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APPLICATION NUMBER:

21-717

**CLINICAL PHARMACOLOGY AND
BIOPHARMACEUTICS REVIEW(S)**

**OFFICE OF CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS
REVIEW**

NDA: 21-717	Submission Date(s): 11/19/2003
Proposed Brand Name(s)	S-Caine Peel; TetraPeel
Generic Name	Lidocaine and Tetracaine topical cream
Reviewer	Srikanth C. Nallani
Team Leader	Suresh Doddapaneni
OCPB Division	Division of Pharmaceutical Evaluation II
ORM division	Division of Anesthetics, Critical Care, and Addiction Drug Products
Sponsor	ZARS, Inc. 1142 W. 2320 S. Suite A, Salt Lake City, UT 84119
Relevant IND(s)	59,801
Submission Type; Code	New Combination (4), Standard Review(S)
Formulation; Strength(s)	Topical Cream; lidocaine 7%, tetracaine 7%
Indication	Local dermal anesthesia on intact skin
Proposed Dose	Minor Dermal Procedures: _____

Major Dermal Procedures: _____
|

Table of Contents

1	Executive Summary	3
1.1	Recommendation	3
1.2	Phase IV Commitments (none).....	3
1.3	Summary of CPB Findings.....	3
2	QBR.....	5
2.1	General Attributes.....	5
2.2	General Clinical Pharmacology.....	5
2.3	Intrinsic Factors	7
2.4	Extrinsic Factors (None evaluated)	8
2.5	General Biopharmaceutics.....	8

2.5.1	Formulation.....	8
2.5.2	In vitro drug release test method.....	8
2.6	Analytical Assay Methodology	10
	Is the analytical method adequately Validated.....	10
3	Labeling.....	12
4	Appendix.....	16
4.1	Proposed labeling	16
4.2	Attachments	28
4.2.1	Drug Release Test Method Validation Report.....	28
4.2.2	OCPB filing Memo:.....	34

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1 Executive Summary

S-Caine Peel is a local anesthetic cream consisting of 7% each of lidocaine and tetracaine in an oil-in-water emulsion. It is meant to produce local dermal anesthesia on intact skin. The cream forms a pliable peel on the skin when exposed to air. Any systemic absorption of lidocaine and tetracaine is unintended. Systemic levels were determined after dermal application to assess if the levels are sufficiently high enough to cause systemic pharmacologic effects. The sponsor adequately assessed systemic exposure to active ingredients, lidocaine and tetracaine in healthy adult subjects, pediatric and geriatric subjects. Overall, systemic exposure to lidocaine and tetracaine in subjects receiving topical S-Caine Peel is minimal and systemic pharmacological effects are not likely to occur following indicated usage.

1.1 Recommendation

From a Clinical Pharmacology and Biopharmaceutics perspective, the submitted data is acceptable provided that;

- (1) mutually acceptable agreement can be reached between the Agency and Zars, Inc., regarding the text in the package insert, and
- (2) release rate specifications are tightened as follows (pending consultation with Dr. Dominic Chiapperino, CMC reviewer for this NDA):

Sampling time	Lidocaine, (LC) = 70 mg		Tetracaine, (LC) = 70 mg	
	Sponsor proposal	FDA proposal	Sponsor Proposal	FDA proposal
20 min	✓			
40 min				
60 min				✓

1.2 Phase IV Commitments (none)

1.3 Summary of CPB Findings

S-Caine Peel is a local anesthetic cream formulated as an oil-in-water emulsion containing a eutectic mixture of lidocaine and tetracaine (1:1 ratio) in the oil phase. The cream dries upon application to intact skin and forms a flexible membrane that easily peels off from the skin after use. Systemic absorption of active ingredients, lidocaine and tetracaine, is unintended for the purpose of providing local dermal anesthesia. Systemic levels were assessed for this product to determine if the absorbed levels could cause systemic pharmacologic effects. Pharmacokinetic studies SCP-30-02 and SCP-31-02 evaluated systemic levels of lidocaine and tetracaine from a safety perspective following application of the topical cream to increasing area of intact skin for upto two hours to simulate conditions when used as directed and when used inappropriately. Attempts were not made to correlate systemic exposure of these drugs with the efficacy. Tetracaine was not detected in plasma samples collected from any of the adult volunteers. Limited number of samples showed low levels of tetracaine in pediatric subjects. On the other hand, lidocaine plasma concentration profiles could be quantified in adults and

