advanced Notice of Proposed Rulemaking
PR = Proposed Rule
FR = Final Rule

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

Studies reviewed within this submission:

Study Title	Document #	Volume
Repeat Dose Toxicology:		
A 28 day dermal toxicity study of S-Caine™ Patch in rabbits	925-004	11
Acute Toxicology/Dermal Irritation:		
Modified Primary Skin Irritation (Rabbits).	X9C009G	10
A dermal irritation study of S-Caine™ Patch in rabbits	925-002	10
Dermal absorption and dermal irritation study of S-Caine™ Patch in neonatal piglets	925-003	10
Genotoxicity:		
Salmonella-Escherichia coli mammalian-microsome reverse mutation assay with a confirmatory assay with lidocaine base	23840-0-409OECD	12
Salmonella-Escherichia coli mammalian-microsome reverse mutation assay with a confirmatory assay with tetracaine base	23841-0-409OECD	12
Chromosomal aberrations in Chinese Hamster Ovary (CHO) cells with lidocaine base	23840-0-437OECD	12

Chromosomal aberrations in Chinese Hamster Ovary (CHO) cells with tetracaine base	23841-0-437OECD	12
In vivo mouse micronucleus assay with lidocaine base	23840-0-455OECD	12
In vivo mouse micronucleus assay with tetracaine base	23841-0-455OECD	12
Reproductive Toxicity		
Pilot Study for effects on embryo-fetal development in rats	925-012	3 BZ
Pilot prenatal development toxicity study in New Zealand white rabbits	925-013	4 BZ
Final toxicology report for study 925-015; Study for effects on embryo-fetal development in rats	925-015	5 BZ
Final toxicology report for study 925-016; Study for effects on embryofetal development in rabbits	925-016	6BZ

The reproductive toxicology studies were submitted on 8/1/2003

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

Study Title	Document #	Volume
Special Toxicology:		
Dermal Sensitization – Buehler Method (previously reviewed by Dr. Kathleen Haberny whose review is reproduced here)	X9C010G	10

3.2 PHARMACOLOGY

3.2.1 Brief summary

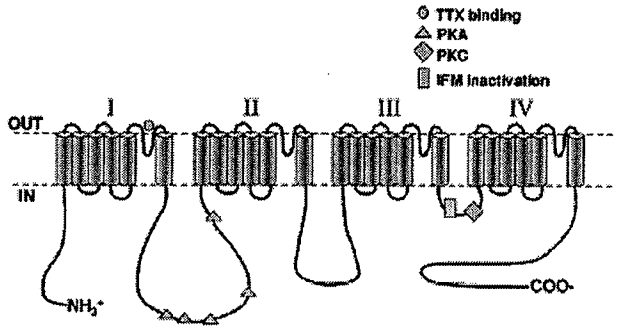
No new pharmacology studies were performed by the sponsor for this application. A review of the pharmacology of local anesthetics in general, and lidocaine and tetracaine specifically, is provided in Goodman and Gilman's The Pharmacological Basis of Therapeutics. When applied locally to nerve tissue 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.

Local anesthetics block conduction by decreasing or preventing the large transient increase in the permeability of excitable membranes to Na^+ that normally is produced by a slight depolarization of the membrane due to direct interaction with voltage-gated Na^+ channels. Local anesthetics can also bind to other membrane proteins such as K^+ channels. However, blockade of conduction is not accompanied by any large or consistent change in resting membrane potential due to block of K^+ channels since the interaction of local anesthetics with K^+ channels requires higher drug concentrations. Lidocaine and tetracaine have similar pharmacological profiles and are about equipotent. Lidocaine is considered to be the faster acting of the two components, although is shorter-acting compared to bupivacaine. Tetracaine is a para-aminobenzoic acid ester that has been used in a variety of formulations, including solutions and cream, gels, ointments, injectable, mouth spray, lozenge and even spinal block.

3.2.2 Primary pharmacodynamics

Lidocaine is an amide-linked local anesthetic, while tetracaine is an ester-linked local anesthetic. Local anesthetics prevent the generation and the conduction of nerve impulses.

Mechanism of action: Local anesthetics block the generation and conduction of nerve impulses in excitable tissues by decreasing or preventing the large transient increase in the permeability of the membrane to sodium ions. Local anesthetics bind directly to voltage-gated sodium channels from the inside of the membrane. The degree of block produced by local anesthetics is dependent upon how the rate of nerve stimulation and on its resting membrane potential. Local anesthetics are only able to bind to sodium channels in their charged form and when the sodium channels are open. In this situation, the local anesthetic is able to bind more tightly to and stabilize the sodium channel. Differences in pKa, lipid solubility, and molecular size influence the binding of local anesthetics to sodium channels. The basic structure of a sodium channel subunit is depicted below:



Subtype	Rat Orthologs	TTX Sensitivity (nM)	Activation Threshold	Inactivation Rate	Tissue Localization
$Na_v1.1$	Brain I	-	Low	Fast	CNS, also in DRG and motor neurons
$Na_v1.2$	Brain IIA	18	Low	Fast	CNS
$Na_v1.3$	Brain III	15	Low	Fast	Embryonic nervous system; adult CNS;
$Na_v1.4$	SkM1	5	Low	Fast	Skeletal muscle
$Na_v1.5$	H1	1,800	Low	Medium	Heart; embryonic DRG
$Na_v1.6$	SCP6, PN4	1	Low	Fast	DRG, motor neurons, also in CNS
$Na_v1.7$	PN1	2	Low	Fast	Mostly DRG, also in CNS
$Na_v1.8$	PN3, SNS	>100,000	High	Slow	DRG (50% small diameter; 20% large
$Na_v1.9$	PN5, NaN	39,000	Low	Medium	DRG (small diameter); also in CNS

Figure 1 Schematic secondary structure of the family of VGSCs, their classification, tissue distribution, and functional characteristics.

In general, small nerve fibers are more sensitive to local anesthetics than large nerve fibers. However, myelinated fibers are blocked before non-myelinated fibers of the same diameter. Autonomic fibers, small unmyelinated C fibers (mediating pain) and small myelinated Aδ fibers (mediating pain and temperature sensation) are blocked before larger myelinated Aγ, Aβ, or Aα fibers (mediating touch, pressure, muscle and postural inputs). Small, sensory fibers are preferentially blocked since nerve conduction is more easily blocked over shorter distances and these fibers have longer action potentials allowing more of the local anesthetic to bind. Clinically, the loss of nerve function proceeds as loss of pain, temperature, touch, proprioception, and then skeletal muscle.

Drug activity related to proposed indication: Blockade of neuronal conduction prevents the action potential of sensory neurons and therefore blocks the transmission of pain signals to the CNS. Lidocaine and tetracaine blockade demonstrates both frequency and voltage-dependency. Both drugs block both open and inactivated Na^+ channels. The frequency dependence of this blockade makes smaller unmyelinated nerve fibers more sensitive to blockade than larger heavily myelinated fibers. Therefore, Type C fibers (dorsal root and sympathetic nerves) and Type B (preganglionic autonomic nerves) are blocked at lower concentrations than heavily myelinated Type A (alpha, beta, gamma and delta) fibers. Of the type A fibers, pain and temperature sensitive neurons (delta) are more susceptible to local anesthetics than muscle spindles (gamma), touch and pressure sensitive neurons (beta) which are, in turn, more sensitive than proprioception and motor neurons (alpha). This sensitivity also correlates with the diameter of the nerve fiber, with smaller fibers being more sensitive to the local anesthetic action.

3.2.3 Secondary pharmacodynamics

In addition to Na+ channels, local anesthetics can bind to other membrane proteins. Specifically, local anesthetics have been shown to bind to K+ channels, at higher concentrations.

In addition to blockade of sensory nerves, local anesthetics also interfere with the functioning of all organs which require the conduction of electrical impulses for their activity. These organs include the CNS, autonomic ganglia, neuromuscular junction and all forms of muscle, including cardiac. The anti-arrhythmic effects of lidocaine are primarily due to action on the myocardium. Lidocaine leads to decreased electrical excitability, conduction rate and force of contraction. The ability for lidocaine to block cardiac conduction is the basis for its use as an anti-arrhythmic drug. This pharmacodynamic action occurs at systemic blood levels that range from 1-5 mg/ml.

3.2.4 Safety pharmacology

Safety pharmacology studies for either lidocaine or tetracaine were not conducted for this NDA, and are not required for drugs that have a long history of clinical use. However, extensive experience with local anesthetics has provided a clear understanding of the effects of these drugs on the critical systems of the body. Toxicity is due to an exaggerated pharmacological activity, primarily on the cardiovascular and central nervous system. Initial effects include mild hypertension and tachycardia, lightheadedness, mild agitation, and confusion. In severe cases this may progress to seizures, coma, respiratory depression, bradycardia, ventricular arrhythmias and asystole. Toxicity may result from an excessive dose, mistaken drug identity, enhanced drug absorption, inadvertent intravascular injection, altered protein binding, slowed redistribution and/or elimination.

Neurological effects: Sufficiently high plasma concentrations of lidocaine (5 μg/ml) can have toxic effects. However, "toxicity may occur with 'therapeutic' drug levels, particularly in patients with low serum protein concentrations who have increased levels if free (nonprotein-bound) drug (Micromedex Online Database)." Therapeutic plasma concentrations of lidocaine range from 1.5 to 5 μg/ml (Micromedex Online Database). CNS effects can include excitation and/or depression, light-headedness, nervousness, apprehension, euphoria, confusion, dizziness, drowsiness, tinnitus, blurred or double vision, vomiting, sensations of heat, cold or numbness, twitching, tremors, convulsions, unconsciousness, respiratory depression and arrest. In the peripheral nervous system, there is evidence that an excessively high concentration of local anesthetics can be toxic to nerve tissue.

High systemic plasma levels of lidocaine as well as other local anesthetics have been associated with convulsions and death. In the mouse model, the median convulsant dose was 111.0 mg/kg, intraperitoneally and the median lethal dose was 133.1 mg/kg, i.p. (de Jong and Bonin, 1980).

Cardiovascular effects: Toxic effects on the cardiovascular system may also occur with sufficiently high blood levels of lidocaine. These may include bradycardia, hypotension, cardiac collapse and arrest. Lidocaine is used therapeutically to suppress cardiac arrhythmia with effective blood concentrations ranging from 1.2 to 5 μg/ml. These effects are mediated both via direct effects on the cardiac and smooth muscle and via effects on the autonomic nerves. Likewise, high concentrations of tetracaine may also lead to depression of the myocardium, hypotension or hypertension, bradycardia, ventricular arrhythmias and cardiac arrest.

Pulmonary effects: There are no known direct pulmonary effects associated with application of either lidocaine or tetracaine to the skin surface. With systemic dosing, apnea, anaphylaxis, and respiratory depression may occur in some patients.

Renal effects: There are no known renal effects following topical application of lidocaine or tetracaine to the oral mucosa.

Gastrointestinal effects: Local anesthetics can depress contraction of the smooth muscle in intact bowel and strips of isolated intestine. Nausea and vomiting may occur with tetracaine.

Abuse liability: The sponsor has not conducted specific studies to examine abuse liability. A review of the literature indicates that neither lidocaine nor tetracaine bind substantially to the dopamine transporter nor do they maintain self-administration in monkeys (Wilcox et al., 2000). Overall, there is no indication that lidocaine or tetracaine would demonstrate any abuse liability concerns.

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

Safety Pharmacology Summary: Formal safety pharmacology studies were not performed for this application and were not required due to the extensive human experience with both lidocaine and tetracaine. As with other local anesthetics, secondary pharmacodynamic effects of lidocaine and tetracaine include stimulation of the CNS which is manifested by restlessness and tremor leading to clonic convulsions. Central stimulation is followed by depression and death is usually caused by respiratory failure. Cardiovascular effects may include decreased electrical excitability, conduction rate, and force of contraction, arteriolar dilatation, and cardiac arrhythmias when plasma levels exceed ~ 10 μmol/L (5 μg/ml) for lidocaine. Cardiovascular effects are thought to be due to a pharmacological effect on cardiac muscle due to sodium channel blockade.

Lidocaine has a biphasic effect on blood flow. Lower concentrations produce vasoconstriction, while higher concentrations produce vasodilatation.

