

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

21-504

CHEMISTRY REVIEW(S)



NDA 21-504

LidoSite™ -Lidocaine/Epinephrine
Iontophoretic Drug Delivery System

Vyteris, Inc.
13-01 Pollitt Drive
Fair Lawn, NJ 07410

CMC Review # 2
Ravi S. Harapanhalli, Ph.D.
Division of Anesthetics, Critical Care, And
Addiction Drug Products
(DACCADP/HFD-170)



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1. NDA 21-504
2. REVIEW # 2
3. REVIEW DATE: April 28, 2004
4. REVIEWER: Ravi S. Harapanhalli, Ph.D.

5. PREVIOUS DOCUMENTS:

<u>Previous Documents</u>	<u>Document Date</u>
Teleconference with Vyteris	12-MAR-2003
CMC IR Letter	02-MAY-2003

<u>Submission(s) Reviewed</u>	<u>Document Date</u>
Original submission	25-SEP-2002
BC	18-DEC-2002
N000 (MR)	26-FEB-2003
BC	10-MAR-2003
N000 (c)	19-MAR-2003
N000 BC	29-APR-2003
N000 (c)	01-MAY-2003
N000 BC	27-MAY-2003
N000 BL	05-JUN-2003
N000 (c)	16-JUN-2003

6. SUBMISSION(S) BEING REVIEWED:

<u>Submission(s) not reviewed</u>	<u>Document Date</u>
N000 (BC): Additional responses to IR letter and additional data to support site transfer.	14-JUL-2003
NDA Resubmission AZ	08-NOV-2003
E-Submission of Stability Data BZ	18-MAR-2004



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N000(NC): Revised Package insert and Labels

28-APR-2004

7. NAME & ADDRESS OF APPLICANT:

Name: Vyteris, Inc.

Address: 13-01 Pollitt Drive
Fair Lawn, NJ 07410

Representative: George M. Baskinger, Manager, Quality
Management and Regulatory Compliance

Telephone: 201-703-2420

8. DRUG PRODUCT NAME/CODE/TYPE:

- a) Proprietary Name: LidoSite™
- b) Non-Proprietary Name (USAN): Lidocaine and Epinephrine Topical Iontophoretic System
- c) Code Name/# (ONDC only): Northstar System
- d) Chem. Type/Submission Priority (ONDC only):
 - Chem. Type: 3
 - Submission Priority: S

9. LEGAL BASIS FOR SUBMISSION: 505 (b) (2). Listed drug: NDA 6-488 for xylocaine; epinephrine Injection (0.5%; 0.005 mg/ml to 2%; 0.01 mg/ml) from Astrazeneca. NDA 21-504 is additionally supported by the literature in Section 5 of the NDA and information submitted in NDA amendment 003.

10. PHARMACOL. CATEGORY: Local dermal anesthesia

11. DOSAGE FORM: Patch for Iontophoretic delivery

12. STRENGTH/POTENCY: - mg Lidocaine HCl and - mg epinephrine bitartrate (- epinephrine).



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13. ROUTE OF ADMINISTRATION: Topical Iontophoresis

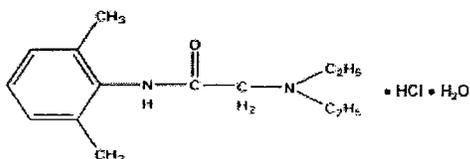
14. Rx/OTC DISPENSED: X Rx OTC

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

SPOTS product – Form Completed

X Not a SPOTS product

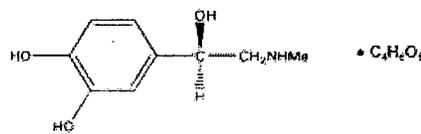
16. CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOLECULAR WEIGHT:



Lidocaine Hydrochloride Monohydrate

Molecular formula: $C_{13}H_{22}N_2O \cdot HCl \cdot H_2O$

Molecular weight: 288.81



(-)-Epinephrine (+) Bitartrate

Molecular formula: $C_9H_{13}NO_2 \cdot C_4H_6O_6$

Molecular weight: 333.29

Acetamide, 2-(diethylamino)-N-(2,6-dimethylphenyl)-
2-(Diethylamino)-2',6'-acetoxylidide
[137-58-6].

