

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

22-395

CHEMISTRY REVIEW(S)

Qutenza™
(Capsaicin) 8% Patch
NDA 22-395

**Summary of the Basis for the Recommended Action
from Chemistry, Manufacturing, and Controls**

Applicant: NeurogesX, Inc.
215 Bridgepointe Parkway, Suite 200, San Mateo
CA 94404-5067

Indication: Treatment of pain due to postherpetic neuralgia.

Presentation: The drug product is a thin, translucent patch of rectangular shape with rounded corners (200 mm x 140 mm). Each patch contains a (b) (4) polyester backing layer coated with 179 mg capsaicin (8% w/w; 640 mcg/cm²) in an adhesive matrix. The backing film is imprinted with “capsaicin 8%” for identification. The other side of the adhesive is covered with a removable polyester release liner that is slit to facilitate removal of the film from the patch prior to use. The patch is packaged in a (b) (4) pouch (b) (4) (b) (4)

The patches are supplied in a carton containing 1 or 2 patches and a 50 g tube of cleansing gel. The cleansing gel is a clear to opalescent, colorless semi-solid gel packaged in a white high density polyethylene tube sealed with a (b) (4) screw cap. The cleansing gel is used as a topical to remove residual capsaicin from the skin after the patch is discarded.

EER Status: Recommendations: Acceptable (8/24/09)

Consults: EA – Categorical exclusion granted under 21 CFR §25.31(c).
Statistics – R. Kelly (4/14/09)
Methods Validation – Revalidation by Agency was not requested

Original Submission: 13-October-2008

Re-submissions: N/A

Post-Approval CMC Agreements: None

Drug Substance:

While capsaicin is a natural substance found in chili peppers, the drug substance for Qutenza is manufactured entirely by (b) (4). Capsaicin is a white to off-white powder that is very soluble in several non-polar and amphiphilic solvents but only slightly soluble in water. The chemical name for capsaicin is (E)-8-methyl-N-vanillyl-6-nonenamide; *trans*-8-methyl-N-vanillyl-6-nonenamide; 6-nonenamide, (E)-N-[(4-hydroxy-3-methoxy-phenyl)methyl]-8-methyl and the molecular weight is 305.42. Two crystalline polymorphs have been identified with the chosen form being the stable at room temperature. A complete structural characterization of the drug substance was performed by IR spectroscopy, 1H and 13C NMR, and mass spectrometry. A USP capsaicin reference standard is employed as the primary reference standard for the capsaicin drug substance, and suitable reference standards have been prepared for the known impurities.

The drug substance is manufactured in a (b) (4). Critical process steps were identified and appropriate in-process controls are included. Drug substance specifications include appearance, color/clarity, identification (Infrared Spectroscopy), assay (HPLC), related compounds and total impurity (HPLC), water content (Coulometric Karl Fischer), residual solvents (GC), heavy metals, residue on ignition, and melting range. The drug substance specifications for impurities were deemed acceptable in consultation with the toxicology division. The retest period for the drug substance is (b) (4) based on real time stability data.

Conclusion: The drug substance is satisfactory

Drug Product:

Qutenza™ is a transdermal topical patch containing 8% capsaicin. The product is used by a medical professional cutting the patch to match the area of the skin affected by postherpetic neuralgia, removing the release liner, and applying the adhesive directly to the patient’s skin. Upon application, a small amount of the capsaicin (approximately 0.9%, according to the applicant) is absorbed into the skin over the 1-hour application time. The time between patch applications is up to 3 months, depending upon the patient’s response and level of pain. After patch removal, residual capsaicin is removed using a cleansing gel, which dissolves the capsaicin.

The drug product is a (b) (4)

(b) (4) include ethylcellulose, (b) (4) Other excipients silicone adhesive, and dimethicone. The manufacturing process employed for the patch (b) (4)

(b) (4) Critical process steps were identified and appropriate in-process controls are included. Drug product specifications include aspect (size and appearance), identification (IR, UV), assay (HPLC), degradation products (HPLC),

content uniformity, residual solvents, DGME content, release test, adhesive force, peel force, pouch integrity, and microbial content.

