CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

21-623

CHEMISTRY REVIEW(S)

NDA 21-623

Synera™
(lidocaine 70 mg and tetracaine 70 mg) topical patch

Zars, Inc.

Jila H. Boal, Ph. D.

Division of Anesthetics, Critical Care, and Addiction Drug Products (DACCADP)
HFD-170

Table of Contents

Chemistry Review Data Sheet

1. NDA 21-623

2. REVIEW #: 2

3. REVIEW DATE: March 10, 2005
   Revised June 21, 2005

4. REVIEWER: Jila H. Boal, Ph. D.

5. PREVIOUS DOCUMENTS:

Previous Documents	Document Date
End of Phase 2 Meeting	09-MAY-2000
End of Phase 2 Meeting Minutes	07-JUN-2000
Pre-NDA Meeting	05-DEC-2002
Original NDA 000	31-MAR- 2003
N-000-SU	01-AUG- 2003
N-000-SL	09-SEP- 2003
N-000 BC	30-DEC-2003

6. SUBMISSION(S) BEING REVIEWED:

Submission(s) Reviewed	Document Date
CMC Conference Call	02-April-2004
Post Action Meeting	17-Jun-2004
N-000 AZ	17-Dec-2004
N-000 BL	03-FEB-2005
N-000BC(submission of raw data for dissolution)	22-FEB-2005
N-000C (Proposal for a new tradename)	17-March-2005
N-000BC (Three supplemental registration batches according to SUPAC-SS)	April 5, 2005
CMC Conference Call	06-June-2005
N000-BC	07-June-2005
CMC Conference call	16-June-2005
E-mail (the label for patch, pouch and carton which included the approved trade name Synera)	17-June-2005
N000-BC (CMC Commitment: Drug Release Test)	17-June-2005

E-mail (Final label for primary and secondary packaging configuration and Package Insert)	June 21, 2005
N-000-BC (Final Label)	June 21, 2005

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:	801-350-0202

8. DRUG PRODUCT NAME/CODE/TYPE:

a) Proprietary Name: Synera™
b) Non-Proprietary Name (USAN): (lidocaine 70 mg and tetracaine 70 mg) topical patch
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) Application

10. PHARMACOL. CATEGORY: Anesthetic

11. DOSAGE FORM: Patch

12. STRENGTH/POTENCY: 70-mg/70-mg

13. ROUTE OF ADMINISTRATION: Topical

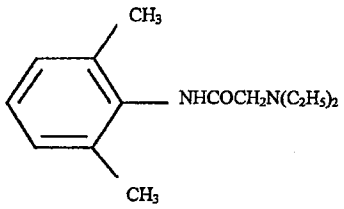
14. Rx/OTC DISPENSED: _X__Rx ___OTC

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

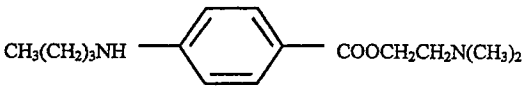
_____ Not a Spots product

__X__ Not a SPOTS product

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



Lidocaine: Acetamide, 2-(diethylamino)-*N*-(2,6-dimethylphenyl), or 2-(Diethylamino)-2',6'-acetoxylidide.
Molecular formula: $C_{14}H_{22}N_2O$
Formula weight: 234.34
CAS #: [137-58-6]



Tetracaine: Benzoic acid, 4-(butylamino)-, 2-(dimethylamino) ethyl ester, or
2-(Dimethylamino) ethyl p (butylamino) benzoate.
Molecular formula: $C_{15}H_{24}N_2O_2$
Formula weight: 264.36
CAS #: [94-24-6]

