# CENTER FOR DRUG EVALUATION AND RESEARCH

*APPLICATION NUMBER:*

**21-623**

# CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW(S)

# CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW

| | |
|---|---|
| NDA: 21-623 N-000 | Submission Date(s): 12/17/2004 |
| Brand Name | S-Caine Patch |
| Generic Name | Lidocaine and Tetracaine |
| Reviewer | Srikanth C. Nallani, Ph.D. |
| Team Leader | Suresh Doddapaneni, Ph.D. |
| OCPB Division | Division of Pharmaceutical Evaluation II |
| ORM Division | Division of Analgesics Anesthetics and Rheumatology Products |
| Sponsor | Zars Inc., Salt lake City, UT 84119 |
| Relevant IND(s) | 58,823 |
| Submission Type; Code | NDA Resubmission; 505b(2) |
| Formulation; Strength(s) | Topical Patch; Lidocaine 70 mg, Tetracaine 70 mg |
| Indication | |

## Executive Summary

The sponsor's response to the Biopharmaceutics query is acceptable. The additional PK study # SC-51-04 data provided is acceptable. Overall, from a Clinical Pharmacology and Biopharmaceutics perspective the submission is a Complete Response and is acceptable provided that a mutually acceptable agreement can be reached between the Agency and Zars, Inc. regarding the text in the package insert.

## Comments

Sponsor should conduct dissolution testing in media-containing concentrations lower than

## Background

In April 2003, Zars Inc., filed an original 505(b)(2) New Drug Application for S-Caine™ Patch for the indication of The Agency found the application approvable and identified several deficiencies to address before approval. The deficiency pertinent to Clinical Pharmacology and Biopharmaceutics discipline was Justify why was used as test media." In response, the sponsor provided drug release profiles in different media.

In addition, the sponsor also submitted data from a pharmacokinetic study SC-51-04 to demonstrate low systemic exposure to lidocaine and tetracaine in adults following single and multiple simultaneous applications of S-Caine Patch. In the original submission, study SC-25-01 was conducted with the same goal; where blood sampling from the site of application of product introduced large variability in the data. While the Agency did recognize the sponsor's argument and did not request further studies, the sponsor repeated the PK study with appropriate steps to avoid blood sampling from the site of application. Data from this study was used to support labeling changes.

**Dissolution Documentation**

In general, use of [redacted] is not encouraged as indicated in USP "< 1088> In Vitro Evaluation: Dissolution and Drug Release Testing". The Agency's consideration behind the requested development data was to ensure the discriminatory power of the dissolution method to adequately capture the dissolution profile of lidocaine and tetracaine from various batches of S-Caine Patch.

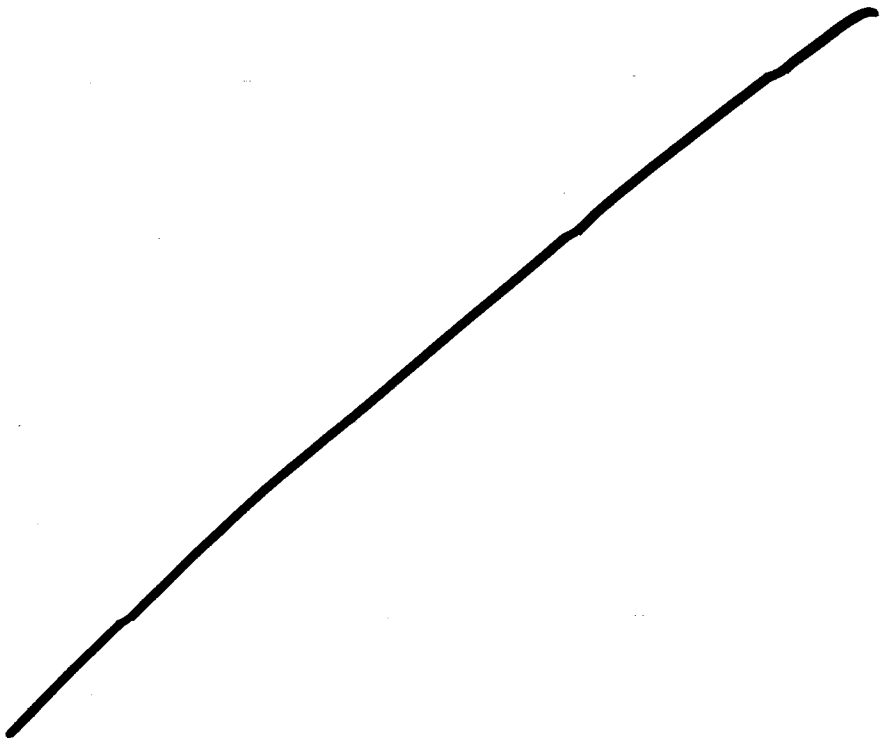
The sponsor indicated that in initial studies, [redacted] containing media did not dissolve tetracaine. The sponsor conducted additional studies to determine the release of both lidocaine and tetracaine in [redacted] The dissolution profile from the [redacted] media was compared with profiles generated employing [redacted] containing [redacted] with [redacted] media. The release rate of lidocaine and tetracaine from S-Caine Patch in the three tested media is shown in the table below.

[redacted]

LC = Label Claim, 70 mg for Lidocaine, 70 mg for Tetracaine

Lidocaine and tetracaine were released from S-Caine patch from all three tested media. The lidocaine and tetracaine release characteristics from [redacted] medium relative to [redacted] appear better for the following reasons:

a) While lidocaine and tetracaine release appears as a curvilinear profile in both [redacted] and [redacted] media, the variability of drug release is higher (Standard deviation is >10%) in [redacted] medium.



**Study # SC-51-04: "A PK Study in Adult Volunteers with Single or Multiple Simultaneous Applications of the S-Caine Patch"**

Previously, in study # SC-25-01, healthy adult subjects received two and four patches of S-Caine for 30 or 60 min of duration in a crossover design. The plasma levels of lidocaine and tetracaine although detectable were very variable within individual treatment groups. Even though the levels of lidocaine and tetracaine were relatively higher after simultaneous application of 2 and 4 patches, these levels were still lower than those expected to cause systemic side effects. The sponsor indicated that several blood samples collected from the same arm as the application site had very high plasma levels.

Study # SC-51-04 was aimed at measuring systemic exposure to lidocaine and tetracaine following application of one, two or four S-Caine Patches for 60 minutes in a parallel design. Six men and six women, 18 – 64 years of age, received different number of S-Caine Patches for 60 minutes. In an additional group, six men and six women at least 65 years received two S-Caine Patches for 60 minutes. Blood samples were collected from an arm contra lateral to the site of application for upto 24 hours. The plasma samples were analyzed for lidocaine and tetracaine employing a validated LC/MS/MS assay. None of the samples from any of the subjects had detectable levels of tetracaine (limit of quantitation 0.9 ng/mL). The study # SC-51-04 synopsis is attached to this review. The following table indicates the PK parameters of lidocaine in various groups of S-Caine Patch exposure:

**Pharmacokinetic Parameters (Mean ± SD) for Lidocaine**

| | $C_{max}$ (ng/mL) | $T_{max}$ (hr) | $AUC_{0-24}$ (ng•hr/mL) | $t_{1/2}$ (hr) |
|---|---|---|---|---|
| ***Group 1-3; 18 - 64 yrs*** | | | | |
| 1 S-Caine Patch, 60 min (n = 11) | 1.50 ± 1.56 | 2.4 ± 1.2 | 7.91 ± 9.76 | 5.3 ± 3.5 (n = 4) |
| 2 S-Caine Patches, 60 min (n = 11) | 4.03 ± 2.49 | 1.9 ± 0.9 | 25.02 ± 11.92 | 4.3 ± 2.1 (n = 9) |
| 4 S-Caine Patches, 60 min (n = 11) | 5.09 ± 1.92 | 2.4 ± 2.1 | 42.73 ± 11.42 | 7.9 ± 4.3 (n = 7) |
| ***Group 4; ≥ 65 yrs*** | | | | |
| 2 S-Caine Patches, 60 min (n = 12) | 1.65 ± 1.65 | 3.4 ± 2.9 | 11.49 ± 11.13 | 18.1 ± 28.2 (n = 4) |

Statistical analysis revealed that the $C_{max}$ and $AUC_{0-24}$ increased significantly with the application of increased number of S-Caine Patches. However, the peak plasma levels in 18 – 64 year subjects receiving four simultaneous applications of S-Caine patch were below 9 ng/mL. In the additional treatment group with ≥65 years of age subjects receiving two simultaneous applications of S-Caine Patch, the peak plasma levels were below 6 ng/mL.

While this PK study is limited in scope to assess safety, no serious adverse events were reported in this study. Overall, it appears that following appropriate use of S-Caine Patch the systemic levels of lidocaine and tetracaine may be very low to cause any systemic side effects.

The sponsor submitted a draft protocol and proposed a time line for the conduct of pediatric PK study (SC-33-04) aimed at determining systemic exposure to lidocaine and tetracaine following S-Caine Patch application. Previously, study # SC-30-01 evaluated systemic exposure to lidocaine and tetracaine in pediatric subjects >4 months upto 12 years of age. The proposed study includes six neonates at least 38 weeks estimated gestational age and 0-4 months weeks postnatal age and three infants 1-4 months age. Newborn subjects will have requirement for topical local anesthesia with an indwelling vascular access for blood sampling already in place at the time of enrollment. The review of draft protocol is attached and appears acceptable pending review of the full final version.

**Changes to Package Insert**

The sponsor proposed labeling text pertinent to Clinical Pharmacology Section is presented below. Additions and deletions to the label is indicated by **bold** and ~~strikethrough~~ font.

# 3 Page(s) Withheld

_____ Trade Secret / Confidential

✓ Draft Labeling

_____ Deliberative Process

*Withheld Track Number: Clin Pharm/Bio-* 8

## Study # SC-51-04 Synopsis:

### 2.0 SYNOPSIS

| | | |
|---|---|---|
| **Name of Company:** ZARS, Inc. | **Individual Study Table Referring to Part of the Dossier** | *(For National Authority Use only)* |
| **Name of Finished Product:** S-Caine™ Patch (lidocaine and tetracaine topical patch) 70 mg/70 mg | **Volume:** | |
| **Name of Active Ingredient:** lidocaine 70 mg and tetracaine 70 mg | **Page:** | |

**Title of Study:** A Pharmacokinetic Study in Adult Volunteers with Single or Multiple Simultaneous Applications of the S-Caine™ Patch (Lidocaine and Tetracaine Topical Patch) 70 mg/70 mg

**Investigators and Study Centers:** [redacted]

**Publication (reference):** None

| | |
|---|---|
| **Study Start Date:** July 13, 2004<br>**Study Completion Date:** July 14, 2004 | **Phase of Development:** 1 |

**Objectives:** To measure and quantify the levels of lidocaine and tetracaine in the plasma of adult volunteers following single or multiple simultaneous applications of the S-Caine Patch. To monitor the nature and frequency of adverse events associated with the safety of the S-Caine Patch.

**Methodology:**

Three groups of 6 men and 6 women 18 - 64 years of age received one, two or four S-Caine Patches applied for 60 minutes. Six men and 6 women at least 65 years of age received two S-Caine Patches applied for 60 minutes. Plasma samples were collected predose and 1, 2, 3, 4, 6, 8 and 24 hr after the initial application of the S-Caine Patches. The lidocaine and tetracaine concentrations were determined by an LC/MS/MS assay with limits of quantitation of 0.9 ng/mL for both drugs.

**Number of Subjects (Planned and Analyzed):** Approximately 48 subjects were planned for the study. Forty-eight subjects entered the study and all were included in the safety analysis, whereas forty-five were included in the analysis of pharmacokinetic parameters.