The Cleansing Gel is a clear to opalescent, viscous topical gel used to remove residual capsaicin from the skin after patch application. The Cleansing Gel contains polyethylene glycol (PEG) as the capsaicin (b) (4) and carbomer copolymer, disodium edentate (EDTA), butylated Hydroxyanisole (BHA), and sodium hydroxide in purified water. Specifications on the cleansing gel include appearance, identification (UV, FT-IR), package integrity, content uniformity (for BHA), viscosity, pH, assay (BHA, PEG, EDTA), water content, fill level and microbial content.

Based on the statistical review and the applicant's supporting stability data, a 36-month shelf life was granted for the finished packaged product, including both the patch and cleansing gel components.

Conclusion: The drug product is satisfactory.

Overall Conclusion: From a CMC perspective, the application is recommended for **approval**.

Christine M. V. Moore, Ph.D.
Division Director, DPA I (acting)
ONDQA/CDER/FDA

| Application Type/Number | Submission Type/Number | Submitter Name | Product Name |
|----------------------------|---------------------------|------------------------|------------------|
| ----- NDA-22395 | ----- ORIG-1 | ----- NEUROGESX INC | ----- Qutenza |

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

/s/

CHRISTINE M MOORE
11/06/2009

NDA 22-395

**Qutenza™
(Capsaicin) 8% Patch**

NeurogesX, Inc.

Theodore Carver

**Division of Pre-Marketing Assessment I, Branch
II, ONDQA**

**for the
Division of Anesthesia Analgesia and
Rheumatology Products (HFD-170)**

Table of Contents

| | |
|---|-----------|
| Table of Contents | 2 |
| Chemistry Review Data Sheet..... | 3 |
| The Executive Summary | 8 |
| I. Recommendations | 8 |
| A. Recommendation and Conclusion on Approvability | 8 |
| B. Recommendation on Phase 4 (Post-Marketing) Commitments, Agreements, and/or Risk Management Steps, if Approvable..... | 8 |
| II. Summary of Chemistry Assessments..... | 8 |
| A. Description of the Drug Product(s) and Drug Substance(s) | 8 |
| B. Description of How the Drug Product is Intended to be Used..... | 9 |
| C. Basis for Approvability or Not-Approval Recommendation..... | 9 |
| III. Administrative..... | 11 |
| A. Reviewer's Signature..... | 11 |
| B. Endorsement Block..... | 11 |
| C. CC Block | 11 |
| Chemistry Assessment | 12 |
| I. Review of CMC IR Response Received on July 30, 2009 | 12 |

Chemistry Review Data Sheet

1. NDA 22-395
2. REVIEW #:3
3. REVIEW DATE: 9/10/2009
4. REVIEWER: Theodore Carver

5. PREVIOUS DOCUMENTS:

| <u>Previous Documents</u> Document | <u>Date</u> |
|------------------------------------|-------------|
| CMC Review #1 and 2? | 5/11/2009 |
| Original NDA | 10-13-2008 |
| Amendment (3.2.P.8) | 03-06-09 |
| Amendment (3.2.S.7, 3.2.P.8) | 03-04-09 |
| Amendment (3.2.P.8) | 02-11-09 |
| Amendment | 06-25-09 |

6. SUBMISSION(S) BEING REVIEWED:

| <u>Submission(s) Reviewed</u> Document | <u>Date</u> |
|--|-------------|
| Amendment containing a CMC IR response | 7/30/2009 |

7. NAME & ADDRESS OF APPLICANT:

Name: NeurogesX, Inc.
Address: 215 Bridgepointe Parkway, Suite 200, San Mateo,
CA 94404-5067
Representative: Susan Rinne, V.P. Regulatory Affairs