1,2-Benzenediol, 4-[1-hydroxy-2-(methylamino)ethyl]-, (R)-
(-)-3,4-Dihydroxy- α -[(methylamino)methyl]benzyl
alcohol
[51-43-4].

17. RELATED/SUPPORTING DOCUMENTS:

A. DMFs:

DMF #	TYPE	HOLDER	ITEM REFERENCED	CODE ¹	STATUS ²	DATE REVIEW COMPLETED	COMMENTS
/	II	/	/	1	Adequate	April 30, 2004	T
/	II	/	/	1	Adequate	April 29, 2004	/
/	II	/	/	1	Adequate	April 30, 2004	Final



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Chemistry Review Data Sheet

III		1	Adequate	July 1, 2003
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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
LidoSite™ Controller	510 K 031551 This 510 K was cleared for marketing on August 20, 2003. (Attachment 4)	Iontophoresis device that provides controlled battery-operated electric supply of 17.7 milliampere-minutes in ten minutes patch application. Kevin Lee, MD is CDRH reviewer

18. STATUS:

ONDC:

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
Biometrics	Agreed with the proposed shelf life of 24 months	April 14, 2004	Tom Permutt, Ph.D.
EES	Firm not ready (WH)	March 19, 2003	Firm indicated that they are not ready for inspection till the end of August 2003.
Pharm/Tox*	Adequate	June 25, 2003	Tim McGovern, Ph.D.
Biopharm	N/A	N/A	N/A
LNC	Recommended established name for the drug product as	July 10, 2003	Dan Boring, Ph.D.



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Methods Validation	To be submitted to the labs upon revision of specifications		Firm should be asked to submit method validation package with revised specifications.
ODS	Tradename "LidoSite" accepted by ODS	February 25, 2004	Scott Dallas
EA	N/A (Exclusion claimed)		
Microbiology	Approval	July 3, 2003	Bryan Riley, Ph.D.
CDRH (electrode subassembly and the electrical specifications of the patch)	Acceptable	March 09, 2004	Kevin Lee found the section on Patch electrical subassembly and electrochemical testing of the patch "acceptable". No deficiencies were identified by the reviewer.

*No issues during the second review cycle. In the first cycle Pharm/Tox consult with Dr. Tim McGovern: The reviewer discussed in detail the components and composition of the patch, including the non-pharmacopoeal components of anti-microbial preservative and any potential effect of these on the skin and on systemic toxicity. No issues with safety were identified by the Pharm-Tox.

**APPEARS THIS WAY
ON ORIGINAL**

Chemistry Review Data Sheet

The Chemistry Review for NDA 21-504

The Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

From CMC standpoint, the NDA is recommended for approval. All the deficiencies identified in the AE letter dated July 25, 2003 have been adequately addressed in the resubmission. The Office of Compliance in their recommendations dated March 12, 2004 deemed all manufacturing and testing facilities to be acceptable from the standpoint of cGMP compliance.

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

Applicant should develop a reliable method for the in vitro drug release that is indicative of the iontophoretic transfer of the drugs lidocaine HCl and epinephrine. The acceptance criteria for the physical quality attributes, the cathode and anode probe tack, the apparent compressive modulus and the probe tack of the adhesive, and the electrode conductivities are considered tentative in nature and should be revised following accrual of manufacturing data on commercial batches. As part of the commitment for the manufacturing site transfer of the electrode solutions from [redacted] to Fair Lawn, New Jersey, Vyteris should provide additional supporting stability data to the NDA.

II. Summary of Chemistry Assessments

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

LisoSite™ Lidocaine and epinephrine topical iontophoretic system consists of the LisoSite topical patch containing the two drugs (Lidocaine HCl 100 mg, and Epinephrine 1 mg per patch) and LidoSite controller that provides uniform electric current of 17.7 milliamperes-min in ten minutes of patch application, during which time approximately 600-µg of lidocaine (0.6% of the label claim) is delivered to the dermis of the skin. A local anesthetic of the amide type, Lidocaine is indicated for dermal anesthesia in the hospital setting. Epinephrine, a sympathomimetic (adrenergic) agent and a vasoconstrictor, is thought to decrease the rate of removal of lidocaine from the site of administration and thus improve its analgesia. The patch is non-sterile and contains anti-microbial preservative [redacted] 2-phenoxyethanol, methyl-, ethyl-, propyl-, butyl-, and isobutyl-p-hydroxybenzoate), is for single use, and consists of a 5 cm² circular anode (positive electrode) containing the drug and a cathode