Safety Pharmacology Conclusions: The primary effects of lidocaine and tetracaine related to safety pharmacology include CNS and cardiovascular effects at plasma levels exceeding ~ 10 μmol/L (5 μg/ml) for either compound. Plasma levels following administration of S-Caine™ Patch are expected to be well below the plasma levels at which these adverse findings are observed.

3.2.5 Pharmacodynamic drug interactions

The potential for local anesthetics to produce pharmacodynamic drug interactions results when coadministration of a drug would lead to altered effects. Coadministration of a vasoconstrictor, such as epinephrine, has been utilized to prolong the activity of injected local anesthetics by decreasing the diffuse of the anesthetic away from the intended site of action.

The effects of drugs that block other ionic currents in excitable membranes may be augmented in the presence of lidocaine. This is certainly true with other local anesthetics or sodium channel blockers such as amiodarone.

Adverse Drug Interactions in Dentistry: Local Anesthetics

Drugs	Interaction	Clinical Implications
Lidocaine/tetracaine with other local anesthetics (i.e., bupivacaine)	Effects are additive	Major Significance: Local anesthetic toxicity is additive when these drugs are given in combination; although combination therapy with local anesthetics is acceptable; total dose should not exceed combined maximum recommended doses.
lidocaine with anithistaminees (i.e., cimetadine)	Inhibition of local anesthetic metabolism	Inhibition of local anesthetic metabolism will have little effect on peak plasma levels of anesthetic when given as a single injection. Plasma clearance of lidocaine may be reduced in the presence of enzyme inducers.
Local anesthetics and opioids (i.e., mepivacaine with meperidine)	Increased sedation	Sedation with opioids may increase the risk of local anesthetic toxicity, particularly with children; local anesthetic dose should be reduced.
Lidocaine with beta-blockers (i.e., propranolol)	Inhibition of local anesthetic metabolism and perhaps reduced hepatic blood flow	Beta-Blockers and/or reduced hepatic blood flow can lead to elevated levels of lidocaine, possibly leading to lidocaine toxicity.

Sources: Drug Interaction Facts Online and (Moore, 1999).

Pharmacodynamic interactions can occur with either lidocaine or tetracaine in the drug product. Briefly, lidocaine may interaction with other antiarrhythmic drugs which also block sodium channels and increase the toxic effects of this class of drugs ultimately leading to seizures, heart failure or cardiac arrest. As listed in the EMLA® (lidocaine; prilocaine) label, the combination of lidocaine:prilocaine should be used with caution in patients receiving class I antiarrhythmics (e.g., disopyramide, encainide, flecainide, mexiletine, moricizine, phenytoin, procainamide, propafenone, quinidine, or tocainide) since the toxic effects are additive and potentially synergistic. Similarly, interaction with other local anesthetics would reduce the amount of lidocaine bound to α-1-acid glycoprotein and thereby increase plasma levels of lidocaine. Similar caution should be taken with the combination of lidocaine and tetracaine.

3.3 PHARMACOKINETICS/TOXICOKINETICS

3.3.1 Brief summary

The S-Caine™ patch contains two active local anesthetic agents, lidocaine and tetracaine. Lidocaine is an amide linked local anesthetic while tetracaine is an ester-linked local anesthetic agent. Tetracaine is rapidly hydrolyzed by esterases in the plasma and tissues. The amide linkage in lidocaine is far less susceptible to hydrolysis than the ester linkage. Lidocaine and tetracaine bases diffuse through the lower membrane of the patch and into the underlying skin. The free bases are absorbed rapidly through mucous membranes, intact and damaged skin, and from the intestines and respiratory tract. The hydrochlorides are absorbed rapidly after parenteral administration, but absorption through intact skin or mucous membranes is poor. Following parenteral injection, lidocaine and tetracaine are widely distributed into highly perfused tissue, followed by redistribution into skeletal muscle and adipose tissue. Distribution is similar for both compounds. 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 has been reported to be between 51 and 85% in humans. Protein binding of tetracaine in humans has been reported to be 76% (Micromedex Online Database). Local anesthetics are bound primarily by α-1-acid glycoprotein.

In general, agents with an amide linkage are metabolized by hepatic microsomal enzymes and their elimination is prolonged by liver disease and decreased hepatic blood flow. Lidocaine is almost completely metabolized by the liver (95%) before excretion in the urine (< 10 % excreted unchanged). As such, any alteration in liver function or hepatic blood flow can have a significant effect on the pharmacokinetics and dosage requirements. Metabolism of lidocaine 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-xylidine were identified as major metabolites. In the urine of man and dogs, the major metabolite (4-hydroxy 2,6-xylidine) accounted for 70% and 35% of the dose, respectively. In rats, the urinary metabolites accounted for 70% of the administered dose and included 3-hydroxy lidocaine and its dealkylated product, 3-hydroxy-MEGX.

In general, agents with an ester type linkage are rapidly metabolized mainly by the plasma pseudocholinesterases yielding para-aminobenzoic acid derivatives. They are also metabolized by liver esterases to some degree. As such, tetracaine is hydrolyzed by plasma esterases to form aminobenzoic acid and diethylaminoethanol. Aminobenzoic acid is used by topical application as a sunscreen. The compound effectively absorbs light throughout the UVB range but not the UVA range. Aminobenozoate sunscreens, therefore can prevent sunburn but would not prevent photosensitivity reactions caused by UVA light. Adverse skin reactions have been reported following the topical administration of aminobenzoic acid sunscreens, including contact and photocontact allergic dermatitis and vitiligo.

3.3.3 Absorption

Lidocaine is readily absorbed from the gastrointestinal tract, from mucous membranes and through damaged skin. Absorption through intact skin, however, is considered to be poor. Absorption from injection sites, including muscle is rapid. The oral bioavailability of lidocaine is about 35%, due to the extensive first-pass metabolism in the liver. Alterations in hepatic blood flow or liver function can have a pronounced effect on the pharmacokinetics and half-life of lidocaine.

Tetracaine is readily absorbed into open wounds. Tetracaine is reported to be about 15% bioavailable following application of a 4% gel to intact skin.

3.3.4 Distribution

Amide local anesthetics are widely distributed after intravenous administration. Intravenous lidocaine demonstrates a rapid distribution phase (into highly perfused tissues) following by slower distribution phases into muscle as well as fat tissues. Lidocaine can cross the blood brain barrier as well as the placenta and can be detected in breast milk. Systemic lidocaine has fairly high protein binding (33-80%) in humans, primarily to α-1-acid glycoprotein. The volume of distribution has been reported to be 1.7 L/kg with a distributional half-life of 15-30 minutes (Thomson et al., 1971;Rowland et al., 1971). In distribution studies examining intravenous administration, there is a large first pass uptake of lidocaine by the lung. Lidocaine crosses the blood brain barrier by passive diffusion. Likewise, lidocaine rapidly crosses the placenta by passive diffusion and levels may be sufficient enough to reach the fetus. Lidocaine is detectable in the fetal circulation within minutes of administration to the mother.

Following intravenous infusion, tetracaine is initially distributed to the lung, and later redistributed to the liver, kidney and adrenals. The distribution of tetracaine has been examined following intravenous and spinal administration in the rabbit model. The table to the right presents the concentration of tetracaine and the metabolite para-butylaminobenzoic acid in selected rabbit tissues following intravenous administration (Hino et al., 2001).

Table 3
Concentrations of tetracaine and its metabolite in rabbit tissues following intravenous administration (ng/g)

Rabbit number	11	
Weight (kg)	3.02	
Dose (mg/kg)	1.08	
Survival time after injection (min)	26	
	Tetracaine	Metabolite
Cerebrum	268.3	4597.5
Cerebellum	199.5	2973.1
Brain stem	ND[a]	800.3
Spinal cord		
Cervical	ND	411.0
Thoracic	ND	332.4
Lumbar	ND	341.8
Heart blood	148.8	521.4
Peripheral blood	403.9	498.4

[a] Not detected.

3.3.5 Metabolism

About 90% of the administered lidocaine is metabolized in the liver (Zito and Reid, 1981;Elvin et al., 1981). Lidocaine is not metabolized by plasma esterases. There is increasing evidence that lidocaine can be metabolized extrahepatically, including the intestines, lung and kidney. Both monoethylglycine xylidide (MGEX) and glycine xylidide (GX) exhibit some local anesthetic activity. In human beings, approximately 75% of the xylidide is excreted in the urine as 4-hydroxy-2,6-dimethylaniline. The 4-hydroxyxylidine is the predominant metabolite excreted in the urine after lidocaine administration. The conversion of lidocaine to MGEX *in vitro* appears to be mediated by CYP3A4 in humans and CYP2C11 and CYP2B1 in rats. Hydroxylation of lidocaine appears to be mediated by CYP2D and CYP1A2 isozymes. There is considerable interspecies variability in the metabolism of lidocaine. N-hydroxyxylidine has been shown to form hemoglobin adducts. Xylidine-hemoglobin adducts have been detected in the blood of tobacco smokers and non-smokers. The figure below details the metabolism of lidocaine to MEGX, GX and Xylidines (Alexson et al., 2002).

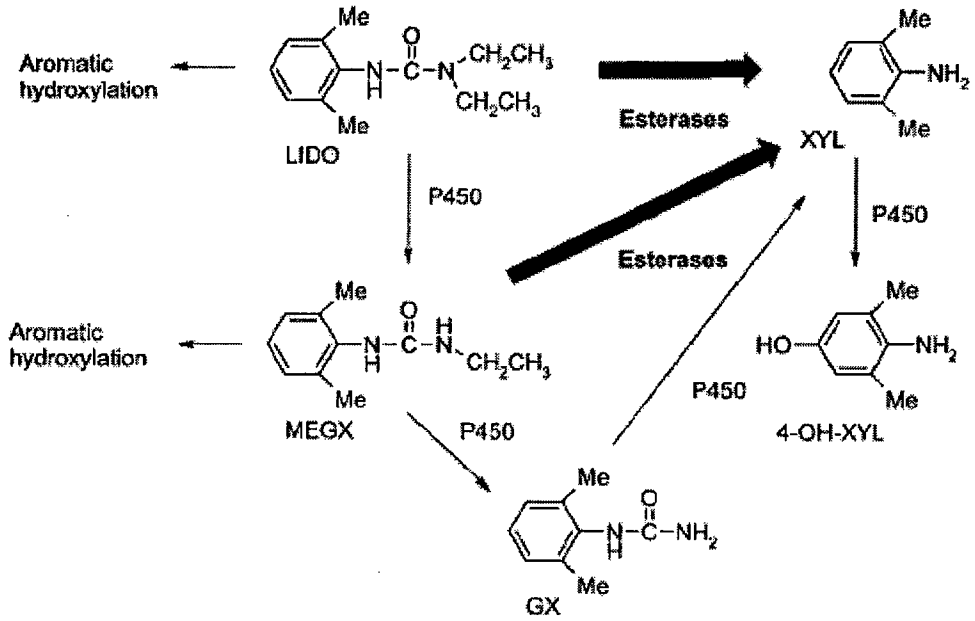
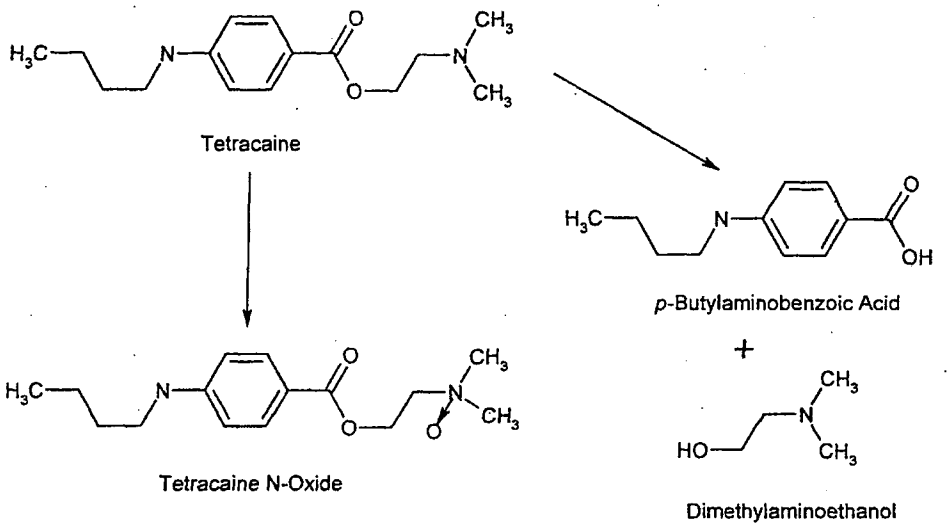


FIG. 5. *Hypothetical scheme for the formation of 4-OH-XYL and other hydroxylated metabolites from LIDO, MEGX, and/or GX via the activity by esterases and/or P450.*

Tetracaine is metabolized by hydrolysis of the ester bond by plasma cholinesterases. Primary metabolites include para-butylaminobenzoic acid and diethylaminoethanol, both of which have an unspecified activity. In rats, rabbits and horses, the N-oxide of tetracaine is also formed.

