CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

202278Orig1s000

CHEMISTRY REVIEW(S)

NDA 202278
Resubmission

Zecuity
(sumatriptan iontophoretic transdermal system)

NuPathe Inc.

Caroline Strasinger, Ph.D.
Branch IV
DNDQA II/ONDQA

CMC Review for
Division of Neurological Products

Table of Contents

Chemistry Review Data Sheet

1. NDA 202278

2. REVIEW #: #4

3. REVIEW DATE: December 26, 2012

4. REVIEWER: Caroline Strasinger, Ph.D. (Drug Product)

5. PREVIOUS DOCUMENTS:

Previous Documents	Document Date
CMC Review #1	30-JUN-2011
CDRH/OC Review	14-JUL-2011
Discipline Review #1	15-JUL-2011
CDRH/ODE Review	20-JUL-2011
CMC Review #2	22-JUL-2011
General Advice Letter	02-AUG-2011
Action Letter – Complete Response	29-AUG-2011
CMC Review #3	09-SEP-2011
Meeting Minutes	09-DEC-2011
Meeting Minutes	04-APR-2012

6. SUBMISSION(S) BEING REVIEWED:

Submission(s) Reviewed	Document Date
Resubmission	16-JUL-2012
Amendment	20-NOV-2012

7. NAME & ADDRESS OF APPLICANT:

Name: NuPathe, Inc.

Chemistry Review Data Sheet

Address:	227 Washington Street Suite 200 Conshohocken, PA 19428
Representative:	Michele A. Roy, RN, MS
Telephone:	484-567-0130 x1103

8. DRUG PRODUCT NAME/CODE/TYPE:

a) Proprietary Name: Zecuity
b) Non-Proprietary Name (USAN): sumatriptan iontophoretic transdermal system

c) Code Name/#: NP101
d) Chem. Type/Submission Priority:
- Chem. Type: 3
- Submission Priority: Standard

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

10. PHARMACOL. CATEGORY: Selective 5-hydroxytryptamine$_1$ (5-HT$_1$) agonist; Vascular headache suppressant

11. DOSAGE FORM: Iontophoretic Transdermal System

12. STRENGTH/POTENCY: 86 mg delivers 6.5 mg (equals [redacted](b) (4) sumatriptan succinate) over 4 hours

13. ROUTE OF ADMINISTRATION: Transdermal

14. Rx/OTC DISPENSED: _X_Rx ___OTC

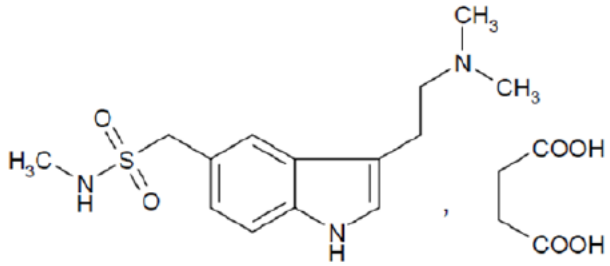
15. SPOTS (SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM):
_____SPOTS product – Form Completed

___X___Not a SPOTS product

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

Sumatriptan Succinate:

1H-Indole-5-methanesulfonamide,3-[2-(dimethylamino)ethyl]-N-methyl-,butanedioate(1:1) [3-[2-(Dimethyl amino) ethyl]-N-methylindole-5-methanesulfonamide succinate (1:1)



Molecular Formula: $C_{18}H_{27}N_3O_6S$
Molecular Weight: 413.5

17. RELATED/SUPPORTING DOCUMENTS:

A. DMFs:

DMF #	TYPE	HOLDER	ITEM REFERENCED	CODE[1]	STATUS[2]	DATE REVIEW COMPLETED	COMMENTS
[redacted]			(b) (4)	1	Adequate	01/11/2011	Dr. C. Strasinger for NDA 202278
				1	Adequate	01/11/2011	Dr. C. Strasinger for NDA 202278
				3	Adequate	01/21/2010	Dr. Y. Hu for NDA (b) (4)
				4	Adequate		
				4	Adequate		
				3	Adequate	09/08/2010	by Andrew Langowski
				3	Adequate	02/01/2010	BingYuan Wu

[1] Action codes for DMF Table:
1 – DMF Reviewed.
Other codes indicate why the DMF was not reviewed, as follows:

2 –Type 1 DMF
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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

18. STATUS:

ONDQA:

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
Biometrics	N/A		
EES	Acceptable	01/14/2013	Office of Compliance
Pharm/Tox	N/A		
Biopharm	In vitro release method and specification is recommended for Approval	12/18/2012	Tapash Ghosh, PhD
LNC	N/A		
Methods Validation	TBD		Requested per ONDQA's policy 03/11/2011
DMEPA	N/A		
EA	Categorical exclusion granted	6/30/11	Raanan Bloom
Microbiology	Adequate	12/6/12	Stephen Langille

The Chemistry Review for NDA 202278

The Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

The Applicant of NDA 202278 has provided sufficient information to assure the identity, strength, purity, and quality of the drug product. All CMC, Biopharmaceutic, CDRH and Microbiological deficiencies identified in the first review cycle have been adequately addressed.

The labels and labeling have been reviewed and all labeling is adequate from the CMC perspective.

The Office of Compliance has issued an overall "Acceptable" recommendation for the facilities involved in the NDA.

Therefore, from the ONDQA perspective, this NDA is recommended for Approval.

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)

Drug Substance:
The drug substance is the succinate salt of sumatriptan. It is a white to almost white powder (b) (4) freely soluble in water. Much of the drug substance CMC information is cross referenced to the DMFs of its (b) (4) respectively). Different manufacturing processes are used at the two sites however the regulatory drug substance specification including impurity limits comply with USP standards – only site-specific solvent tests are part of the specification. Batch analysis results of lots from both sites met specifications. Stability data support a (b) (4) retest period for material from either site.