pediatrics. In general, maximum concentration (C_{max}) of lidocaine was observed at the end of the application period. The highest level seen in any adult subject was 217 ng/mL. The highest level seen in any pediatric subject was 71 ng/mL. Overall, systemic exposure to active drugs lidocaine and tetracaine is minimal when S-Caine Peel is used as directed.

An *in vitro* drug release test method, employing Franz cells and 30% ethanol as the dissolution medium, was developed for assessing the over all consistency and variability within and across different lots of S-Caine Peel. The rationale for the selection of 30% ethanol as the dissolution medium was not provided. Based on analysis of samples from four different S-Caine Peel lots, the sponsor proposed the following drug release rate specifications:

Sampling Time	Lidocaine, (LC) = 70 mg	Tetracaine, (LC) = 70 mg
20 min.	✓	
40 min.		
60 min.		✓

However, the individual and mean data from the four lots supports the following release rate specifications (pending concurrence from reviewing chemist):

Sampling time	Lidocaine, (LC) = 70 mg	Tetracaine, (LC) = 70 mg
20 min	✓	
40 min		
60 min		✓

**APPEARS THIS WAY
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2 QBR

2.1 General Attributes

Zars Inc., filed this 505(b)(2) New Drug Application for S-Caine™ Peel for the indication of local dermal anesthesia on intact skin. The product is a topical cream containing a eutectic mixture of 7% each of lidocaine and tetracaine that forms a pliable peel on the skin some time after application for easy removal. The sponsor cited EMLA cream (lidocaine 2.5% and tetracaine 2.5%) as the reference listed drug product as the basis for this submission (NDA 19-941).

The mechanism of action of lidocaine and tetracaine entails inhibition of ionic fluxes required for the initiation and conduction of impulses. Usage of S-Caine peel involves application of (a) _____

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 µg/mL is generally considered to be the threshold for the onset of systemic pharmacologic effects, while a level greater than 5 µg/mL is considered to produce toxic effects. 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 also 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 of these drugs may include bradycardia, hypotension and cardiovascular collapse leading to arrest.

The clinical pharmacology program for S-Caine Peel was designed to assess the systemic levels of lidocaine and tetracaine from a safety perspective following application of the topical cream to increasing area of intact skin for upto two hours to simulate conditions 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 of lidocaine and tetracaine seen after single application of S-Caine Peel? Are any clinically relevant side effects anticipated at the concentrations of the drug absorbed from the dosage form?

Tetracaine was not detected in any of the blood samples collected in adult PK studies. Although detected, lidocaine concentrations observed were low and may not elicit systemic pharmacological effects following recommended usage.

2.3 Intrinsic Factors

a) Elderly: In Study # SCP-30-02, detectable levels of lidocaine alone were observed following single application of S-Caine Peel to 200- and 400 cm² for 60 min in subjects of age >65 years. The maximum lidocaine concentration observed in any individual subject was 74 ng/mL following 60 min application of S-Caine peel to 400 cm² surface area. Although limited in number, none of the subjects in this age group exhibited any serious adverse events.

b) Pediatric patients: The exposure to active ingredients of S-Caine Peel following 30-minute application was studied (Study # SCP-31-02) in pediatric subjects stratified in subgroups of premature infants, 0-2 years old, 3 to 6 years old and 7 – 12 years old. Tetracaine plasma levels were measurable in eight of 33 subjects, while samples from other subjects were below the lower limit of quantitation (2.25 ng/mL). Highest individual tetracaine level, of these eight subjects, was 15 ng/mL, while two outlier tetracaine concentrations of 56 ng/mL and 93 ng/mL were discounted as samples that were possibly contaminated. All subjects had measurable lidocaine levels. The highest lidocaine concentration in prematurely born infants was 71 ng/mL. Two outliers, attributed to possible contamination showed concentrations of 83.7 and 54.8 ng/mL. Among all the individuals in all other age groups of 0-2 years old, 3 to 6 years old and 7 – 12 years old, highest lidocaine concentration of 29 ng/mL was seen. A summary of lidocaine and tetracaine pharmacokinetic parameters are shown in the table below.