**Diagnosis and Main Criteria for Inclusion:** Males or females of any race at least 18 years old and in stable health were eligible to participate if they had no known allergies or sensitivities to lidocaine, tetracaine or other local anesthetics and if they had signed a written informed consent. Subjects were excluded if they had a known sensitivity to any components of the test materials; had damaged, denuded, or broken skin at the designated patch site; had a history of cocaine addiction; had donated blood or plasma within the prior 30 days; had participated in a study using an investigational drug within the prior 30 days; had been administered a local or systemic anesthetic, including OTC products, within the prior 14 days; or who were pregnant or breastfeeding.

| | | |
|---|---|---|
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| **Name of Active Ingredient:** lidocaine 70 mg and tetracaine 70 mg | **Page:** | |

**Test Product, Dose and Mode of Administration, Batch Number:** S-Caine Patch (lidocaine 70 mg and tetracaine 70 mg patch) contains a 1:1 eutectic mixture of lidocaine base, USP and tetracaine base, USP. Batch No. FP-04-037 was used.

**Duration of Treatment:** Single application of one, two or four S-Caine Patches for 60 minutes.

**Reference Therapy, Dose and Mode of Administration, Batch Number:** None.

**Criteria for Evaluation:**

Pharmacokinetic Variables: Maximum concentration, $C_{max}$, time of maximum concentration, $T_{max}$, and area under the plasma concentration curve, $AUC_{0-24}$.

Safety: Safety and tolerability were evaluated based on the frequency of adverse events, and on the evaluation of skin reactions following removal of study patches, and after the collection of the 8 and 24 hr blood samples. The occurrence of erythema and eschar formation was jointly evaluated using a 5-point categorical scale ranging from no erythema through severe erythema to slight eschar formation. Edema was independently evaluated using a 5-point categorical scale ranging from no erythema through severe edema.

**Statistical Methods:** Demographic, history, and examination variables were summarized using descriptive statistics.

Levels of lidocaine were summarized by time of sampling and administration. Treatment groups were compared for pharmacokinetic parameters $AUC_{0-24}$ and $C_{max}$, using a one-way analysis of variance of log transformed parameters. The parameters $T_{max}$, $t_{1/2}$, and $AUC_{0-\infty}$ were summarized descriptively. Two subjects were excluded from the pharmacokinetic analysis due to protocol deviations, and one subject was excluded due to an early withdrawal from the study.

Skin evaluations and vital sign measurements were summarized.

RESULTS AND CONCLUSIONS

Pharmacokinetic Results: None of the samples from any of the subjects had measurable levels of tetracaine. The limit of quantitation of the assay was 0.9 ng/mL. The highest lidocaine concentrations observed for younger subjects receiving one, two or four S-Caine Patches for 60 minutes were [redacted], respectively. The highest lidocaine concentration for the elderly subjects receiving two S-Caine Patches for 60 minutes was Pharmacokinetic parameters for lidocaine are summarized below:

| **Name of Company:** ZARS, Inc. | **Individual Study Table Referring to Part of the Dossier** | *(For National Authority Use only)* |
|---|---|---|
| **Name of Finished Product:** S-Caine™ Patch (lidocaine and tetracaine topical patch) 70 mg/70 mg | **Volume:** | |
| **Name of Active Ingredient:** lidocaine 70 mg and tetracaine 70 mg | **Page:** | |

**Pharmacokinetic Parameters (Mean ± SD) for Lidocaine**

| | $C_{max}$ (ng/mL) | $T_{max}$ (hr) | $AUC_{0-24}$ (ng•hr/mL) | $t_{1/2}$ (hr) |
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| ***Group 1-3; 18 - 64 yrs*** | | | | |
| 1 S-Caine Patch, 60 min (n = 11) | 1.50 ± 1.56 | 2.4 ± 1.2 | 7.91 ± 9.76 | 5.3 ± 3.5 (n = 4) |
| 2 S-Caine Patches, 60 min (n = 11) | 4.03 ± 2.49 | 1.9 ± 0.9 | 25.02 ± 11.92 | 4.3 ± 2.1 (n = 9) |
| 4 S-Caine Patches, 60 min (n = 11) | 5.09 ± 1.92 | 2.4 ± 2.1 | 42.73 ± 11.42 | 7.9 ± 4.3 (n = 7) |
| ***Group 4; ≥ 65 yrs*** | | | | |
| 2 S-Caine Patches, 60 min (n = 12) | 1.65 ± 1.65 | 3.4 ± 2.9 | 11.49 ± 11.13 | 18.1 ± 28.2 (n = 4) |

For Groups 1 - 3 with the younger subjects, $C_{max}$ and $AUC_{0-24}$ increased with an increasing number of S-Caine Patches. For $C_{max}$, the estimated ratio of geometric means of Group 2 to Group 1 was 217%, and the estimated ratio of Group 3 to Group 2 was 129%. For $AUC_{0-24}$, the corresponding estimates are 555% and 182%. The larger estimate for $AUC_{0-24}$ for the comparison of Groups 2 and 1 is probably due to four subjects in Group 1 having all values below the level of quantitation. Two S-Caine Patches applied to the younger subjects produced statistically significantly higher values for $C_{max}$ and $AUC_{0-24}$ than the application of one S-Caine Patch (one-way ANOVA, pairwise p-values ≤ 0.0014). Four S-Caine Patches produced higher $AUC_{0-24}$ and $C_{max}$ values than the application of two patches, but did not achieve statistical significance (one-way ANOVA, pairwise p-values = 0.172 and 0.268 respectively). Comparison of Group 4 to Group 2 showed that both the $C_{max}$ and $AUC_{0-24}$ values were statistically significantly lower for the elderly subjects receiving two S-Caine Patches (one-way ANOVA, pairwise p-values ≤ 0.0063). The $T_{max}$ values occurring after patch removal in many subjects and the $t_{1/2}$ values that are substantially longer than the reported half-life for lidocaine of 1.8 hr indicate that lidocaine may be stored in a depot in the skin. The apparently longer mean $t_{1/2}$ for the elderly subjects is due to a single $t_{1/2}$ value of 60 hr and may not reflect an intrinsic difference since the other values for $t_{1/2}$ ranged from 3.0 - 6.2 hr, similar to the younger subjects.

Safety Results: Six mild adverse events were reported for five subjects. The events included upset stomach and lightheadedness (same subject), headache, head cold, numbness in fingers of right hand (single S-Caine Patch applied to left arm for this subject), and shakiness. The upset stomach and lightheadedness resolved in a few minutes, the headache in 7.5 hr, the head cold in 6 days, the numbness in the fingers in 4 hr, and the shakiness in 5 hr. The adverse events were considered to be not related or unlikely to be related to study drug. None of the subjects with adverse events withdrew from the study.

There were ten subjects with decreases in one or more vital signs that met criteria defined in

prior studies. No subjects had increases meeting the defined criteria. With the exception of Subject 1302, who had decreased pulse rate at both 1 and 2 hr, none of the changes were sustained beyond a single measurement. The decreases in vital signs were distributed across the treatment groups, with two changes for two subjects in Group 1, five changes for four subjects in Group 2, two changes for two subjects in Group 3, and three changes for two subjects in Group 4. None of the changes in vital signs for the ten subjects were reported as adverse events.

Twenty-six of the 36 younger subjects in Groups 1 through 3 had well-defined erythema at one or more application sites, and 8 subjects had very slight erythema. The elderly subjects in Group 4 had less severe skin reactions, with only three subjects showing well-defined erythema and 8 with very slight erythema at one or more of the application sites. None of the subjects in any of the groups had moderate or severe erythema or eschar formation. At 8 hr, the incidence and severity of the erythema was less than immediately after patch removal. At 24 hr, no erythema was observed for any subject. Five subjects had slight or very slight edema at one S-Caine Patch site immediately after patch removal. All other subjects had no evidence at patch removal, and none of the subjects showed evidence of edema at 8 or 24 hr.

**Conclusions:** For the subjects aged 18 to 64 years, the plasma levels of lidocaine increased with increasing number of S-Caine Patches applied. Two S-Caine Patches produced significantly higher $C_{max}$ and $AUC_{0-24}$ values than one S-Caine Patch. The parameters for four S-Caine Patches were higher than those for two S-Caine Patches, but the differences did not achieve statistical significance. The plasma levels of lidocaine were lower for subjects 65 years of age or more than for younger subjects, when both groups received two S-Caine Patches. $C_{max}$ and $AUC_{0-24}$ values were significantly lower for the older subjects. $T_{max}$ occurred after removal of the S-Caine Patches for many subjects, and $t_{1/2}$ tended to be longer than the reported half-life for lidocaine, 1.8 hr, indicating that lidocaine was absorbed from the S-Caine Patch and remained as a depot in the skin with later transfer to the systemic circulation. The highest observed concentration of lidocaine was [redacted] which is less than $1/500^{th}$ the lower end on the concentration range associated with lidocaine toxicity (> 5,000 ng/mL).

The tetracaine concentrations in all samples from all subjects in this study were below the limit of quantitation, [redacted] Thus, the systemic exposure to tetracaine from S-Caine Patches was less than $1/200^{th}$ of reported tetracaine concentrations that were not associated with adverse events [redacted]

Simultaneous application of one, two or four S-Caine Patches for 60 minutes was well tolerated in this study. Five mild adverse events affecting four of 48 subjects occurred, and all were considered unlikely or not related to the application of S-Caine Patches. There were ten subjects with decreases in one or more vital signs that met pre-defined criteria, but none of the changes were regarded as adverse events. As expected following topical local anesthetic application, most subjects experienced a mild skin reaction following treatment. No subject

| | | |
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| **Name of Active Ingredient:** lidocaine 70 mg and tetracaine 70 mg | **Page:** | |
| experienced a moderate or severe dermal reaction to the patch. The safety results of this study are consistent with what would be expected following the use of a local anesthetic preparation. | | |
| **Date of Report:** 3 December 2004 | | |

Pediatric PK Study # SC-33-04 Synopsis:

**IND: 58, 823**

**Study Type:** Phase I safety tolerability and pharmacokinetics study

**Protocol Title:** Evaluation of Systemic Exposure to Lidocaine and Tetracaine Produced by the S-Caine Patch in Neonates and Infants.

**Study Objectives:**

- To evaluate systemic exposure to lidocaine and tetracaine following application of the S-Caine Patch to neonates and infants.

- To monitor the nature and frequency of any adverse events associated with the S-Caine Patch

**Study Design:** Open label study in neonates and infants to evaluate plasma levels of lidocaine and tetracaine following application of single S-Caine patch for 30 minutes

**Subject Breakdown:** Neonates and infants requiring medically indicated procedures for which the use of a topical local anesthetic would provide a benefit to the patient.

| **Number** | 6 | 3 |
|---|---|---|
| **Mean Age (Range)** | At least 38 weeks estimated gestational age and 0-4 months postnatal age | 1-4 months |

**Blood sampling Scheme:** 1 mL blood samples will be collected from an indwelling catheter at 0, 0.5, 1.5 or 4 hours, one between 8-10 hours, and one between 24 – 30 hours post dose. Blood sampling will be performed on a limb contra lateral to the planned site of S-Caine patch application. Plasma samples will be analyzed for lidocaine and tetracaine employing a validated LC/MS/MS method.

If the plasma samples have detectable levels of drug, PK parameters such as $T_{max}$, $C_{max}$ and AUC will be calculated and their descriptive statistics will be provided.

**Safety Assessments:** 1) Post-treatment skin assessment of erythema, edema and blanching at the time of patch removal; 2) second skin assessment after 24 – 30 hour blood sample collection; 3) methemoglobin concentrations; and 4) other adverse events.