Chemistry Review Data Sheet

(negative electrode) containing the buffered solution for electrical circuitry (return reservoir). Besides the drugs, the drug reservoir contains sodium chloride, glycerin, citric acid as a buffer and chelator, edetate disodium as a chelator, and sodium metabisulfite as an antioxidant, in a non-sterile hydrogel. The elongated return reservoir contains glycerin, sodium chloride, and monobasic sodium phosphate as an acidulating agent

Positively charged lidocaine and epinephrine are delivered simultaneously from the anode reservoir through a process known as iontophoresis to achieve local dermal anesthesia. Iontophoresis is based on the principle that a soluble salt or drug can be transported across the skin barrier as a part of an electric current induced in the skin. The patch is individually packaged in a chevron-shaped foil-foil pouch. The marketing package configurations are

The two drug substances, namely lidocaine hydrochloride and epinephrine bitartrate are provided by the

There are no differences between the pre-clinical and clinical drug product, and hence comparability studies were not necessary.

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

Even though the product is provided as along with a controller, each patch is packaged primarily in a peelable chevron-shaped foil-foil patch and is meant for single use only. Typically, one to two patches may be used in a day. The drug is designed to effect dermal anesthesia and is used in a hospital setting. It is for single time use and is not meant for chronic administration. There is only one strength (100-mg lidocaine HCl and epinephrine) and only about 600- μ g (0.6%) of the drug is delivered to the dermis. There are no unusual steps or procedures for dose preparation. The detailed procedure for the use of the controller and the patch is provided in the package insert. The proposed expiration dating is 24-months and the recommended storage is 20-25°C (room temperature), and this is supported by the real time stability data of 24 months.



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C. Basis for Approvability or Not-Approval Recommendation***Device Review of Lidosite™ Contoller:***

The 510K (K031551) for the Lidosite™ contoller was reviewed in the CDRH by Kevin Lee, M.D. and was cleared for marketing on August 20, 2003. A copy of the CDRH letter confirming determination of substantial equivalence to the predicate device is attached at the end of the review.

Chemistry, Manufacturing and Controls of Lidosite™ patch:

In response to the AE letter dated July 25, 2003, Vyteris provided adequate responses. The updated DMF's for lidocaine HCl and epinephrine bitartrate are now adequate to support the application. The drug substance specifications, the in-process controls, and the controls over the starting materials were revised adequately. Adequate specifications for assay and impurities for the active components in the drug product have now been established.

A sampling plan for the in-process tests, representative of the patch manufacturing process, has been provided. Requested information on the manufacture of the electrode subassembly has also been provided. The data indicate that Vyteris exerts adequate manufacturing controls over the process and that the intended commercial process is the same as the one followed in the manufacture of the Phase III study materials and the primary stability batches.

The data on the chemical stability of the lidocaine and epinephrine in the drug product during the 10-minute patient use have been provided. The data indicates that the electrical current during iontophoresis does not contribute to the product degradation.

Lidocaine HCL solubility is 680-mg/ml and that of epinephrine is 333-mg/ml in water at 25°C. By USP definition, both drugs are freely soluble in water and are formulated at _____ along with other excipients. Considering the solubility threshold for lidocaine and the presence of nearly _____ glycerine in the formulation, the potential for _____ lower temperatures are now addressed. The data clearly indicates that lidocaine HCl does not _____

— Even though the temperature cycling studies between -20°C and ambient temperatures showed no effect on the product quality for the attributes tested, the issue is exacerbated by the lack of a reliable in vitro release method that could measure the patch performance following temperature cycling. The wet chemistry methods alone are insufficient to assess the patch performance following the temperature insult. Therefore, Vyteris was asked to include a warning statement in the labeling to indicate that the patch should not be cooled to freezing temperatures. Vyteris revised their labeling accordingly.

Drug product stability trends of concern included declining trace conductance and increasing peripheral probe tack. There were several instances of skin damage associated

**Chemistry Review Data Sheet**

with patch removal that may have been related to increased probe tack over storage. Instances of patient withdrawal due to high impedance may be related to declining trace conductance. The sponsor submitted 24-months of stability data and proposed 24-months expiration dating period. Based on the statistical analysis of all the stability-indicating attributes in the revised stability data and in consultation with the reviewing statistician, the reviewer determined that an expiration dating period of 24 months can be granted for this product.