Drug Product:

The sumatriptan iontophoretic transdermal system, is a disposable, single-use co-packaged drug/device combination product that utilizes iontophoretic technology to deliver sumatriptan transdermally for the treatment of acute migraine attacks. The drug component portion of Zecuity is referred to as the reservoir card and consists of two separate reservoir pads imbibed with either (b) (4) g of sumatriptan formulation ((b) (4) sumatriptan succinate containing (b) (4) equivalent to 86 mg of sumatriptan base) or (b) (4) g of salt formulation (b) (4) sodium chloride). The device portion of Zecuity is the Electrode Patch (E-Patch) containing a positively charged (b) (4) electrode and a negatively charged (b) (4) electrode. The system measures approximately 8 inches by 4 inches.

The system is manufactured as (b) (4)

Drug delivery is approximately four hour (b) (4) hours) after which time the system is automatically deactivated by the pre-programmed circuit. The quality of the system is controlled by tests for appearance, assay, (b) (4) identification, drug release, pouch tightness, impurities, microbial limits, water content, methyl paraben content and drug release. The electrode pad is controlled by connectivity, capacity, and fixed resistance testing. (b) (4) months of stability data of the co-packaged product has been provided.

The reservoir card pads are (b) (4). It is intended that the commercial cartons will contain 6 pouched transdermal drug delivery systems (TDDS). The Applicant is requesting (b) (4) months of expiration dating. Labels and Labeling have been reviewed and deficiencies are to be communicated in the final action letter.

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

Sumatriptan iontophoretic transdermal system, 6.5 mg/4 hours is a drug device combination designed to be applied to the upper arm or thigh and activated by pressing a button. After 4 hours of delivery, the system will deactivate and should be removed and disposed of out of reach of children and pets. The product should be stored at room temperature.

C. Basis for Approvability or Not-Approval Recommendation

The Applicant has provided sufficient information on raw material controls, manufacturing processes and process controls, and adequate specifications for assuring consistent product quality of the drug substance and drug product. The Applicant has provided sufficient stability information for the drug product to assure strength, purity, and quality of the drug product during the proposed expiration dating period.

Label and Labeling are adequate.

Office of Compliance has issued an "Acceptable" overall recommendation for all facilities involved.

III. Administrative

A. Reviewer's Signature

B. Endorsement Block

ChemistName/Date: Caroline Strasinger, PhD 26-DEC-2012
ChemistryTeamLeaderName/Date: Martha Heimann, PhD; 26-DEC-2012
ProjectManagerName/Date: Teshara Bouie; 26-DEC-2012

C. CC Block

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/s/

CAROLINE STRASINGER
01/15/2013

TERRANCE W OCHELTREE
01/15/2013

NDA 202-278
ADDENDUM

Zecuity
(sumatriptan) Iontophoretic Transdermal System

NuPathe Inc.

Caroline Strasinger, Ph.D.
Branch IV
DNDQA II/ONDQA

David J. Claffey, Ph.D.
Branch I
DNDQA I/ONDQA

CMC Review for
Division of Neurological Products

Chemistry Review Data Sheet

1. NDA 202-278

2. REVIEW #: #3

3. REVIEW DATE: August 25, 2011

4. REVIEWER: Caroline Strasinger, Ph.D.
David Claffey, Ph.D.

5. PREVIOUS DOCUMENTS:

Previous Documents	Document Date
N/A	

6. SUBMISSION(S) BEING REVIEWED:

Submission(s) Reviewed	Document Date
Original	29-OCT-2010

7. NAME & ADDRESS OF APPLICANT:

Name:	NuPathe, Inc.
Address:	227 Washington Street Suite 200 Conshohocken, PA 19428
Representative:	Michele A. Roy, RN, MS
Telephone:	484-567-0130 x1103

8. DRUG PRODUCT NAME/CODE/TYPE:

a) Proprietary Name:	Zecuity (formerly NP101)
b) Non-Proprietary Name (USAN):	sumatriptan iontophoretic transdermal system

c) Code Name/#: NP101
d) Chem. Type/Submission Priority:

- Chem. Type: 3
- Submission Priority: Standard

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

10. PHARMACOL. CATEGORY: Selective 5-hydroxytryptamine$_1$ (5-HT$_1$) agonist; Vascular headache suppressant

11. DOSAGE FORM: Iontophoretic Transdermal System

12. STRENGTH/POTENCY: (b) (4) delivers 6.5 mg (equals (b) (4) mg sumatriptan succinate) over 4hours

13. ROUTE OF ADMINISTRATION: Transdermal

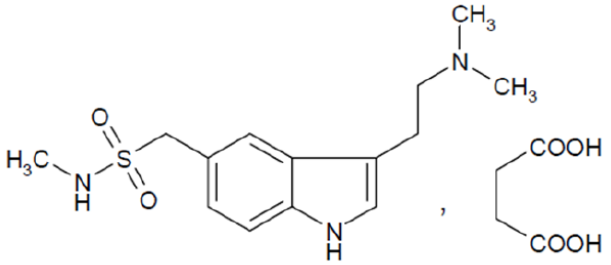
14. Rx/OTC DISPENSED: _X_Rx ___OTC

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:

Sumatriptan Succinate:
1H-Indole-5-methanesulfonamide,3-[2-(dimethylamino)ethyl]-N-methyl-,butanedioate(1:1) [3-[2-(Dimethyl amino) ethyl]-N-methylindole-5-methanesulfonamide succinate (1:1)



Molecular Formula: $C_{18}H_{27}N_3O_6S$
Molecular Weight: 413.5

17. RELATED/SUPPORTING DOCUMENTS:

A. DMFs:

DMF #	TYPE	HOLDER	ITEM REFERENCED	CODE[1]	STATUS[2]	DATE REVIEW COMPLETED	COMMENTS
(b) (4)				1	Adequate	01/11/2011	Dr. C. Strasinger for NDA 202-278
				1	Adequate	01/11/2011	Dr. C. Strasinger for NDA 202-278
				3	Adequate	01/21/2010	Dr. Y. Hu for NDA (b) (4)
				4	Adequate		
				4	Adequate		
				3	Adequate	09/08/2010	by Andrew Langowski
				3	Adequate	02/01/2010	BingYuan Wu
				7	N/A		To be reviewed in next review cycle due to late receipt
				7	N/A		To be reviewed in next review cycle due to late receipt
				7	N/A		To be reviewed in next review cycle due to late receipt