An overview of study procedures and assessments is provided in the table below:

**Study Chart 1. Overview of Procedures for Study**

| Procedure | Screening | Day 1<br>Pre-dose | Day 1<br>Post-dose | Day 2<br>24 to 30 hrs. Post Application |
|---|---|---|---|---|
| Informed Consent | X | | | |
| Physical Exam and Medical History | X | | | |
| Inclusion and Exclusion Criteria | X | | | |
| Patch Application for 30 minutes | | | X | |
| Blood Samples for PK | | X | X<br>0.5, 1.5, 4, 8-12<br>hr after patch application. | X<br>must be 24-30 hrs<br>after patch application. |
| Methemoglobin collection (0.4 mL) | | X | X<br>4, 8-12<br>hr after patch application. | X<br>must be 24-30 hrs<br>after patch application. |
| Vital Signs and Oxygen Saturation | | X | X<br>0.5, 1.5, 4, 8-12<br>hr after patch application. | X<br>must be 24-30 hrs<br>after patch application. |
| Collection of Used Patch & Gauze | | | X | |
| Skin Evaluation; immediately after patch removal and after 24-30 hr blood collection | | | X<br>after patch removal | X |
| Concomitant Medications Recorded | X | X | X | X |
| Adverse Event Recording | | X | X | X |
| Discharge from Study | | | | X |

[1]If the subject experiences a delayed skin reaction or if investigator determines that the subject requires follow-up due to an adverse event, the study termination report will be completed once all follow-up interactions are completed.

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

/s/
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Srikanth Nallani
6/6/05 04:33:47 PM
BIOPHARMACEUTICS

Suresh Doddapaneni
6/7/05 10:32:46 AM
BIOPHARMACEUTICS

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

*General Information About the Submission*

| | Information | | Information |
|---|---|---|---|
| NDA Number | 21-623 | Brand Name | S-CAINE™ Patch |
| OCPB Division (I, II, III) | DPE II | Generic Name | lidocaine and tetracaine |
| Medical Division | DACCADP | Drug Class | Topical anaesthetic |
| OCPB Reviewer | Srikanth C. Nallani | Indication(s) | |
| OCPB Team Leader | Suresh Doddapaneni | Dosage Form | topical patch |
| | | Dosing Regimen | lidocaine 70 mg, tetracaine 70 mg |
| Date of Submission | 4/4/2003 | Route of Administration | topical |
| Estimated Due Date of OCPB Review | 1/5/2003 | Sponsor | ZARS, Inc.<br>350 W. 800 N. Suite 320<br>Salt Lake City, UT 84103 |
| PDUFA Due Date | 2/4/2004 | Priority Classification | Standard |
| Division Due Date | 1/8/2004 | | |

## *Clin. Pharm. and Biopharm. Information*

| | "X" if included at filing | Number of studies submitted | Number of studies reviewed | Critical Comments If any |
|---|---|---|---|---|
| STUDY TYPE | | | | |
| Table of Contents present and sufficient to locate reports, tables, data, etc. | X | | | |
| Tabular Listing of All Human Studies | | | | Tabular list of PK, Safety and Efficacy studies presented separately. |
| HPK Summary | X | | | |
| Labeling | X | | | |
| Reference Bioanalytical and Analytical Methods | X | | | |
| I. Clinical Pharmacology | | | | |
| Mass balance: | | | | |
| Isozyme characterization: | | | | |
| Blood/plasma ratio: | | | | |
| Plasma protein binding: | | | | |
| Pharmacokinetics (e.g., Phase I) - | | | | |
| Healthy Volunteers- | | | | |
| single dose: | X | 4 | 4 | |
| multiple dose: | X | 1 | 1 | |
| Patients- | | | | |
| single dose: | | | | |
| multiple dose: | | | | |
| Dose proportionality - | | | | |
| fasting / non-fasting single dose: | | | | |
| fasting / non-fasting multiple dose: | | | | |
| Drug-drug interaction studies - | | | | |
| In-vivo effects on primary drug: | | | | |
| In-vivo effects of primary drug: | | | | |
| In-vitro: | | | | |
| Subpopulation studies - | | | | |
| ethnicity: | | | | |
| gender: | | | | |
| pediatrics: | | 1 | 1 | |

| | | | | |
|---|---|---|---|---|
| geriatrics: | | 1 | 1 | |
| renal impairment: | | | | |
| hepatic impairment: | | | | |
| **PD:** | | | | |
| Phase 2: | | | | |
| Phase 3: | | | | |
| **PK/PD:** | | | | |
| Phase 1 and/or 2, proof of concept: | | | | |
| Phase 3 clinical trial: | | | | |
| **Population Analyses -** | | | | |
| Data rich: | | | | |
| Data sparse: | | | | |
| **II. Biopharmaceutics** | | | | |
| **Absolute bioavailability:** | | | | |
| **Relative bioavailability -** | | | | |
| solution as reference: | | | | |
| alternate formulation as reference: | | | | |
| **Bioequivalence studies -** | | | | |
| traditional design; single / multi dose: | | | | |
| replicate design; single / multi dose: | | | | |
| **Food-drug interaction studies:** | | | | |
| **Dissolution:** | | | | |
| **(IVIVC):** | | | | |
| **Bio-wavier request based on BCS** | | | | |
| **BCS class** | | | | |
| **III. Other CPB Studies** | | | | |
| **Genotype/phenotype studies:** | | | | |
| **Chronopharmacokinetics** | | | | |
| **Pediatric development plan** | | | | |
| **Literature References** | | | | |
| **Total Number of Studies** | | 5 | 5 | |

**Filability and QBR comments**

| | "X" if yes | Comments |
|---|---|---|
| **Application filable ?** | X | Reasons if the application is not filable (or an attachment if applicable) For example, is clinical formulation the same as the to-be-marketed one? |
| **Comments sent to firm ?** | | Comments have been sent to firm (or attachment included). FDA letter date if applicable. |
| **QBR questions (key issues to be considered)** | **Are the active ingredients significantly absorbed into the systemic circulation?<br>Are any clinically relevant side effects anticipated at the concentrations of the drug absorbed from the dosage form?** | |
| **Other comments or information not included above** | | |
| **Primary reviewer Signature and Date** | | |
| **Secondary reviewer Signature and Date** | | |

# CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW

| | |
|---|---|
| NDA: 21-623 | Submission Date(s): 4/4/2003 |
| Brand Name | S-Caine™ Patch |
| Generic Name | Lidocaine and Tetracaine |
| Reviewer | Srikanth C. Nallani, Ph.D. |
| Team Leader | Suresh Doddapaneni, Ph.D. |
| OCPB Division | Division of Pharmaceutical Evaluation II |
| ORM Division | Division of Anesthetics Critical Care and Addiction Drug Products, HFD-170 |
| Sponsor | ZARS Inc.<br>350 W. 800 N. Suite 320<br>Salt Lake City, UT 84103 |
| Relevant IND(s) | 58,823 |
| Submission Type; Code | Original NDA; 505b(2) |
| Formulation; Strength(s) | Topical Patch; Lidocaine 70 mg, Tetracaine 70 mg |
| Indication | [redacted] |
| Proposed Dosage Regimen | [redacted] |

**Table of Contents**

# 1 Executive Summary

## 1.1 Recommendation

S-Caine Patch is a topical drug product developed for the indication of [redacted] The formulation contains inactive ingredients necessary to generate a controlled chemical reaction with resulting heat upon atmospheric exposure. The resultant heat is theorized to warm the skin and enhance permeation of the local anesthetics lidocaine and tetracaine contained in the patch. Adequate data was provided to evaluate the systemic levels of lidocaine and tetracaine following single and multiple-repetitive or multiple-simultaneous S-Caine Patch application in healthy adults, pediatric and geriatric subjects. Overall, systemic exposure to the local anesthetics in subjects receiving topical S-Caine Patch is minimal and systemic pharmacological effects may not occur following the indicated usage. From a Clinical Pharmacology and Biopharmaceutics perspective, the submitted data is acceptable provided that a mutually acceptable agreement can be reached between the Agency and Zars, Inc. regarding the text in the package insert and *in vitro* release method specifications. The release specifications should be modified (pending agreement of the reviewing Chemist) as follows;

| Sampling Time | Lidocaine | Tetracaine |
|---|---|---|
| 20 min | [redacted] | |
| 40 min | | |
| 60 min | | |

LC – Label Claim of 70 mg each of lidocaine and tetracaine

## 1.2 Phase IV Commitments (None)

## 1.3 Summary of Clinical Pharmacology and Biopharmaceutics Findings

S-Caine Patch comprises of (a) a eutectic mixture of lidocaine and tetracaine bases in a 1:1 weight ratio suspended as fine oil droplets (oil in water emulsion) and (b) an integrated oxygen-activated heating component (activated carbon, iron powder, sodium chloride, wood [redacted] Immediately upon removal out of the airtight package, the heating component activates and upon application, supposedly increases the skin temperature between [redacted] This is thought to result in enhanced permeation of the local anesthetics, decreased onset time and increased depth of local anesthesia of the skin. A potential safety concern for this topical product is unintended systemic exposure to high levels of lidocaine and tetracaine. Systemic exposure of lidocaine and tetracaine was determined in adult (SC-05-99, SC-25-01, SC-26-01), geriatric (SC-31-01), and pediatric subjects (Study#SC-30-01), applied with single or multiple S-Caine Patches, simulating several possible scenarios of use in the clinical setting. In healthy adults, following application of single S-Caine Patch for 30 minutes (min) or 60 min, tetracaine levels were not detected in plasma, while lidocaine levels were very variable and when detected were in the range of 1 – 6 ng/mL. Multiple applications involved application of two and four S-Caine Patches for 30 and 60 min. Repetitive treatment involved application of four S-Caine Patches for 30 min with a 30 min

interval between each patch application and three S-Caine Patches for 60 min with a 60 min interval between each application. Overall, systemic levels of lidocaine and tetracaine were very variable and higher drug concentrations were observed following multiple simultaneous compared to multiple repetitive or single applications of S-Caine Patch in healthy adults. In subjects with detectable drug concentrations, maximum plasma concentrations were observed between 30 – 180 min of patch application in the ranges of 2 – 400 ng/mL and 1 – 250 ng/mL for lidocaine and tetracaine, respectively. In two subjects, high levels (~1 μg/mL) of lidocaine were seen. This was attributed by the sponsor to possible blood sampling from the site of application. Considering that concentrations observed before and after the time of observed high levels are comparatively very low (3- to 100-fold low), the sponsor's justification appears reasonable. Eventhough, the pharmacokinetic studies enrolled relatively small number of subjects, in general, the product was well tolerated and no severe adverse events were reported. The only notable drug-related adverse events were skin blanching and erythema at the application site of the S-Caine Patch.

In geriatric subjects applied with single S-Caine Patch for 20 min duration, lidocaine or tetracaine were not detected.

In pediatrics (age groups of 4 months – 2 years, 3 – 6 years and 7 – 12 years), application of one or two S-Caine Patches was well tolerated and no serious adverse events were reported in subjects of any age group. In subjects with detectable levels of lidocaine and tetracaine, maximum plasma concentrations ranged from 1 – 330 ng/mL and 1 – 65 ng/mL, respectively. Four subjects in a particular clinical site (# 302) were applied two S-Caine Patches on the antecubital fossa and blood samples were collected from the site of application. Two subjects had very high levels of lidocaine and tetracaine-subject 30208 had maximum lidocaine and tetracaine concentrations of [redacted] at 1 hour post application, while subject 30210 had [redacted] of lidocaine and no detectable levels of tetracaine. However, lidocaine levels were only [redacted] in these subjects at the 2 hour time point. In spite of blood sampling from the site of application, in subjects 30206 and 30209, lidocaine and tetracaine levels were [redacted] respectively. Overall, systemic exposure of pediatric population to lidocaine and tetracaine may be low to cause any systemic side effects.

An *in vitro* release method was developed for the purpose of determining lot to lot variability employing the final formulation that was used in the clinical trials. The US pharmacopeia specified Drug release <724> Apparatus # 5 – Paddle over disk was employed with two modifications to accommodate for the size of the patch (watch glass instead of glass disk) and the anticipated temperature (40°C instead of 32°C) of the patch upon activation of the heating component. The dissolution media (1:4 acetonitrile:phosphate buffer, pH 3.0) was employed at 40°C with the paddle speed of 50 rpm, and samples were collected at 20, 40 and 60 min. Based on the drug release profile, the sponsor has arrived at the following dissolution specifications provided in the table below.