Chemistry Review Data Sheet

Telephone: 650-358-3329

8. DRUG PRODUCT NAME/CODE/TYPE:

- a) Proprietary Name: Qutenza™
- b) Non-Proprietary Name (USAN): capsaicin patch, 8%
- c) Code Name/# (ONDC only):
- d) Chem. Type/Submission Priority (ONDC only):
 - Chem. Type:
 - Submission Priority: S

9. LEGAL BASIS FOR SUBMISSION: Original submission

10. PHARMACOL. CATEGORY: analgesic

11. DOSAGE FORM: dermal patch

12. STRENGTH/POTENCY: 8% capsaicin (640 mcg/cm²)

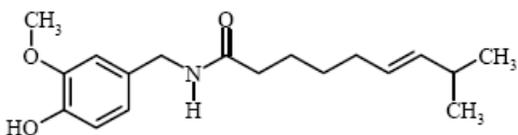
13. ROUTE OF ADMINISTRATION: topical

14. Rx/OTC DISPENSED: Rx OTC15. [SPOTS \(SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM\):](#) SPOTS product – Form Completed X Not a SPOTS product16. CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA,
MOLECULAR WEIGHT:

Chemistry Review Data Sheet

Chemical Names:

(E)-8-methyl-N-vanillyl-6-nonenamide; *trans*-8-methyl-N-vanillyl-6-nonenamide; 6-nonenamide, (E)-N-[(4-hydroxy-3-methoxy-phenyl)methyl]-8-methyl

Structural Formula:

Molecular Formula: C₁₈H₂₇NO₃

Molecular Weight: 305.42

17. RELATED/SUPPORTING DOCUMENTS:

A. DMFs:

| DMF # | TYPE | HOLDER I | TEM REFERENCED | CODE ¹ | STATUS ² | DATE REVIEW COMPLETED | COMMENTS |
|---------|------|----------|----------------|-------------------|---------------------|-----------------------|------------------------|
| (b) (4) | I | | (b) (4) | 1 | Adequate | 1/29/2009 | Reviewer: T. Carver |
| | V | | 4 | N/A | | | |
| | V | | 4 | N/A | | | |
| | V | | 4 | N/A | | | |
| | II | | 4 | N/A | | | |
| | II | | 4 | N/A | | | |
| | II | | 4 | N/A | | | |
| | II | | 4 | N/A | | | |
| | II | | 4 | N/A | | | |

Chemistry Review Data Sheet

| DMF # | TYPE | HOLDER I | TEM REFERENCED | CODE ¹ | STATUS ² | DATE REVIEW COMPLETED | COMMENTS |
|---------|------|----------|----------------|-------------------|---------------------|-----------------------|---------------------------------|
| (b) (4) | V | | (b) (4) | 4, 7 | N/A | C | ertified compendial (NF) in NDA |

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 APPL | ICATION NUMBER | DESCRIPTION |
|---------------|----------------|-------------|
| IND | (b) (4) | (b) (4) |

18. STATUS:

ONDC:

| CONSULTS/ CMC RELATED REVIEWS | RECOMMENDATION | DATE | REVIEWER |
|-------------------------------|---------------------------------------|--------------------------|------------------------|
| Biometrics | (b) (4) | 4/14/2009 Roswitha Kelly | |
| EES Accept | able | 8/24/09 | |
| Pharm/Tox Accept | able | 7/17/09 | Lawrence Leshin, Ph.D. |
| Biopharm N/A | | | |
| LNC | | | |
| Methods Validation | N/A according to ONDQA current policy | | |



CHEMISTRY REVIEW



Chemistry Review Data Sheet

| | | | |
|--------------|------------------------------|----------|--------------------------------|
| DMEPA | Acceptable | 5/5/2009 | Cathy A. Miller, M.P.H. B.S.N. |
| EA N/A | | | |
| Microbiology | N/A; non-sterile dosage form | | |

OGD:

| CONSULTS/ CMC RELATED REVIEWS | RECOMMENDATION | DATE RE | VIEWER |
|--------------------------------------|-----------------------|----------------|---------------|
| Microbiology | | | |
| EES | | | |
| Methods Validation | | | |
| Labeling | | | |
| Bioequivalence | | | |
| EA | | | |
| Radiopharmaceutical | | | |

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: n/a

The Chemistry Review for NDA 22-395

The Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

The CMC recommendation is approval. All outstanding CMC issues have been addressed by the applicant, and the Office of Compliance has issued an overall cGMP recommendation of acceptable.