17. RELATED/SUPPORTING DOCUMENTS:

A. DMFs:

DMF #	TYPE	HOLDER	ITEM REFERENCED	CODE	STATUS	DATE REVIEW COMPLETED	COMMENTS
[redacted]	2	[redacted]	[redacted]	1	Adequate	April 4, 2005	Reviewed by J. H. Boal
[redacted]	2	[redacted]	[redacted]	1	Adequate	April 4, 2005	Reviewed by J. H. Boal
[redacted]	3	[redacted]	[redacted]	1	Adequate	February 2, 2004	Reviewed by R. S. Harapanhalli
[redacted]	3	[redacted]	[redacted]	1	Adequate	May 4, 2005	Reviewed by J. H. Boal
[redacted]	3	[redacted]	[redacted]	1	Adequate	February 3, 2004	Reviewed by R. S. Harapanhalli,

[1] 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")

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

B. Other Documents:

DOCUMENT	APPLICATION NUMBER	DESCRIPTION
IND	IND 58, 823	Originally submitted on July 26, 1999.
EOP2 Meeting	IND 58,823	May 9, 2000
Pre-NDA Meeting	IND 58,823	December 5, 2002
CMC Review # 1	NDA 21-623	January 23, 2004
CMC Conference Call with FDA	NDA 21-623	March 16, 2004
FDA & Zars Post Action Meeting for the S-Caine Patch	NDA 21-623	May 03, 2004

18. STATUS:

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
Biometrics	Grantable expiration dating of 18 months	10/01/03	Tom Permutt, Ph.D.
	Based on the evidence presented from study SC-55-04, the heating component contributed to the efficacy of the S-Caine Patch.	4/26/05	Joan Buenconsejo
	Biometrics consult was not needed for the evaluation of stability data submitted in the complete response		

	submission of December 17, 2004 and the amendments thereafter.		
EES	The facilities were resubmitted to OC for re-evaluation on 2/1-4/05. A new overall recommendation as acceptable has been entered on June-17-2005.	06/9/05	Office of Compliance/ Ferguson, Shirnette D
Pharm/Tox	Tetracaine degradants are human metabolites and qualify for the proposed high limits. No pharmTox consult was needed for the evaluation of the resubmission.	01/05/04	Dan Mellon, Ph.D.
Biopharm	[redacted] However, it is recommended that the applicant study the patch drug		Srikanth C. Nallani, Ph.D. June 7, 2005
Methods Validation	Not required for submission to FDA labs		
DMETS	The trade name Synera was approved.	June 10, 2005	ODS/DMETS Felicia Duffy
EA	Exclusion from EA (< 1 PPB)	01/16/04	Florian W. Zielinski, Ph.D.
Microbiology	"Acceptable" for antimicrobial effectiveness of the parabens	01/23/04	Bryan Riley. (Does not need to be sterile)

Executive Summary Section

The Chemistry Review for NDA 21-623

The Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

From CMC standpoint, the NDA is recommended for approval. The deficiencies identified in the AE letter dated February 04, 2004 have been adequately addressed.

Overall recommendation from the Office of Compliance is acceptable dated June-17-2005.

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

None

II. Summary of Chemistry Assessments

A. Description of the Drug Product(s) and Drug Substance(s)

Synera™ (lidocaine 70 mg and tetracaine 70 mg) topical patch consists of a thin, uniform layer of a new local anesthetic formulation (S-Caine™ Bulk Material) with an integrated, oxygen-activated heating element (CHADD™ [Controlled Heat-Aided Drug Delivery] Heating Pod) that enhances the delivery of the local anesthetics to the skin. The patch is an oval, multi-layer system. Synera™ patch is an oil-in-water emulsion formulation. The delivery of the drugs is enhanced through the application of the CHADD™ heating element. The patch application should numb the human skin within 20-30 minutes for a variety of painful medical procedures.

The various layers in the order of addition in the final patch manufacturing process are summarized below:
These are,

1. [redacted]
2.
3.
4.
5.
6.
7.