Figure 2. Metabolic Pathways for Tetracaine



Information from Foldes, 1966 and Momose, 1976.

3.3.6 Excretion

Lidocaine and its metabolites are excreted in the urine. The elimination half-life of the parent compound is between 1.5 and 2 hours (Thomson et al., 1971;Rowland et al., 1971). MEGX has a half-life of 1-6 hours and GX has a half-life of about 1 hour. The metabolite 2,6-xylidine has been detected in the breast milk of human females. Urinary excretion of local anesthetics is pH-dependent. Acidification of the urine results in increased concentrations of local anesthetics and some metabolites in urine. Alkalinization of the urine decreased levels of local anesthetics. Very little local anesthetic is eliminated in the feces of humans.

Tetracaine metabolites (aminobenzoic acid and diethylmanioethanol) are primarily excreted in the urine. Tetracaine has a long duration compared to other local anesthetics. The duration of local anesthesia following spinal anesthesia is 2-3 hours without epinephrine and 4-6 hours with epinephrine. It is not known if tetracaine can be excreted in breast milk.

3.3.7 Pharmacokinetic drug interactions

Local anesthetics such as lidocaine and tetracaine are largely metabolized in the liver and therefore any alteration in liver function or blood flow through the liver will alter the plasma levels of prilocaine.

The speed of onset of a local anesthetic may be increased by the addition of a vasoconstrictor. This prevents the drug from diffusing into the general circulation from the injection site. Epinephrine is commonly combined with a local anesthetic in a ratio of 1:100,000 or 1:200,000. The total amount of epinephrine injected should not be greater than 500 mg. Local anesthetics are generally administered in an acidic solution and alkalization of the solution with sodium carbonate is thought to increase the speed of onset. Alkalization of the solution increases the proportion of the lipid soluble non-ionized free base allowing the active molecule to pass through the cell membrane. The buffering of the solution with sodium bicarbonate reduces the acidity and thereby also reduces the pain associated with their injection.

Amiodarone or one of its metabolites may inhibit lidocaine metabolism via CYP3A4 possibly leading to increased lidocaine plasma concentrations and lidocaine toxicity.

3.3.10 Tables and figures to include comparative TK summary

The plasma levels of lidocaine and tetracaine were examined in the 28-day repeat-dose toxicology study and are reproduced below:

Figure 1a. Mean Concentrations of Lidocaine in Male Rabbits, Non-Abraded

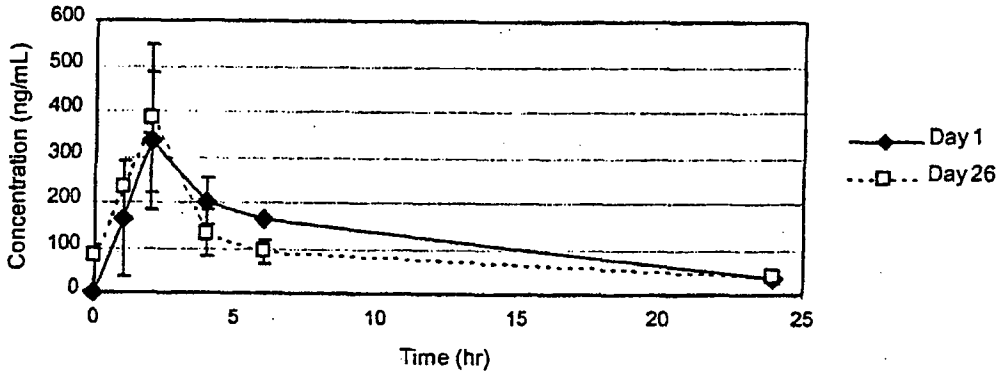


Figure 1b. Mean Concentrations of Tetracaine in Male Rabbits, Non-Abraded

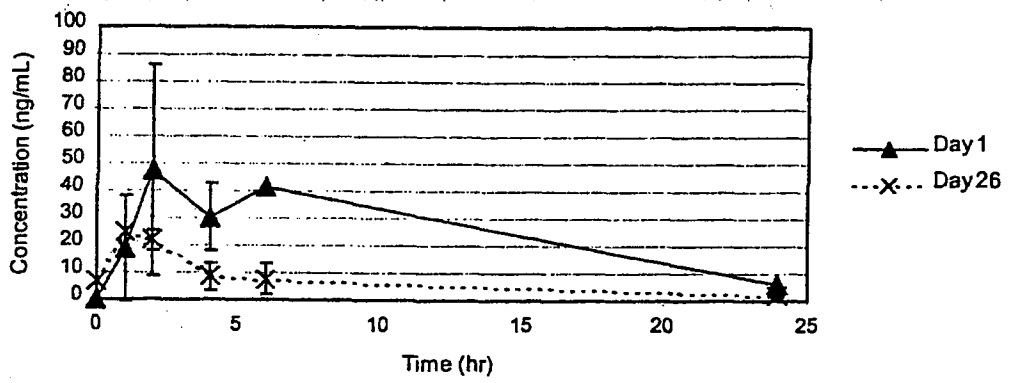


Figure 1c. Mean Concentrations of Lidocaine and Tetracaine in Male Rabbits, Non Abraded

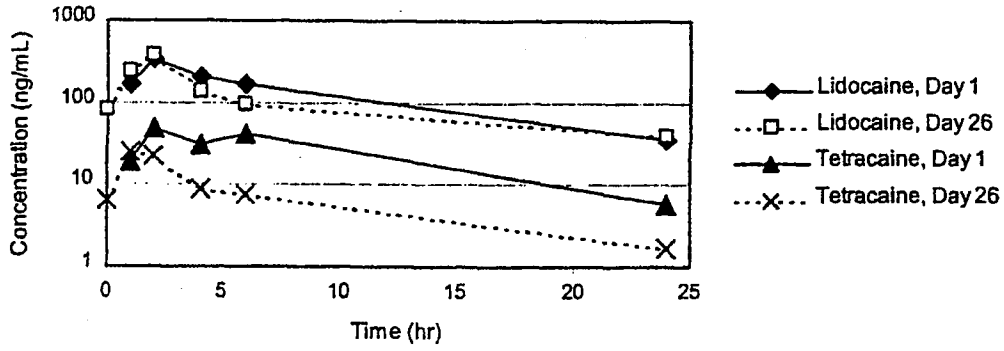


Figure 4a. Mean Concentrations of Lidocaine in Female Rabbits, Abraded

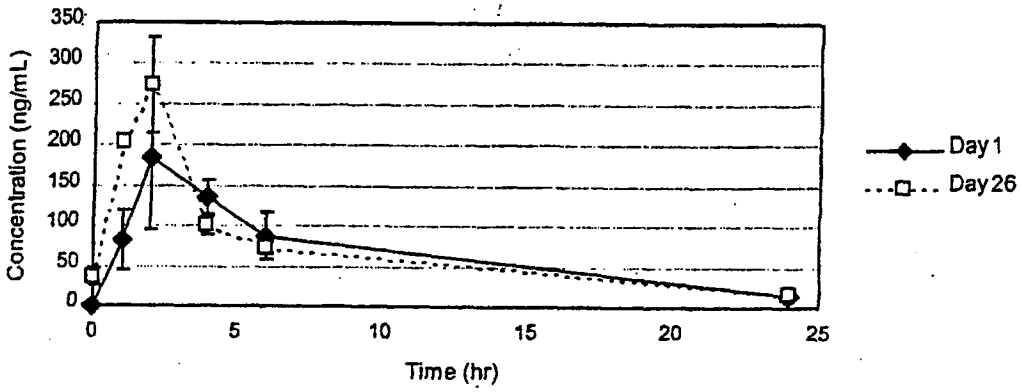


Figure 4b. Mean Concentrations of Tetracaine in Female Rabbits, Abraded

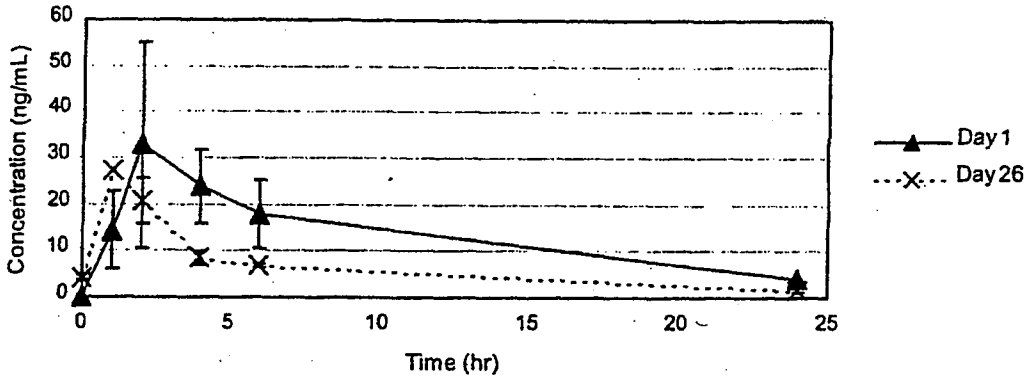


Figure 4c. Mean Concentrations of Lidocaine and Tetracaine in Female Rabbits, Abraded

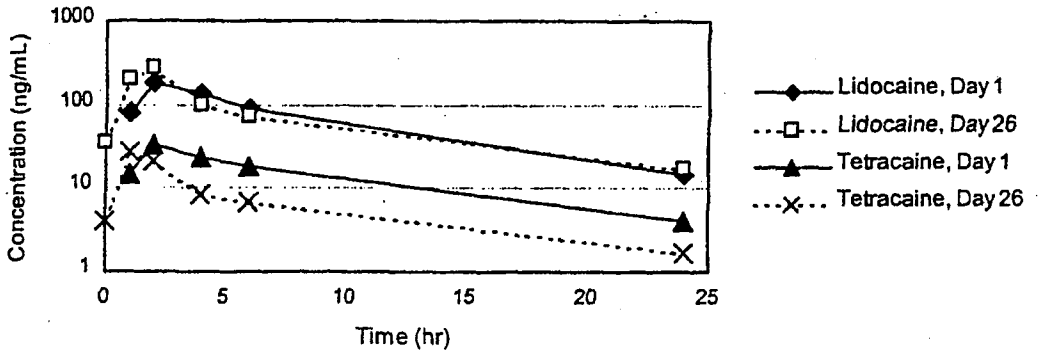


Table 5.1.2.1.-3. Results of 28-Day Nonclinical ADME Study Conducted by ZARS

Species	Study No.	No. of Animals, Sex	Skin	Day	Mean PK Parameters for Lidocaine				Mean PK Parameters for Tetracaine			
					C_{max} (ng/mL)	T_{max} (hr)	AUC_{0-24} (ng•hr/mL)	$t_{1/2}$* (hr)	C_{max} (ng/mL)	T_{max} (hr)	AUC_{0-24} (ng•hr/mL)	$t_{1/2}$* (hr)
Rabbit	925-004	3 M	Intact	1	335	2.0	3,076	8.0	49	2.7	640	7.4
				26	383	2.0	2,431	12.6	23	1.7	180	8.5
		3 F	Intact	1	366	2.0	2,813	6.9	55	2.0	461	7.1
				26	286	2.0	1,962	9.4	16	2.7	119	6.2
		3 M	Abraded	1	314	2.0	2,143	6.1	47	2.0	363	5.5
				26	299	2.0	2,156	9.4	28	1.0	140	8.5
		3 F	Abraded	1	185	2.7	1,452	6.4	34	2.7	263	8.1
				26	277	1.7	1,684	8.1	28	1.7	156	8.8

All animals received three S-Caine patches applied for 2 hr daily.