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

The applicant agreed to submit the proposal to reduce the frequency of microbial testing as a postmarketing supplement. Additional data on at least 10 commercial batches will be presented as part of a CBE-30 postmarketing supplement.

II. Summary of Chemistry Assessments

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

Qutenza™ is a transdermal topical patch containing 8% capsaicin. The patch utilizes a matrix reservoir delivery system, wherein the active ingredient, capsaicin, (b) (4)

Upon application, the capsaicin solution becomes supersaturated as the DGME rapidly migrates into the dermis. A small amount of the capsaicin (approximately 0.9%, according to the applicant) is then absorbed into the skin over a 1-hour application time.

Drug Substance

Capsaicin is a white to off-white powder, very soluble in several non-polar and amphiphilic solvents but only slightly soluble in water. (b) (4)

(b) (4) A USP capsaicin reference standard is employed as the primary reference standard for the capsaicin drug substance, and suitable reference standards have been prepared for the known impurities. The drug substance

Executive Summary Section

specifications for impurities were deemed acceptable in consultation with the toxicology division. The retest period is (b) (4), based on real time stability data.

Drug Product

The patch is thin, translucent and has a rectangular shape with rounded corners. The patch area is 280 cm² (200 mm x 140 mm) and contains a total of 179 mg of capsaicin or 640 mcg of capsaicin per square cm of patch (8% w/w in the adhesive matrix). The patch consists of (b) (4)

The drug product is supplied in a carton containing 1 or 2 patches and a 50 g tube of cleansing gel to remove residual capsaicin from the skin after the patch is discarded. A shelf life of 36 months is granted for the finished product.

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

Qutenza® is an 8% capsaicin patch intended to be applied directly to areas of skin where patients are experiencing pain due to postherpetic neuralgia. Capsaicin, the active pharmaceutical ingredient, works by binding to the transient potential vanilloid 1 receptor, causing cutaneous nociceptors to become less sensitive (defunctionalized). The effect is intended to be local to the affected area and prolonged in duration. The time between patch applications is up to 3 months, depending upon the patient's response and level of pain. The patch is administered by a medical professional and may be cut into smaller pieces to match the area of the skin affected by postherpetic neuralgia. After patch removal, residual capsaicin is removed using a cleansing gel containing polyethylene glycol (b) (4) which dissolves the capsaicin.

C. Basis for Approvability or Not-Approval Recommendation

The active ingredient in this product is capsaicin, the spicy component of chili peppers. It is currently marketed as an unapproved drug in several topical products; however, it is considered to be a new molecular entity for the purpose of this review. All of the information required to evaluate the relatively straightforward manufacturing process was included in the application, with the exception of (b) (4) which is a purchased intermediate referenced to DMF (b) (4). DMF (b) (4) and the drug substance portions of the application were found to be acceptable. (b) (4)

The proposed drug substance specifications, including the specifications for the impurity cis-capsaicin and the residual solvent (b) (4), were found to be acceptable after consultation with the toxicology division.

Executive Summary Section

The manufacturing process employed for the patch

(b) (4)

(b) (4)

The patch may be cut by a medical professional into any desired shape to fit an affected area of the patient's skin. The applicant claimed that no leakage of drug occurs from the (b) (4) after cutting but did not provide data regarding the physical properties of or clinical experiences with, the patches after cutting. Additional justification was requested to support the assertion that cutting the patch into smaller pieces does not impact the (b) (4) function and the overall performance of the patch. The applicant provided summaries of the physical testing of cut pieces and experience from clinical use during trials that adequately address this issue. The patch is held in place by an overwrap or mechanical support in a clinical setting; therefore, the risk of patch movement or unintended exposure of mucous membranes to capsaicin is small.