Mean (range) Pharmacokinetic Parameters

Parameter	Premature	0 to 2 yr		3 to 6 yr		7 to 12 yr	
	10 cm ²	30 cm ²	30 cm ²	50 cm ²	30 cm ²	80 cm ²	
Lidocaine	n = 3	n = 6	n = 7	n = 6	n = 4 ^c	n = 6	
C _{max} (ng/mL)	42.5 (23.9-71.0)	20.1 (13.5-28.9)	7.4 (1.3-15.3)	9.3 ^a (5.0-19.8)	8.6 ^c (4.4-17.9)	10.5 (2.8-22.4)	
T _{max} (hr)	3.8 (0.7-6.3)	5.0 (1.5-8.3)	5.7 (1.0-10.4)	6.9 ^a (2.0-10.5)	3.0 ^c (1.0-8.0)	5.0 (2.0-8.0)	
AUC ₀₋₂₄ (ng•hr/mL)	626 (347-946)	302 (169-439)	86 (16-125)	141 ^a (69-281)	76 ^c (36-110)	125 (39-224)	
Tetracaine	n = 3	n = 4	n = 7	n = 6	n = 4 ^c	n = 6	
C _{max} (ng/mL)	3.8 (0-11.5)	0	0.4 (0-2.8)	1.0 (0-3.2)	3.4 ^c (0-13.7)	0.2 (0-1.2)	
T _{max} (hr)	0.7 ^b	na	0.5 ^b	0.8 (0.5-1.0)	1.0 ^{b,c}	1.0 ^b	
AUC ₀₋₂₄ (ng•hr/mL)	7.1 (0-21.3)	0	0.9 (0-6.4)	3.2 ^a (0-14.8)	7.4 ^c (0-29.7)	0.2 (0-1.4)	

2.4 Extrinsic Factors (None evaluated)

2.5 General Biopharmaceutics

2.5.1 Formulation

S-Caine Peel is a local anesthetic cream which dries upon application to intact skin and forms a flexible membrane which easily peels from the skin. The formulation is an oil-in-water emulsion containing a eutectic mixture of lidocaine and tetracaine (1:1 ratio) in the oil phase. The composition of final commercial S-Caine Peel formulation used in the pivotal clinical studies is presented in the table below.

Component	Weight Percentage (%w/w)
Lidocaine, USP	7.00
Tetracaine, USP	7.00
Dibasic Calcium Phosphate, Anhydrous, USP	
Purified Water, USP	
Polyvinyl Alcohol, USP	
Petrolatum, USP	
Sorbitan Monopalmitate, NF	
Methylparaben, NF	
Propylparaben, NF	

2.5.2 In vitro drug release test method

Are the proposed *in vitro* drug release test method and specifications acceptable?

Based on the data provided, the in vitro drug release test method appears sufficiently precise and robust with adequate linearity. However, the basis for the use of 30% ethanol in water as receptor fluid is not clear. Lidocaine and tetracaine release specifications should be tightened.

An *in vitro* drug release test method was developed for assessing the over all consistency and variability of lidocaine and tetracaine amount released from S-Caine Peel within and across different lots.

Method description: Samples were prepared by loading the S-Caine Peel into the dosage wafer of Franz-type diffusion cell. The samples were placed on the _____ and drug dissolution was assessed using the following conditions:

Membrane: _____ 25 mm, 0.45- μ m pore
Receptor Fluid: 30% ethanol in water
Temperature: 32°C
Stirring speed: 400 rpm
Collection times: 20, 40 and 60 minutes

Collection volume: 500 µL
 Waster volume: 700 µL

The samples were analyzed using a validated HPLC-UV detection method. Based on the data provided, the *in vitro* drug release test method appears sufficiently precise and robust with adequate linearity. However, the basis for use of 30% ethanol in water as receptor fluid is not clear. The *in vitro* drug release test validation report is appended to this review.