* Derived from mean concentration values. For all other parameters, the parameters were calculated from the plasma concentrations for the individual animals and then averaged.

Table 5.1.2.1.-4. Results of Pilot Reproductive Studies Conducted by ZARS

Species	Study No.	Animals, Sex per Group	Gestation Day	Drug, Dose (mg/kg)	Mean PK Parameters for Lidocaine				Mean PK Parameters for Tetracaine			
					C_{max} (ng/mL)	T_{max} (hr)	AUC_{0-24} (ng•hr/mL)	$t_{1/2}$ (hr)	C_{max} (ng/mL)	T_{max} (hr)	AUC_{0-24} (ng•hr/mL)	$t_{1/2}$* (hr)
Rat	925-012	3F	17	L: 15	1,267	0.5	3,281	0.8				
				L: 30	2,060	0.5	5,595	2.0				
				L: 60	2,788	1	11,408	2.4				
				L: 75	3,019	0.5	11,847	2.4				
Rabbit	925-013	3F	20	L: 15	2,928	0.5	8,001	1.8				
				L: 30	7,209	0.5	16,477	1.0				
				L: 60*	10,703	0.7	28,954	1.7				
				T: 1					45.7	0.5	59.2	1.1
				T: 2					22.8	0.5	30.5	0.8
				T: 5					123.2	0.7	209.0	1.2
				T: 10					618.3	0.5	683.5	0.8

All administrations were daily subcutaneous injections.

* All animals receiving 75 mg/kg died before Day 20; thus, no parameters for that dose group.

3.4 TOXICOLOGY

3.4.1 Overall toxicology summary

General toxicology: Systemic toxicology studies were not conducted for this NDA. The general toxicology of lidocaine and tetracaine reflect an exaggeration of their pharmacological effect, as described in the safety pharmacology section of this review.

Genetic toxicology: A standard battery of genetic toxicology studies were completed by the sponsor testing lidocaine base and tetracaine base independently. Lidocaine tested negative in the *in vitro* Bacterial Reverse Mutation Assay (Ames test), *in vitro* chromosome aberrations assay, and the *in vivo* mouse micronucleus assay. Tetracaine tested negative in the *in vitro* bacterial reverse mutation assay (Ames test) and the *in vivo* mouse micronucleus assay. However, tetracaine was equivocal in the *in vitro* chromosome aberrations assay.

Carcinogenicity: The sponsor did not conduct carcinogenicity assessment for either lidocaine or tetracaine. There are no data in the public domain that indicates that either compound is carcinogenicity. The ICH M3 Guidance indicates that carcinogenicity assessment would not be required for a drug that would not be used either continuously for $\geq$ 6 months or intermittently over a lifetime such that total exposure would add up to approximately six months time. At this point in time, carcinogenicity assessment is not required for this drug product.

The metabolite of lidocaine, 2,6-xylidine, has been tested for carcinogenic potential in Sprague-Dawley rats by the National Toxicology Program in 1990. Dietary administration of 2,6-xylidine to the rat at 0, 300, 1000 or 3000 ppm for 102 weeks produced a significant increase in the incidence of nasal cavity adenomas, carcinomas and adenocarcinomas in both males and females. Rhabdomyosarcomas, previously unreported in this rat strain, were detected in two high-dose males and two high-dose females (none in the controls) (National Toxicology Program, 1990).

Reproductive toxicology: To support the current NDA application, the sponsor completed Segment II reproductive toxicology studies (embryo-fetal development) in the rat and rabbit model with lidocaine, tetracaine and the combination of lidocaine:tetracaine. Dosing for the definitive Segment II studies was determined by a pilot study. Under the conditions of the assay, neither lidocaine nor tetracaine produced evidence of alterations in the development of the fetus. By previous agreement with the Division, the sponsor was informed that they could submit segment I and segment III studies for tetracaine alone post approval (i.e., as a phase 4 commitment). The sponsor therefore is relying upon the published literature to characterize the effect of lidocaine on fertility and early embryonic development (segment I studies). The sponsor summarizes the results of Fijinaga and Mazze (1986) as the primary data for lidocaine's effects. Although the sponsor provided a large number of publications, this citation was not provided in the NDA package. Likewise, the sponsor cites Smith et al. (1989) as a critical publication to characterize the effects of lidocaine on peri- and post-natal

development in the rat (segment III studies). However, this citation was also not provided in the NDA.

The published literature provides some data regarding the effects of lidocaine in the fertility and early embryonic development in the rat. Fujinaga and Mazza reported that treatment of rats with lidocaine (100 and 250 mg/kg/day) via chronically implanted osmotic pumps for two weeks prior to mating and throughout pregnancy. A high dose treatment group (500 mg/kg/day) were treated from gestation day 3 to 17 for evaluate potential teratogenic effects. Examination of the 1040 offspring for external, visceral, and skeletal abnormalities failed to detect any evidence of teratogenicity. Reproductive indices were reported at normal. There was treatment-related decrease in mean fetal weight in the high dose group that was determined to be secondary to slightly delayed fetal development (Fujinaga and Mazze, 1986). It is not clear from this study summary if the males were also treated in this study report. Current protocols recommend treatment of the males for at least 4 weeks prior to mating and females at least 2 weeks prior to mating. There does not appear to be any discussion of how these studies compare to the current standards for a segment I study, as requested during the pre-NDA meeting. The sponsor should provide copies of all literature references and their analysis of the data as apart of the second submission.

Special toxicology: The sponsor examined the potential for S-Caine™ Patch induced contact sensitization via the Buehler Method. The results suggested that the S-Caine™ patch has the potential to produce dermal sensitization in the guinea pig model. As this study was not conducted with the final formulation of the S-Caine™ Patch proposed for clinical use, the human sensitization study may serve as the definitive analysis of the potential for dermal sensitization.

3.4.2 Single-dose toxicity

The results of acute toxicity studies of lidocaine hydrochloride have been reported in the Hazardous Substances Database (HSDB). The human equivalent dose conversion is based upon body surface area and expressed for a 60 kg individual.

Species	Route	LD_{50} (mg/kg)	Human Equivalent Dose mg/60 kg person
Mouse	Oral	292	1,424
	i.p.	105	512
	s.c.	238	1,161
	i.v.	19.5	95
Rat	Oral	317	3,068
	i.p.	133	1,287
	s.c.	335	3,242
	i.v.	25	242

The acute toxicity of tetracaine is described in the RTECs database and is summarized below:

TDLO/TCLO – Lowest Published Toxic Dose/Concentration			
Species	**Route**	**Dose**	**Toxic Effects**
Human, Woman	Parenteral	4 mg/kg	*Behavioral – Excitation* *Behavioral – Coma* *Cardiac – Arrhythmias (including changes in conduction)*
LDLO/LCLO – Lowest Published Lethal Dose/Concentration			
Human, Man	Parenteral	1 mg/kg	*Behavioral – Muscle contraction or spacticity* *Behavioral – Coma* *Lung, Thorax, or Respiration – Cyanosis*
Rabbit	Intraspinal	4.9 mg/kg	
	Intravenous	6 mg/kg	*Lung, Thorax, or Respiration – Other changes*
	Subcutaneous	20 mg/kg	*Lung, Thorax, or Respiration – Other changes*
LD50/LC50 –Lethal Dose/Concentration 50% Kill			
Rat	intraperitoneal Intratracheal Intravenous	33 mg/kg 4 mg/kg 6 mg/kg	
Mouse	Intraperitoneal Intravenous Oral Subcutaneous	20 mg/kg 6 mg/kg 300 mg/kg 41.5 mg/kg	
Rabbit	Intratracheal Parenteral	6.5 mg/kg 33.5 mg/kg	

According to Martindale's online, tetracaine has high systemic toxicity and is absorbed rapidly from mucous membranes. As such, adverse reactions can occur abruptly without warning and fatalities have been reported. Topical application is frequently associated with mild erythema.

3.4.3 Repeat-dose toxicity

The sponsor did not submit any systemic repeat dose toxicology studies with either tetracaine or lidocaine for this NDA application. The potential for systemic toxicity following repeated application of S-Caine™ Patches to the rabbit were characterized in the study described below:

Study title: A 28-Day Dermal Toxicity Study of S-Caine™ Patch in Rabbits (with toxicokinetics)

Key study findings: A repeat-dose dermal toxicology study was conducted in rabbits to evaluate the dermal toxicity of S-Caine™ patch following daily dermal application of 3 patches for 2 hours a day for a total of 28 days on abraded and non abraded skin. The key findings are as follows:

1. There was no evidence of systemic toxicity in any group under the conditions of this assay.
2. Repeated application of S-Caine™ patch (once every three days) produced a greater degree of skin irritation compared to the placebo patch for both abraded and non-abraded skin.
3. There were no differences in the blood levels of lidocaine or tetracaine between abraded and non-abraded animals or males and females.
4. Histological changes were limited to the test-article application sites and included epidermal surface exudates, epidermal necrosis, acute dermatitis, trace to moderate epithelial hyperplasia and fibrosis of the dermis.
5. The incidence and severity of histological changes were comparable between males and females and abraded and non-abraded sites.

Study no.: 925-004
Volume #, and page #: Volume 11, Page 1
Conducting laboratory and location: [redacted]

Date of study initiation: May 9, 2002
GLP compliance: Yes
QA report: yes (X) no ( )
Drug, lot #, and % purity: Active S-Caine™ Patch, Lots 1262 and

Placebo Patch, Lot 1264

Methods

Doses: 3 S-Caine™ Patch (70 mg lidocaine; 70 mg tetracaine) applied for 2 hours per day for 28 days.

Species/strain: New Zealand White Hra(NZW)SPF albino rabbits

Number/sex/group or time point (main study): The following groups were tested in this study:

Group Assignment				
			Number of Animals	
Group	Treatment	Test Site	Male	Female
1	S-Caine™ Placebo Patch	Non-Abraded	3	3
2	S-Caine™ Patch	Non-Abraded	3	3
3	S-Caine™ Placebo Patch	Abraded	3	3
4	S-Caine™ Patch	Abraded	2	4

The use of only 2 males and 4 females in group 4 animals was due to incorrect sexing that was noticed upon necropsy.

Route, formulation, volume, and infusion rate: Transdermal administration, via S-Caine™ Patch or Placebo S-Caine™ Patch. Groups 2 and 4 had patches applied to three of 9 sites and rotated such that each site was only exposed once every three days. Groups 1 and 3 had patches applied to two of six sites and rotated such that each site was only exposed once every three days. Patches were applied to the dorsal surface of each animal in a grid pattern of either three sites wide by three sites long or two sites wide by three sites long. The self adhesive patches were applied on Day 1 in a row across the two or three most cranial sites on the dorsal surface. The patches were applied for approximately 2 hours each day. They were held in contact with the skin with a gauze dressing and covered with a nonirritating tape. Elizabethan-type collars were applied and remained in place throughout the study.

Satellite groups used for toxicokinetics or recovery: None

Age: ~ 4 months

Weight (nonrodents only): Males 2.36 to 2.68 kg
Females 2.33 to 3.08 kg

Unique study design or methodology (if any): Patch sites were rotated such that each site received patch application once every three days.

Observation times and results

Mortality: Observations for mortality and clinical signs were completed twice during each day, once prior to test article administration and once at the end of the exposure period.

One female rabbit in the abraded placebo patch group was sacrificed *in extremis* on Day 25. The animal had fluid in the thoracic cavity at necropsy and microscopically had mild pulmonary arterial hypertrophy. According to the sponsor, the lesions were considered to be incidental to treatment. There were no other mortalities noted.

Clinical signs: Detailed clinical examination was completed twice each day, once prior to test article administration and once at the end of the exposure period. Physical examination was conducted on all animals by a staff veterinarian both pretest and prior to terminal necropsy. There were no clear test article-related clinical findings observed. Minor skin changes noted included abrasions, hair absent or scabbed areas were noted in one female per group but do not appear to be clearly attributable to the treatment.