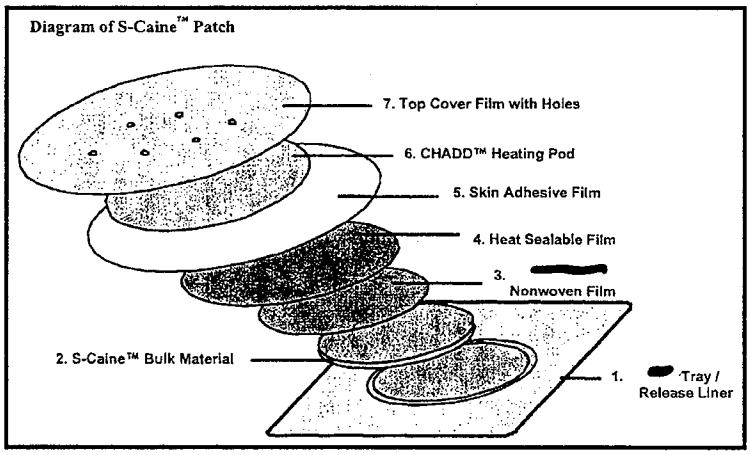
Components of each layer are listed below:
Components of the S-Caine Bulk Material are: Lidocaine base, USP, Tetracaine Base,

Executive Summary Section

USP, [redacted] Polyvinyl Alcohol, (PVA) USP, [redacted] Sorbitan Monopalmitate NF [redacted] and [redacted] water, USP. Methylparaben and propylparaben [redacted]

CHADD Heating Pod Components are: Iron powder [redacted] Activated Carbon [redacted] Sodium Chloride [redacted] [redacted] Wood flour [redacted] . Filter paper [redacted]

A diagram showing the construction and various components of the Synera™ Patch is provided in the following figure:



The Function of each layer is summarized:

- [redacted]

Lidocaine is an amide-type local anesthetic agent and tetracaine is an ester-type local anesthetic agent. Both drugs are thought to stabilize neuronal membranes by initiating the ionic fluxes required for the initiation and conduction of impulses, thereby effecting local anesthesia.

Lidocaine manufacturer is [redacted]

CHEMISTRY REVIEW

Executive Summary Section

This DMF is up to date and has been reviewed by this reviewer to be adequate to support the use of lidocaine in this NDA. The office of compliance recommendation for inspection of the facility is acceptable, dated February 15, 2005.

Note that the NDA contained an acceptance criteria for the process impurity [redacted] at NMT [redacted] whereas [redacted] is controlled at NMT [redacted] or NMT [redacted] in the [redacted] This discrepancy was resolved during the teleconference of June 6, 2005 that was held between Zars and the agency. Zars has submitted an amendment in response to the June 6, 2005 teleconference. The amendment contains a revised specification table for lidocaine drug substance that includes an acceptance criteria of NMT [redacted]

Tetracaine manufacturer is [redacted] This DMF was also reviewed by this reviewer and was determined to be adequate for use in the NDA. Facility inspection is acceptable dated February 15, 2005.

S-Caine Bulk Material (SBM) is manufactured and stability tested by [redacted] The inspection of this facility was completed and an overall acceptable recommendation was entered on June 17, 2005.

Drug Product Synera Patch is manufactured by Tapemark Company. CFN # 2182681.
The facility had inspection with acceptable recommendation on April 27, 2005.

The application received an overall withhold recommendation when it was originally entered into EES in 2003. The facilities were resubmitted to OC for re-evaluation 2/1/4/05. The last facility to be inspected was [redacted] and this facility was inspected on June 16, 2005 (inspection report on these facilities in reference to this NDA are in EES).
A new overall acceptable recommendation has been entered on June 17, 2005 for the NDA.

S-Caine Bulk Material (SBM) commercial scale is [redacted] The expiration date for the S-Caine Bulk Material is 90 days and there is [redacted] The viscosity test with the acceptance criteria of [redacted] for SBM was lacking in the original NDA submission. The applicant has agreed to include the viscosity test at release and on stability in the specifications for the SBM. This issue was resolved during the teleconference that was held on June 6, 2005.

