

**CENTER FOR DRUG EVALUATION AND  
RESEARCH**

*APPLICATION NUMBER:*

**21-717**

**CHEMISTRY REVIEW(S)**

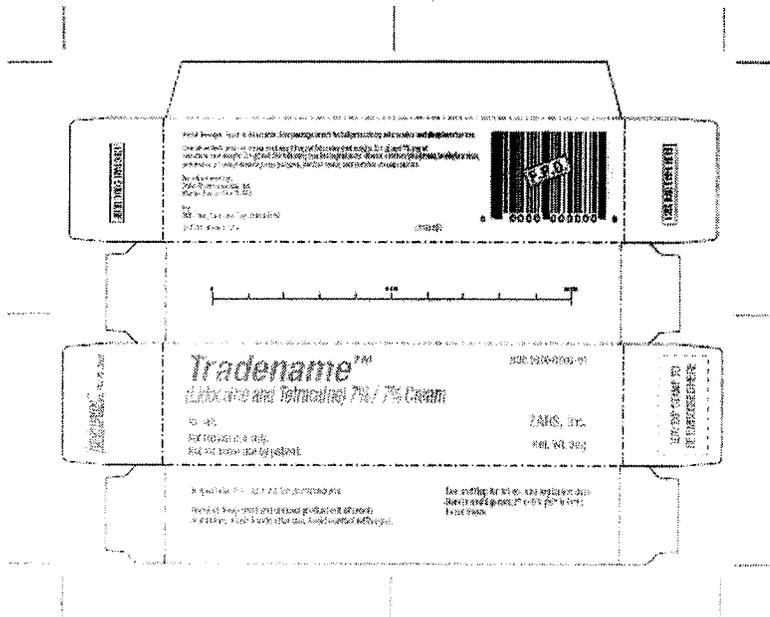
CMC Branch Chief Memo: NDA 21-717  
S-Caine (Lidocaine and tetracaine) 7%/7% Cream  
Ravi S. Harapanhalli, Ph.D.  
DPAMS, ONDQA  
June 29, 2006

This memo serves to document outstanding issues with this NDA paving the way for an approval recommendation from CMC standpoint. On June 29, 2006, The Office of Compliance provided acceptable overall recommendation for this NDA based on the file review as well as inspection of \_\_\_\_\_ facility. Based on the assessment of the stability data, an expiration dating period of 24 months may be granted when stored at 2-8°C. This should be included in the action letter along with a listing of three agreements below.

Summary:

All outstanding CMC issues were resolved during the first review cycle. In his review dated Ali Alhakim, Ph.D. indicated that acceptable recommendation was listed in the EER dated September 10, 2004 and that recommendation for a FUR (facility update report) was still pending. His review also indicated that the applicant was asked to revise the container and carton labels as per the recommendations from the ODS/DMETs. Specifically, DMETs asked the applicant to reduce the size of the blue curved line on the container and carton labels to bring down its prominence. However, after negotiations, the firm opted not to include the curved line on the labels. Additionally, the firm was asked to delete the word ' \_\_\_\_\_ ' from the "For topical \_\_\_\_\_ use only" statement and to change "gm" to "g" for the weight unit. Also, the tradename "S-Caine" was not accepted and the firm was asked to propose a new tradename within thirty days from the date of approval of the NDA. The following are the final labels submitted by the firm on June 27, 2006 and are accepted by the Agency.

**APPEARS THIS WAY  
ON ORIGINAL**



**Tradename™**  
(Lidocaine and Tetracaine) 7% / 7% Cream

NDC 0000-0000-00

**Rx only**  
For topical use only.  
Not for home use by patient.

**ZAFSS, Inc.**  
Net. Wt. 30g

To Open Tube: Push cap in and turn counterclockwise.

See crimped end for lot  
no. and expiration date.  
Store in a refrigerator,  
2° to 8°C (36° to 46°F).  
Do not freeze.