Preapproval inspections were carried out and the overall recommendation of acceptance was obtained from the Office of Compliance on March 12, 2004. The summary report is provided in Attachment 3 (pages 69-71 of the review).

The revised patch, pouch, and carton labels are provided following extensive revisions recommended by the Agency in the AE letter and through teleconferences. The revised labels are copied at the end of the review and are deemed acceptable.

Vyteris has addressed all the CMC approvability issues identified in the AE letter. However, there are some pending commitments and some new issues that have been identified as post-marketing commitments. Vyteris should be asked to agree to these commitments since the "approval" recommendation from CMC is predicated on Vyteris' acceptance of these commitments described below.

Applicant should develop a reliable method for the in vitro drug release that is indicative of the iontophoretic transfer of the drugs lidocaine HCl and epinephrine. The acceptance criteria for the physical quality attributes, the cathode and anode probe tack, the apparent compressive modulus and the probe tack of the adhesive, and the electrode conductivities are considered tentative in nature and should be revised following accrual of manufacturing data on commercial batches. As part of the commitment for the manufacturing site transfer of the electrode solutions from Fair Lawn, New Jersey, Vyteris should provide additional supporting stability data to the NDA.

In summary, the NDA is recommended for approval with the caveat that Vyteris should agree to fulfill the post-marketing commitments listed at the end of the review.

III. Administrative**A. Reviewer's Signature****B. Endorsement Block**

Ravi S. Harapanhalli, Ph.D, CMC Team Leader/April 28, 2004
Eric Duffy, Ph.D., DNDC-II Division Director
Kim Compton, Project Manager/

C. CC Block

65 Page(s) Withheld

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

§ 552(b)(5) Deliberative Process

§ 552(b)(4) Draft Labeling

**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
4/30/04 05:51:21 PM
CHEMIST

Please sign off. All corrections made to the review.
Approval recommended. Two Phase 4 commitments and one
reminder

Eric Duffy
5/3/04 11:36:11 AM
CHEMIST
Division Director Secondary Review



NDA 21-504

**LidoSite™ -Lidocaine/Epinephrine Iontophoretic Drug
Delivery System**

**Vyteris, Inc.
13-01 Pollitt Drive
Fair Lawn, NJ 07410**

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



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1. NDA 21-504
2. REVIEW # 1
3. REVIEW DATE: June 18, 2003 (Revised July 11, 2003)
4. REVIEWER: Ravi S. Harapanhalli, Ph.D.

5. PREVIOUS DOCUMENTS:

<u>Previous Documents</u>	<u>Document Date</u>
Teleconference with Vyteris	12-MAR-2003
CMC IR Letter	02-MAY-2003

6. SUBMISSION(S) BEING REVIEWED:

<u>Submission(s) Reviewed</u>	<u>Document Date</u>
Original submission	25-SEP-2002
BC	18-DEC-2002
N000 (MR)	26-FEB-2003
BC	10-MAR-2003
N000 (c)	19-MAR-2003
N000 BC	29-APR-2003
N000 (c)	01-MAY-2003
N000 BC	27-MAY-2003
N000 BL	05-JUN-2003
N000 (c)	16-JUN-2003

SUBMISSIONS NOT REVIEWED:



Chemistry Review Data Sheet

Submission(s) not reviewed

N000 (BC): Additional responses to IR letter and additional data to support site transfer. The submission is substantial and the PDUFA date is 25-JUL-2003 and the Division is taking an "approvable" action from all disciplines.

Document Date

14-JUL-2003

7. NAME & ADDRESS OF APPLICANT:

Name: Vyteris, Inc.

Address: 13-01 Pillitt Drive
Fair Lawn, NJ 07410

Representative: George M. Baskinger, Manager, Quality
Management and Regulatory Compliance

Telephone: 201-703-2420

8. DRUG PRODUCT NAME/CODE/TYPE:

- a) Proprietary Name: LidoSite™
- b) Non-Proprietary Name (USAN): Lidocaine and Epinephrine Topical Iontophoretic System
- c) Code Name/# (ONDC only): Northstar System
- d) Chem. Type/Submission Priority (ONDC only):
 - Chem. Type: 3
 - Submission Priority: S

9. LEGAL BASIS FOR SUBMISSION: 505 (b) (2). Listed drug: NDA 6-488 for xylocaine; epinephrine Injection (0.5%; 0.005 mg/ml to 2%; 0.01 mg/ml) from Astrazeneca. NDA 21-504 is additionally supported by the literature in Section 5 of the NDA and information submitted in NDA amendment 003.