The commercial scale of Synera patch is [redacted] patches and the expiration dating of the Synera patch is [redacted] which begins from the date the S-Caine Bulk material is manufactured [redacted] lag time was accounted for the holding of SBM). The expiration dating takes into account the [redacted] lag time in the start of the stability testing as well as the [redacted] of hold time for the SBM (more detail on the stability data evaluation / discussion can be found in the review notes sections).

The packaging is a continuation of the manufacturing process in that as soon as the final Synera patch is manufactured and cut out of the web of material, it is immediately packaged in a heat – sealed barrier film pouch [redacted] . As the sealed packaging material moves down

the machine, it is cut at appropriate intervals into individual 4.00" X 5.75" white air-tight, heat-sealed, barrier-film, child-resistant pouches (as defined by the U.S. Consumer Product Safety Commission regulations), each containing one Synera™ patch. The packaging film is printed with the labeling information prior to the manufacture and packaging of the Synera™ patch. The final label has been revised on June 21, 2005.

The CMC deficiencies are addressed by Zars and are being evaluated in this review. A comprehensive evaluation is given by this reviewer to each of Zars responses in the body of the review.

Most of the CMC issues identified during the first cycle review were related to lack of or inadequate explanation of the specifications for some of the materials used in the manufacture of the various components of the patch and these were adequately addressed by the applicant.

The primary issue that was originally identified during the first cycle of review was mostly related to the product's integrated heating element. Basically, inadequate justification was given for the patch temperature test. The specification of mean temperature over time interval from 20-120 minutes being within [redacted] was not justified. The response to this deficiency now clearly addressed this issue. The time course of the exothermic reaction, the temperature range and the maximum temperature achieved, are well characterized now, and do support claims or dosing instructions on the proposed product label, and match how the product is likely to be used in clinical practice. Specifically, the label indicates that the patch warms from [redacted] and the acceptance criteria indicates that the patch warms to [redacted] The important factor is the delta T i.e., the rise in temperature from the initial temperature value to the targeted value once the CHADD heating Pod component is exposed to oxygen of the air by opening the seal of the packaged patch and applying the patch on the patient skin. This value is consistent and is approximately [redacted] whether the measurement is performed in in-vitro study on the Plexiglas or measured in in-vivo study on human skin.

The absolute amounts of lidocaine and tetracaine present in each Synera™ Patch are fixed, as are patch dimensions. Drug dose delivered is dependent for the most part, on the duration of patch contact with the skin. Patch and drug temperature, as well as skin temperature, could also be expected to effect transdermal drug delivery.

Although the in-vitro drug release acceptance criteria is a quality control measure for the drug product and is not indicative of the clinical drug release amount which is approximately [redacted] of the amount on the patch. The specifications for the Synera™ Patch dissolution/release have been the matter of discussion since the original submission in 2003. The division had asked the applicant to explain the use of an [redacted] and had also asked the applicant to tighten the release specifications. Review of submitted data in the resubmission revealed that while an [redacted] was included for the drug (lidocaine & tetracaine) release, the variability was high without it.
Due to limited amount of drug release data both on stability and at initial time of T=0, plus the

observation of slight tailing of drug release from patches on stability, it was decided to accept Zars proposed three point drug release acceptance criteria on interim bases and to revisit the drug release specifications for the Synera™ patch once sufficient data becomes available upon commercial manufacture of patches. The acceptance of drug release on interim bases was agreed upon during the teleconference of June 6, 2005. The applicant has submitted an amendment on June 7, 2005 agreeing that the proposed drug release acceptance criteria is accepted on interim bases. It was decided to request from Zars to perform additional experiment to justify the [redacted] concentration in the dissolution media of 0.1M potassium phosphate buffer pH = 3. In a brief Teleconference held on June 16, 2005 the applicant was informed of this request. Zars has agreed to submit dissolution / drug release data using [redacted] media in the future (see the amendment titled "CMC Commitment: Drug Release Test" dated June 17, 2005 that was received from Zars). The drug release data will be submitted under a post-marketing commitment or a supplement depending on future agreement between the division and Zars.