The proposed finished product consists of either one or two patches and a 50g tube of cleansing gel packaged in a carton. The applicant provided 36-48 months long-term (25°C/60%RH) stability data for three primary lots of the patch product and 9-48 months long-term stability data for lots of the cleansing gel, as well as 6 months of stability data under accelerated conditions for both products. No significant stability issues were found in either product, and the patch limiting stability attribute was the *in vitro* drug release rate. The statistical analysis review (see review in DFS filed by Roswitha Kelly, biometrics reviewer) of the patch and cleansing gel data limited the shelf life to twice the amount of data provided for the cleansing gel (20 months, per ICH guidelines). Based on the statistical review and the applicant's supporting stability data, a 36-month shelf life was granted for the finished packaged product, including both the patch and cleansing gel components.

The applicant has satisfactorily addressed all issues and deficiencies raised during the CMC review. The Office of Compliance has issued an overall "acceptable" cGMP recommendation, following the evaluation of a contract microbiology drug product testing

Executive Summary Section

facility added to this NDA in the amendment dated 7/30/09. Therefore, the CMC recommendation for this NDA is approval.

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

T. Carver/CMC Reviewer, 04/24/09
A. Al-Hakim/Branch Chief, ONDQA

C. CC Block

Danae Christodoulou/Lead Chemist, ONDQA
Tanya Clayton/RPM, DAARP

2 pages of chemistry review has been withheld in full immediately following this page as B4 CCI/TS

| Application Type/Number | Submission Type/Number | Submitter Name | Product Name |
|-------------------------|------------------------|----------------|-------------------------------|
| NDA-22395 | ORIG-1 | NEUROGESX INC | NGX-4010 (CAPSAICIN PATCH 8%) |

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

/s/

THEODORE E CARVER

09/15/2009

Overall acceptable to OC and final CMC approval

ALI H AL HAKIM

09/15/2009

NDA 22-395

**Qutenza™
(Capsaicin) 8% Patch**

NeurogesX, Inc.

Theodore Carver

**Division of Pre-Marketing Assessment I, Branch
II, ONDQA**

**for the
Division of Anesthesia Analgesia and
Rheumatology Products (HFD-170)**

Table of Contents

| | |
|---|-----------|
| Table of Contents | 2 |
| Chemistry Review Data Sheet..... | 3 |
| The Executive Summary | 8 |
| I. Recommendations | 8 |
| A. Recommendation and Conclusion on Approvability | 8 |
| B. Recommendation on Phase 4 (Post-Marketing) Commitments, Agreements, and/or Risk Management Steps, if Approvable..... | 8 |
| II. Summary of Chemistry Assessments..... | 8 |
| A. Description of the Drug Product(s) and Drug Substance(s) | 8 |
| B. Description of How the Drug Product is Intended to be Used..... | 9 |
| C. Basis for Approvability or Not-Approval Recommendation..... | 9 |
| III. Administrative..... | 11 |
| A. Reviewer's Signature..... | 11 |
| B. Endorsement Block..... | 11 |
| C. CC Block | 11 |
| Chemistry Assessment | 12 |
| I. Review of CMC IR Response Received on June 24, 2009..... | 12 |
| II. Review of Drug Substance Specification | 20 |
| III. Labeling Comment to Applicant..... | 24 |