Dissolution Specifications for S-Caine Patch

| Sampling Time | [redacted] |
|---|---|
| 20 min. | |
| 40 min. | |
| 60 min. | |

LC = Label Claim, which is 70 mg for both lidocaine and tetracaine

## 2 QBR

### 2.1 General Attributes

Zars Inc., filed this original 505(b)(2) New Drug Application for S-Caine™ Patch for the indication of [redacted] The patch consists of separate layers of (a) an oil in water emulsion of eutectic mixture of lidocaine and tetracaine, (b) an integrated oxygen-activated heating component to enhance dermal permeation of lidocaine and tetracaine. The mechanism of action of lidocaine and tetracaine entails inhibition of ionic fluxes required for the initiation and conduction of impulses. The proposed S-Caine Patch dosage based on the indication is as follows: a) between 20 – 30 min application on intact skin for minor dermal procedures such as [redacted] b) at least 30 min application to intact skin for major dermal procedures such as excision, shave biopsy [redacted]

### 2.2 General Clinical Pharmacology

In this product, both lidocaine and tetracaine are meant to act at the application site producing superficial anesthesia. Any systemically absorbed drug is unintended. Generally, a blood level greater than 1.5 µg/mL is generally considered to be the threshold for the onset of systemic pharmacologic effects, while a level greater than 6 µg/mL is considered toxic. Systemic adverse effects of lidocaine and tetracaine include CNS excitation and/or depression (light-headedness, nervousness, apprehension, euphoria, confusion, dizziness, drowsiness, tinnitus, blurred or double vision, vomiting, sensation of heat, cold or numbness, twitching, tremors, convulsions, unconsciousness, respiratory depression and arrest). Lidocaine is a cardiac antiarrhythmic agent and does not produce any changes in ECG. Effect of tetracaine specifically on human cardiac electrophysiology is not clearly known. However, cardiovascular toxicity manifestations may include bradycardia, hypotension and cardiovascular collapse leading to arrest.

The clinical pharmacology program for S-Caine was designed to assess the systemic levels of lidocaine and tetracaine from a safety perspective following single- and multiple-application of S-Caine Patches when used as directed and when used inappropriately. Attempts were not made to correlate systemic exposure of these drugs with the efficacy.

Are significant systemic levels seen after single application of S-Caine patch?

*Lidocaine levels were very low while tetracaine levels were undetectable when used as directed.*

Lidocaine and tetracaine were not detected in any of the plasma samples obtained from study # SC-05-99, where healthy subjects were applied with a single S-Caine Patch for 30 min. However, the plasma samples from this study were analyzed by a GC-MS method with a detection limit of 100 ng/mL for both lidocaine and tetracaine. In later studies, a sensitive LC/MS/MS method was employed for detection of lidocaine (LOQ<0.9 ng/mL) and tetracaine (LOQ <0.9 ng/mL) in plasma samples. In study # SC-26-01, single application of S-Caine Patch for 30 or 60 min did not result in detectable tetracaine levels and where detected, lidocaine levels were very low (1 – 6 ng/mL) to cause any systemic side effects.

Are significant systemic levels seen after sequential application of single S-Caine patches?

*After the application of four S-Caine patches (30 min duration each) 30 minutes apart or three S-caine patches (60 minutes duration each) 60 minutes apart, lidocaine levels were very low while tetracaine levels were undetectable.*

In study # SC-26-01, subjects were applied four S-Caine Patches for duration of 30 min each with a 30 min interval between treatments, or in another group subjects received three S-Caine Patches for duration of 60 min each with a gap of 60 min between treatments.

Tetracaine was not detected in plasma following single or multiple application of S-Caine Patch for 30 or 60 min duration while lidocaine levels were very low. The table below summarizes the mean pharmacokinetic parameters of lidocaine observed in plasma following single or repeat application.

**Mean Pharmacokinetic Parameters for Lidocaine**

| Study # SC-26-01 | Single Application | | Repeat Application | |
|---|---|---|---|---|
| | 30 Minutes | 60 Minutes | 30 Minutes | 60 Minutes |
| $C_{max}$ (ng/mL) | 1.65 ± 1.56 | 2.04 ± 1.83 | 6.35 ± 3.01 | 4.42 ± 1.69 |
| $T_{max}$ (hr) | 1.7 ± 2.0 | 3.3 ± 2.4 | 3.6 ± 0.5 | 5.2 ± 1.2 |
| $AUC_{0-6}$ (ng•hr/mL) | 8.38 ± 9.20 | 14.37 ± 11.12 | 47.33 ± 18.68 | 49.59 ± 18.71 |
| $t_{1/2}$ (hr) | 5.9 ± 1.3 | 7.4 ± 5.0 | 4.2 ± 2.5 | 8.0 ± 3.5 |

Are significant systemic levels seen after simultaneous application of multiple S-Caine patches?

*After application of two or four patches simultaneously for 30 min and 60 min duration, systemic levels of lidocaine were still lower than those expected to cause systemic side effects.*

In study # SC-25-01, healthy adult subjects received two and four patches of S-Caine for 30 or 60 min of duration in a crossover design. The pharmacokinetic parameters of lidocaine and tetracaine, following simultaneous application of two or four S-Caine Patches for 30 or 60 min duration are shown below.

Study # SC-25-01 **Mean Pharmacokinetic Parameters**

| **Lidocaine** | 30-Minute Application | | 60-Minute Application | |
|---|---|---|---|---|
| | 2 Patches | 4 Patches | 2 Patches | 4 Patches |
| $C_{max}$ (ng/mL) | 94.4 ± 113.5 | 192.6 ± 303.1 | 312.0 ± 401.4 | 190.8 ± 204.0 |
| $T_{max}$ (hr) | 2.6 ± 1.9 | 1.1 ± 0.7 | 1.8 ± 1.7 | 1.5 ± 1.5 |
| $AUC_{0-6}$ (ng•hr/mL) | 221.2 ± 325.0 | 220.5 ± 211.3 | 363.6 ± 363.9 | 300.6 ± 286.5 |
| $t_{1/2}$ (hr) | 1.1 ± 0.2 | 3.9 ± 2.5 | 1.6 ± 1.8 | 2.4 ± 1.5 |
| **Tetracaine** | 30-Minute Application | | 60-Minute Application | |
| | 2 Patches | 4 Patches | 2 Patches | 4 Patches |
| $C_{max}$ (ng/mL) | 9.9 ± 28.8 | 9.1 ± 13.3 | 48.1 ± 71.6 | 32.5 ± 69.4 |
| $T_{max}$ (hr) | 1.0 ± 1.8 | 0.5 ± 0.8 | 0.7 ± 0.4 | 1.0 ± 1.6 |
| $AUC_{0-6}$ (ng•hr/mL) | 5.71 ± 15.29 | 6.27 ± 8.41 | 34.22 ± 52.58 | 28.29 ± 61.50 |

The plasma levels of lidocaine and tetracaine although detectable were very variable within individual treatment groups. Eventhough, the levels of lidocaine and tetracaine were relatively higher after simultaneous application of 2 and 4 patches, these levels were still lower than those expected to cause systemic side effects.

What is the estimated absorbed dose of lidocaine and tetracaine?

*Out of 70 mg in the formulation, approximately 1.5 mg each of lidocaine and tetracaine seems to be absorbed in adults while in pediatrics about 3 mg each of lidocaine and tetracaine is absorbed.*

Dose of lidocaine and tetracaine released from S-Caine Patches was determined by analyzing the residual amounts in the patches removed following an application interval from study SC-26-01. The estimated maximum absorbed dose (EMAD) calculated by subtracting the residual amount of drug from the labeled amount for that particular lot 30 min or 60 min application for both drugs was about 1.5 mg each was not significantly different between the duration of application. A summary of the lidocaine and tetracaine amounts in S-Caine Patches used in study # SC-26-01 is presented below.

**Table indicating residual lidocaine and tetracaine in S-Caine Patches used in PK study # SC-26-01**

| | 30-Minute Single Application | | 60-Minute Single Application | |
|---|---|---|---|---|
| Parameter | Lidocaine | Tetracaine | Lidocaine | Tetracaine |
| Residual Amount (mg) | | | | |
| Mean ± SD | 67.4 ± 1.1 | 65.8 ± 1.1 | 67.6 ± 0.9 | 66.1 ± 1.0 |
| Median | 67.9 | 66.4 | 67.8 | 66.1 |
| Range | 65.2 - 68.7 | 63.9 - 67.1 | 65.9 - 69.3 | 64.5 - 68.2 |
| n | 12 | 12 | 12 | 12 |
| Estimated Maximum Absorbed (mg) | | | | |
| Mean ± SD | 1.7 ± 1.1 | 1.6 ± 1.1 | 1.5 ± 0.9 | 1.4 ± 1.0 |
| Median | 1.2 | 1.1 | 1.3 | 1.4 |
| Range | 0.4 - 3.9 | 0.4 - 3.6 | -0.2 - 3.2 | -0.7 - 3.0 |
| n | 12 | 12 | 12 | 12 |

The residual amount of active ingredients in S-Caine Patches used in the pediatric PK study (SC-30-01) showed higher absorbed amounts of lidocaine and tetracaine. A summary of the lidocaine and tetracaine amounts in S-Caine Patches used in study # SC-30-01 is presented below.

Table indicating residual lidocaine and tetracaine in S-Caine Patches used in PK Study # SC-30-01

| | Lidocaine | | Tetracaine | |
|---|---|---|---|---|
| | Single patch (n = 6) | Two Patches (n = 14) | Single patch (n = 6) | Two Patches (n = 14) |
| Residual amount (mg) | 65.5 ± 1 | 64.1 ± 2* | 63.9 ± 1.01 | 62.6 ± 1.7* |
| Range (mg) | 64.1 – 66.6 | 62.4 – 67.5* | 62.7 – 65 | 59.8 – 63.6* |
| Estimated maximum absorbed dose (mg) | 3.3 ± 0.9 | 9.5 ± 3.3+ | 3 ± 0.8 | 8.7 ± 2.8+ |
| Range (mg) | 2.1 – 4.7 | 5.7 – 14.4+ | 2.3 – 4.1 | 4.9 – 13.2+ |

* For two patch application, residual amount from one patch is presented

+ Estimated maximum absorbed dose was calculated for two patches with essentially seven observations

## 2.3 Intrinsic Factors

The pharmacokinetics of active ingredients of S-Caine Patch was evaluated in subjects of different age groups in separate studies employing different treatment strategies. In general, the plasma levels of lidocaine and tetracaine were minimal to cause any systemic pharmacological or toxicological effects.

a) Elderly: In the geriatric pharmacokinetic Study # SC-31-01, none of the collected blood samples had detectable levels of lidocaine or tetracaine following single S-Caine Patch application in subjects for 20 min.

b) Pediatric patients: The exposure to active ingredients of S-Caine Patch was studied (Study # SC-30-01) in pediatric subjects stratified in subgroups of 4 months – 2 years, 3 – 6 years and 7 – 12 years. The pharmacokinetic parameters of lidocaine and tetracaine are tabulated below.

**Mean Pharmacokinetic Parameters**

| | 4 mo to 2 yr | | 3 to 6 yr | | 7 to 12 yr | |
|---|---|---|---|---|---|---|
| Parameter | 1 Patch (n = 2) | 2 Patches (n = 6) | 1 Patch (n = 7) | 2 Patches (n = 7) | 1 Patch (n = 9) | 2 Patches (n = 6) |
| Lidocaine | | | | | | |
| $C_{max}$ (ng/mL) | 14.3 ± 11.0 | 141 ± 145 | 13.4 ± 22.2 | 16.8 ± 10.8 | 4.7 ± 3.9 | 2.1 ± 2.1 |
| $T_{max}$ (hr) | 2.8 ± 3.2 | 1.4 ± 1.0 | 1.4 ± 0.8 | 1.2 ± 1.3 | 2.7 ± 2.6 | 3.3 ± 0.6 |
| $AUC_{0-24}$ (ng•hr/mL) | 128.8 | 826 ± 1,180 | 50.7 ± 38.6 | 92.1 ± 34.9 | 11.2 ± 16.0 | 49.5 ± 31.9 |
| Tetracaine | | | | | | |
| $C_{max}$ (ng/mL) | < 0.9 | 0.2 ± 0.5 | 0.7 ± 1.5 | < 0.9 | 7.2 ± 21.6 | < 0.9 |
| $T_{max}$ (hr) | na | 0.6 | 1.2 ± 0.1 | na | 2.0 | na |
| $AUC_{0-24}$ (ng•hr/mL) | 0 | 0 | 0.6 ± 1.2 | 0 | 0 | 0 |

na = not applicable due to all values < 0.9 ng/mL.
For $AUC_{0-24}$, n < n for $C_{max}$ due to missing 24-hr values.