Summary of Clinical Findings Day (# times observed/# animals affected)								
	Males				Females			
Group	**1**	**2**	**3**	**4**	**1**	**2**	**3**	**4**
Treatment	**Placebo Non-Abraded**	**Active Non-Abraded**	**Placebo Abraded**	**Active Abraded**	**Placebo Non-Abraded**	**Active Non-Abraded**	**Placebo Abraded**	**Active Abraded**
N	**3**	**3**	**3**	**2**	**3**	**3**	**3**	**4**
Skin								
Abrasions	0/0	0/0	0/0	0/0	2/1	3/1	3/1	3/1
Hair absent	0/0	0/0	0/0	0/0	0/0	8/1	0/0	0/0
Scabbed area	0/0	0/0	0/0	0/0	5/1	0/0	0/0	0/0

Body weights: Body weights were recorded twice prior to randomization and weekly during the study.

All rabbits lost weight during the study. The weight loss was similar in all groups and was likely due to the wearing of the Elizabethan collars continuously during the entire study. There was no evidence that the S-Caine™ treated animals lost any more or less weight than the placebo groups.

Food consumption: Food consumption was measured and recorded daily during the pretest and study periods and reported on a weekly basis. Occasionally food consumption was excluded due to spillage or wet food. There was no evidence for a treatment-related alteration in food consumption between groups.

Ophthalmoscopy: Ophthalmologic examinations were conducted prior to exposure and prior to the scheduled sacrifice by a certified veterinary ophthalmologist. All findings were within normal limits.

EKG: Not examined.

Hematology: Blood samples were obtained from the central ear artery of all animals at pretest and study termination. Hematology parameters were evaluated for all animals at pretest and at study termination. There were no test article-related alterations in hematological parameters noted. An occasional value was significantly different from the placebo group, however, the sponsor did not consider these changes to be related to the test article. Of note, the number of samples examined for hematological changes were frequently limited to one per group, apparently due to technical errors. Therefore, statistical analysis was not possible to compare the values obtained. The hematological and clinical chemistry changes noted, therefore are of little utility. However, based upon comparison of the values obtained, there does not appear to be any strong signal for S-Caine™ patch induced alterations in hematological parameters.

Clinical chemistry: Blood samples were obtained from the central ear artery of all animals at pretest and study termination. Clinical chemistry parameters were evaluated for all animals at pretest and at study termination. There were no test article-related alterations in clinical chemistry parameters noted. An occasional value was significantly different from the placebo group, however, these were not considered to be related to the test article.

Urinalysis: Not completed.

Gross pathology: Complete necropsy was performed following euthanasia via overdose of sodium pentobarbital solution and exsanguinations. Animals were examined carefully for external abnormalities including palpable masses. The skin was reflected from a ventral midline incision and any gross lesions collected. The abdominal, thoracic and cranial cavities were examined for abnormalities. The organs were removed, examined,

and placed in neutral buffered formalin (eye was placed Davidson's fixative). Lungs were infused via the trachea with formalin.

Macroscopic changes noted were limited to the skin and noted in both male and female rabbits and in both abraded and non-abraded skin sites. When skin changes were noted in groups treated with the S-Caine™ patch non-abraded sites, the effect was not mimicked in the corresponding abraded sites. Overall, the lack of correlation is consistent with a mild inflammatory change induced by the S-Caine™ patch in some animals; however, the clinical significance of these changes appears minimal. These changes are summarized in the table below:

Incidence of Macroscopic Findings								
	Males				Females			
Group	**1**	**2**	**3**	**4**	**1**	**2**	**3**	**4**
Treatment	**Placebo Non-Abraded**	**Active Non-Abraded**	**Placebo Abraded**	**Active Abraded**	**Placebo Non-Abraded**	**Active Non-Abraded**	**Placebo Abraded**	**Active Abraded**
N	3	3	3	2	3	3	3	4
Skin								
Discolored, red, mild	0	1	0	0	0	0	1	2
Scab, mild	0	1	0	0	0	1	0	1
Abrasion, mild	0	0	0	0	0	1	0	0

Organ weights (specify organs weighed if not in histopath table): Organ weights were obtained at necropsy. Paired organs were weighed together. Organ weights were obtained for the following: adrenal gland, brain, epididymis, heart, kidney, liver, ovary, pituitary, spleen, testis and thyroid with parathyroid. There were no test-article related changes in organ weights detected.

Histopathology: Adequate Battery: yes (X), no ( )—explain
Peer review: yes ( ), no (X)

For the skin histology, the protocol indicated that 3 samples from each of the 4 exposure sites and 1 sample from an untreated site were to be examined. Test article microscopic observations were limited to the treated skin sites. These changes were noted in males and females in both abraded and non-abraded sites. Most non-abraded and abraded placebo treated sites were normal, with only trace hyperkeratosis, trace epithelial hyperplasia and trace chronic dermatitis noted in a few sites. The summary of the histological changes note are presented in the tables below:

Example of the Incidence of Microscopic Histological Findings in Treated Skin A Samples								
	Males				Females			
Group	**1**	**2**	**3**	**4**	**1**	**2**	**3**	**4**
Treatment	**P**	**S**	**P**	**S**	**P**	**S**	**P**	**S**
Skin Condition	**NA**	**NA**	**A**	**A**	**NA**	**NA**	**A**	**A**
N	**3**	**3**	**3**	**2**	**3**	**3**	**3**	**4**
Dermatitis, acute	0	2	0	0	0	2	0	0
Trace	0	1	0	0	0	1	0	0
Moderate	0	1	0	0	0	1	0	0
Exudate, epidermal, surface	0	1	0	2	0	1	0	2
Trace	0	0	0	2	0	0	0	2
Mild	0	1	0	0	0	1	0	0
Fibrosis, trace	0	0	0	1	0	0	0	1
Hyperkeratosis, trace	0	1	0	1	0	1	0	1
Hyperplasia, epithelial, trace	0	1	0	2	0	1	0	2
Necrosis, epidermal	0	2	0	0	0	2	0	0
Mild	0	1	0	0	0	1	0	0
Severe	0	1	0	0	0	1	0	0

Key: P = Placebo Patch, S = S-Caine™ Active Patch, A=Abraded Tissue, NA = Non-Abraded tissue

Toxicokinetics: Blood samples were collected from the central ear artery of all animals in Groups 2 and 4 only for determination of the plasma concentrations of the test article. Samples were collected prior to exposure and at 1, 2, 4, 6 and 24 hours after application of patches on Days 1 and 26. Samples were placed in tubes containing potassium EDTA and neostigmine and stored on ice until centrifuged. Plasma was stored at -70°C until assayed.

The figures below depict the mean plasma concentrations of lidocaine and tetracaine in male rabbits with intact skin:

Figure 1a. Mean Concentrations of Lidocaine in Male Rabbits, Non-Abraded

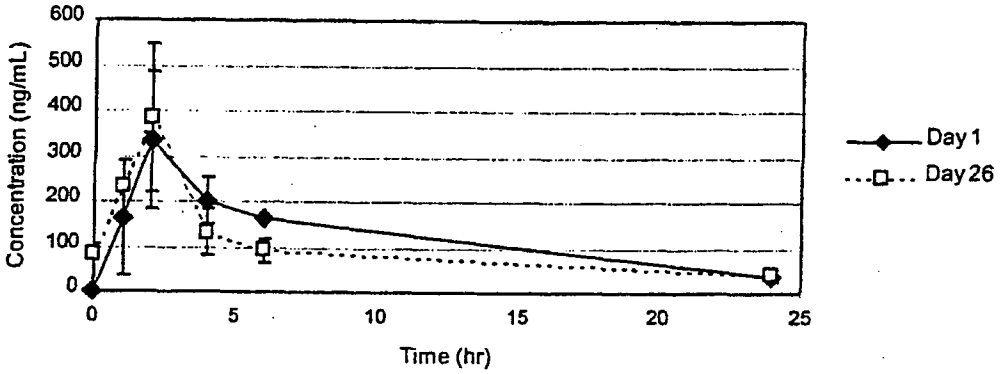


Figure 1b. Mean Concentrations of Tetracaine in Male Rabbits, Non-Abraded

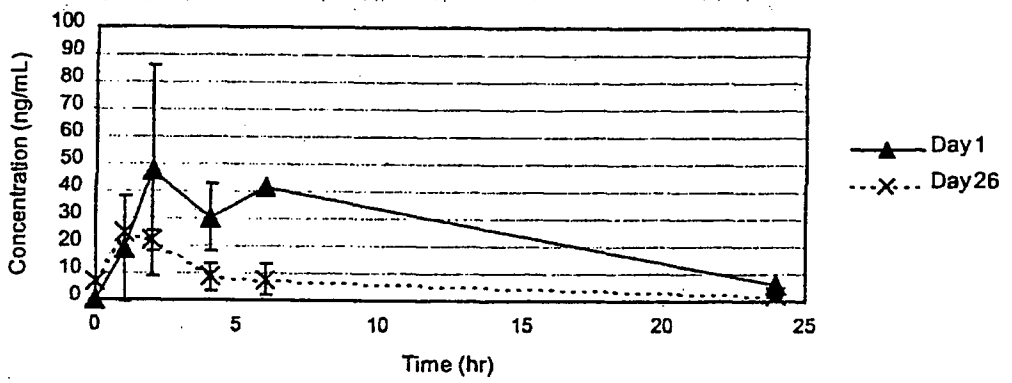
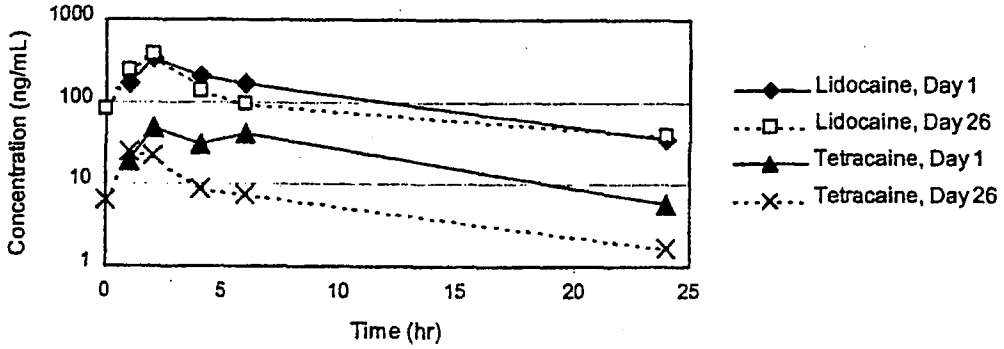


Figure 1c. Mean Concentrations of Lidocaine and Tetracaine in Male Rabbits, Non Abraded



The figures below depict the mean plasma concentration of lidocaine and tetracaine in female rats with intact skin:

Figure 2a. Mean Concentrations of Lidocaine in Female Rabbits, Non-Abraded

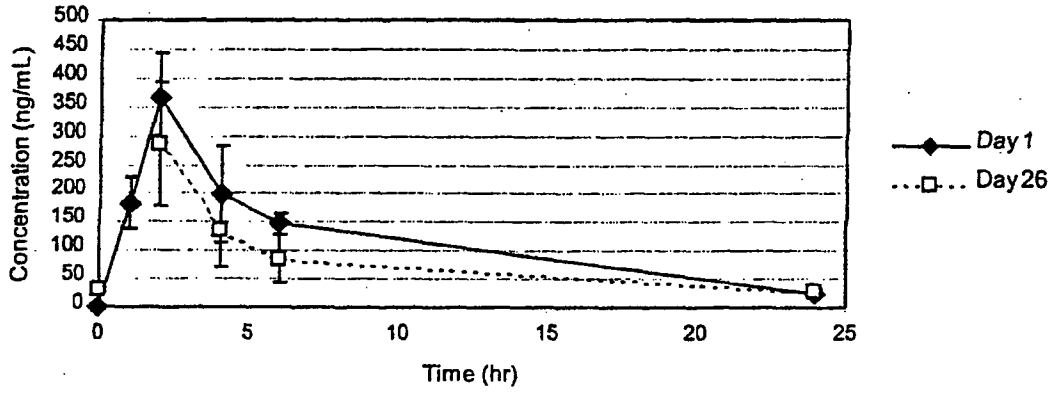


Figure 2b. Mean Concentrations of Tetracaine in Female Rabbits, Non-Abraded

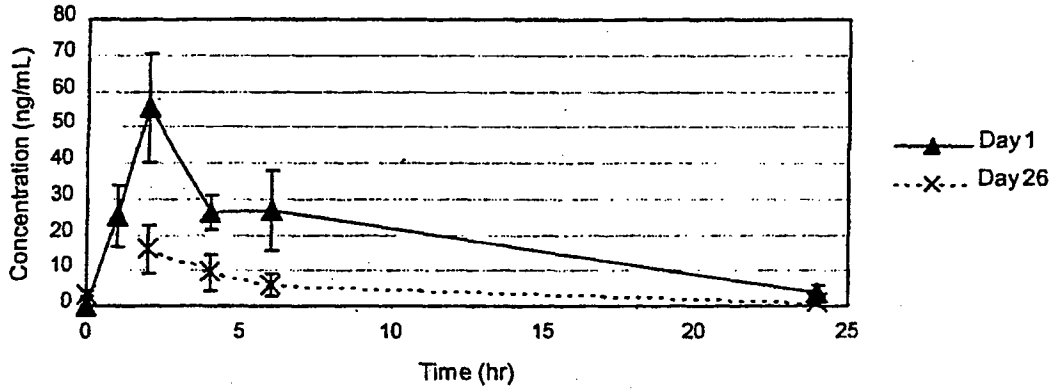
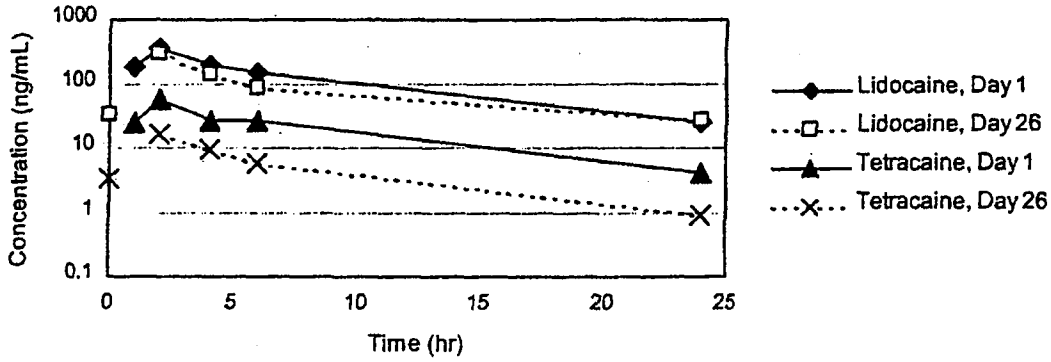


Figure 2c. Mean Concentrations of Lidocaine and Tetracaine in Female Rabbits, Non-Abraded



The figures below depict the mean plasma concentrations of lidocaine and tetracaine in male rats with abraded skin:

Figure 3a. Mean Concentrations of Lidocaine in Male Rabbits, Abraded

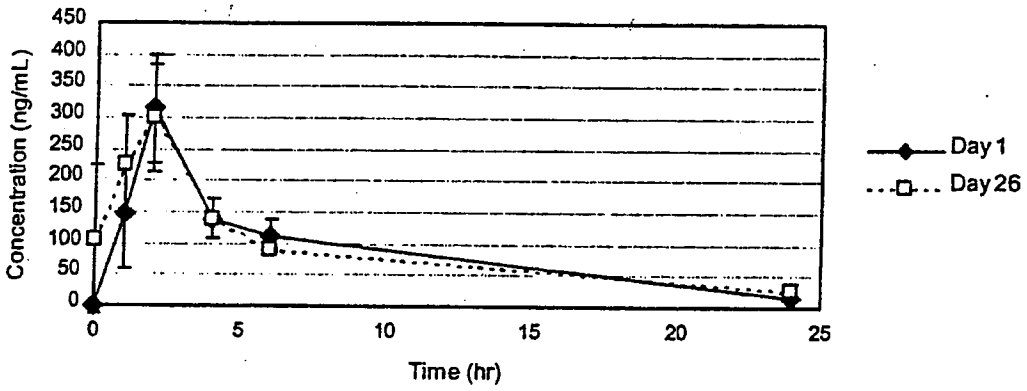


Figure 3b. Mean Concentrations of Tetracaine in Male Rabbits, Abraded

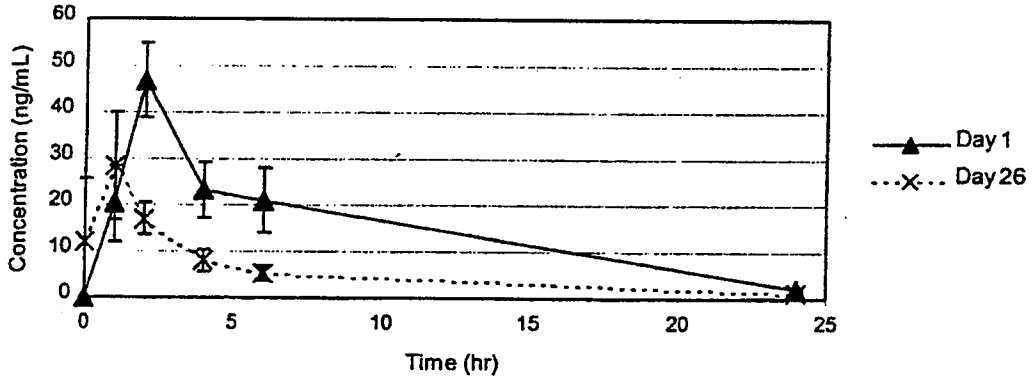
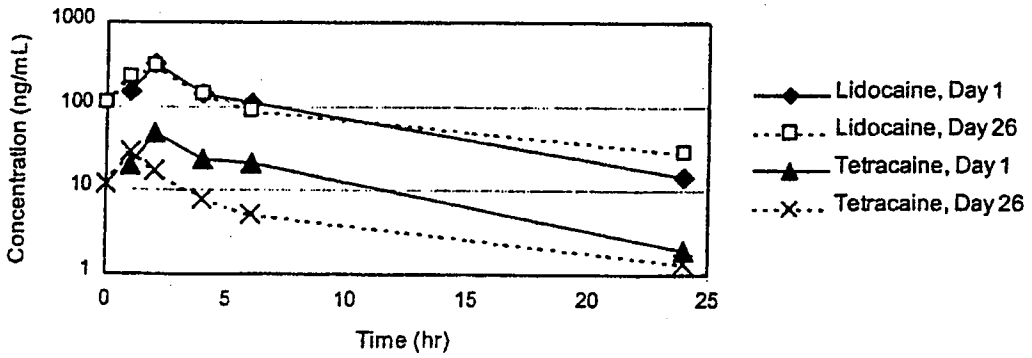


Figure 3c. Mean Concentrations of Lidocaine and Tetracaine in Male Rabbits, Abraded



The figures below depict the mean plasma concentrations of lidocaine and tetracaine in female rats with abraded skin.

Figure 4a. Mean Concentrations of Lidocaine in Female Rabbits, Abraded

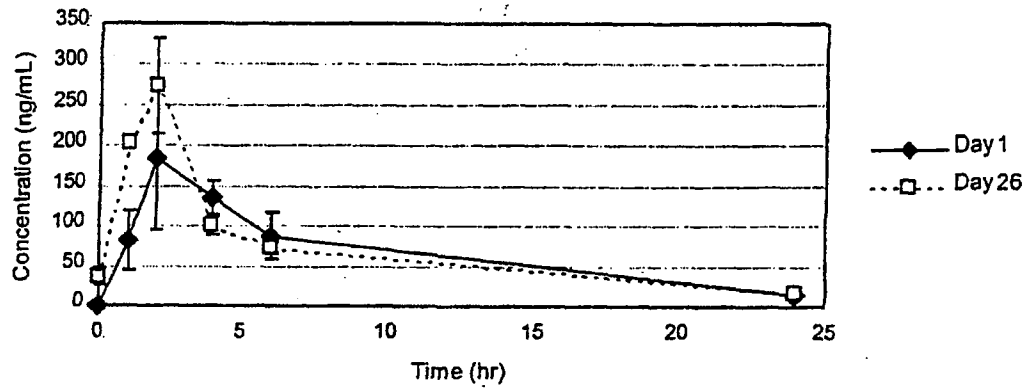


Figure 4b. Mean Concentrations of Tetracaine in Female Rabbits, Abraded

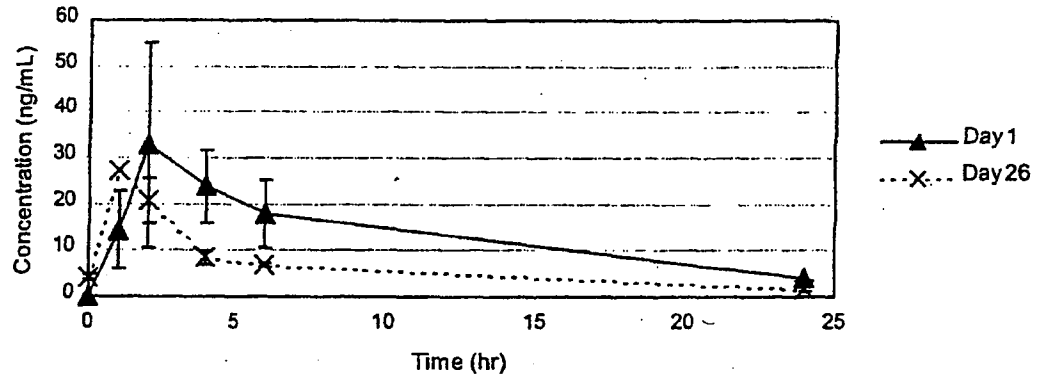
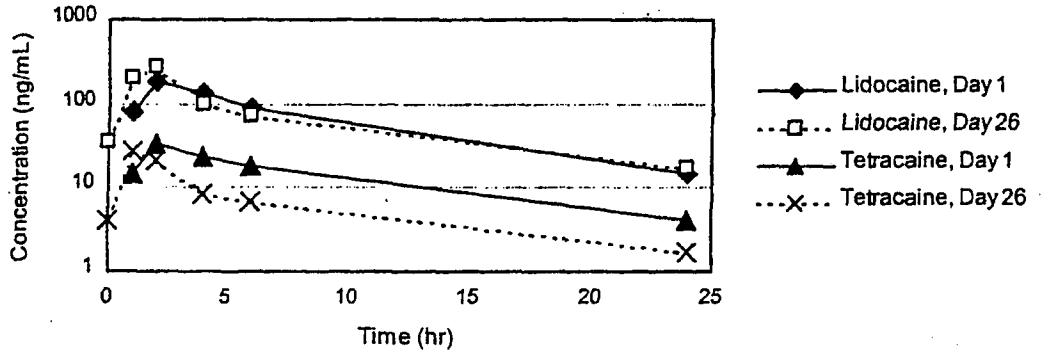


Figure 4c. Mean Concentrations of Lidocaine and Tetracaine in Female Rabbits, Abraded



The table below provides the pharmacokinetics parameters for lidocaine in rabbits treated with 3 S-Caine™ patches applied for 2 hours daily:

Table 3. Pharmacokinetic Parameters for Lidocaine for Rabbits with 3 S-Caine Patches Applied for 2 Hours Daily

Group	Skin	Sex	Day	C_{max} (ng/mL) Mean ± SD	T_{max} (ng/mL) Mean ± SD	AUC_{0-24} (ng•hr/mL) Mean ± SD
2	Non-abraded	M	1	335 ± 151	2.0 ± 0.0	3,076 *
			26	383 ± 163	2.0 ± 0.0	2,431 *
			Mean % Change	15%		-19% *
		F	1	366 ± 77	2.0 ± 0.0	2,813 ± 454
			26	286 ± 107	2.0 ± 0.0	1,962 ± 794
			Mean % Change	-21%		-32%
4	Abraded	M	1	314 ± 84	2.0 ± 0.0	2,143 ± 496
			26	299 ± 85	2.0 ± 0.0	2,156 ± 186
			Mean % Change	2%		6%
		F	1	185 ± 88	2.7 ± 1.2	1,452 *
			26	277 ± 55	1.7 ± 0.6	1,684 ± 162
			Mean % Change	75%		28% *

n = 3 unless otherwise noted.
* n = 2
Standard deviation values were not calculated for n < 3.