Chemistry Review Data Sheet

1. NDA 22-395
2. REVIEW #:2
3. REVIEW DATE: 6/26/2009
4. REVIEWER: Theodore Carver

5. PREVIOUS DOCUMENTS:

| <u>Previous Documents</u> | <u>Document Date</u> |
|------------------------------|----------------------|
| CMC Review #1 | 5/11/2009 |
| Original NDA | 10-13-2008 |
| Amendment (3.2.P.8) | 03-06-09 |
| Amendment (3.2.S.7, 3.2.P.8) | 03-04-09 |
| Amendment (3.2.P.8) | 02-11-09 |

6. SUBMISSION(S) BEING REVIEWED:

| <u>Submission(s) Reviewed</u> | <u>Document Date</u> |
|--|----------------------|
| Amendment containing a CMC IR response | 6/24/2009 |

7. NAME & ADDRESS OF APPLICANT:

Name: NeurogesX, Inc.
Address: 215 Bridgepointe Parkway, Suite 200, San Mateo,
CA 94404-5067
Representative: Susan Rinne, V.P. Regulatory Affairs

Chemistry Review Data Sheet

Telephone: 650-358-3329

8. DRUG PRODUCT NAME/CODE/TYPE:

- a) Proprietary Name: Qutenza™
- b) Non-Proprietary Name (USAN): capsaicin patch, 8%
- c) Code Name/# (ONDC only):
- d) Chem. Type/Submission Priority (ONDC only):
 - Chem. Type:
 - Submission Priority: S

9. LEGAL BASIS FOR SUBMISSION: Original submission

10. PHARMACOL. CATEGORY: analgesic

11. DOSAGE FORM: dermal patch

12. STRENGTH/POTENCY: 8% capsaicin (640 mcg/cm²)

13. ROUTE OF ADMINISTRATION: topical

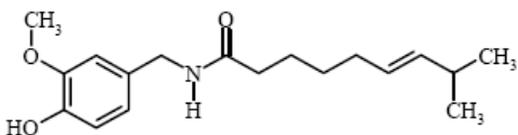
14. Rx/OTC DISPENSED: Rx OTC15. [SPOTS \(SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM\):](#) SPOTS product – Form Completed X Not a SPOTS product16. CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA,
MOLECULAR WEIGHT:

Chemistry Review Data Sheet

Chemical Names:

(E)-8-methyl-N-vanillyl-6-nonenamide; *trans*-8-methyl-N-vanillyl-6-nonenamide; 6-nonenamide, (E)-N-[(4-hydroxy-3-methoxy-phenyl)methyl]-8-methyl

Structural Formula:



Molecular Formula: C₁₈H₂₇NO₃

Molecular Weight: 305.42

17. RELATED/SUPPORTING DOCUMENTS:

A. DMFs:

| DMF # | TYPE | HOLDER | ITEM REFERENCED | CODE ¹ | STATUS ² | DATE REVIEW COMPLETED | COMMENTS |
|---------|------|--------|-----------------|-------------------|---------------------|-----------------------|------------------------|
| (b) (4) | II | | (b) (4) | 1 | Adequate | 1/29/2009 | Reviewer: T. Carver |
| | IV | | 4 | N/A | | | |
| | IV | | 4 | N/A | | | |
| | IV | | 4 | N/A | | | |
| | III | | 4 | N/A | | | |
| | III | | 4 | N/A | | | |
| | III | | 4 | N/A | | | |
| | III | | 4 | N/A | | | |
| | III | | 4 | N/A | | | |
| | III | | 4 | N/A | | | |

Chemistry Review Data Sheet

| DMF # | TYPE | HOLDER | ITEM REFERENCED | CODE ¹ | STATUS ² | DATE REVIEW COMPLETED | COMMENTS |
|---------|------|--------|-----------------|-------------------|---------------------|-----------------------|----------------------------------|
| (b) (4) | IV | | (b) (4) | 4, 7 | N/A | | Certified compendial (NF) in NDA |