**Warning: Keep used and unused product out of reach  
of children. Wash hands after use. Avoid contact with eyes.**

**Usual Dosage:** Apply to intact skin. See package insert for full prescribing information and directions for use.

**Contains:** Each gram of cream contains 70 mg of lidocaine (net weight 2.1 g) and 70 mg of tetracaine (net weight 2.1 g) and the following inactive ingredients: dibasic calcium phosphate, methylcellulose, petrolatum, polyvinyl alcohol, propylparaben, purified water, and sorbitan monopalmitate.

Manufactured by:  
Ortho Pharmaceutical, Inc.  
Monroeville, PA 15146-0074  
For: ZAFSS, Inc., Salt Lake City, Utah 84119

UCC-RSS 14 FPO  
000000000000

© 2005 Made in USA

10151400

Outstanding agreements to be listed in the action letter:

The following agreements were made during the first review cycle and were listed in the NDA amendment dated September 10, 2004. These should be conveyed to the applicant.

We remind you of your agreement to address the following issues listed in your amendment dated Sep. 10, 2004.

1. To reevaluate the drug release specifications once data from multiple commercial batches during the first year of production.
2. To provide the Agency with data on three validation batches demonstrating the correlation between assay homogeneity of the bulk drug product before it is

packaged into — tubes with assay data on finished tubes to support the adequacy of assay testing only on the bulk drug product.

3. To provide additional specifications if the data does not demonstrate the above correlation.

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/s/

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Ravi Harapanhalli  
6/29/2006 03:28:29 PM  
CHEMIST

## MEMORANDUM

From: Ali Al-Hakim, PAL, DPAMS/ONDQA  
Through: Ravi Harapanhalli, Branch Chief, DPAMS/ONDQA  
To: NDA 21-717 S-Caine  
Date: June 23, 2006  
Applicant: ZARS, Inc.  
Subject: Resolving labeling issues for the container/closure system for the above NDA

### Background

There were two container/closure unresolved labeling issues which were described in the initial rearview for the above NDA (see approval review in DFS dated June 15, 2006). The issues were related to the revision of the established name and to adding the net weight of each of the active ingredients on the container/closure system (see review dated June 15, 2006). The following requests were submitted to the sponsor:

- Revise the established name by keeping only "*lidocaine and tetracaine*" inside the parenthesis and moving "*7%/7% cream*" outside the parenthesis as it was reported in the original submission.
- The net weight of each of the active ingredients should be included on the container/closure system.

These issues are being communicated to the sponsor during the ongoing labeling negotiation. The sponsor provided responses dated June 22, 2006 (see attachments) which were in agreement with the above recommendations regarding revising labeling for the container closure system. The revisions are satisfactory.

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X § 552(b)(4) Draft Labeling

       § 552(b)(5) Deliberative Process

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/s/  
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Ali Al-Hakim  
6/23/2006 02:19:35 PM  
CHEMIST

The sponsor submitted satisfcarory responses regarding revised labels for  
the container/closure systems (revision of establsihed name and  
addition of net weight of active ingredients) as  
per FDA requests.

Ravi Harapanhalli  
6/23/2006 02:35:20 PM  
CHEMIST



## Chemistry Assessment Section

Office of New Drug Quality Assessment  
Division of Pre-Marketing Assessment III and Manufacturing Science  
Branch V

**S-Caine™ (lidocaine and tetracaine) 7%/7% Cream****ZARS, Inc.**

Division of Anesthesia, Analgesia and Rheumatology Drug  
(Products, HFD-170)

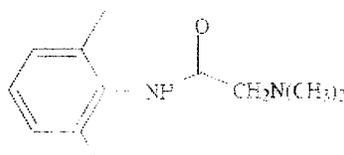
Review No. 2 Reviewer: Ali Al-Hakim Date June 15, 2006

- DRUG PRODUCT NAME/CODE/TYPE:
- Proprietary Name: S-Caine™ (lidocaine and tetracaine) 7%/7% Cream
- Non-Proprietary Name (USAN):
- Code Name/# (ONDC only): N/A
- Chem. Type: 3
- Submission Priority: S
- LEGAL BASIS FOR SUBMISSION: 505 (b) (2)
- PHARMACOL. CATEGORY: local anesthetic
- DOSAGE FORM: Topically applied cream
- STRENGTH/POTENCY: 2.1 mg lidocaine, 2.1 mg tetracaine
- ROUTE OF ADMINISTRATION: Topical
- Rx/OTC DISPENSED:  Rx  OTC
- CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA AND MOLECULAR WEIGHT:

**Tetracaine** $\text{C}_{15}\text{H}_{24}\text{N}_2\text{O}_2$ 

Mol. Wt. = 264.36

CAS#: [94-24-6]

**Lidocaine** $\text{C}_{14}\text{H}_{22}\text{N}_2\text{O}$ 

Mol. Wt. = 234.34

CAS#: [137-58-6]



## Chemistry Assessment Section

## Review Notes

This is a resubmission dated January 03, 2006, which contains responses to the not-approvable letter dated September 15, 2004. The original CMC review (chemistry review no. 1) for the above NDA was conducted by Dominic Chiapperino on September 14, 2004. The reviewer concluded, at that time, that the application is approved from the CMC stand point of view (see review in DFS). However, the NDA was not-approvable due to some non-CMC issues (protocol deviation, protocol deviation, etc).

The applicant did not submit any CMC amendment since September 15, 2004. The EER for all sites were acceptable (EER dated September 10, 2004). However, a new EER for all sites was re-submitted based on the compliance recommendation.

There were some CMC issues related to the label insert (missing molecular weight and molecular formula), container/closure labels and established name. These issues were communicated to the sponsor. The sponsor revised the label insert to include the molecular weight and molecular formula of the active ingredients. Regarding the labeling issue for the container/closure system, the applicant incorporated the following changes as per the FDA request:

- Lot number and Expiry dating on the immediate and secondary container
- Bar code information on the immediate and secondary container
- NDC number
- See attachments which contain container/closure labeling revisions described above.

However, additional labeling issues need to be addressed by the sponsor. These are related to the revision of the established name and to adding the net weight of each of the active ingredients on the container/closure system (see below).

- ✓ ○ The sponsor should revise the established name by keeping only "*lidocaine and tetracaine*" inside the parenthesis and moving "*7%/7% cream*" outside the parenthesis as it was reported in the original submission (see Chemistry Review no. 1).
- ✓ ○ The net weight of each of the active ingredients should be included on the container/closure system

These issues are being communicated to the sponsor during the ongoing labeling negotiation.



Chemistry Assessment Section

**Comment:**

DEMETS recommended that the sponsor should reduce the size of the blue curved line on the container/closure system so that it becomes less prominent.

**Conclusion**

Based on the above information, the application is recommended for approval from the CMC stand point of view.

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X § 552(b)(4) Draft Labeling

       § 552(b)(5) Deliberative Process



Chemistry Assessment Section

Ali Al-Hakim  
Pharmaceutical Assessment Lead

CC  
DAARP/HFD-170 NDA 21-717 Division Files  
DAARP/D. Chiapperino  
ONDQA/K. Stiller  
ONDQA/DPAMS/A. Al-Hakim  
ONDQA/DPAMS/R. Harapanhalli  
ONDQA/DPAMS/R. Lostritto  
06/15/06 Wordfile/NDA/21-717

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/s/

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Ali Al-Hakim  
6/15/2006 04:30:53 PM  
CHEMIST

Ravi Harapanhalli  
6/15/2006 04:39:35 PM  
CHEMIST



**NDA 21-717**

**S-Caine™ Peel**  
**(lidocaine and tetracaine) 7%/7% Cream**  
**ZARS, Inc.**

**Chemistry Reviewer: Dominic Chiapperino, Ph.D.**  
**Division of Anesthetic, Critical Care and Addiction Drug**  
**Products, HFD-170**



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# Chemistry Review Data Sheet

1. NDA 21-717
2. REVIEW # 1
3. REVIEW DATE: 14-SEP-2004
4. REVIEWER: Dominic Chiapperino, Ph.D.
5. PREVIOUS DOCUMENTS:

<u>Previous Documents</u>	<u>Document Date</u>
End of Phase 2 Meeting	06-FEB-2002
End of Phase 2 Meeting Minutes	08-MAR-2002
Pre-NDA Meeting	16-JUL-2003