The table below provides the pharmacokinetics parameters for tetracaine in rabbits treated with 3 S-Caine™ patches applied for 2 hours daily:

Table 4. Pharmacokinetic Parameters for Tetracaine for Rabbits with 3 S-Caine Patches Applied for 2 Hours Daily

Group	Skin	Sex	Day	C_{max} (ng/mL) Mean ± SD	T_{max} (ng/mL) Mean ± SD	AUC_{0-24} (ng•hr/mL) Mean ± SD
2	Non-abraded	M	1	48.6 ± 37.5	2.7 ± 1.2	640 *
			26	22.8 ± 4.0	1.7 ± 0.6	180 *
			Mean % Change	-38%		-70% *
		F	1	55.3 ± 15.4	2.0 ± 0.0	461 ± 111
			26	16.4 ± 6.5	2.7 ± 1.2	119 ± 52
			Mean % Change	-67% *		-73%
4	Abraded	M	1	46.7 ± 8.1	2.0 ± 0.0	363 ± 96
			26	28.4 ± 11.7	1.0 ± 0.0	140 ± 39
			Mean % Change	-39%		-61%
		F	1	33.9 ± 21.3	2.7 ± 1.2	263 *
			26	28.0 ± 9.9	1.7 ± 0.6	156 ± 7
			Mean % Change	-16%		-38% *

n = 3 unless otherwise noted.
* n = 2
Standard deviation values were not calculated for n < 3.

As noted in the tables above, plasma levels of lidocaine were approximately 6 times higher than those of tetracaine. There were no differences noted between males and females or between abraded and intact skin.

Other: Dermal Scoring: Each exposure site on the back was evaluated for erythema and edema according to skin reaction scales based upon those of Draize and reproduced below:

Erythema and Eschar Formation	
Score	Observation
0	No erythema
1	Very slight erythema (barely perceptible)
2	Well-defined erythema
3	Moderate to severe erythema
4	Severe erythema (beet redness) to slight eschar formation (injuries in depth)
	Maximum possible score = 4

Edema Formation	
Score	Observation
0	No edema
1	Very slight edema (barely perceptible)
2	Slight edema (edges of area well-defined by definite raising)
3	Moderate edema (raised approximately 1 mm)
4	Severe edema (raised more than 1 mm and extending beyond area of exposure)
	Maximum possible score = 4

Mean primary irritation index (PII) is the average erythema score after patch removal plus the average edema score after patch removal. The descriptive range is as follows:

Mean Primary Irritation Index	
Descriptive Rating	Range of Index Values
Non-Irritating	0
Mildly Irritating	0.1 - 2
Moderately Irritating	2.1 - 5
Severely Irritating	5.1 - 8

In placebo patch groups, there was a very slight to slight erythema noted in the six application sites (both abraded and non-abraded) in both males and females. The incidence was generally similar between abraded and non-abraded and male and females.

Table 2 Cont. Summary of Dermal Irritation Scores (Incidence At All Sites Combined) - Erythema/Eschar + - MALE

Group	Severity	Study Interval (Day) 15	16	17	18	19	20	21	22	23	24	25	26	27	28
S-Caine™ Placebo Patch (Non-Abraded)	0-no erythema	11	13	14	18	17	15	12	12	10	12	18	13	12	14
	1-very slight	7	5	4	0	1	3	6	6	8	6	0	5	6	3
	2-slight	0	0	0	0	0	0	0	0	0	0	0	0	0	1
S-Caine™ Patch (Non-Abraded)	0-no erythema	1	1	2	2	2	4	1	0	2	1	5	4	5	1
	1-very slight	5	4	9	10	2	8	7	4	3	4	10	6	5	2
	2-slight	10	8	8	4	9	7	11	15	14	14	6	9	12	13
	3-moderate	6	8	3	5	8	6	6	6	5	7	4	6	4	8
	4-severe	5	6	5	6	6	2	2	2	3	1	2	2	1	3
S-Caine™ Placebo Patch (Abraded)	0-no erythema	12	15	11	18	12	12	12	9	10	9	17	12	13	9
	1-very slight	6	3	7	0	6	6	6	9	8	9	0	6	4	8
	2-slight	0	0	0	0	0	0	0	0	0	0	1	0	1	1
S-Caine™ Patch (Abraded)	0-no erythema	3	3	2	8	1	5	1	0	3	1	5	4	1	1
	1-very slight	4	6	5	1	1	6	4	8	4	4	0	2	2	1
	2-slight	3	3	4	3	6	2	10	5	4	6	6	5	8	5
	3-moderate	4	4	4	4	6	5	3	3	4	2	3	5	5	8
	4-severe	4	2	3	2	4	0	0	2	3	5	4	2	1	3

+ - Number of times observed

Table 2 Summary of Dermal Irritation Scores (Incidence At All Sites Combined) - Erythema/Eschar + - MALE

Group	Severity	Study Interval (Day) 1	2	3	4	5	6	7	8	9	10	11	12	13	14
S-Caine™ Placebo Patch (Non-Abraded)	0-no erythema	6	12	18	18	17	18	18	9	13	17	10	18	10	9
	1-very slight	0	0	0	0	1	0	0	7	5	1	8	0	8	9
	2-slight	0	0	0	0	0	0	0	2	0	0	0	0	0	0
S-Caine™ Patch (Non-Abraded)	0-no erythema	7	15	17	19	21	24	19	8	5	13	6	6	4	3
	1-very slight	2	3	10	8	6	1	6	10	12	7	7	6	6	11
	2-slight	0	0	0	0	0	2	1	5	7	6	7	8	8	4
	3-moderate	0	0	0	0	0	0	1	4	3	1	5	6	7	3
	4-severe	0	0	0	0	0	0	0	0	0	0	2	1	2	6
S-Caine™ Placebo Patch (Abraded)	0-no erythema	6	11	18	18	18	18	18	9	7	18	13	16	9	11
	1-very slight	0	1	0	0	0	0	0	7	10	0	5	2	9	7
	2-slight	0	0	0	0	0	0	0	2	1	0	0	0	0	0
S-Caine™ Patch (Abraded)	0-no erythema	5	10	17	15	13	18	10	8	4	11	8	7	3	6
	1-very slight	1	2	1	3	5	0	6	5	6	3	3	1	7	3
	2-slight	0	0	0	0	0	0	2	2	6	3	3	4	3	2
	3-moderate	0	0	0	0	0	0	0	3	2	0	2	5	3	3
	4-severe	0	0	0	0	0	0	0	0	0	1	2	1	2	4

+ - Number of times observed

Table 2 Cont. Summary of Dermal Irritation Scores (Incidence At All Sites Combined) - Erythema/Eschar* - FEMALE

Group	Severity	Study Interval (Day) 1	2	3	4	5	6	7	8	9	10	11	12	13	14
S-Caine™ Placebo Patch (Non-Abraded)	0-no erythema	6	11	17	18	18	18	18	11	12	18	11	16	5	7
	1-very slight	0	1	1	0	0	0	0	5	6	0	7	2	13	11
	2-slight	0	0	0	0	0	0	0	2	0	0	0	0	0	0
S-Caine™ Patch (Non-Abraded)	0-no erythema	8	11	18	15	15	25	14	8	5	4	6	3	2	4
	1-very slight	1	6	8	11	11	1	11	5	8	17	4	5	2	1
	2-slight	0	1	1	1	1	0	1	13	12	4	9	14	14	8
	3-moderate	0	0	0	0	0	1	1	1	1	1	6	4	4	9
	4-severe	0	0	0	0	0	0	0	0	1	1	2	1	5	5
S-Caine™ Placebo Patch (Abraded)	0-no erythema	6	12	17	18	18	18	18	9	10	17	13	12	9	9
	1-very slight	0	0	1	0	0	0	0	7	5	1	4	4	9	9
	2-slight	0	0	0	0	0	0	0	2	3	0	1	2	0	0
S-Caine™ Patch (Abraded)	0-no erythema	7	15	25	26	28	31	16	10	6	14	13	9	6	7
	1-very slight	4	9	9	10	5	1	14	10	10	7	3	2	7	4
	2-slight	1	0	2	0	3	2	5	6	11	11	7	14	8	8
	3-moderate	0	0	0	0	0	2	1	10	8	3	7	9	10	11
	4-severe	0	0	0	0	0	0	0	0	1	1	6	2	5	6

+ - Number of times observed

Table 2 Cont. Summary of Dermal Irritation Scores (Incidence At All Sites Combined) - Erythema/Eschar* - FEMALE

Group	Severity	Study Interval (Day) 15	16	17	18	19	20	21	22	23	24	25	26	27	28
S-Caine™ Placebo Patch (Non-Abraded)	0-no erythema	13	13	10	18	14	11	13	7	11	11	16	14	14	16
	1-very slight	4	5	8	0	4	7	5	11	7	7	2	4	3	1
	2-slight	1	0	0	0	0	0	0	0	0	0	0	0	1	1
S-Caine™ Patch (Non-Abraded)	0-no erythema	2	4	5	7	5	6	2	1	3	0	11	11	10	10
	1-very slight	3	3	7	6	2	8	11	9	12	11	6	5	3	4
	2-slight	8	9	5	7	7	6	9	9	4	11	3	6	9	7
	3-moderate	10	4	4	1	6	3	1	3	3	1	1	2	2	3
	4-severe	4	7	6	6	7	4	4	5	5	4	6	3	3	3
S-Caine™ Placebo Patch (Abraded)	0-no erythema	10	14	9	18	14	8	12	10	10	10	12	9	11	10
	1-very slight	8	4	9	0	4	10	6	8	8	8	0	3	1	2
S-Caine™ Patch (Abraded)	0-no erythema	3	4	2	7	5	6	3	6	6	4	10	8	4	9
	1-very slight	6	7	9	12	1	10	10	3	6	10	7	7	8	7
	2-slight	14	9	7	10	12	7	10	13	10	11	7	13	16	14
	3-moderate	7	7	8	0	11	10	10	12	10	8	8	5	5	3
	4-severe	6	9	10	7	7	3	3	2	4	3	4	3	3	3

+ - Number of times observed

For the S-Caine™ patch treated groups, there was a very slight to slight erythema noted in male and female animals in both the non-abraded and abraded S-Caine™ Patch groups during the initial treatment days. Moderate erythema was noted at one site in one male (non-abraded) and one site in one female (non-abraded) and two sites in two females (abraded) during week 1. Very slight to severe erythema was seen in most application sites in male and female non-abraded and abraded S-Caine™ patch sites after the first week of the study. The incidence and severity was greater in females than in males.

No edema was observed in male and female non-abraded and abraded placebo patch sites under the conditions tested. There was a low incidence of very slight to slight edema in males and females in both the abraded and non-abraded groups.

The overall Mean Primary Irritation Index for Weeks 1 through 28 is given below.

Mean Primary Irritation Index		
	Males	Females
S-Caine™ Placebo Patch (Non-Abraded)	0.21	0.25
S-Caine™ Patch (Non-Abraded)	1.59	1.58
S-Caine™ Placebo Patch (Abraded)	0.26	0.26
S-Caine™ Patch (Abraded)	1.49	1.63

These data indicate that the severity of the irritation was greater in the S-Caine™ patch group compared to placebo regardless of the site of application being intact or abraded.

Histopathology inventory (optional)

Study	**925-004**
Species	**Rabbit**
Adrenals	*X
Aorta	X
Bone Marrow smear	X
Bone (femur)	X
Brain	*X
Cecum	X
Cervix	X
Colon	X
Duodenum	X
Epididymis	*X
Esophagus	X
Eye	X
Fallopian tube	
Gall bladder	X
Gross lesions	X
Harderian gland	X
Heart	*X
Ileum	X
Injection site	
Jejunum	X
Kidneys	*X
Lachrymal gland	
Larynx	
Liver	*X
Lungs	X
Lymph nodes,	X

ileococococolic	
Lymph nodes, cervical	
Lymph nodes mandibular	X
Lymph nodes, mesenteric	
Mammary Gland	X
Nasal cavity	
Optic nerves	
Ovaries	*X
Pancreas	X
Parathyroid	
Peripheral nerve	
Pharynx	
Pituitary	*X
Prostate	X
Rectum	X
Salivary gland	X
Sciatic nerve	X
Seminal vesicles	X
Skeletal muscle	X
Skin	X
Spinal cord (Cervical, lumbar, thoracic)	X
Spleen	*X
Sternum	
Stomach	X
Testes	*X
Thymus	X
Thyroid	*X
Tongue	X
Trachea	X
Urinary bladder	X
Uterus	X
Vagina	X
Zymbal gland	

X, histopathology performed
*, organ weight obtained

3.4.4. Genetic toxicology

Study title: Salmonella-Escherichia coli/Mammalian-Microsome Reverse Mutation Assay with a Confirmatory Assay with Lidocaine Base

Key findings: Under the test conditions, lidocaine base was not mutagenic in the bacterial reverse mutation assay in the tested species examined.