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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

18. STATUS:

ONDQA:

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
Biometrics	N/A		
EES	Acceptable	8/25/2011	Office of Compliance
Pharm/Tox	N/A		
Biopharm	In vitro release method and specification is recommended for Complete Response	6/22/2011	Tapash Ghosh, PhD
LNC	N/A		
Methods Validation	TBD		Requested per ONDQA's policy 03/11/2011
DMEPA	N/A		
EA	Categorical exclusion granted	6/30/11	Raanan Bloom
Microbiology	N/A		

The Chemistry Review for NDA 202-278

The Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

NDA 202-287 for sumatriptan iontophoretic transdermal system is recommended for Complete Response from the CMC perspective. The applicant has not provided sufficient information to assure identity, strength, purity, and quality of the drug product. The Applicant needs to respond adequately to the CMC issues outlined in this review.

An overall "Acceptable" recommendation was issued for the manufacturing and testing sites by the Office of Compliance on 25-AUG-2011.

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)

Drug Substance:
The drug substance is the succinate salt of sumatriptan. It is a white to almost white powder (b) (4) freely soluble in water. Much of the drug substance CMC information is cross referenced to the DMFs of its (b) (4) respectively). Different manufacturing processes are used at the two sites however the regulatory drug substance specification including impurity limits comply with USP standards – only site-specific solvent tests differ for the specifications. Batch analysis results of lots from both sites met specifications. Stability data support a (b) (4) retest period for material from either site.

Drug Product:
The sumatriptan iontophoretic transdermal system, Zecuity, is a disposable, single-use co-packaged drug/device combination product that utilizes iontophoretic technology to deliver sumatriptan transdermally for the treatment of acute migraine attacks The drug component portion of Zecuity is referred to as the reservoir card and consists of two separate reservoir pads imbibed with either (b) g of sumatriptan formulation ((b) (4) sumatriptan succinate containing (b) (4) mg equivalent to 86 mg of sumatriptan base) or (b) (4) g of salt formulation ((b) (4) sodium chloride). The device portion of Zecuity is the Electrode Patch (E-Patch) containing a positively charged

(b) (4) electrode and a negatively charged (b) (4) electrode. The system measures approximately 8 inches by 4 inches.

The system is manufactured as (b) (4)

Drug delivery is approximately four hours (b) (4) hours) after which time the system is automatically deactivated by the pre-programmed circuit. The quality of the system is controlled by tests for appearance, assay, (b) (4) identification, drug release, pouch tightness, impurities, microbial limits, water content, methyl paraben content and drug release. The electrode pad is controlled by connectivity, capacity, and fixed resistance testing. 9 months of stability data of the co-packaged product has been provided.

The reservoir card pads are (b) (4) It is intended that the commercial cartons will contain (b) (4) 6 pouched transdermal drug delivery systems (TDDS). The Applicant is requesting 12 months of expiration dating. Labeling has not been reviewed at this time. Labeling negotiations will not take place during this review cycle because of the Complete Response recommendation.

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

Sumatriptan iontophoretic transdermal system, 6.5 mg/4 hours is a drug device combination designed to be applied to the upper arm or thigh and activated by pressing a button. After 4 hours of delivery, the system will deactivate and should be removed and disposed of out of reach of children and pets. The product should be stored at room temperature.

C. Basis for Approvability or Not-Approval Recommendation

Specifications cannot be established per 21.CFR.314.50 to adequately assure identity, strength, quality, purity, potency and bioavailability of the product. A lack of drug formulation containment, and issues associated with drug formulation uniformity, (b) (4) and residual drug raise concerns about the safety and efficacy of the product.

The Applicant has not provided sufficient information on raw material controls, manufacturing processes and process controls, and adequate specifications for assuring consistent product quality of the drug substance and drug product. The applicant has not provided sufficient stability information for the drug product to assure strength, purity, and quality of the drug product during the proposed expiration dating period.

Labeling of the drug product backing is insufficient to assure the product can be appropriately identified during use. Carton and product insert labeling are not reviewed in this review cycle given the significant number of deficiencies.

Office of Compliance has issued an "Acceptable" overall recommendation for all facilities involved.

III. Administrative

A. Reviewer's Signature

B. Endorsement Block

Chemist Name/Date: Caroline Strasinger, PhD 25-AUG-2011
Director Name/Date: Terrance Ocheltree, PhD, RPh 25-AUG-2011
Chemistry Team Leader Name/Date: Martha Heimann, PhD; 25-AUG-2011
Project Manager Name/Date: Teshara Bouie; 25-AUG-2011

C. CC Block

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/s/

CAROLINE STRASINGER
09/09/2011

TERRANCE W OCHELTREE
09/09/2011

NDA 202-278
ADDENDUM

NP 101
(sumatriptan) Iontophoretic Transdermal System

NuPathe Inc.

Caroline Strasinger, Ph.D.
Branch IV
DNDQA II/ONDQA

David J. Claffey, Ph.D.
Branch I
DNDQA I/ONDQA

CMC Review for
Division of Neurological Products

Chemistry Review Data Sheet

1. NDA 202-278

2. REVIEW #: #2

3. REVIEW DATE: July 21, 2011

4. REVIEWER: Caroline Strasinger, Ph.D.
David Claffey, Ph.D.

5. PREVIOUS DOCUMENTS:

Previous Documents	Document Date
N/A	

6. SUBMISSION(S) BEING REVIEWED:

Submission(s) Reviewed	Document Date
Original	29-OCT-2010
Amendment 0011	11-APR-2011
Amendment 0014	10-JUN-2011

7. NAME & ADDRESS OF APPLICANT:

Name:	NuPathe, Inc.
Address:	227 Washington Street Suite 200 Conshohocken, PA 19428
Representative:	Michele A. Roy, RN, MS
Telephone:	484-567-0130 x1103