Drug release rate results from four lots of S-Caine Peel are as follows:

Lot No.	Collection Times (min)	Lidocaine (mg)			Tetracaine (mg)		
		Range	Mean	% CV	Range	Mean	% CV
PE-1806	20	0.70-1.10	0.9	22%	0.27-0.44	0.3	33%
	40	1.03-1.65	1.3	15%	0.42-0.69	0.5	20%
	60	1.38-2.18	1.8	17%	0.60-0.96	0.8	13%
PE-1808	20	0.78-1.11	0.9	11%	0.32-0.49	0.4	25%
	40	1.26-1.51	1.4	7%	0.53-0.65	0.6	0%
	60	1.77-2.15	1.9	5%	0.78-0.96	0.9	11%
PE-1829	20	0.80-1.05	0.9	11%	0.33-0.42	0.4	0%
	40	1.22-1.53	1.4	7%	0.52-0.67	0.6	17%
	60	1.70-2.19	1.9	11%	0.74-1.04	0.9	11%
PE-1944	20	0.67-0.85	0.7	9%	0.26-0.32	0.3	9%
	40	1.28-1.46	1.3	5%	0.52-0.57	0.5	3%
	60	1.81-2.06	1.9	5%	0.77-0.85	0.8	4%

The sponsor provided stability data for several S-Caine Peel lots that is under review by Dr. Dominic Chiapperino, chemistry reviewer.

Based on the above results, the sponsor proposed following drug release specifications:

Sampling Time	Lidocaine, (LC) = 70 mg	Tetracaine, (LC) = 70 mg
20 min.	✓	
40 min.		
60 min.		✓

However, the individual and mean data from the four lots supports the following release rate specifications (pending concurrence from reviewing chemist):

Sampling time	Lidocaine, (LC) = 70 mg	Tetracaine, (LC) = 70 mg
20 min	✓	
40 min		
60 min		✓

2.6 Analytical Assay Methodology

Is the analytical method adequately Validated

The sponsor adequately employed validated the LC/MS/MS method used for the determination of lidocaine and tetracaine in plasma samples generated in pharmacokinetic studies SCP-30-02 and SCP-31-02.

The analytical validation summary is as follows:

Assay method: LC/MS/MS

Assay Sensitivity: Tetracaine – Lower limit of quantitation (LLOQ) of 0.9 ng/mL with a linear range of 0.9- 226 ng/mL.

Lidocaine - LLOQ of 0.1 ng/mL with a linear range of 0.9-500 ng/mL.

Between-Run Assay Accuracy and Precision: *Lidocaine*

Study # SCP-30-02 Quality Control Samples n = 28							
	4 ng/mL		50 ng/mL		180 ng/mL		
Accuracy (%)	99.8		103.6		105.0		
Precision (CV%)	7.5		6.6		5.4		
Study # SCP-30-02 Standard Concentrations (ng/mL) n = 8							
	0.9	1.8	5	20	80	200	340
Accuracy (%)	100.2	95.1	97.1	102.4	100.2	98.7	99.6
Precision (%)	2.4	12.2	5.6	4.7	4.3	4.6	4.5
Study # SCP-31-02 Quality Control Samples n = 16							
	4 ng/mL		50 ng/mL		180 ng/mL		
Accuracy (%)	98.2		102.3		103.5		
Precision (CV%)	12.3		4.7		4.1		
Study # SCP-31-02 Standard Concentrations (ng/mL) n = 8							
	0.9	1.8	5	20	80	200	340
Accuracy (%)	99	105.5	101.8	101.1	97.9	101.1	98.9
Precision (%)	2.8	16.3	10.2	4	2.3	2.0	2.4

Between-Run Assay Accuracy and Precision: *Tetracaine*

Study # SCP-30-02 Quality Control Samples n = 30							
	2 ng/mL		25 ng/mL		90 ng/mL		
Accuracy (RE%)	109.1		94.1		100.0		
Precision (CV%)	5.3		5.0		5.4		
Study # SCP-30-02 Standard Concentrations (ng/mL) n = 14							
	0.9	1.8	5	20	50	120	170
Accuracy (%)	107.6	101.3	93.6	99.2	97.3	97.7	100.3
Precision (%)	5.3	3.1	6.5	5.0	3.3	4.5	3.0
Study # SCP-31-02 Quality Control Samples n = 16							
	2 ng/mL		25 ng/mL		90 ng/mL		
Accuracy (RE%)	103.6		102.3		103.1		