10. PHARMACOL. CATEGORY: Local dermal anesthesia

11. DOSAGE FORM: Patch



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12. STRENGTH/POTENCY: \checkmark 1-mg Lidocaine HCl and \checkmark mg epinephrine bitartrate (\checkmark epinephrine).

13. ROUTE OF ADMINISTRATION: Topical

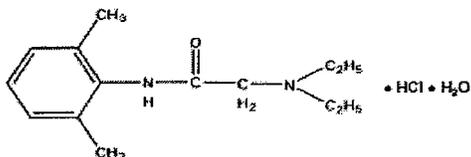
14. Rx/OTC DISPENSED: X Rx OTC

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

SPOTS product – Form Completed

X Not a SPOTS product

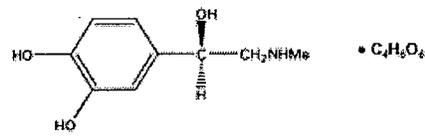
16. CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOLECULAR WEIGHT:



Molecular formula: $C_{14}H_{22}N_2O \cdot HCl \cdot H_2O$

Molecular weight: 288.81

Acetamide, 2-(diethylamino)-N-(2,6-dimethylphenyl)-
2-(Diethylamino)-2',6'-acetoxylidide
[137-58-6].



Molecular formula: $C_9H_{13}NO_3 \cdot C_4H_6O_6$

Molecular weight: 333.29

1,2-Benzenediol, 4-[1-hydroxy-2-(methylamino)ethyl]-, (R)-.
(-)-3,4-Dihydroxy- α -
[(methylamino)methyl]benzyl alcohol
[51-43-4].

17. RELATED/SUPPORTING DOCUMENTS:

A. DMFs:

DMF	TYPE	HOLDER	ITEM	CODE ¹	STATUS ²	DATE	COMMENTS
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Chemistry Review Data Sheet

#	REFERENCED	REVIEW COMPLETED
II	1	Inadequate June 24, 2003
II	1	Inadequate July 3, 2003
II	1	Inadequate July 3, 2003
III	1	Adequate July 1, 2003

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
LidoSite™ Controller	510 K 031551 (Under review)	Iontophoresis device that provides controlled battery-operated electric supply of 17.7 milliamperes-minutes in ten minutes patch application. Kevin Lee, MD is CDRH reviewer

18. STATUS:

ONDC:

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
Biometrics	Not consulted	N/A	Will be consulted after firm submits revised stability data.
EES	Firm not ready (WH)	March 19, 2003	Firm indicated that they are not



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Chemistry Review Data Sheet

			ready for inspection till the end of August 2003.
Pharm/Tox*	Adequate	June 25, 2003	Tim McGovern, Ph.D.
Biopharm	N/A	N/A	N/A
LNC	Recommended established name for the drug product as	July 10, 2003	Dan Boring, Ph.D.
Methods Validation	To be submitted to the labs upon revision of specifications		Firm should be asked to submit method validation package with revised specifications.
ODS	Pending	May 15, 03: Consult for "LidoSite" tradename June 17, 03: Consult for " " a backup tradename June 16, 03: Consult for carton and container labels	Pending
EA	N/A (Exclusion claimed)		
Microbiology	Approval	July 3, 2003	Bryan Riley, Ph.D.
CDRH (electrode subassembly and the electrical specifications of the patch)	Acceptable	June 18, 2003	Kevin Lee found the section on Patch electrical subassembly and electrochemical testing of the patch "acceptable". No deficiencies were identified by the reviewer.

*Pharm/Tox consult with Dr. Tim McGovern: The reviewer discussed in detail the components and composition of the patch, including the non-pharmacopoeal components of — anti-microbial preservative and any potential effect of these on the skin and on systemic toxicity. No issues with safety were identified by the Pharm-Tox.

19. ORDER OF REVIEW (OGD Only)

The application submission(s) covered by this review was taken in the date order of receipt. ___ Yes ___ No If no, explain reason(s) below:



CHEMISTRY REVIEW

Chemistry Assessment Section

The Chemistry Review for NDA 21-504

The Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

From CMC standpoint, the NDA is “approvable” pending satisfactory resolution of the deficiencies listed at the end of the review and upon satisfactory completion of pre-approval inspections of the Vysteris facility for compliance with cGMPs.