8. DRUG PRODUCT NAME/CODE/TYPE:

a) Proprietary Name: NP101 (Proprietary Name is to be determined)

b) Non-Proprietary Name (USAN): sumatriptan iontophoretic transdermal system

c) Code Name/#: NP101

d) Chem. Type/Submission Priority:

- Chem. Type: 3
- Submission Priority: Standard

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

10. PHARMACOL. CATEGORY: Selective 5-hydroxytryptamine$_1$ (5-HT$_1$) agonist; Vascular headache suppressant

11. DOSAGE FORM: Iontophoretic Transdermal System

12. STRENGTH/POTENCY: (b) (4) delivers 6.5 mg (equals (b) (4) mg sumatriptan succinate) over 4hours

13. ROUTE OF ADMINISTRATION: Transdermal

14. Rx/OTC DISPENSED: _X_Rx ___OTC

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

_____SPOTS product – Form Completed

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

Sumatriptan Succinate:

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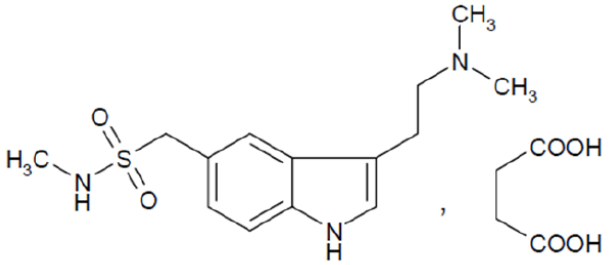

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				1	Adequate	01/11/2011	Dr. C. Strasinger for NDA 202-278
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Biopharm	In vitro release method and specification is recommended for Complete Response	6/22/2011	Tapash Ghosh, PhD
LNC	N/A		
Methods Validation	TBD		Requested per ONDQA's policy 03/11/2011
DMEPA	N/A		
EA	Categorical exclusion granted	6/30/11	Raanan Bloom
Microbiology	N/A		

The Chemistry Review for NDA 202-278

The Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

NDA 202-287 for sumatriptan iontophoretic transdermal system is recommended for Complete Response from the CMC perspective. The applicant has not provided sufficient information to assure identity, strength, purity, and quality of the drug product. The Applicant needs to respond adequately to the CMC issues outlined in this review.

An overall "Pending" recommendation has been issued for the manufacturing and testing sites by the Office of Compliance.

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)

Drug Substance:
The drug substance is the succinate salt of sumatriptan. It is a white to almost white powder (b) (4) freely soluble in water. Much of the drug substance CMC information is cross referenced to the DMFs of its (b) (4), respectively). Different manufacturing processes are used at the two sites however the regulatory drug substance specification including impurity limits comply with USP standards – only site-specific solvent tests differ for the specifications. Batch analysis results of lots from both sites met specifications. Stability data support a (b) (4) retest period for material from either site.

Drug Product:
The sumatriptan iontophoretic transdermal system (NP 101), is a disposable, single-use co-packaged drug/device combination product that utilizes iontophoretic technology to deliver sumatriptan transdermally for the treatment of acute migraine attacks The drug component portion of NP 101 is referred to as the reservoir card and consists of two separate reservoir pads imbibed with either (b) (4) g of sumatriptan formulation ((b) (4) sumatriptan succinate containing (b) (4) equivalent to 86 mg of sumatriptan base) or (b) g of salt formulation ((b) (4) sodium chloride). The device portion of NP 101 is the Electrode Patch (E-Patch) containing a positively charged

(b) (4) electrode and a negatively charged (b) (4) electrode. The system measures approximately 8 inches by 4 inches.

The system is manufactured as (b) (4)

Drug delivery is approximately four hours (b) (4) hours) after which time the system is automatically deactivated by the pre-programmed circuit. The quality of the system is controlled by tests for appearance, assay, (b) (4) identification, drug release, pouch tightness, impurities, microbial limits, water content, methyl paraben content and drug release. The electrode pad is controlled by connectivity, capacity, and fixed resistance testing. 9 months of stability data of the co-packaged product has been provided.

The reservoir card pads are (b) (4) It is intended that the commercial cartons will contain (b) (4) 6 pouched transdermal drug delivery systems (TDDS). The Applicant is requesting 12 months of expiration dating. Labeling has not been reviewed at this time. Labeling negotiations will not take place during this review cycle because of the Complete Response recommendation.

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

Sumatriptan iontophoretic transdermal system, 6.5 mg/4 hours is a drug device combination designed to be applied to the upper arm or thigh and activated by pressing a button. After 4 hours of delivery, the system will deactivate and should be removed and disposed of out of reach of children and pets. The product should be stored at room temperature.

C. Basis for Approvability or Not-Approval Recommendation

Specifications cannot be established per 21.CFR.314.50 to adequately assure identity, strength, quality, purity, potency and bioavailability of the product. A lack of drug formulation containment, and issues associated with drug formulation uniformity, (b) (4), and residual drug raise concerns about the safety and efficacy of the product.

The Applicant has not provided sufficient information on raw material controls, manufacturing processes and process controls, and adequate specifications for assuring consistent product quality of the drug substance and drug product. The applicant has not provided sufficient stability information for the drug product to assure strength, purity, and quality of the drug product during the proposed expiration dating period.

Labeling of the drug product backing is insufficient to assure the product can be appropriately identified during use. Carton and product insert labeling are not reviewed in this review cycle given the significant number of deficiencies.

Office of Compliance has issued a "Pending" overall recommendation for all facilities involved.

III. Administrative

A. Reviewer's Signature

B. Endorsement Block

Chemist Name/Date: David Claffey, PhD; Caroline Strasinger, PhD 21-JUL-2011
Director Name/Date: Terrance Ocheltree, PhD, RPh 21-JUL-2011
Chemistry Team Leader Name/Date: Martha Heimann, PhD; 21-JUL-2011
Project Manager Name/Date: Teshara Bouie; 21-JUL-2011

C. CC Block

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/s/

CAROLINE STRASINGER
07/21/2011

TERRANCE W OCHELTREE
07/22/2011

DATE: May 11, 2011

TO: NDA 202-278

FROM: Tapash Ghosh, Ph.D.