In general, the drugs were not detected in plasma samples from several subjects, and where detected the plasma levels were very low and variable. Tetracaine levels were not detected in most of the pediatric subjects following either one or two patch applications. There was no statistical difference in exposure ($C_{max}$ or AUC) to lidocaine following single patch application in the subjects of different age groups. However, following application of two S-Caine Patches, $C_{max}$ and $AUC_{0-24}$ of lidocaine were significantly higher in the subjects of 4 months – 2 years age group compared to the other two groups. The above table does not include data from five subjects from whom the blood samples were collected from the site of S-Caine Patch application.

2.4 Extrinsic Factors (None evaluated)

2.5 General Biopharmaceutics

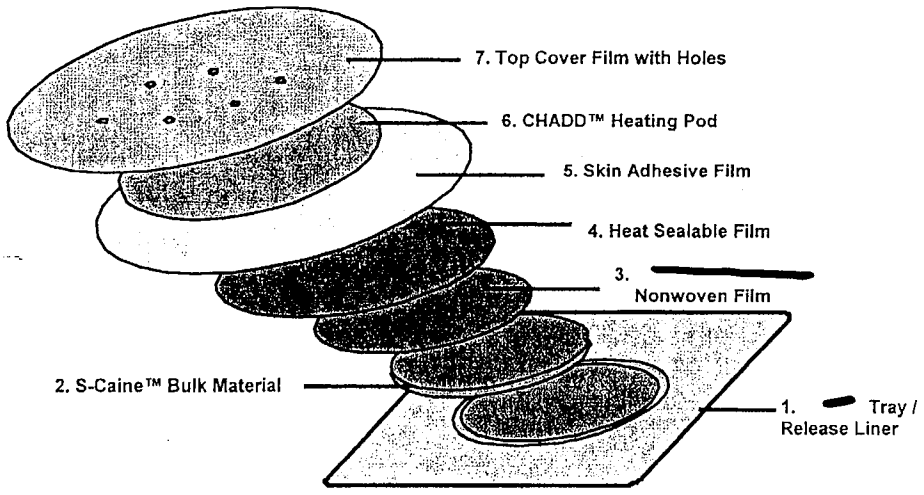
2.5.1 Formulation

As shown in the diagram below, S-Caine Patch has a thin, uniform layer of local anesthetic formulation (S-Caine™ Bulk Material) with an integrated, oxygen-activated heating component (CHADD or controlled heat-Aided drug delivery, Heating Pod). The S-Caine™ Bulk Material is an oil-in-water emulsion containing a eutectic mixture of lidocaine and tetracaine. The components of the bulk material are indicated in the table below. CHADD™ Heating Pods are filled with a chemical mixture of iron powder, activated carbon, sodium chloride, and wood flour. The heating component of the S-Caine Patch is activated by exposure to oxygen in ambient air upon removal from the air-tight pouch.

**Table S-Caine™ Bulk Material components and their function**

| Component | Function | Weight | |
|---|---|---|---|
| | | Percentage (%) | per patch (mg) |
| Lidocaine Base, USP | | | 70 |
| Tetracaine Base, USP | | | 70 |
| Polyvinyl Alcohol, USP (PVA) | | | |
| Sorbitan Monopalmitate, NF | | | |
| Water, USP | | | |
| Methylparaben, NE | | | |
| Propylparaben, NE | | | |

**Diagram of S-Caine™ Patch**



2.5.2 In Vitro Release Method

Are the proposed in vitro release method and specifications acceptable?

*The proposed method may be used for assessing lot to lot variability and may not be used to link formulation changes in lieu of in vivo data. The in vivo relevance of the conditions employed in the method is unknown. Release specifications should be tightened.*

Dissolution Results for Three Lots of S-Caine Patch

| | Lidocaine, Mean ± SD % LC (Range) | | | Tetracaine, Mean ± SD % LC (Range) | | |
|---|---|---|---|---|---|---|
| | 20 min | 40 min | 60 min | 20 min | 40 min | 60 min |
| Lot 1261 | | | | | | |
| Lot 1262 | | | | | | |
| Lot 1263 | | | | | | |

LC = Label Claim, which is 70 mg for both lidocaine and tetracaine

An *in vitro* drug release method was developed for assessing the over all consistency and variability of drug release rate from S-Caine Patches within lots and across different lots. Final formulation of S-Caine Patch was used in the drug release studies. Approximately

S-Caine Patches were manufactured in each of the lot numbers #1261, #1262, #1263. Two modifications were made to the method specified in US Pharmacopeia, 24th Edition, page # 1944, Drug Release <724> describing the dissolution method for testing drug release from transdermal delivery systems. The first modification involved use of a 65 mm watch glass in place of a glass disk in Apparatus # 5 – Paddle over Disk (Distek 2100B), in order to accommodate the size of the patch. The second modification involved increasing bath temperature from 32°C to 40°C to reflect the temperature of the patch, upon activation of the heating component. The dissolution media (1:4 acetonitrile:phosphate buffer, pH 3.0) was employed at 40°C with the paddle speed of 50 rpm, and samples were collected at 20, 40 and 60 min. A validated HPLC/UV method was used for the determination of lidocaine and tetracaine. The sponsor proposed specifications are;

Dissolution Specifications for S-Caine Patch

| Sampling Time | Lidocaine | Tetracaine |
|---|---|---|
| 20 min. | | |
| 40 min. | | |
| 60 min. | | |

LC = Label Claim, which is 70 mg for both lidocaine and tetracaine

However, the specifications should be changed as mentioned in the Recommendations section.

# 9 Page(s) Withheld

_____ Trade Secret / Confidential

✓ Draft Labeling

_____ Deliberative Process

*Withheld Track Number: Clin Pharm/Bio-* 9

## 4 Appendix

4.1 proposed labeling

4.2 Individual Study Reviews

**Study # SC-05-99 (single application PK, safety and efficacy)**

**Study Type:** Single application Safety, Efficacy and PK study.

**Protocol Title:** Randomized, double-blind, placebo-controlled, crossover study evaluating the S-Caine patch to induce local anesthesia of the skin prior to vascular access procedure in normal healthy volunteers.

**NDA:** 21-623 **Submission Date:** 4/4/2003 **Volume:**15 of 63 **Protocol:**SC-05-99

**Study Design:** Randomized, double-blind, placebo-controlled, crossover study involving single 30-minute patch application with a washout period of 1 week.

**Subject Breakdown:**

| **Demographics** | |
|---|---|
| Number | 22 healthy adult volunteers |
| Mean Age (range) | 26 (20-34) years |
| Mean Weight (range) | 117 (50-214) lbs |

**Formulation:**

| **Treatment Group** | **Dose** | **Dosage form** | **Strength** | **Lot#** |
|---|---|---|---|---|
| Placebo | - | Topical Patch | - | IP-01-31-00B<br>IP-02-08-00B<br>IP-03-24-00B |
| S-Caine Patch | 70 mg lidocaine<br>70 mg tetracaine | Topical patch | 70 mg lidocaine<br>70 mg tetracaine | IP-02-08-00A<br>IP-03-24-00A |

**Treatment Strategy:** The patch (placebo or treatment) was placed directly over the antecubital vein for 30 min. Following patch removal, the application area is evaluated for erythema, edema, and any other adverse skin reactions. This is followed by vascular access procedure at the designated patch site. Efficacy evaluations included observations such as, subject and investigator's ratings of procedural pain and adequacy of anesthesia.

**Blood sampling Scheme:** Predose, 30, 60, 120, 180, and 240 min post application.

**Analytical Methodology:**

Assay method: GC-nitrogen phosphorus detection.

Assay Sensitivity: Tetracaine- LLOQ [redacted]
Lidocaine- LLOQ

Assay Accuracy and Precision: The between-run precision (%CV) of the method for tetracaine was 2.93 - 4.23% with an accuracy range of 103 – 106%.

The between-run precision (%CV) of the method for lidocaine was 4.58 - 5.3% with an accuracy range of 100 – 107%.

The accuracy and precision of the detection method for tetracaine are acceptable.

**Results and Discussion:**

Pharmacokinetics: Plasma concentrations of lidocaine and tetracaine were below [redacted] ng/mL, respectively) the lower limit of quantitation for all the samples collected in this study. Hence, pharmacokinetic analysis was not performed.

Safety: The single application of S-Caine Patch was well tolerated in volunteers. No severe dermal reaction was observed at the application. Although not statistically significant p=0.058), erythema was observed in S-Caine treatment group compared to placebo. One adverse event, unrelated to study medication, involving a vasovagal episode was reported and that volunteer was terminated from the study.

Efficacy: Efficacy evaluations included observations such as, subject and investigator's ratings of procedural pain and adequacy of anesthesia.

*Subject rating*: Ninety percent of subjects reported adequate anesthesia following S-Caine treatment compared to 24% in placebo group. A median VAS pain score of 2 mm was reported in S-Caine treatment compared to 30 mm for placebo.

*Investigator rating*: The investigator rated 55% of subjects as having no pain with S-Caine treatment compared with 10% in placebo group. In addition, the investigator reports adequate anesthesia in 85% of subjects in S-Caine treatment group, compared to 14% subjects in placebo group.

## Study # SC-26-01 (Single and repetitive application PK study)

**Study Type:** PK study following single and repetitive application of S-Caine Patch

**Protocol Title:** A pharmacokinetic study in adult volunteers measuring plasma levels of lidocaine and tetracaine produced by single and repetitive applications of the S-Caine local anesthetic patch.

**NDA:** 21-623 **Submission Date:** 4/4/2003 **Volume:** 16 of 63 **Protocol:** SC-26-01

**Clinical Investigator(s):** [redacted]

**Study Design:** This is a randomized, two-period, crossover study performed in two groups of 12 subjects receiving either single or repeat applications of S-Caine Patch for 30 min or 60 min.

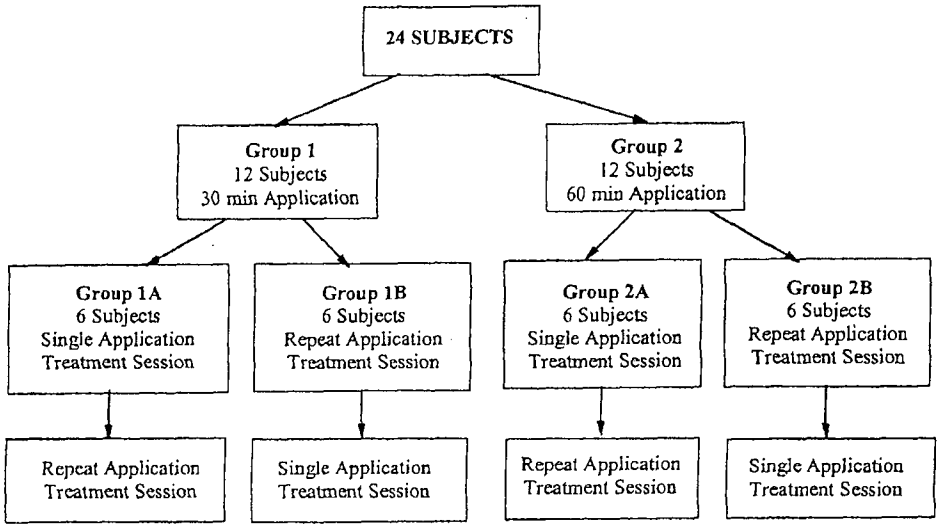
**Subject Breakdown:**

| **Demographics** | 30 min | 60 min |
|---|---|---|
| Number | 12 | 12 |
| Mean Age (Range) | 27.2 (19-47) | 34.4 (21-58) |
| Mean Weight (Range) | 183.7 (123-292) | 192.9 (120-269) |

**Formulation:**

| **Treatment Group** | **Dose** | **Dosage form** | **Strength** | **Lot#** |
|---|---|---|---|---|
| 30 min or 60 min, single or repeat S-Caine Patch application | 70 mg lidocaine 70 mg tetracaine | Topical patch | 70 mg lidocaine + 70 mg tetracaine | 1261 (Final Formulation) |

**Treatment Strategy:**




Schematic of Treatment Groups

Subjects randomized into a 30 min S-Caine Patch application group or a 60 min patch application group. Within each treatment group, subjects attended 2 treatment sessions, a treatment of single or repeat patch application followed by the converse treatment, with a week long washout period. During single application session, the S-Caine Patch was placed on subject's antecubital surface, opposite the site of venipuncture for blood sampling. During repetitive application, session, the S-Caine Patch was repeatedly placed on the antecubital surface, opposite the venipuncture site.