Precision (CV%)	5.8		4.7		3.9		
Study # SC-31-02 Standard Concentrations (ng/mL) n = 8							
	0.9	1.8	5	20	50	120	170
Accuracy (%)	108.0	101.9	94.6	97.8	96.5	100.5	99.8
Precision (%)	3.7	3.8	2.2	1.8	2.2	2.4	2.3

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16 Page(s) Withheld

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

X § 552(b)(4) Draft Labeling

 § 552(b)(5) Deliberative Process

6 Page(s) Withheld

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

X § 552(b)(4) Draft Labeling

 § 552(b)(5) Deliberative Process

4.2.2 OCPB filing Memo:

Office of Clinical Pharmacology and Biopharmaceutics				
New Drug Application Filing and Review Form				
General Information About the Submission				
	Information		Information	
NDA Number	21-717	Brand Name	S-Caine® Peel	
OCPB Division (I, II, III)	DPE II	Generic Name	lidocaine 7% and tetracaine 7%	
Medical Division	DACCADP	Drug Class	Topical anesthetic	
OCPB Reviewer	Srikanth C. Nallani	Indication(s)	Local dermal anesthesia on intact skin	
OCPB Team Leader	Suresh Doddapaneni	Dosage Form	tonical cream	
Date of Submission	11/17/2003	Dosing Regimen		
Estimated Due Date of OCPB Review	7/15/2004	Route of Administration	Topical	
PDUFA Due Date	9/17/2004	Sponsor	Zars, Inc. 1142 W. 2320 S. Suite A Salt Lake City, UT 84119	
Division Due Date	8/15/2004	Priority Classification	Standard	
Clin. Pharm. and Biopharm. Information				
	"X" if included at filing	Number of studies submitted	Number of studies reviewed	Critical Comments If any
STUDY TYPE				
Table of Contents present and sufficient to locate reports, tables, data, etc.	X			
Tabular Listing of All Human Studies	X			
HPK Summary	X			
Labeling	X			
Reference Bioanalytical and Analytical Methods	X			
I. Clinical Pharmacology				
Mass balance:				
Isozyme characterization:				
Blood/plasma ratio:				
Plasma protein binding:				
Pharmacokinetics (e.g., Phase I) -				
<i>Healthy Volunteers-</i>				
single dose:		3	3	
multiple dose:				
Patients-				
single dose:				
multiple dose:				
Dose proportionality -				
fasting / non-fasting single dose:				
fasting / non-fasting multiple dose:				
Drug-drug interaction studies -				
In-vivo effects on primary drug:				
In-vivo effects of primary drug:				
In-vitro:				
Subpopulation studies -				
ethnicity:				
gender:				
pediatrics:		1	1	
geriatrics:				
renal impairment:				
hepatic impairment:				
PD:				
Phase 2:				
Phase 3:				
PK/PD:				

Phase 1 and/or 2, proof of concept:				
Phase 3 clinical trial:				
Population Analyses -				
Data rich:				
Data sparse:				
II. Biopharmaceutics				
Absolute bioavailability:				
Relative bioavailability -				
solution as reference:				
alternate formulation as reference:				
Bioequivalence studies -				
traditional design; single / multi dose:				
replicate design; single / multi dose:				
Food-drug interaction studies:				
Dissolution:				
(IVIVC):				
Bio-wavier request based on BCS				
BCS class				
III. Other CPB Studies				
Genotype/phenotype studies:				
Chronopharmacokinetics				
Pediatric development plan				
Literature References				
Total Number of Studies		3	2	
Filability and QBR comments				
	"X" if yes	Comments		
Application filable ?		Reasons if the application <u>is not</u> 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? 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				

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/s/

Srikanth Nallani
8/30/04 09:51:04 AM
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