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

Applicant should develop a reliable method for the in vitro drug release that is indicative of the iontophoretic transfer of the drugs lidocaine HCl and epinephrine.

In the interim, as part of risk management step, a warning statement should be included in the product labeling that the product should not be subject to lower temperatures such as freezing. Additionally, the acceptance criteria for the physical and electrical tests should be tightened with upper and lower limits and the expiration dating should be restricted.

II. Summary of Chemistry Assessments

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

LisoSite™ Lidocaine and epinephrine topical iontophoretic system consists of the LisoSite topical patch containing the two drugs (Lidocaine HCl 100 mg, and Epinephrine 2 mg per patch) and LidoSite controller that provides uniform electric current of 17.7 milliamperes-min in ten minutes of patch application, during which time approximately 600-µg of lidocaine (0.6% of the label claim) is delivered to the dermis of the skin. A local anesthetic of the amide type, Lidocaine is indicated for dermal anesthesia in the hospital setting. Epinephrine, a sympathomimetic (adrenergic) agent and a vasoconstrictor, is thought to decrease the rate of removal of lidocaine from the site of administration and thus improve its analgesia. The patch is non-sterile and contains anti-microbial preservative 2-phenoxyethanol, methyl-, ethyl-, propyl-,



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Chemistry Assessment Section

butyl-, and isobutyl-p-hydroxybenzoate), is for single use, and consists of a 5 cm² circular anode (positive electrode) containing the drug and a cathode (negative electrode) containing the buffered solution for electrical circuitry (return reservoir). Besides the drugs, the drug reservoir contains sodium chloride, glycerin, citric acid as a buffer and chelator, edetate disodium as a chelator, and sodium metabisulfite as an antioxidant, in a non-sterile hydrogel. The elongated return reservoir contains glycerin, sodium chloride, and monobasic sodium phosphate as an acidulating agent

Positively charged lidocaine and epinephrine are delivered simultaneously from the anode reservoir through a process known as iontophoresis to achieve local dermal anesthesia. Iontophoresis is based on the principle that a soluble salt or drug can be transported across the skin barrier as a part of an electric current induced in the skin. The patch is individually packaged in a chevron-shaped foil-foil pouch. The marketing package configurations are

containing the LidoSite® patches. The two drug substances, namely lidocaine hydrochloride and epinephrine bitartrate are provided by

Lidocaine HCL solubility is 680-mg/ml and that of epinephrine is 333-mg/ml in water at 25°C. By USP definition, both drugs are freely soluble in water and are formulated along with other excipients.

Considering the solubility threshold for lidocaine and the presence of nearly of glycerine in the formulation, the potential for are not addressed.

Even though the temperature cycling studies between -20°C and ambient temperatures showed no effect on the product quality for the attributes tested, the issue is exacerbated by the lack of a reliable in vitro release method that could measure the patch performance following temperature cycling. The wet chemistry methods alone are insufficient to assess the patch performance following the temperature insult.



CHEMISTRY REVIEW

Chemistry Assessment Section

There are no differences between the pre-clinical and clinical drug product, and hence comparability studies were not necessary.

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

Even though the product is provided as along with a controller, each patch is packaged primarily in a peelable chevron-shaped foil-foil patch and is meant for single use only. Typically, one to two patches may be used in a day. The drug is designed to effect dermal anesthesia and is used in a hospital setting. It is for single time use and is not meant for chronic administration. There is only one strength (100-mg lidocaine HCl and epinephrine) and only about 600- μ g (0.6%) of the drug is delivered to the dermis. There are no unusual steps or procedures for dose preparation. The detailed procedure for the use of the controller and the patch is provided in the package insert. The proposed expiration dating is 24-months and the recommended storage is 20-25°C (room temperature).

C. Basis for Approvability or Not-Approval Recommendation

Device Review of Lidosite™ Controller:

The 510K (K031551) for the Lidosite™ controller is currently being reviewed in CDRH by Kevin Lee, M.D.

Chemistry, Manufacturing and Controls of Lidosite™ patch:

The electrode subassembly and the electrical specifications of Lidosite™ patch were evaluated via consult by CDRH reviewer Kevin Lee, M.D. Dr. Lee determined that the manufacturing process and specifications for the iontophoretic patch, the pouch container closure, the pH hydrogen surface of the anode and cathode, the anode-specific capacity of the anode and cathode, the dielectric leakage current, the patch leakage current, the patch conductance, the hydrogel/electrical conductivity of the anode and cathode, and the overall container closure were acceptable.