THROUGH: Terrance Ocheltree, Ph.D., R.Ph.

SUBJECT: Product Quality and Manufacturing Memo for *in-vitro* release testing site of Zelrix™ (sumatriptan) iontophoretic transdermal system of NuPathe, Inc; Reservoir Card and Electrode Patch, (b) (4) for NDA 202-278

The purpose of this memo is to provide a brief description of the customized apparatus, "Transdermal Patch Testing System" (TPTS) and procedure (VTM 120-001-02) for *in vitro* testing of the drug product in NDA 202-278. The memo is meant to provide an aid for investigators and compliance officers in preparing for inspection of the testing site; it is not intended to provide inspectional instructions.

NDA 202-278 from NuPathe, Inc provides for Zelrix (sumatriptan iontophoretic transdermal system), a drug/device combination. It is a highly complex transdermal system which incorporates the use of an iontophoretic device to deliver sumatriptan succinate from a drug imbibed pad. The application of low electrical potential results in movement of ionized sumatriptan molecules through the skin. Though other iontophoretic drug delivery systems have been previously approved by the FDA, this system is unique in design, use, and size and presents various safety issues associated with the manufacturing process.

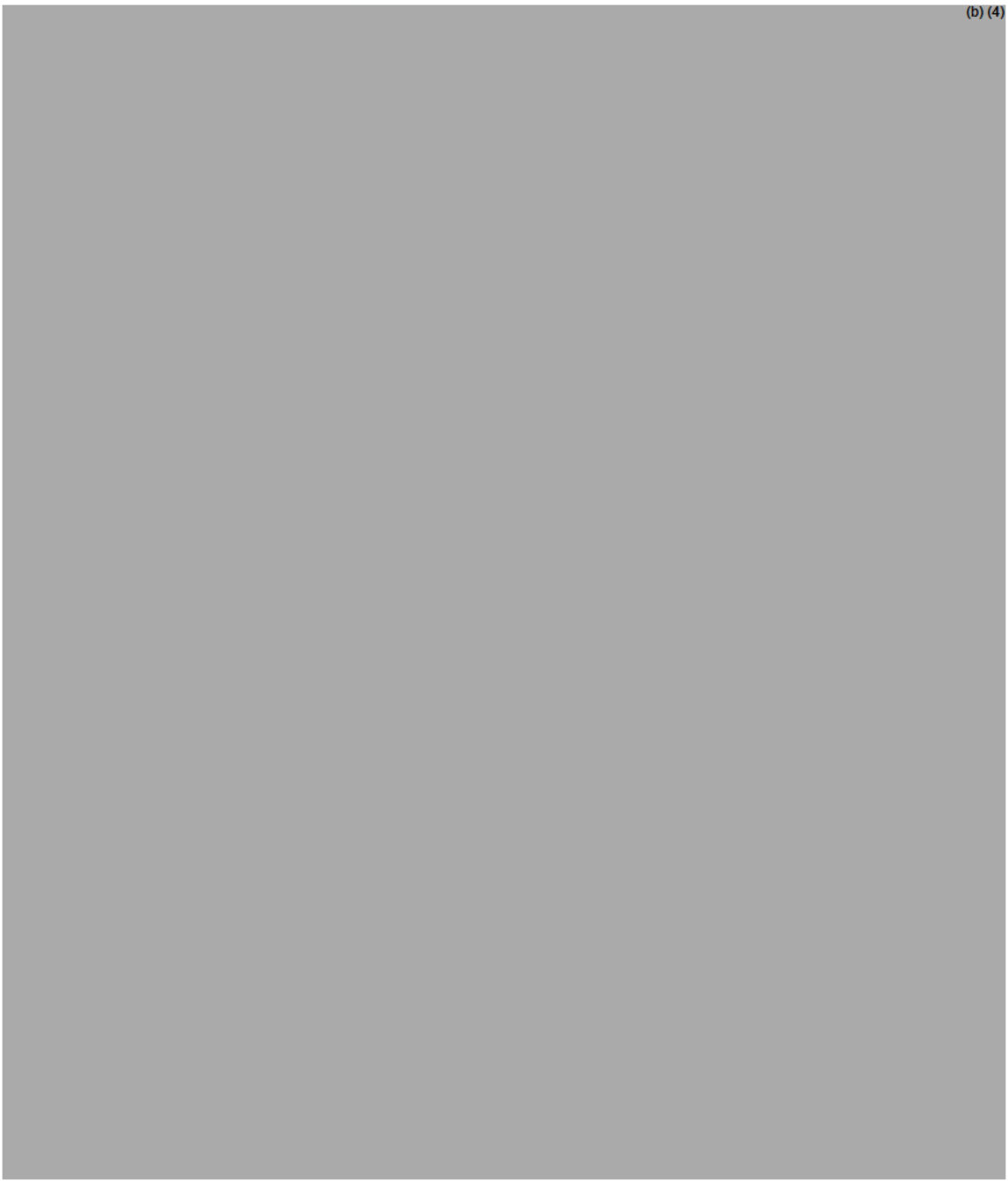
The *in-vitro* release apparatus test method is performed at the (b) (4) site as part drug product release. The *in-vitro* drug release analysis uses a testing instrument customized for the NP101 drug product and is described as being able to actuate the product and collect the drug delivered over the proposed use period of the product. Diagrams of the apparatus follow.

While the method is still undergoing validation and optimization, the following parameters remain unresolved to assure robustness and reproducibility of the final method:

- Can the sampling area be reproducibly moved without disturbing the integrity of the system?
- Can the electronics be precisely controlled especially in changing the (b) (4) (b) (4)
- How is the total amount of drug delivered calculated?
- Is the system able to detect and precisely prevent passive transport of the drug?

In summary, a rigorous control over each batch's release performance is of paramount importance from product quality control and assurance point of view. Therefore,

investigation of this complex in-vitro release procedure for this custom designed apparatus is necessary to validate its suitability to assure batch to batch uniformity of NP101.