B. Description of How the Drug Product is intended to be used:

Synera™ patch when applied to intact skin is claimed to provide local dermal [redacted] by the release of lidocaine and tetracaine from the patch into the epidermis and dermal layers of the skin and the accumulation of the drugs in the vicinity of dermal pain receptors and nerve endings. To provide sufficient [redacted] or minor dermal procedures such as [redacted] the Synera™ patch should be applied for 20-30 minutes. For major dermal procedures such as excision and shave biopsy [redacted] the patch should be applied for at least 30 minutes. There is a Patient Application Instructions that demonstrates the method of application of the patch. See also the Drug Package Insert which contains instructions on dosage and administration.

C. Basis for Approvability or Not-Approval Recommendation

In response to the AE letter dated February 4, 2004, Zars provided adequate information. However, the following issues required further clarification. On June 6, 2005 a teleconference was held between Zars, this reviewer and Dr. Duffy the Division Director to resolve the following four issues. **(1)** The specification for the level of [redacted] required modification to NMT [redacted] in order to correlate with the relevant specification in [redacted]. Zars provided a revised specification table for lidocaine drug substance which includes the modification of NMT [redacted] **(2)** [redacted]. **(3)** Zars and the agency agreed that the proposed three point drug release specifications for the Synera™ patch be accepted on an interim bases and to be revisited at later time once more patches are manufactured. **(4)** The specification for viscosity of the SBM is to be carried out both at time of the release of the Bulk as well as during the stability testing of the SBM.

In addition, on June 16, 2005 a Teleconference was held between Dr. Eric Duffy, Dr. Ravi Harapanhalli, Dr. Jila H. Boal, Dr. Suresh Doddapaneni, Dr. Srikanth Nallani, and Ms. Lisa Malandro of the FDA and representatives from Zars to further clarify the drug release specification. The applicant has agreed to further justify the use of [redacted] in drug release media by submitting dissolution / drug release data using [redacted] in the media and submitting the data in a supplement or post marketing commitment depending on the Division's decision. Zars committed to the request through the amendment of June 17, 2005 titled "CMC Commitment: Drug Release Test".

The updated DMFs for lidocaine and tetracaine are now adequate to support the application. [redacted] is cross referenced. The DMF was reviewed by this reviewer and is adequate to support the approval of the NDA.

III. Administrative

A. Reviewer's Signature

B. Endorsement Block

Jila H. Boal, P.h.D./
R. S. Harapanhalli, Ph.D./
Eric Duffy, Ph.D./
Allison Meyer/

C. CC Block

cc: Orig. NDA 21-623
HFD-170/NDA Division File
HFD-170/chemist/BoalJ
HFD-170/MO/JosefbergH
HFD-170/Pharmacologist/Dan Mellon
HFD-170/CSO/MeyerA
R/D Init by: Eric P. Duffy.

filename: c:/data/mydocs/NDA/21-623 review2.doc

120 Page(s) Withheld

✓ Trade Secret / Confidential

_____ Draft Labeling

_____ Deliberative Process

Withheld Track Number: Chemistry- 3

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

/s/

Jila Boal
6/21/05 05:32:18 PM
CHEMIST

Eric Duffy
6/21/05 05:43:29 PM
CHEMIST

NDA 21-623

S-Caine™ Patch
(Lidocaine and Tetracaine Topical patch) 70 mg/70 mg

Zars, Inc.

Ravi S. Harapanhalli, Ph.D.
Division of Anesthetics, Critical Care, and Addiction Drug Products (DACCADP)
HFD-170

Table of Contents

Chemistry Review Data Sheet

1. NDA 21-623

2. REVIEW #: 1

3. REVIEW DATE: January 23, 2004

4. REVIEWER: Ravi S. Harapanhalli, Ph.D.

5. PREVIOUS DOCUMENTS:

Previous Documents	Document Date
End of Phase 2 Meeting	09-MAY-2000
End of Phase 2 Meeting Minutes	07-JUN-2000
Pre-NDA Meeting	05-DEC-2002
Original NDA 000	31-MAR- 2003
N-000-SU	01-AUG- 2003
N-000-SL	09-SEP- 2003
N-000 BC	30-DEC-2003

6. SUBMISSION(S) BEING REVIEWED:

Submission(s) Reviewed	Document Date
Original NDA 000	31-MAR- 2003
N-000-SU	01-AUG- 2003
N-000-SL	09-SEP- 2003
N-000 BC	30-DEC-2003

7. NAME & ADDRESS OF APPLICANT:

Name: Zars, Inc.