6. SUBMISSION(S) BEING REVIEWED:

<u>Submission(s) Reviewed</u>	<u>Document Date</u>
Original NDA 21-717-000	14-NOV-2003
N-000-BC	15-JUN-2004
N-000-BC	10-SEP-2004
N-000-BC	13-SEP-2004

7. NAME & ADDRESS OF APPLICANT:

Name: Zars, Inc.  
Address: 350 W. 800 N Suite 320  
Salt Lake City, UT 84103  
Representative: T. Andrew Crockett  
Director, Clinical and Regulatory  
Telephone: 801-350-0200



## CHEMISTRY REVIEW



### Chemistry Review Data Sheet

8. DRUG PRODUCT NAME/CODE/TYPE:

- a) Proprietary Name: S-Caine™ Peel (lidocaine 7% and tetracaine 7% cream)
- b) Non-Proprietary Name (USAN): lidocaine 7% and tetracaine 7% cream
- c) Code Name/# (ONDC only): N/A
- d) Chem. Type/Submission Priority (ONDC only):
  - Chem. Type: 3
  - Submission Priority: S

9. LEGAL BASIS FOR SUBMISSION: 505 (b) (2)

10. PHARMACOL. CATEGORY: local anesthetic

11. DOSAGE FORM: Topically applied cream

12. STRENGTH/POTENCY: 2.1 mg lidocaine, 2.1 mg tetracaine

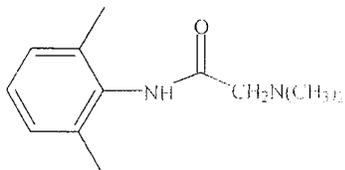
13. ROUTE OF ADMINISTRATION: Topical

14. Rx/OTC DISPENSED:  Rx  OTC

15. SPOTS (SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM):

SPOTS product – Form Completed  
 Not a SPOTS product

16. CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA,  
MOLECULAR WEIGHT:



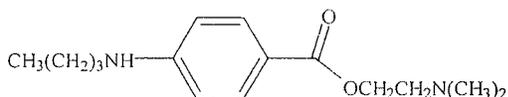
Lidocaine  
 $C_{14}H_{22}N_2O$   
Mol. Wt. = 234.34  
CAS#: [137-58-6]



# CHEMISTRY REVIEW



## Chemistry Review Data Sheet



Tetracaine  
 $C_{15}H_{24}N_2O_2$   
 Mol. Wt. = 264.36  
 CAS#: [94-24-6]

### 17. RELATED/SUPPORTING DOCUMENTS:

#### A. DMFs:

DMF #	TYPE	HOLDER	ITEM REFERENCED	CODE <sup>1</sup>	STATUS <sup>2</sup>	DATE REVIEW COMPLETED	COMMENTS
			Tetracaine drug substance	1	Adequate	16-AUG-2004	Complete response to previous deficiencies is adequate
				3	Adequate	30-AUG-2004	OGD Reviewer, A. Langowski
				4	Adequate	N/A	None
				4	Adequate	N/A	None.

#### <sup>1</sup> Action codes for DMF Table:

1 – DMF Reviewed.

Other codes indicate why the DMF was not reviewed, as follows:

2 – Type 1 DMF

3 – Reviewed previously and no revision since last review

4 – Sufficient information in application

5 – Authority to reference not granted

6 – DMF not available

7 – Other (explain under Comments)



# CHEMISTRY REVIEW



## Chemistry Review Data Sheet

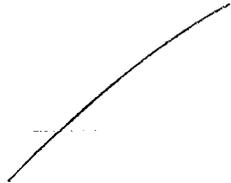
<sup>2</sup> Adequate, Inadequate, or N/A (There is enough data in the application, therefore the DMF did not need to be reviewed)

### B. Other Documents:

None.