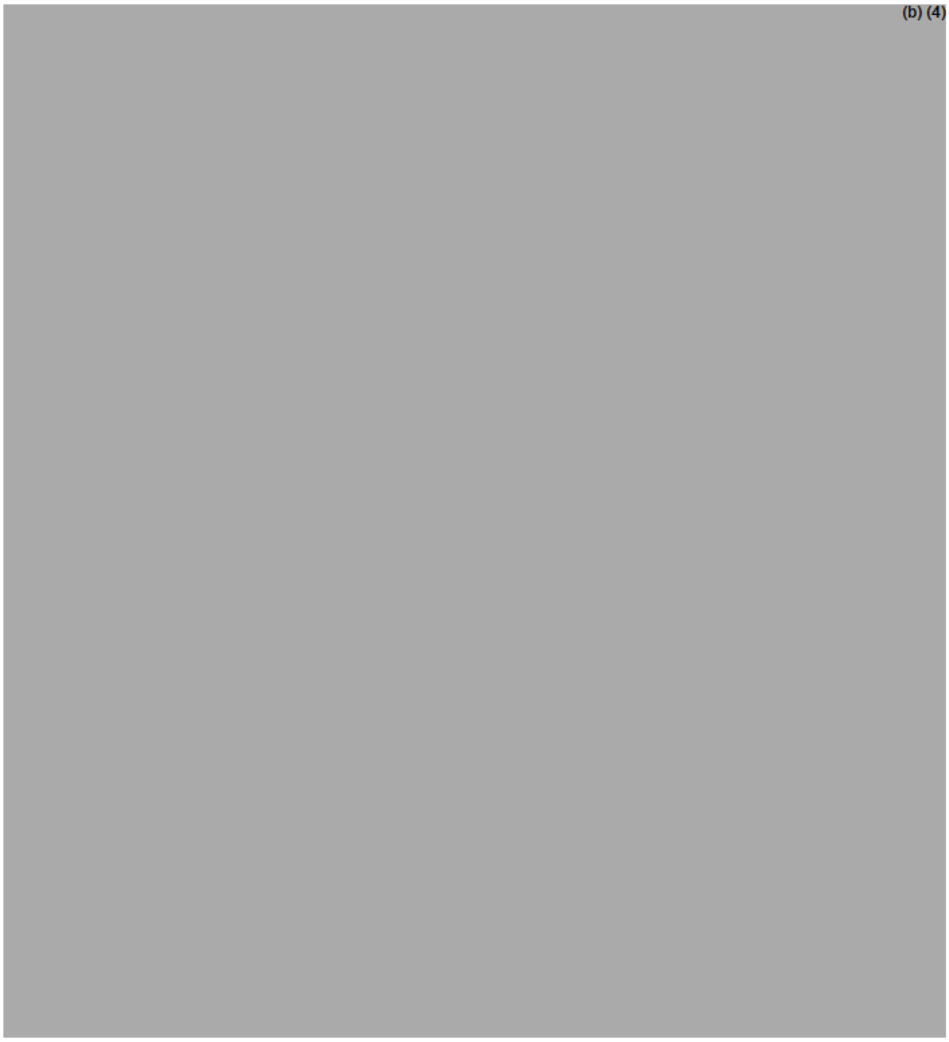


(b) (4)

Description from NDA 202-278:

(b) (4)

(b) (4) . Figure 1 illustrates the sampling pattern. Refer to table 1 for dial position.


(b) (4)

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/s/

TAPASH K GHOSH
05/11/2011

PATRICK J MARROUM
05/11/2011

DATE: May 5, 2011

TO: NDA 202-278

FROM: Caroline Strasinger, Ph.D.

THROUGH: Terrance Ocheltree, Ph.D., R.Ph.

SUBJECT: Product Quality and Manufacturing Memo for NP101 (sumatriptan) iontophoretic transdermal system of NuPathe, Inc; Reservoir Card and Electrode Patch, (b) (4) for NDA 202-278

The purpose of this memo is to outline the product description, manufacturing process and associated risks for NDA 202-278. It is meant to provide an aid for investigators and compliance officers in preparing for inspection; it is not intended to provide inspectional instructions.

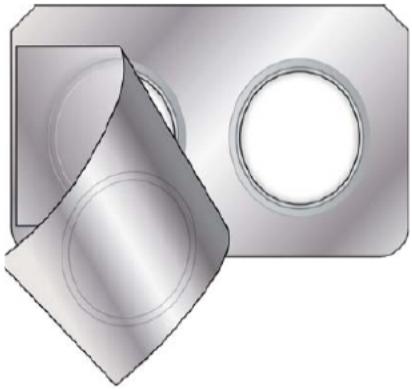
NDA 202-278 from NuPathe, Inc provides for NP101 (sumatriptan iontophoretic transdermal system), a drug/device combination. It is a highly complex transdermal system which incorporates the use of an iontophoretic device to deliver sumatriptan succinate from a drug imbibed pad. The application of low electrical potential results in movement of ionized sumatriptan molecules through the skin. Though other iontophoretic drug delivery systems have been previously approved by the FDA, this system is unique in design, use, and size. The design and associated manufacturing process for NP101 pose potential safety and efficacy risks.

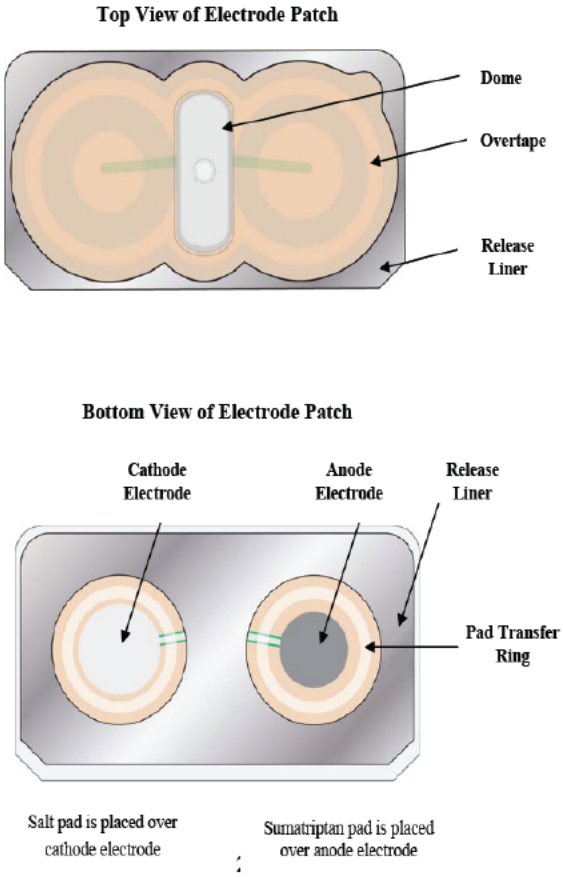
The purpose of this memo is to provide an overview of the delivery system and an outline for the investigator on the manufacturing steps that take place at the (b) (4) site. In particular, the reservoir card and electrode patch will be described and the potential risks associated with a lack of rigorous manufacturing control will be outlined.