An IR letter was sent to the sponsor on May 2, 2003. A number of issues delineated in that letter have since been sufficiently addressed by the sponsor. However, several important CMC issues related to product quality remain unresolved. These issues are enumerated below:

1. Pre-approval Inspection



CHEMISTRY REVIEW

Chemistry Assessment Section

In the original NDA submission, Becton Dickinson Medical Systems (BDMS) was identified as the contract manufacturer of the bulk electrode solutions. However, during this review cycle BDMS informed Vyteris, Inc. of their intent not to continue production of the two bulk electrode solutions. Thus, Vyteris is moving the manufacture of the bulk electrode solutions to their facility in Fair Lawn, New Jersey. In a teleconference on March 12, 2003, Vyteris requested that the Agency defer the inspection of their manufacturing facilities until July, 2003. However, the production of a test batch of the drug product following equipment installation at the new manufacturing site could not be completed by the user fee date. At the time of this action, the new facility is still not ready for inspection and the sponsor reports that they anticipate being prepared for inspection in September, 2003. Additional stability data from the Vyteris site is also required and will not likely be available until 3rd quarter 2003. CDER and CDRH Offices of Compliance determined that the potential need to inspect the manufacturer of electrode subassembly will be assessed after the inspection of Vyteris, who manufactures the finished patch.

2. Drug Product Assay and Impurity Specifications

Adequate specifications for assay and impurities for the active components in the drug product have not been provided.

3. Drug Product In-use Stability Data

Data for the chemical stability of the lidocaine and epinephrine in the drug product during the 10-minute patient use have not been provided; the electrical current during iontophoresis may degrade the drug substances.

4. Drug Product Stability

Drug product stability trends of concern include declining trace conductance and increasing peripheral probe tack. There were several instances of skin damage associated with patch removal that may have been related to increased probe tack over storage. Instances of patient withdrawal due to high impedance may be related to declining trace conductance. The sponsor submitted _____ of stability data and proposed 24-months expiration dating period. Due to the concerns over the trends on stability, the lack of analysis of these trends, the lack of justification for appropriate acceptance criteria for these attributes, and the lack of 24-months real-time data, the appropriateness of the proposed expiration dating period of 24 months cannot be assessed and furthermore the appropriateness of a shorter expiration dating cannot be assessed.

5. In-process Manufacturing Tests



CHEMISTRY REVIEW

Chemistry Assessment Section

A sampling plan for the in-process tests, representative of the patch manufacturing process, has not been submitted. Without this information, the adequacy of the controls over the manufacturing process cannot be assessed.

6. Electrode Subassembly Manufacturing

Information on the manufacture of the electrode subassembly has not been submitted. Without this information, the continued effectiveness and quality of the drug product cannot be assessed.

7. _____ of Drug

As the electrode solution is formulated close to the solubility of lidocaine HCl, and the presence of glycerine and other ingredients could reduce the solubility of this active component, data on potential _____, and its impact on product performance is necessary. This has not been addressed in the submission.

8. Lack of an in vitro or in vivo drug release method:

A drug release test (*in vitro or in vivo*) to measure the product performance has not been provided. The absence of a test for drug release presents difficulty in assessing and assuring the adequate performance of the drug product at release and assessment of its expiration dating period.

9. Inadequate DMF's

The product quality issues identified above are fixable and the firm is working to address them within a defined timeframe. In view of these outstanding deficiencies, the NDA is "approvable" from the standpoint of CMC pending satisfactory resolution of the listed issues and upon satisfactory completion of pre-approval inspections for cGMP compliance.

III. Administrative

A. Reviewer's Signature



CHEMISTRY REVIEW

Chemistry Assessment Section

B. Endorsement Block

Ravi S. Harapanhalli, Ph.D, CMC Reviewer/June 18, 2003
Dale Koble, Ph.D., Chemistry Team Leader/
Kim Compton, Project Manager/

C. CC Block

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/s/

Ravi Harapanhalli
7/25/03 01:40:38 PM
CHEMIST
"AE" recommendation from CMC

Dale Koble
7/25/03 01:47:38 PM
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