Repeat application treatment session scheme: In this session, two regimens were followed: A) four patches applied for 30 min each with an interval of 30 min between each application; B) three patches applied for 60 min each with an interval of 60 min between each application.

TREATMENT GROUPS 1A and 1B

| Patch On | Patch Off | Patch On | Patch Off | Patch On | Patch Off | Patch On | Patch Off |
|---|---|---|---|---|---|---|---|
| / 30 min | / 30 min | / 30 min | / 30 min | / 30 min | / 30 min | / 30 min | / 30 min |

TREATMENT GROUPS 2A and 2B

| Patch On | Patch Off | Patch On | Patch Off | Patch On | |
|---|---|---|---|---|---|
| / 60 min | / 60 min | / 60 min | / 60 min | / 60 min | / |

**Blood sampling Scheme:**

*Single application sampling*: pre-application, 0.5, 1, 1.5, 2, 4, 6, 8 and 24 hours post dose.
*Repeat 30 min application sampling*: pre-application, 0.5, 1, 1.5, 2, 2.5, 3, 3.5, 4, 6, 8, and 24 hours following application of first patch.
*Repeat 60 min application sampling*: pre-application, 0.5, 1, 1.5, 2, 2.5, 3, 3.5, 4, 4.5, 5, 5.5, 6, 8, and 24 hours following application of first patch.

Following patch removal, the amounts of each drug in the used patch and the gauze used for wiping the area were determined for calculating the maximum dosage of drugs absorbed.

**Analytical Methodology:**

Assay method: An LC/MS/MS method with following validation specifications was employed for analysis of plasma tetracaine and lidocaine concentrations in study SC-26-01:

Assay Sensitivity: Tetracaine - LLOQ [redacted] with linear range of [redacted]
Lidocaine - LLOQ with linear range of

Between-run Assay Accuracy and Precision:

*Lidocaine*

| Study # SC-26-01 Quality Control Samples n = 18 | | | | | | | |
|---|---|---|---|---|---|---|---|
| | 4 ng/mL | | 50 ng/mL | | 180 ng/mL | | |
| Accuracy (%) | 102 | | 106.6 | | 109 | | |
| Precision (CV%) | 3.8 | | 1.8 | | 1.6 | | |
| Study # SC-26-01 Standard Concentrations (ng/mL) n = 4 | | | | | | | |
| | 0.9 | 1.8 | 5 | 20 | 80 | 200 | 340 |
| Accuracy (%) | 102.8 | 95.4 | 94.6 | 96.7 | 99.2 | 102.1 | 105 |
| Precision (%) | 2.3 | 5 | 3.4 | 2 | 1.5 | 0.9 | 1.5 |

*Tetracaine*

| Study # SC-26-01 Quality Control Samples n = 18 | | | | | | | |
|---|---|---|---|---|---|---|---|
| | 2 ng/mL | | 25 ng/mL | | 90 ng/mL | | |
| Accuracy (RE%) | 100.4 | | 98.3 | | 101.3 | | |
| Precision (CV%) | 3.7 | | 2.4 | | 4.5 | | |
| Study # SC-26-01 Standard Concentrations (ng/mL) n = 4 | | | | | | | |
| | 0.9 | 1.8 | 5 | 20 | 50 | 120 | 170 |
| Accuracy(%) | 114.4 | 98.8 | 96.8 | 94.1 | 94.4 | 99.7 | 100.2 |
| Precision(%) | 0.8 | 1.9 | 2.5 | 2.4 | 1.9 | 0.8 | 1.5 |

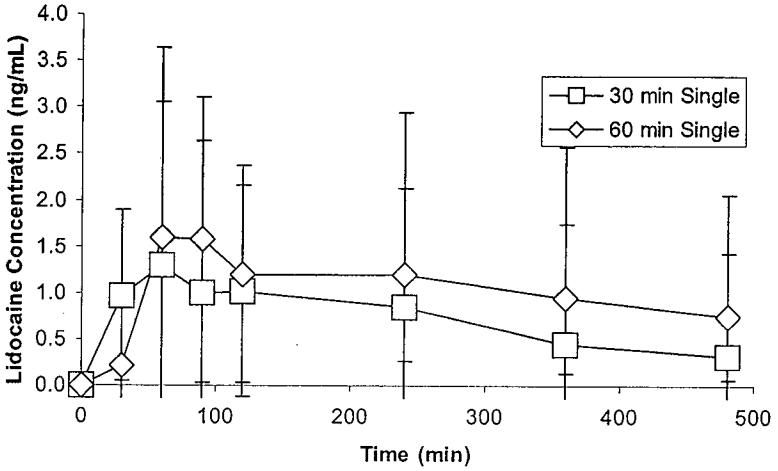
**Results and Discussion:**

Pharmacokinetics: At the end of each application session the patches were removed and analyzed for determining the remaining amount of lidocaine and tetracaine and there after the dose was calculated by subtracting the initial dose with remaining amounts. None of the samples had measurable tetracaine levels (LLOQ [redacted]) following single or multiple application of S-Caine Patch for 30 min or 60 min. Hence, pharmacokinetic data analysis was not performed. The data below pertains to lidocaine absorption following single or repeat application for 30 min or 60 min of S-caine Patch.

*Single Patch Application*: Following 30 min S-Caine Patch application, the absorption of lidocaine was very variable with only 7 out of 12 subjects showing detectable levels of lidocaine. Where detected, the maximum plasma lidocaine concentrations ranged from 1 – 4.4 ng/mL and were achieved between 0.5 – 6 hours following patch application.

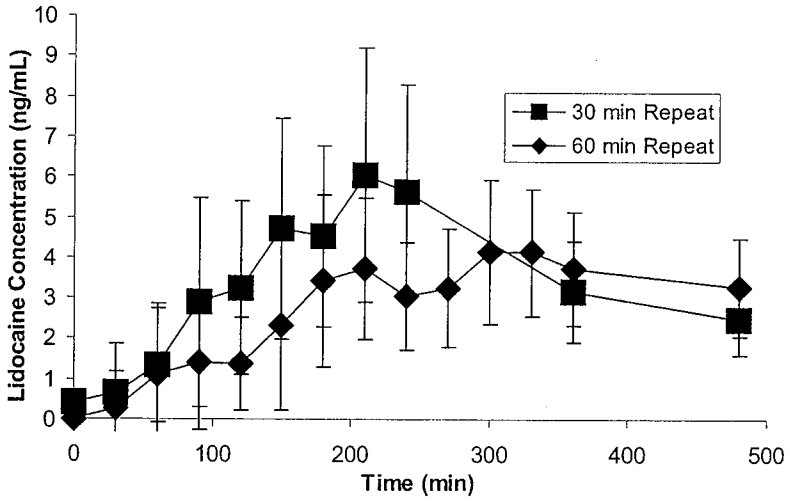
Following 60 min S-Caine Patch application, lidocaine was not detected in 2 out of 12 subjects. In the remaining 10 subjects, the maximum plasma lidocaine concentrations ranged from 1 – 6.1 ng/mL and were achieved between 1 – 8 hours after patch application.

The $C_{max}$ and $AUC_{0-24}$ derived from the plasma lidocaine profiles were not significantly different between the 30 min and 60 min single patch applications.




*Repeat Patch Application*:
In general, all the subjects receiving both the regimen's had detectable lidocaine levels and none of the subjects had detectable tetracaine levels.

Following regimen A, peak plasma concentrations of lidocaine ranging from 2.2 – 11.7 ng/mL were reached between 2.5 – 4 hours after application of first patch. In regimen B, lidocaine peak plasma concentrations of 1.6 – 7.7 ng/mL were reached in 3 – 8 hours of first patch application.




The $C_{max}$ and $AUC_{0-24}$ were not significantly different for plasma lidocaine achieved following repeat application of S-Caine Patch for 30 min and 60 min. Lidocaine $C_{max}$ and $AUC_{0-24}$ following 30 min × four patch regimen were 3.8- and 5.6-fold higher ($p<0.001$) than single 30 min S-Caine Patch application, respectively. Compared to single 60 min S-Caine application, a 2.2- and 3.4-fold increase ($p<0.001$) in $C_{max}$ and $AUC_{0-24}$, respectively, was observed following 60 min × three patch application regimen.

**Mean Pharmacokinetic Parameters for Lidocaine**

| Study # SC-26-01 | Single Application | | Repeat Application | |
|---|---|---|---|---|
| | 30 Minutes | 60 Minutes | 30 Minutes | 60 Minutes |
| $C_{max}$ (ng/mL) | 1.65 ± 1.56 | 2.04 ± 1.83 | 6.35 ± 3.01 | 4.42 ± 1.69 |
| $T_{max}$ (hr) | 1.7 ± 2.0 | 3.3 ± 2.4 | 3.6 ± 0.5 | 5.2 ± 1.2 |
| $AUC_{0-6}$ (ng•hr/mL) | 8.38 ± 9.20 | 14.37 ± 11.12 | 47.33 ± 18.68 | 49.59 ± 18.71 |
| $t_{1/2}$ (hr) | 5.9 ± 1.3 | 7.4 ± 5.0 | 4.2 ± 2.5 | 8.0 ± 3.5 |

## Study # SC-25-01 (Multiple, simultaneous patch application PK study)

**Study Type:** Multiple, simultaneous S-Caine Patch application PK study.

**Protocol Title:** A pharmacokinetic study in adult volunteers measuring the plasma levels of lidocaine and tetracaine produced by multiple, simultaneous applications of the S-Caine Local Anesthetic patch.

**NDA:** 21-623 **Submission Date:** 4/4/2003 **Volume:** 16 of 63 **Protocol:** SC-25-01

**Study Design:** This is a randomized, two-period, crossover study evaluating pharmacokinetics of lidocaine and tetracaine following multiple (2 or 4), simultaneous application of S-Caine Patch for 30 min or 60 min in 25 subjects.

**Subject Breakdown:**

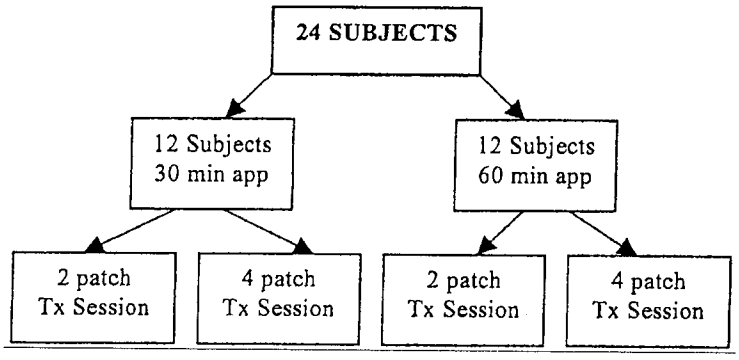
| **Demographics** | |
|---|---|
| Number | 25 |
| Mean Age (Range) | 43.5 (19 – 62) years |
| Mean Weight (Range) | 153.3 (120 – 230) lbs |

**Formulation:**

| **Treatment Group** | **Dose** | **Dosage form** | **Strength** | **Lot#** |
|---|---|---|---|---|
| 30 min or 60 min, single or repeat S-Caine Patch application | 70 mg lidocaine<br>70 mg tetracaine | Topical patch | 70 mg lidocaine<br>+<br>70 mg tetracaine | 1261<br>(Final Formulation) |

**Treatment Strategy:** Subjects were randomized into two treatment groups a) 30 min patch group, b) 60 min patch group, receiving two or four patches of S-Caine simultaneously. For the two patch treatment session, patches were simultaneously placed on subject's forearms, whereas in the four patch treatment session, patches were simultaneously placed on subject's forearms and shoulders.