CHEMISTRY REVIEW

Chemistry Review Data Sheet

Address:	350 W 800 N Suite 320 Salt Lake City, UT 84103
Representative:	T. Andrew Crockett Director, Clinical and Regulatory
Telephone:	801-350-0202

8. DRUG PRODUCT NAME/CODE/TYPE:

a) Proprietary Name: S-Caine™ Patch
b) Non-Proprietary Name (USAN): (Lidocaine and tetracaine topical patch) 70-mg/70-mg
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) Application:
Listed Drug (LD): Emla® Disc (lidocaine and prilocaine) 2.5%/2.5%
Dosage form: Topical disc
NDA holder: AstraZeneca
NDA or ANDA number should be given for the LD.

10. PHARMACOL. CATEGORY: Anesthetic

11. DOSAGE FORM: Patch

12. STRENGTH/POTENCY: 70-mg/70-mg

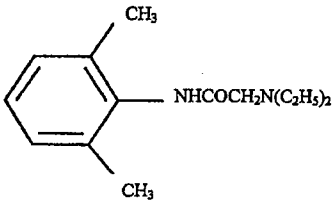
13. ROUTE OF ADMINISTRATION: Topical

14. Rx/OTC DISPENSED: _x__Rx ___OTC

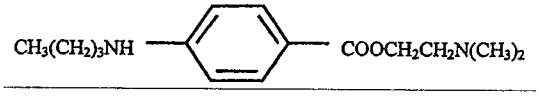
15. SPOTS (SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM):
__Not a Spots product

___x___Not a SPOTS product

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



Lidocaine: Acetamide, 2-(diethylamino)-*N*-(2,6-dimethylphenyl)-2-(Diethylamino)-2',6'-acetoxylidide.
Molecular formula: $C_{14}H_{22}N_2O$
Formula weight: 234.34
CAS #: [137-58-6]



Benzoic acid, 4-(butylamino)-, 2-(dimethylamino) ethyl ester.
2-(Dimethylamino)ethyl p (butylamino)benzoate.
Molecular formula: $C_{15}H_{24}N_2O_2$
Formula weight: 264.36
CAS #: [94-24-6]

17. RELATED/SUPPORTING DOCUMENTS:

A. DMFs:

DMF #	TYPE	HOLDER	ITEM REFERENCED	CODE[1]	STATUS[2]	DATE REVIEW COMPLETED	COMMENTS
[redacted]	2	[redacted]	[redacted]	1	Adequate	A. Langowski, 08/30/03	No amendments subsequent to this review.
	2			1	Inadequate	R. S. Harapanhalli 02/03/04	
	3			1	Adequate	R. S. Harapanhalli, 02/02/04	None
	3			1	Adequate	R. S. Harapanhalli, 02/03/04	None

B. Other Documents:

DOCUMENT	APPLICATION NUMBER	DESCRIPTION
IND	IND 58, 823	Originally submitted on July 26, 1999.
EOP2 Meeting	IND 58,823	May 9, 2000
Pre-NDA Meeting	IND 58,823	December 5, 2002