### 18. STATUS:

#### ONDC:

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
Biometrics	Stability data manipulations only	23-AUG-2004	Tom Permutt, Ph.D.
EES	Acceptable (Satisfactory cGMP compliance)	10-SEP-2004	John M. Dietrick
Pharm/Tox		18-AUG-2004	Suzanne Thornton-Jones, Ph.D. Dan Mellon, Ph.D.
Biopharm	Change in the in vitro dissolution specification	18-AUG-2004	Srikanth Nallani, Ph.D.
LNC	None (Not needed)		
Methods Validation	To be requested for novel test methods (e.g. drug release by Franz diffusion cell method)	Pending	Dominic Chiapperino, Ph.D.
ODS/DMETS	None		
EA	None (Categorical exclusion)		
Microbiology	None		



## Executive Summary Section

**The Chemistry Review for A/NDA 21-717****The Executive Summary****I. Recommendations****A. Recommendation and Conclusion on Approvability**

The application for S-Caine™ Peel is **recommended for approval**, with regards to the CMC portion of the submission. The agreements made between the Applicant and the Agency, listed on page 66, should be included as a reminder in the action letter.

This drug product addresses the need for a fast-acting anesthetic for minor and major dermal procedures. S-Caine™ Peel has a fairly straightforward manufacturing procedure in which an oil and an aqueous phase are combined and emulsified. The cream is very viscous and can be applied with a spatula, a gloved finger, or a tongue depressor (or something similar). Quality Controls on the two APIs, Lidocaine USP and Tetracaine USP, and all excipients, which are all compendial, are acceptable at this time. There are no degradant compounds of concern, and the product mixture is quite stable when stored at the recommended refrigerated temperature. Drug product specifications address assay values of the APIs, and drug-related impurities of both. The identity of the APIs in the product mixture is established by two independent tests, as well as the assay retention times in HPLC. All issues of concern have been addressed within the review cycle by a series of comments to and responses from the Applicant, Zars. The easy usage of this drug product has been facilitated by recommendations for the product labeling, which have been adopted by the Applicant. The Dosage and Administration section of the package insert now advises both a method of application, and a numeric table that helps express the recommended dosage in terms of the length of the extruded cream from the tube's opening. A calibration scale relating to extruded length has been incorporated into the packaging carton's label.

**B. Recommendation on Phase 4 (Post-Marketing) Commitments, Agreements, and/or Risk Management Steps, if Approvable**

Drug product specifications may be fortified pending the availability of release testing data of three validation batches. The need for content uniformity testing will be based on whether an adequate correlation can be determined regarding the homogeneity of the bulk drug product and assay values on finished drug product units in 30 g tubes. The in vitro release testing acceptance criteria will also be finalized on the basis of a larger data pool. There is some question as to whether the testing method is inherently subject to significant variability. The semi-solid product is quite viscous and difficult to handle in accurate amounts for testing. It may be that as proficiency and experience with the procedure is acquired the variability in the data will diminish. The current specification is adequate, but the Applicant is concerned that we required it to be too strict, and good batches may be rejected. New data will be examined to come to a final agreement. The

**Executive Summary Section**

following agreements were reached through a teleconference on September 10, 2004 and amendment dated September 10, 2004 addressed these issues. The applicant should be reminded of these agreements in the action letter.

\*\*List the three agreements here.

**II. Summary of Chemistry Assessments****A. Description of the Drug Product(s) and Drug Substance(s)**

The drug product is a local anesthetic, so far referred to as S-Caine™ Peel. The product is a topically applied cream that contains 2.1 g each of both lidocaine and tetracaine, representing 7% by weight of each in the 30 g contents of each unit. Lidocaine is a compendial drug substance, which contains an aryl amide structure (a derivative of acetanilide) that is substituted on the acyl methyl group with a diethylamino group. Tetracaine is also a compendial drug substance, which contains an ester moiety covalently linked in the para position of an aniline derivative (an aryl amine structure). The two solid drug substances when mixed form a eutectic 1:1 mixture that is an oil at room temperature. This oil is used in the manufacture of a drug product that is an oil-in-water emulsified cream for topical use. The cream once applied on the dermal surface hardens over time so that at the end of the recommended application time, when the active ingredient has been absorbed through the skin, the applied cream can be easily peeled away as a latex-like solid layer. The anesthetic is designed to be a rapidly anesthetizing product, working in approximately 20-60 minutes.