Schematic of Treatment Groups



**Blood sampling Scheme:** Predose, 0.5, 1, 2, 2.5, 3, 3.5, 4, 4.5, 5, 5.5 and 6 hours after application of patches. Samples were collected employing a 3-way stopcock attached to an IV catheter inserted in an antecubital vein. The sponsor indicates that the sampling site (draining vein) might be in close proximity to the S-Caine Patch application site.

**Analytical Methodology:**

Assay method: LC/MS/MS method was employed for determining plasma lidocaine and tetracaine levels.

Assay Sensitivity: Tetracaine - LLOQ [redacted] with linear range of [redacted]
Lidocaine - LLOQ [redacted] with linear range of

Between-run Assay Accuracy and Precision:

*Lidocaine*

| Study # SC-25-01 Quality Control Samples n = 26 | | | | | | | |
|---|---|---|---|---|---|---|---|
| | 4 ng/mL | | 50 ng/mL | | 180 ng/mL | | |
| Accuracy (%) | 103.3 | | 101.9 | | 103 | | |
| Precision (CV%) | 5.5 | | 3.3 | | 3.4 | | |
| Study # SC-25-01 Standard Concentrations (ng/mL) n = 13 | | | | | | | |
| | 0.9 | 1.8 | 5 | 20 | 80 | 200 | 340 |
| Accuracy (%) | 99.9 | 101.1 | 98.8 | 99.6 | 98.7 | 99.4 | 102.7 |
| Precision (%) | 4.8 | 9.7 | 5.2 | 2.9 | 2.2 | 2.3 | 3.1 |

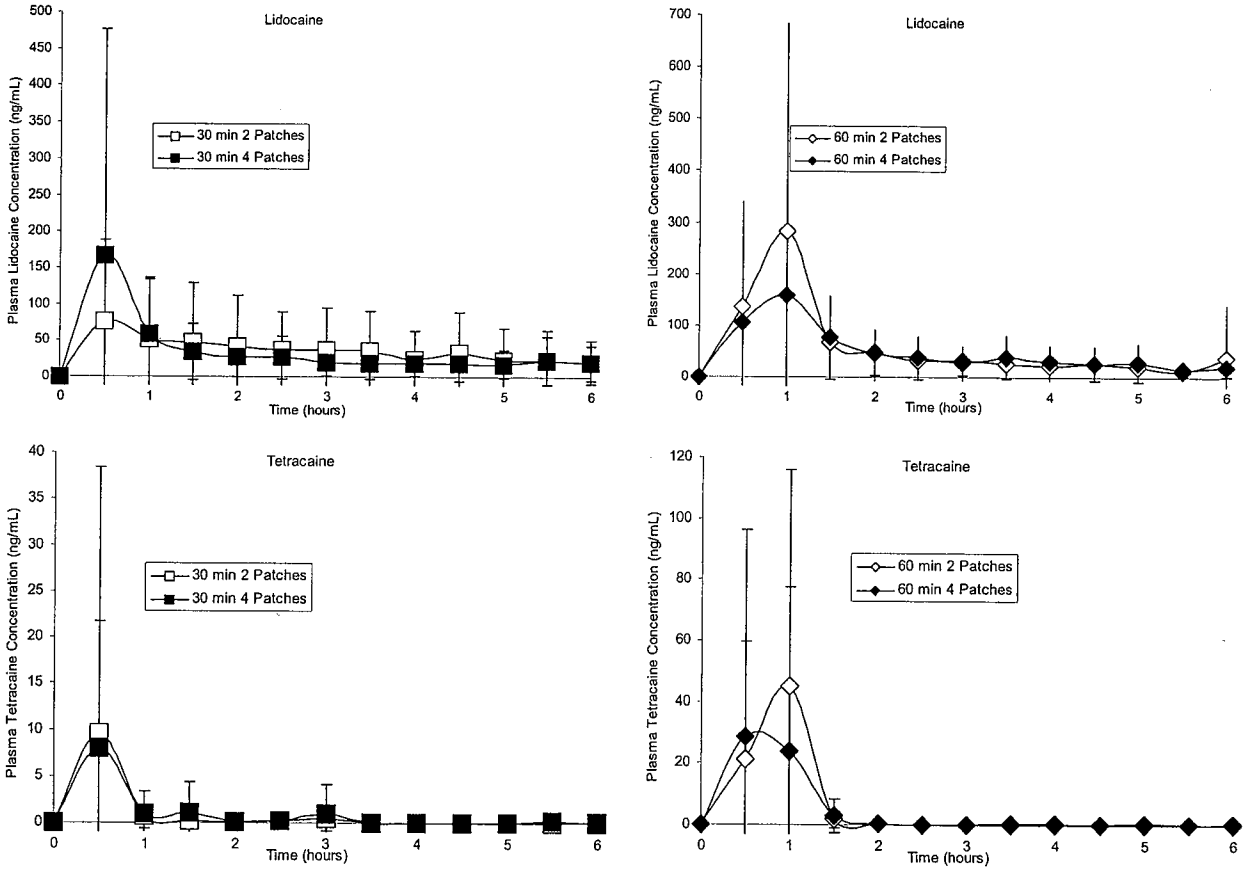
*Tetracaine*

| Study # SC-25-01 Quality Control Samples n = 26 | | | | | | | |
|---|---|---|---|---|---|---|---|
| | 2 ng/mL | | 25 ng/mL | | 90 ng/mL | | |
| Accuracy (RE%) | 101.6 | | 97.4 | | 96.7 | | |
| Precision (CV%) | 5.2 | | 3.2 | | 3.2 | | |
| Study # SC-25-01 Standard Concentrations (ng/mL) n = 13 | | | | | | | |
| | 0.9 | 1.8 | 5 | 20 | 50 | 120 | 170 |
| Accuracy (%) | 106.8 | 101.7 | 96.1 | 97.4 | 97.3 | 99.6 | 100.4 |
| Precision (%) | 2.5 | 2.7 | 2.6 | 1.2 | 1.7 | 1.4 | 1.2 |

**Results and Discussion:**

Plasma lidocaine and tetracaine levels, although detectable, were found to be very variable in different subjects and different treatments (See Table below). Statistical comparison of $C_{max}$ and $AUC_{0-6}$ of lidocaine and tetracaine across different duration and patch application treatment groups revealed they were not significantly different. Perhaps, this may be due to the large variability in the plasma levels of lidocaine and tetracaine observed among different subjects. Lidocaine levels associated with antiarrhythmic activity (>1 µg/mL) were observed in 2 subjects (Subject # 25117 at 1h, [redacted] in 60 min × two patch group and Subject # 25119 at 0.5 h, [redacted] in 30 min × four patch group). During crossover in their

respective treatments, the same subjects had plasma lidocaine levels less than 60 ng/mL. Exposure to tetracaine appears to be low. Interestingly, the average lidocaine $C_{max}$ and $AUC_{0-6}$ observed following 30 min × two patch values (from Study # SC-25-01) are ~ 57- and 26-fold higher than those observed following single 30 min patch application (from Study # SC-26-01 discussed above). Taken together, the variability in the plasma levels of lidocaine and tetracaine is possibly due to inconsistent collection of blood from draining vein or vein opposite to the site of patch application. In conclusion, the plasma lidocaine concentrations are well within limits to cause any pharmacological effects and the significance of observed tetracaine levels is either unknown or possibly minimal.



**Mean Pharmacokinetic Parameters**

| **Lidocaine** | 30-Minute Application | | 60-Minute Application | |
|---|---|---|---|---|
| | 2 Patches | 4 Patches | 2 Patches | 4 Patches |
| $C_{max}$ (ng/mL) | 94.4 ± 113.5 | 192.6 ± 303.1 | 312.0 ± 401.4 | 190.8 ± 204.0 |
| $T_{max}$ (hr) | 2.6 ± 1.9 | 1.1 ± 0.7 | 1.8 ± 1.7 | 1.5 ± 1.5 |
| $AUC_{0\text{-}6}$ (ng•hr/mL) | 221.2 ± 325.0 | 220.5 ± 211.3 | 363.6 ± 363.9 | 300.6 ± 286.5 |
| $t_{1/2}$ (hr) | 1.1 ± 0.2 | 3.9 ± 2.5 | 1.6 ± 1.8 | 2.4 ± 1.5 |
| **Tetracaine** | 30-Minute Application | | 60-Minute Application | |
| | 2 Patches | 4 Patches | 2 Patches | 4 Patches |
| $C_{max}$ (ng/mL) | 9.9 ± 28.8 | 9.1 ± 13.3 | 48.1 ± 71.6 | 32.5 ± 69.4 |
| $T_{max}$ (hr) | 1.0 ± 1.8 | 0.5 ± 0.8 | 0.7 ± 0.4 | 1.0 ± 1.6 |
| $AUC_{0\text{-}6}$ (ng•hr/mL) | 5.71 ± 15.29 | 6.27 ± 8.41 | 34.22 ± 52.58 | 28.29 ± 61.50 |

## Study # SC-31-01 (single application Geriatric PK, safety and efficacy)

**Study Type:** Single application PK, safety and efficacy study in geriatric subjects

**Protocol Title:** A randomized, double-blind, placebo-controlled, pharmacokinetic study evaluating the S-Caine Patch for induction of local anesthesia prior to vascular access procedures in geriatric subjects.

**NDA:** 21-623 **Submission Date:** 4/1/2003 **Volume:** 18 of 63 **Protocol:** SC-31-01

**Study Design:** This is a randomized, double-blind, placebo-controlled evaluating the S-Caine Patch for induction of local anesthesia prior to vascular access procedures in at least 40 geriatric subjects. Blood samples were collected from 10 subjects for pharmacokinetic evaluation.

**Subject Breakdown:**

| **Demographics** | |
|---|---|
| Number | 10 |
| Mean Age (Range) | 72 (66 – 78) years |
| Mean Weight (Range) | 178 (128 – 206) lbs |

**Formulation:**

| **Treatment Group** | **Dose** | **Dosage form** | **Strength** | **Lot#** |
|---|---|---|---|---|
| single S-Caine Patch | 70 mg lidocaine 70 mg tetracaine | Topical patch | 70 mg lidocaine + 70 mg tetracaine | 1264 (Final Formulation) |

**Treatment Strategy:** Subjects were applied a single S-Caine Patch or Placebo patch to the volar surface of left and right forearms (one patch on the left and one patch on the right). for 20 min. In one group of 10 subjects, pharmacokinetic and efficacy evaluations were performed, while, the second group (30 subjects) were employed for efficacy evaluation only. Visual Analog Pain Scale for evaluating the pain associated with a vascular access procedure was administered for efficacy evaluation.

**Blood sampling Scheme:** Blood samples were collected for determining plasma lidocaine and tetracaine levels at pre dose, 0.5, 1, 2, 3, 4, 8, and one sample between 24-30 hours post application. All samples were drawn from an area other than the volar surface of each forearm in order to avoid proximity to either of the patch application areas.

**Analytical Methodology:**

Assay method: LC/MS/MS method was employed for determining plasma lidocaine and tetracaine levels.