18. STATUS:

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
Biometrics	Grantable expiration dating of 18 months	10/01/03	Tom Permutt, Ph.D.
EES	"Withhold"	01/30/04	Office of Compliance/Randy Woods
Pharm/Tox	Tetracaiene degradants are human metabolites and qualify for the proposed high limits	01/05/04	Dan Mellon, Ph.D.
Biopharm	Tighter drug release specifications	01/13/04	Shreekant Nallani, Ph.D.
LNC	Revised established name	12/11/03	Dan Boring, Ph.D.
Methods Validation	In preparation		DPA Laboratories, St. Louis, MO
OPDRA	Acceptable tradename "S-Caine™ Patch"		ODS/DMETS
EA	Exclusion from EA (< 1 PPB)	01/16/04	Florian W. Zielinski, Ph.D.
Microbiology	"Acceptable" for antimicrobial effectiveness of the parabens	01/23/04	Bryan Riley. (Does not need to be sterile)

CHEMISTRY REVIEW

Executive Summary Section

The Chemistry Review for NDA 21-623

The Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

The NDA is "approvable" pending satisfactory resolution of CMC deficiencies and comments listed at the end of the review.

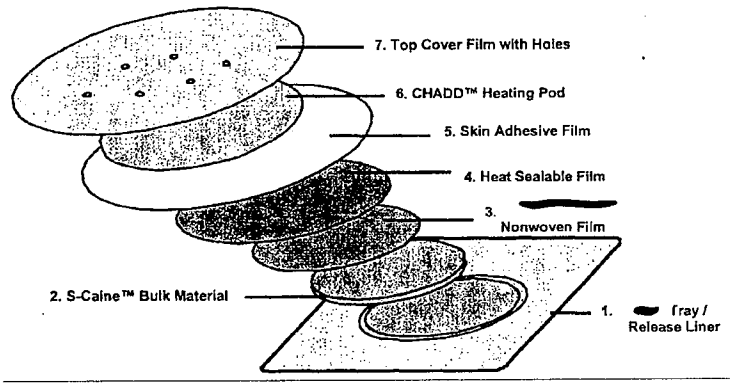
B. Recommendation on Phase 4 (Post-Marketing) Commitments, Agreements, and/or Risk Management Steps, if Approvable

None

II. Summary of Chemistry Assessments

A. Description of the Drug Product(s) and Drug Substance(s)

Diagram of S-Caine™ Patch



The S-Caine™ patch (lidocaine and tetracaine topical patch)70-mg/70-mg, is claimed to use controlled heat to enhance the delivery of local [redacted] through skin and to effectively numb human skin within 20-30 minutes for a variety of painful medical procedures. The patch consists of a thin, uniform layer of a local anesthetic formulation, an oil-in-water emulsion consisting of a eutectic mixture of lidocaine and tetracaine with an integrated, oxygen-activated heating element. The following are the components of the multi-layer patch (from innermost skin contact to the outermost).

[redacted]

Executive Summary Section

Lidocaine is an amide-type local anesthetic agent and tetracaine is an ester-type local anesthetic agent. Both drugs are thought to stabilize neuronal membranes by initiating the ionic fluxes required for the initiation and conduction of impulses, thereby effecting local anesthesia.

B. Description of How the Drug Product is intended to be used

S-Caine patch when applied to intact skin is claimed to provide local dermal [redacted] by the release of lidocaine and tetracaine from the patch into the epidermis and dermal layers of the skin and the accumulation of the drugs in the vicinity of dermal pain receptors and nerve endings. To provide sufficient [redacted] for minor dermal procedures such as [redacted] the S-Caine patch should be applied for 20-30 minutes. For major dermal procedures such as excision and shave biopsy [redacted] the patch should be applied for at least 30 minutes.

C. Basis for Approvability or Not-Approval Recommendation

The CMC section of the NDA lacks adequacy and clarity in all areas of drug product quality, namely the drug substance specifications, the controls over the raw materials and the components of the S-Caine patch, the manufacturing controls, the drug product specifications and their relevance to the intended use and the claims of the benefits of the CHADD heating pod.