Study no.: 23840-0-409OECD
Volume #, and page #: Volume 12, Page 1

Conducting laboratory and location: [redacted]

Date of study initiation: May 13, 2002
GLP compliance: Yes
QA reports: yes (X) no ( )
Drug, lot #, and % purity: Lidocaine base, Lot # 811D0013 (expiration date of June 15, 2005), purity was verified by the sponsor.

Methods

Tester strains were exposed to the test article via the plate incorporation method originally described by Ames. In the plate incorporation methodology, test article, tester strain and the S9 mix were combined in molten agar which was overlaid onto a minimal agar plate. Following incubation, revertant colonies were counted. All doses of the test article, vehicle control and positive controls were plated in triplicate. The condition of the bacterial lawn was evaluated macroscopically and microscopically (dissecting microscope) for indications of cytotoxicity and test article precipitate. Revertant colonies were counted by automated colony counter or by hand.

The acceptable ranges for spontaneous revertants (negative controls ranges) in protocol are listed in the table below:

Strain	Low-High
TA98	8-60
TA100	60-240
TA1535	4-45
TA1537	2-25
WP2*uvr*A	5-40

A positive result with tester strains TA98, TA100 and WP2uvrA was obtained when the test article produced at least a 2-fold increase in the mean revertants per plate over the mean revertants per plate of the appropriate vehicle control. This increase had to be accompanied by a dose response to increasing concentrations of test article. A positive response for tester strains TA1535 and TA1537 was obtained when the test article produce at least a 3-fold increase in the mean revertants per plate over the mean revertants in the vehicle control. This increase had to show evidence of a dose response.

Strains/species/cell line: *Salmonella typhimurium* TA98, TA100, TA1535 and TA1537 (histidine auxotrophs) and *Escherichia coli* WP2*uvr*A (tryptophan auxotroph).

Doses used in definitive study: 33.3, 100, 333, 1000, 3330 and 5000 μg/plate with and without S9 for all 5 tester strains for both the initial mutagenicity assay and the independent confirmatory experiment.

Basis of dose selection: Dose range finding assay on lidocaine using tester strain TA100 (generally representative of the other strains) and WP2*uvr*A. The test article was freely soluble at all doses and conditions evaluated. Ten doses were tested, from 6.67 to 5000 μg/plate both with and without metabolic activation (S9). Evaluation of growth inhibition was completed by a decreased number of revertant colonies per plate and/or thinning or disappearance of the bacterial background lawn. Growth inhibition (number of revertants per plate) was observed in tester strain WP2*uvr*A at 5000 μg/plate with S9

(↓68%). The background lawn was considered to be reduced in tester strain TA100 at concentrations of ≥ 3330 µg/plate in the absence of S9. This reduction appeared to be in relation to a slight stimulation over the 333 to 1000 µg/plate cultures while comparable to the appearance of the vehicle control lawns.

Negative controls: Vehicle control used a 50 µl aliquot of DMSO (the highest concentration used for the test article dilution).

Positive controls: The positive controls for the assay are summarized in the sponsor's table below:

Table II. Positive Controls

Tester Strain	S9 Mix	Positive Control	Dose (µg/plate)
TA98	+	benzo[a]pyrene	2.5
TA98	–	2-nitrofluorene	1.0
TA100	+	2-aminoanthracene	2.5
TA100	–	sodium azide	2.0
TA1535	+	2-aminoanthracene	2.5
TA1535	–	sodium azide	2.0
TA1537	+	2-aminoanthracene	2.5
TA1537	–	ICR-191	2.0
WP2*uvr*A	+	2-aminoanthracene	25.0
WP2*uvr*A	–	4-nitroquinoline-N-oxide	1.0

Incubation and sampling times: Plates were incubated for 52 ± 4 hours at 37°C.

Results

Study validity (comment on replicates, counting method, criteria for positive results, etc.): [redacted] criteria for a valid assay included validation of tester strain integrity and acceptable levels of spontaneous revertants. The positive controls must produce at least a 3-fold increase over the mean value of the vehicle control. Upon review, the study appears to be valid for the following reasons: 1) the methodology was consistent with currently acceptable protocols, 2) the positive controls produced a clear increase in the number of revertants per plate compared to the vehicle control group 3) the vehicle control group levels were within historical control ranges, and 4) although there were slight increases in lidocaine treated bacteria, there was no evidence of a dose-dependent alteration in the number of revertants per plate.

Study outcome: The results of the mutagenicity assay are summarized in sponsor's table 4 reproduced below. Briefly,

Table 4 : Mutagenicity Assay Results – Summary

Test Article ID: Lidocaine Base

Experiment ID: 23840-B1

Date Plated: 11-Jun-02 Vehicle: DMSO

Date Counted: 17-Jun-02 Plating Aliquot: 50 µL

	Dose/Plate	Mean Revertants Per Plate with Standard Deviation										Background Lawn[a]
		TA98		TA100		TA1535		TA1537		WP2*uvr*A		
		Mean	S.D.	Mean	S.D.	Mean	S.D.	Mean	S.D.	Mean	S.D.	
Microsomes: Rat Liver												
Vehicle Control		18	5	67	3	19	2	8	2	22	2	N
Test Article	33.3 µg	26	7	70	8	16	2	10	4	18	7	N
	100 µg	25	5	66	6	20	6	9	2	24	7	N
	333 µg	22	4	72	6	16	9	9	2	17	6	N
	1000 µg	26	11	79	16	17	1	7	4	14	4	N
	3330 µg	23	6	88	21	16	3	7	2	19	6	N
	5000 µg	26	3	88	8	11	1	5	4	13	5	N
Positive Control[b]		366	41	254	37	86	18	70	14	480	19	N
Microsomes: None												
Vehicle Control		12	6	99	12	12	4	8	3	18	1	N
Test Article	33.3 µg	17	7	105	7	13	2	9	4	14	4	N
	100 µg	15	3	87	3	17	4	9	3	15	1	N
	333 µg	14	5	87	12	14	3	8	1	16	3	N
	1000 µg	15	2	105	2	19	1	9	3	15	1	N
	3330 µg	14	2	104	21	29	9	8	3	10	3	N
	5000 µg	16	2	95	1	20	4	7	4	12	4	N
Positive Control[c]		226	35	901	-	702	43	878	150	152	18	N

[a] Background Lawn Evaluation Codes:
N = normal R = reduced O = obscured A = absent P = precipitate

[b] TA98	benzo[a]pyrene	2.5 µg/plate	[c] TA98	2-nitrofluorene	1.0 µg/plate
TA100	2-aminoanthracene	2.5 µg/plate	TA100	sodium azide	2.0 µg/plate
TA1535	2-aminoanthracene	2.5 µg/plate	TA1535	sodium azide	2.0 µg/plate
TA1537	2-aminoanthracene	2.5 µg/plate	TA1537	ICR-191	2.0 µg/plate
WP2*uvr*A	2-aminoanthracene	25.0 µg/plate	WP2*uvr*A	4-nitroquinolone-N-oxide	1.0 µg/plate

The results of the confirmatory assay were in agreement with the mutagenicity assay, i.e., under the conditions of the assay, lidocaine was not mutagenic in the bacterial reverse mutation assay.

Study title: **Salmonella-Escherichia coli/Mammalian-Microsome Reverse Mutation Assay with a Confirmatory Assay with Tetracaine Base**

Key findings: Under the test conditions, tetracaine base was not mutagenic in the bacterial reverse mutation assay in the tested species examined.

Study no.: 23841-0-409OECD
Volume #, and page #: Volume 12, Page 32
Conducting laboratory and location: [redacted]

Date of study initiation: May 13, 2002
GLP compliance: Yes
QA reports: yes (X) no ( )
Drug, lot #, and % purity: Tetracaine base, Lot # 721725 (expiration date of August 3, 2005), purity was verified by the sponsor.

Methods

Tester strains were exposed to the test article via the plate incorporation method originally described by Ames. In the plate incorporation methodology, test article, tester strain and the S9 mix were combined in molten agar which was overlaid onto a minimal agar plate. Following incubation, revertant colonies were counted. All doses of the test article, vehicle control and positive controls were plated in triplicate. The condition of the bacterial lawn was evaluated macroscopically and microscopically (dissecting microscope) for indications of cytotoxicity and test article precipitate. Revertant colonies were counted by automated colony counter or by hand.

The acceptable ranges for spontaneous revertants (negative controls ranges) in protocol are listed in the table below:

Strain	Low-High
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A positive result with tester strains TA98, TA100 and WP2uvrA was obtained when the test article produced at least a 2-fold increase in the mean revertants per plate over the mean revertants per plate of the appropriate vehicle control. This increase had to be accompanied by a dose response to increasing concentrations of test article. A positive response for tester strains TA1535 and TA1537 was obtained when the test article produce at least a 3-fold increase in the mean revertants per plate over the mean revertants in the vehicle control. This increase had to show evidence of a dose response.

Strains/species/cell line: *Salmonella typhimurium* TA98, TA100, TA1535 and TA1537 (histidine auxotrophs) and *Escherichia coli* WP2*uvr*A (tryptophan auxotroph).

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Basis of dose selection: Dose range finding assay on lidocaine using tester strain TA100 (generally representative of the other strains) and WP2*uvr*A. The test article was freely soluble at all doses and conditions evaluated. Ten doses were tested, from 6.67 to 5000 µg/plate both with and without metabolic activation (S9). Evaluation of growth

inhibition was completed by a decreased number of revertant colonies per plate and/or thinning or disappearance of the bacterial background lawn. The background lawn was considered to be reduced in both tester strains at the one or two highest concentrations of tetracaine tested both with and without S9. Growth inhibition was noted in strain TA100 at concentrations of 3330 and 5000 µg/plate without S9 (↓52% and ↓93%, respectively) and at 5000 µg/plate (↓85%) with S9. Growth inhibition (number of revertants per plate) was observed in tester strain WP2*uvr*A at 5000 µg/plate with S9 (↓89%). Without S9, the number of revertants per plate was reduced at tetracaine concentrations of 3330 and 5000 µg/plate by 100% and 78%, respectively. The background lawn was considered to be reduced in tester strain WP2*uvr*A only at the concentration of 5000 µg/plate in the absence of S9. The apparent thinning of the background lawns observed in the absence of a decrease in revertant frequency toxicity is generally not considered to be an indication of toxicity.

Negative controls: Vehicle control used a 50 µl aliquot of DMSO (the highest concentration used for the test article dilution).

Positive controls: The positive controls for the assay are summarized in the sponsor's table below:

Table II. Positive Controls

Tester Strain	S9 Mix	Positive Control	Dose (µg/plate)
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TA100	–	sodium azide	2.0
TA1535	+	2-aminoanthracene	2.5
TA1535	–	sodium azide	2.0
TA1537	+	2-aminoanthracene	2.5
TA1537	–	ICR-191	2.0
WP2*uvr*A	+	2-aminoanthracene	25.0
WP2*uvr*A	–	4-nitroquinoline-N-oxide	1.0

Incubation and sampling times: Plates were incubated for 52 ± 4 hours at 37°C.

Results

Study validity (comment on replicates, counting method, criteria for positive results, etc.): [redacted] criteria for a valid assay included validation of tester strain integrity and acceptable levels of spontaneous revertants. The positive controls must produce at least a 3-fold increase over the mean value of the vehicle control. Upon review, the study appears to be valid for the following reasons: 1) the methodology was consistent with currently acceptable protocols, 2) the positive controls produced a clear increase in the number of revertants per plate compared to the vehicle control group 3) the vehicle