**B. Description of How the Drug Product is Intended to be Used**

S-Caine™ Peel is intended as a local anesthetic to be used for minor procedures requiring pain relief at the site of application. It should not be used on areas having open wounds, and is intended only for intact areas of skin. It is considered appropriate for use as a non-invasive method of anesthetizing the skin prior to procedures such as hair removal, tattoo removal, and laser resurfacings.

**C. Basis for Approvability or Not-Approval Recommendation**

There are several comments that have been sent to Zars within the review cycle to attempt to resolve all outstanding CMC issues and all the outstanding CMC issues have been resolved either through required data or through post-approval agreements.. These will be discussed below. All facilities for which inspections were required have been found acceptable.

These are the following comments sent to Zars to address deficiencies in the application in an attempt of a first-cycle approval on CMC issues.



Executive Summary Section

Sent 9/3/2004:

1. Provide a detailed sampling plan for finished drug product units from the packaging line, including the number of units to be tested and details regarding periodic sampling.
2. Amend the Release Rate specification's acceptance criteria to have tightened limits such as those recommended below.

Lidocaine:

20 min

40 min

60 min



Tetracaine:

20 min

40 min

60 min



Sent 9/8/2004

3. Until proven otherwise, it will be assumed [based on the Fick's law of diffusion] that absorption of lidocaine and tetracaine from the topical application of S-Caine peel depends on the amount applied as well as the surface area of application. It is important that both these parameters are controlled to within the practical level of variation such that the thickness of application is also controlled, and that adequate instructions for use are provided in order for practitioners to do so. Therefore, provide the following additional data.
  - a) Density of the cream.
  - b) Amount and thickness of the cream to be applied in volume (cc) for the 0.5 g and 1.0 g applications described in the proposed Dosage and Administration section.
  - c) Provide available data to support the proposed 0.5 and 1 g applications given that all phase 3 final formulation clinical trials appear to have instructed investigators to apply to 1 mm thickness.
  - d) Detailed description of the applicator device utilized in some trials and rationale for not marketing the applicator with the S-Caine peel product.
  - e) Diameter (cm) of the orifice of the container closure system (tube).
  - f) Based on the amount in volume of the cream to be applied and the diameter of the tube opening, calculate the length of the cream (cm) to be squeezed out (assuming cylindrical volume) to provide a 1 mm



## Executive Summary Section

- thickness application over per a given surface area. Tabulate these results for various surface areas up to 400 cm<sup>2</sup>.**
- g) Provide a calibration scale (in cm) covering 0-5 cm or 0-10 cm on the tube or on the carton or separately as appropriate.**
  - h) Provide additional description in the labeling indicating the amount of the cream to be squeezed out (in cm.) and the surface area of application (e.g. 10 X 10 cm) in order to achieve a 1-mm application thickness and how the calibration scale on the tube may be used for this purpose.**

9/10/04 Teleconference

- 4. Amend Drug Product specification for total drug related impurities in Lidocaine to —% to reflect sum of specified and total unknown impurities allowed.**

The responses received on these issues will be discussed in detail at the end of this review document. In summary, Zars has adequately addressed all of these comments, and an approval action is appropriate from the CMC perspective.

**III. Administrative****A. Reviewer's Signature**

Dominic Chiapperino, Ph.D. (electronic signature in DFS)

**B. Endorsement Block**

ChemistName/Date: Same date as draft review  
Dominic Chiapperino, Ph.D., 28-AUG-2004

ChemistryTeamLeaderName/Date  
Ravi Harapanhalli, Ph.D., 02-SEP-2004

ProjectManagerName/Date  
Pratihba Rana, M.S., 02-SEP-2004

**C. CC Block**

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/s/

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CHEMIST

Ravi Harapanhalli  
9/14/04 11:09:11 PM  
CHEMIST  
AP with reminder