[redacted] the manufacturer of the S-Caine bulk material have not provided adequate specifications for the acceptance of lidocaine and tetracaine from the respective DMF holders. Clarity is lacking regarding the acceptance testing of the batches of the drug substances and how the [redacted] is determined. The drug product is a multi-laminate patch with several components and the specifications for the acceptance of the individual raw materials and the components are not adequately described. The quality of each of the components needs to be adequately controlled and built into the system to assure the performance of the finished patch. Specifically, the physical test attributes for the [redacted], certificate of analysis for the CHADD pods from the vendor, [redacted], and the information on the extent of protection provided by the packaging of the CHADD pods are not provided in the NDA. The specifications for S-Caine bulk material lack physical test attributes such as viscosity and syneresis without which the physical integrity of the bulk material as an oil-in-water emulsion cannot be guaranteed. Similarly, the hold time of the bulk material and its impact on the computation of the expiration dating of the drug product have not been discussed sufficiently.

The manufacturing process needs to be described adequately to assure batch-to-batch consistency and comparability to the patches used in the pivotal clinical studies that formed the basis for establishing efficacy. The master batch production records need to be revised to include additional in-process controls, namely the [redacted] h. The

in-process test frequency needs to be increased to hourly testing for a better control over the in-process content uniformity of the fill line.

The drug product specifications need to be revised from the point of safety and performance. Being a rat carcinogen, [redacted] should be tightened to as low levels as achievable. The acceptance criteria for the temperature testing of the patch need to be revised to reflect the clinical utility of the heating pod and the intended use of the patch. In its current form, the acceptance criterion for the temperature testing does not relate to the intended use of the patch and therefore the true clinical utility of the heating pod is questionable. The in vitro drug release rate declined significantly over time and its impact on the in vivo drug release and hence the efficacy of the aged patches is not addressed in the NDA. The acceptance criteria for drug release need to be significantly tightened to better reflect the patch quality from batch-to-batch and through the intended expiration dating of 18 months. The pharmaceutical development section did not clearly justify why revised formulation was selected and what is the utility of using a [redacted] in the patch. Data to demonstrate the safety of the CHADD heating pods containing activated iron powder in the actual use scenario was not provided. Such data should have included the thermodynamic calculations showing extent of heat generation and data demonstrating that accidental mishandling of the patch did not result in the leakage of iron powder and that an oxygen rich environment such as the oxygen breathing circuit did not cause any overheating of the patch.

The manufacturing facilities for lidocaine and S-Caine Patch are out of cGMP compliance. [redacted] the manufacturer of lidocaine, and Tapemark, the manufacturer of S-Caine patch are on "withhold" status for cGMP compliance. The Office of Compliance made an overall recommendation of "withhold" on January 30, 2004 for this NDA. Satisfactory inspections are needed prior to the approval of the NDA.

DMF 4065 was deemed inadequate to support the CMC information for tetracaine drug substance and a correspondence has been sent to the DMF holder.

In view of the above critical CMC issues, the NDA cannot be approved at this time. The NDA is "approvable" pending satisfactory resolution of the deficiencies and comments listed at the end of the review.

III. Administrative

A. Reviewer's Signature

B. Endorsement Block

R. S. Harapanhalli, Ph.D./January 26, 2004
Eric Duffy, Ph.D./January 26, 2004
Lisa Malandros/January 26, 2003

C. CC Block

cc: Orig. NDA 21-623

CHEMISTRY REVIEW

Executive Summary Section

HFD-170/NDA Division File
HFD-170/chemist/Harapanhalli
HFD-170/MO/ArtSimmone
HFD-170/Pharmacologist/Dan Mellon
HFD-170/CSO/LMalandros
R/D Init by: Eric Duffy, Ph.D.

filename: c:/data/mydocs2/NDAs/21623review1.doc

123 Page(s) Withheld

✓ Trade Secret / Confidential

_____ Draft Labeling

_____ Deliberative Process

4

Withheld Track Number: Chemistry-[redacted]

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

/s/

Ravi Harapanhalli
2/4/04 04:47:59 PM
CHEMIST
AE

Eric Duffy
2/4/04 04:53:30 PM
CHEMIST