Assay Sensitivity: Tetracaine - LLOQ [redacted] with linear range of [redacted]
Lidocaine - LLOQ [redacted] with linear range of

Between-run Assay Accuracy and Precision:

*Lidocaine*

| Study # SC-31-01 Quality Control Samples n = 4 | | | | | | | |
|---|---|---|---|---|---|---|---|
| | 4 ng/mL | | 50 ng/mL | | 180 ng/mL | | |
| Accuracy (%) | 96.4 | | 105.4 | | 105.4 | | |
| Precision (CV%) | 12.8 | | 1.7 | | 3.4 | | |
| Study # SC-31-01 Standard Concentrations (ng/mL) n = 2 | | | | | | | |
| | 0.9 | 1.8 | 5 | 20 | 80 | 200 | 340 |
| Accuracy (%) | 101.1 | 85.8 | 101.5 | 101.4 | 98.2 | 99.6 | 100.8 |
| Precision (%) | 3.1 | 15.1 | 9.1 | 0.3 | 2.5 | 1.2 | 3.7 |

*Tetracaine*

| Study # SC-31-01 Quality Control Samples n = 4 | | | | | | | |
|---|---|---|---|---|---|---|---|
| | 2 ng/mL | | 25 ng/mL | | 90 ng/mL | | |
| Accuracy (RE%) | 112 | | 93.2 | | 100.2 | | |
| Precision (CV%) | 0.8 | | 0.7 | | 0.7 | | |
| Study # SC-31-01 Standard Concentrations (ng/mL) n = 2 | | | | | | | |
| | 0.9 | 1.8 | 5 | 20 | 50 | 120 | 170 |
| Accuracy (%) | 100 | 102.2 | 102 | 98.8 | 96.3 | 100.2 | 99.8 |
| Precision (%) | 3.1 | 0.8 | 1.9 | 0.9 | 0.4 | 0.8 | 0.9 |

**Results and Discussion:**

Single application of S-Caine Patch for 20 min in geriatric patients did not yield detectable levels of lidocaine and tetracaine in any of the plasma samples. Subjects receiving S-Caine Patch experienced slightly more erythema than Placebo and no serious adverse events were reported. While 65% subjects receiving S-Caine Patch recorded lower VAS scores (i.e., less pain), only 28% subjects indicated less pain during the vascular access procedure on the arm receiving placebo treatment.

## Study # SC-30-01 (Single application Pediatric PK study)

**Study Type:** Single application PK study

**Protocol Title:** A randomized clinical study in pediatric patients evaluating the systemic exposure to lidocaine and tetracaine produced by the S-Caine local anesthetic patch.

**NDA:** 21-623 **Submission Date:** 8/1/2003 **Volume:** 7 of 9 **Protocol:** SC-30-01

[redacted]

**Study Design:** This was an open label, single-dose pharmacokinetic study in which the subjects were stratified by age to groups with age ranges of 4 months to 2 years. 3 to 6 years, and 7 to 12 years.

**Subject Breakdown:**

| **Demographics** | Group 1 4months – 2 years | | Group 2 3 -6 years | | Group 3 7-12 years | |
|---|---|---|---|---|---|---|
| Treatment (Number of patches) | 1 | 2 | 1 | 2 | 1 | 2 |
| Total Number of Patients | 3 | 6 | 8 | 8 | 10 | 7 |
| # by Study Center | | | | | | |
| 301 | 0 | 1 | 2 | 2 | 4 | 3 |
| 302 | 1 | 2 | 2 | 2 | 2 | 2 |
| 303 | 1 | 1 | 2 | 2 | 1 | 0 |
| 304 | 1 | 2 | 2 | 2 | 3 | 2 |
| Mean Age (Range) | 0.7 (0-2) years | 0.5 (0-1) years | 4.5 (3-6) years | 4.3 (3-6) years | 9.5 (7-12) years | 11 (9-12) years |
| Mean Weight (Range) | 21.7 (18-29) lbs | 18.3 (15-21) lbs | 42.3 (30-50) lbs | 39.2 (32-64) lbs | 96.9 (49-197) lbs | 100.9 (71-125) lbs |

**Formulation:**

| **Treatment Group** | **Dose** | **Dosage form** | **Strength** | **Lot#** |
|---|---|---|---|---|
| one or two S-Caine Patch applications | 70 mg lidocaine 70 mg tetracaine per patch | Topical patch | 70 mg lidocaine + 70 mg tetracaine per patch | 1261 and 1262 (Final Formulation) |

**Treatment Strategy:** The subjects were randomized to receive either one or two S-Caine Patches to be applied for 30 min. At study site 302 and 303 hospitalized patients requiring a procedure and a 24-hr hospital stay were recruited for the study. In sites 301 and 304,

healthy subjects on an out-patient setting were recruited. S-Caine Patch was applied to thigh exclusively by clinical sites 301, 303 and 304. At Site 302, S-Caine Patches were applied to the hand, antecubital fossa or thigh.

**Blood sampling Scheme:**

| Site | Treatment: | Blood sampling scheme | Comments |
|---|---|---|---|
| 302 | In-patient setting, One or two S-Caine Patches applied to the hand, antecubital fossa, or thigh. | Group 1: 0.5, 1.5, 4, 8 and 24hr Groups 2 and 3: 0.5,1,2,4,8, and 24 hr plus a sample between 10 and 16 hr. | Blood collection site was same as the patch application site for at least four subjects. |
| 303 | In-patient setting, One or two S-Caine Patches applied to each thigh or other areas. | Group 1: 0.5, 1.5, 4, 8and 24hr Groups 2and 3: predose, 0.5, 1, 2, 4, 8, and 24 hr plus a sample between 10 and 16 hr. | PK sampling was performed while subjects were anesthetized by inhalation for a scheduled surgical procedure. |
| 301 | Out-patient setting (returning overnight), one or two S-Caine Patches applied to each thigh or other areas. | Group 1: 0.5, 1, 2, 4 and 24-30hr Groups 2 and 3: predose, 0.5, 1, 2, 4 and 24 hr. | These sites were added by sponsor after detecting problems with site's 302 & 303. Blood collection site was different from patch application site. |
| 304 | Out-patient setting (returning overnight), one or two S-Caine Patches applied to each thigh or other areas. | Group 1: 0.5, 1, 2, 4 and 24-30hr Groups 2 and 3: predose, 0.5, 1, 2, 4 and 24 hr. | |

**Analytical Methodology:**

Assay method: LC/MS/MS method was employed for determining plasma lidocaine and tetracaine levels.

Assay Sensitivity: Tetracaine - LLOQ [redacted] with linear range of [redacted]
Lidocaine - LLOQ [redacted], with linear range of [redacted]

Between-Run Assay Accuracy and Precision:

*Lidocaine*

| Study # SC-30-01 Quality Control Samples n = 4 | | | | | | | |
|---|---|---|---|---|---|---|---|
| | 4 ng/mL | | 50 ng/mL | | 180 ng/mL | | |
| Accuracy (%) | 102.5 | | 98.7 | | 99.6 | | |
| Precision (CV%) | 10.9 | | 5.7 | | 6.4 | | |
| Study # SC-30-01 Standard Concentrations (ng/mL) n = 2 | | | | | | | |
| | 0.9 | 1.8 | 5 | 20 | 80 | 200 | 340 |
| Accuracy (%) | 101 | 95.1 | 98.7 | 99.9 | 98.6 | 100.8 | 100.9 |
| Precision (%) | 3.8 | 21.9 | 7.2 | 4.3 | 2 | 2.6 | 3.1 |

*Tetracaine*

| Study # SC-30-01 Quality Control Samples n = 4 | | | | | | | |
|---|---|---|---|---|---|---|---|
| | 2 ng/mL | | 25 ng/mL | | 90 ng/mL | | |
| Accuracy (RE%) | 103.3 | | 95.3 | | 97.9 | | |
| Precision (CV%) | 8.1 | | 2.5 | | 4.5 | | |
| Study # SC-30-01 Standard Concentrations (ng/mL) n = 2 | | | | | | | |
| | 0.9 | 1.8 | 5 | 20 | 50 | 120 | 170 |
| Accuracy (%) | 106.7 | 104 | 94 | 96.6 | 98.2 | 99.7 | 99.8 |
| Precision (%) | 6.2 | 6.2 | 4.3 | 4.8 | 2.6 | 1.7 | 1.4 |

**Results and Discussion:**

The treatment and blood sampling strategy were slightly different among the different clinical sites performing this study. The observed lidocaine and tetracaine levels were very variable among subjects within different groups and in different clinical sites.

As indicated above, at the clinical site 302 applied S-Caine Patches were applied close to the antecubal fossa in several subjects and blood was drawn from the application site in four subjects. Two subjects (# 30208, 12 yrs and #30210, 11 yrs) had very high levels of lidocaine at ~1 hr following application of two S-Caine Patches. The maximum plasma concentrations for lidocaine and tetracaine of [redacted], respectively were observed in subject # 30208. Peak lidocaine plasma levels of [redacted] were observed in subject # 30210 without detectable levels of tetracaine. No drug related severe adverse events were recorded in these two subjects specifically, or any other subject in general. A rapid decline in plasma concentrations of lidocaine, to [redacted], was noted at 2 hr sample in both the subjects. It is noteworthy that in spite of blood sample collection from the site of patch application, subjects #30206 and 30209 had plasma lidocaine and tetracaine levels [redacted] ng/mL and < [redacted], respectively. It is safe to conclude that the observed high levels of drug are probably due to improper sampling approach.

At clinical sites 301 and 304 which recruited 24 subjects, tetracaine levels were below the limit of quantitation in all of them. Out of the seven subjects at site 303, five subjects had tetracaine levels lower than the LOQ, the remaining two subjects had [redacted] ng/mL, respectively at any given time. Three subjects at site 301 did not have measurable lidocaine levels and remaining subjects had lidocaine levels of [redacted]. At site 303 six out of seven had detectable plasma levels of lidocaine and one infant subject receiving two S-Caine Patches had the highest plasma concentration of 330 ng/mL. Eleven out of twelve subjects at site 304 had detectable, but [redacted] of lidocaine in plasma.

Overall, following single S-Caine Patch application the peak plasma concentrations of lidocaine and tetracaine ranged between 0-63 ng/mL and 0-65 ng/mL, respectively. Following application of two S-Caine patches peak plasma levels of lidocaine and tetracaine ranged between 0 – 331 ng/mL and 0 - 1.33 ng/mL, respectively.

**Mean Pharmacokinetic Parameters**

| | 4 mo to 2 yr | | 3 to 6 yr | | 7 to 12 yr | |
|---|---|---|---|---|---|---|
| Parameter | 1 Patch (n = 2) | 2 Patches (n = 6) | 1 Patch (n = 7) | 2 Patches (n = 7) | 1 Patch (n = 9) | 2 Patches (n = 6) |
| Lidocaine | | | | | | |
| $C_{max}$ (ng/mL) | 14.3 ± 11.0 | 141 ± 145 | 13.4 ± 22.2 | 16.8 ± 10.8 | 4.7 ± 3.9 | 2.1 ± 2.1 |
| $T_{max}$ (hr) | 2.8 ± 3.2 | 1.4 ± 1.0 | 1.4 ± 0.8 | 1.2 ± 1.3 | 2.7 ± 2.6 | 3.3 ± 0.6 |
| $AUC_{0-24}$ (ng•hr/mL) | 128.8 | 826 ± 1,180 | 50.7 ± 38.6 | 92.1 ± 34.9 | 11.2 ± 16.0 | 49.5 ± 31.9 |
| Tetracaine | | | | | | |
| $C_{max}$ (ng/mL) | < 0.9 | 0.2 ± 0.5 | 0.7 ± 1.5 | < 0.9 | 7.2 ± 21.6 | < 0.9 |
| $T_{max}$ (hr) | na | 0.6 | 1.2 ± 0.1 | na | 2.0 | na |
| $AUC_{0-24}$ (ng•hr/mL) | 0 | 0 | 0.6 ± 1.2 | 0 | 0 | 0 |

na = not applicable due to all values < 0.9 ng/mL.
For $AUC_{0-24}$, n < n for $C_{max}$ due to missing 24-hr values.

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