The drug product is composed of two main components, a reservoir card (figure 1) and an electrode patch (figure 2). Both are manufactured at the (b) (4). The electrode patch can also be manufactured at (b) (4).

Figure 2: Electrode Patch (Top and Bottom View)

Figure 1: Reservoir Card





1 **Reservoir Card**: The drug component of the system is referred to as the reservoir card and consists of two separate reservoir pads imbibed with either [(b)(4)] g of sumatriptan formulation [(b) (4)] sumatriptan succinate equivalent to 86 mg of sumatriptan base; a [(b) (4)] solution) or [(b) (4)] g of salt formulation ([(b) (4)] sodium chloride). Each reservoir is sealed separately and upon use the patient places the sumatriptan pad on the positively charge electrode (anode) and the salt pad on the negatively charged electrode (cathode) of the device.

2 **Electrode Patch**: The device component contains [(b) (4)]

The manufacturing steps at the [(b) (4)] site for the reservoir card consist of [(b) (4)]. The

manufacturing steps for the electrode patch have not been provided in the Application. Additional considerations for inspection for the electrode patch may be provided in the future.

Critical manufacturing controls at the (b) (4) for the reservoir card include (b) (4) Variations of any one or a combination of these parameters could result in clinically significant changes in drug product performance.

The following are the major risks to product quality, as identified by the CMC reviewer:

Homogeneity
According to the Applicant, (b) (4)

Dispensing
During the manufacturing process (b) (4)

(b) (4)
(b) (4)

Hold Time
According to the Applicant, a hold time is necessary to (b) (4)

[redacted]. The Applicant should define that product expiry period [redacted]. The Applicant should further assign the shelf life of the final product based on the shortest expiration date for the components of the system.

The following deficiencies were identified by the CMC reviewer in the NDA and may be of interest to the inspection team:

Manufacturing Process

1. Assure that [redacted] and alter the manufacturing flow chart to reflect this.
2. Provide justification for the [redacted] hold time of the drug formulation.
3. Establish an IPC for [redacted] per USP <905> of the bulk drug and salt formulations prior to [redacted].

Specification

4. Establish a test method and acceptance criterion for crystals and visible particles for the sumatriptan containing and salt containing pads.
5. Establish an appropriate Identification Test, including a congruent identification test that provides a quantitative measure for the drug and salt pads. [redacted] is not an adequate identification description.
6. Establish a specification, including acceptance criteria for salt content for the salt pad.
7. Establish a specification, including acceptance criteria for appearance of the electrode card.
    - Include an observation for [redacted] of the adhesives.
    - Include appearance of each electrode and lack of surface flaws, such as scratches.

Container Closure

8. Assess extractables and leachables for all packaging components.

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/s/

CAROLINE STRASINGER
05/11/2011

TERRANCE W OCHELTREE
05/11/2011

NDA 202-278

NP 101
(sumatriptan) Iontophoretic Transdermal System

NuPathe Inc.

Caroline Strasinger, Ph.D.
Branch IV
DNDQA II/ONDQA

David J. Claffey, Ph.D.
Branch I
DNDQA I/ONDQA

CMC Review for
Division of Neurological Products

Table of Contents

Chemistry Review Data Sheet

1. NDA 202-278

2. REVIEW #: #1

3. REVIEW DATE: April 1, 2011

4. REVIEWER: Caroline Strasinger, Ph.D. (Drug Product)
David Claffey, Ph.D. (Drug Substance)

5. PREVIOUS DOCUMENTS:

Previous Documents	Document Date
N/A	

6. SUBMISSION(S) BEING REVIEWED:

Submission(s) Reviewed	Document Date
Original	29-OCT-2010
Amendment 0003	03-FEB-2011
Amendment 0005	25-FEB-2011
Amendment 0006	9-MAR-2011
Amendment 0007	17-MAR-2011
Amendment 0008	18-MAR-2011
Amendment 0012	16-MAY-2011

7. NAME & ADDRESS OF APPLICANT:

Name: NuPathe, Inc.

Address: 227 Washington Street
Suite 200
Conshohocken, PA 19428

Representative:	Michele A. Roy, RN, MS
Telephone:	484-567-0130 x1103

8. DRUG PRODUCT NAME/CODE/TYPE:

a) Proprietary Name: NP101 (Proprietary Name is to be determined)

b) Non-Proprietary Name (USAN): sumatriptan iontophoretic transdermal system

c) Code Name/#: NP101

d) Chem. Type/Submission Priority:

- Chem. Type: 3
- Submission Priority: Standard

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

10. PHARMACOL. CATEGORY: Selective 5-hydroxytryptamine$_1$ (5-HT$_1$) agonist; Vascular headache suppressant

11. DOSAGE FORM: Iontophoretic Transdermal System

12. STRENGTH/POTENCY: (b) (4) delivers 6.5 mg (equals (b) (4) sumatriptan succinate) over 4hours

13. ROUTE OF ADMINISTRATION: Transdermal

14. Rx/OTC DISPENSED: _X_Rx ___OTC

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

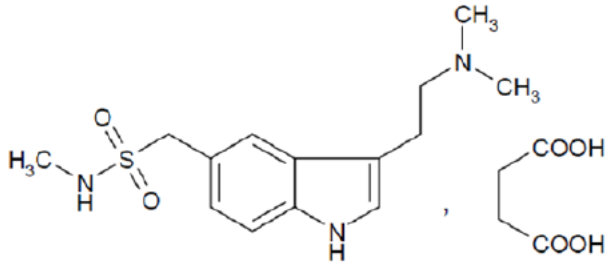
_____SPOTS product – Form Completed

___X___Not a SPOTS product

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

Sumatriptan Succinate:

1H-Indole-5-methanesulfonamide,3-[2-(dimethylamino)ethyl]-N-methyl-,butanedioate(1:1) [3-[2-(Dimethyl amino) ethyl]-N-methylindole-5-methanesulfonamide succinate (1:1)



Molecular Formula: $C_{18}H_{27}N_3O_6S$
Molecular Weight: 413.5

17. RELATED/SUPPORTING DOCUMENTS:

A. DMFs:

DMF #	TYPE	HOLDER	ITEM REFERENCED	CODE[1]	STATUS[2]	DATE REVIEW COMPLETED	COMMENTS
[redacted]			(b) (4)	1	Adequate	01/11/2011	Dr. C. Strasinger for NDA 202-278
				1	Adequate	01/11/2011	Dr. C. Strasinger for NDA 202-278
				3	Adequate	01/21/2010	Dr. Y. Hu for NDA (b) (4)
				4	Adequate		
				4	Adequate		
				3	Adequate	09/08/2010	by Andrew Langowski
				3	Adequate	02/01/2010	BingYuan Wu

[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

18. STATUS:

ONDQA:

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
Biometrics	N/A		
EES	Pending	6/30/2011	Office of Compliance
Pharm/Tox	N/A		
Biopharm	In vitro release method and specification is recommended for Complete Response	6/22/2011	Tapash Ghosh, PhD
LNC	N/A		
Methods Validation	TBD		Requested per ONDQA's policy 03/11/2011
DMEPA	N/A		
EA	Categorical exclusion granted	6/30/11	Raanan Bloom
Microbiology	N/A		

The Chemistry Review for NDA 202-278

The Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

NDA 202-287 for sumatriptan iontophoretic transdermal system is recommended for Complete Response from the CMC perspective. The applicant has not provided sufficient information to assure identity, strength, purity, and quality of the drug product. The Applicant needs to respond adequately to the CMC issues outlined in this review.

An overall "Pending" recommendation has been issued for the manufacturing and testing sites by the Office of Compliance.

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)

Drug Substance:
The drug substance is the succinate salt of sumatriptan. It is a white to almost white powder (b) (4) freely soluble in water. Much of the drug substance CMC information is cross referenced to the DMFs of its (b) (4) respectively). Different manufacturing processes are used at the two sites however the regulatory drug substance specification including impurity limits comply with USP standards – only site-specific solvent tests are part of the specification. Batch analysis results of lots from both sites met specifications. Stability data support a (b) (4) retest period for material from either site.

Drug Product:
The sumatriptan iontophoretic transdermal system (NP 101), is a disposable, single-use co-packaged drug/device combination product that utilizes iontophoretic technology to deliver sumatriptan transdermally for the treatment of acute migraine attacks The drug component portion of NP 101 is referred to as the reservoir card and consists of two separate reservoir pads imbibed with either (b) g of sumatriptan formulation ((b) (4) sumatriptan succinate containing (b) (4)

mg equivalent to 86 mg of sumatriptan base) or [(b)] g of salt formulation ([(b) (4)] sodium chloride). The device portion of NP 101 is the Electrode Patch (E-Patch) containing a [(b) (4)]

The system is manufactured as [(b) (4)]

Drug delivery is approximately four hours [(b) (4)] hours) after which time the system is automatically deactivated by the pre-programmed circuit. The quality of the system is controlled by tests for appearance, assay, [(b) (4)] identification, drug release, pouch tightness, impurities, microbial limits, water content, methyl paraben content and drug release. The electrode pad is controlled by connectivity, capacity, and fixed resistance testing. 9 months of stability data of the co-packaged product has been provided.

The reservoir card pads are [(b) (4)] It is intended that the commercial cartons will contain [(b) (4)] 6 pouched transdermal drug delivery systems (TDDS). The Applicant is requesting 12 months of expiration dating. Labeling has not been reviewed at this time. Labeling negotiations will not take place during this review cycle because of the Complete Response recommendation.

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

Sumatriptan iontophoretic transdermal system, 6.5 mg/4 hours is a drug device combination designed to be applied to the upper arm or thigh and activated by pressing a button. After 4 hours of delivery, the system will deactivate and should be removed and disposed of out of reach of children and pets. The product should be stored at room temperature.

C. Basis for Approvability or Not-Approval Recommendation

Specifications cannot be established per 21.CFR.314.50 to adequately assure identity, strength, quality, purity, potency and bioavailability of the product. A lack of uniformity of drug formulation distribution, and issues with drug formulation containment, safe disposal procedures, and patient usability raise concerns about the safety and efficacy of the product.

The Applicant has not provided sufficient information on raw material controls, manufacturing processes and process controls, and adequate specifications for assuring

consistent product quality of the drug substance and drug product. The applicant has not provided sufficient stability information for the drug product to assure strength, purity, and quality of the drug product during the proposed expiration dating period.

Labeling of the drug product backing is insufficient to assure the product can be appropriately identified during use. Carton and product insert labeling are not reviewed in this review cycle given the significant number of deficiencies.

Office of Compliance has issued a "Pending" overall recommendation for all facilities involved.

III. Administrative

A. Reviewer's Signature

B. Endorsement Block

ChemistName/Date: David Claffey, PhD; Caroline Strasinger, PhD 1-JUN-2011
ChemistryTeamLeaderName/Date: Martha Heimann, PhD; 1-JUN-2011
ProjectManagerName/Date: Teshara Bouie; 1-JUN-2011

C. CC Block

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/s/

CAROLINE STRASINGER
06/30/2011

THOMAS F OLIVER
06/30/2011
Signed for Dr. Terrance Ocheltree