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

18. STATUS:

ONDC:

| CONSULTS/ CMC RELATED REVIEWS | RECOMMENDATION | DATE | REVIEWER |
|-------------------------------|---------------------------------------|-----------|------------------------|
| Biometrics | (b) (4) | 4/14/2009 | Roswitha Kelly |
| EES | Pending | | |
| Pharm/Tox | Acceptable | | Lawrence Leshin, Ph.D. |
| Biopharm | N/A | | |
| LNC | | | |
| Methods Validation | N/A according to ONDQA current policy | | |



CHEMISTRY REVIEW



Chemistry Review Data Sheet

| | | | |
|--------------|------------------------------|----------|--------------------------------|
| DMEPA | Acceptable | 5/5/2009 | Cathy A. Miller, M.P.H. B.S.N. |
| EA | N/A | | |
| Microbiology | N/A; non-sterile dosage form | | |

OGD:

| CONSULTS/ CMC RELATED REVIEWS | RECOMMENDATION | DATE RE | VIEWER |
|--------------------------------------|-----------------------|----------------|---------------|
| Microbiology | | | |
| EES | | | |
| Methods Validation | | | |
| Labeling | | | |
| Bioequivalence | | | |
| EA | | | |
| Radiopharmaceutical | | | |

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: n/a

The Chemistry Review for NDA 22-395

The Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

The CMC recommendation is approval, pending the overall cGMP recommendation from the Office of Compliance. All outstanding CMC issues have been addressed by the applicant.

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

The applicant agrees to submit the proposal to reduce the frequency of microbial testing as a postmarketing supplement. Additional data on at least 10 commercial batches will be presented as part of a CBE-30 postmarketing supplement.

II. Summary of Chemistry Assessments

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

Qutenza™ is a transdermal topical patch containing 8% capsaicin. The patch utilizes a matrix reservoir delivery system, wherein the active ingredient, capsaicin, (b) (4)

Upon application, the capsaicin solution becomes supersaturated as the DGME rapidly migrates into the dermis. A small amount of the capsaicin (approximately 0.9%, according to the applicant) is then absorbed into the skin over a 1-hour application time.

Drug Substance

Capsaicin is a white to off-white powder, very soluble in several non-polar and amphiphilic solvents but only slightly soluble in water. (b) (4)

A USP capsaicin reference standard is employed as the primary reference standard for the capsaicin drug substance, and suitable

Executive Summary Section

The manufacturing process employed for the patch is (b) (4)

[REDACTED]

The patch may be cut by a medical professional into any desired shape to fit an affected area of the patient's skin. The applicant claimed that no leakage of drug occurs from the (b) (4) after cutting but did not provide data regarding the physical properties of or clinical experiences with, the patches after cutting. Additional justification was requested to support the assertion that cutting the patch into smaller pieces does not impact the (b) (4) function and the overall performance of the patch. The applicant provided summaries of the physical testing of cut pieces and experience from clinical use during trials that adequately address this issue. The patch is held in place by an overwrap or mechanical support in a clinical setting; therefore, the risk of patch movement or unintended exposure of mucous membranes to capsaicin is small.

The proposed finished product consists of either one or two patches and a 50g tube of cleansing gel packaged in a carton. The applicant provided 36-48 months long-term (25°C/60%RH) stability data for three primary lots of the patch product and 9-48 months long-term stability data for lots of the cleansing gel, as well as 6 months of stability data under accelerated conditions for both products. No significant stability issues were found in either product, and the patch limiting stability attribute was the *in vitro* drug release rate. The statistical analysis review (see review in DFS filed by Roswitha Kelly, biometrics reviewer) of the patch and cleansing gel data limited the shelf life to twice the amount of data provided for the cleansing gel (20 months, per ICH guidelines). Based on the statistical review and the applicant's supporting stability data, a 36-month shelf life was granted for the finished packaged product, including both the patch and cleansing gel components.

The list of deficiencies sent to the applicant included the above issues as well as additional issues relating to the drug product specifications, labeling, and use of secondary testing

Executive Summary Section

facilities. The applicant has satisfactorily addressed all issues and deficiencies raised during the CMC review. Therefore, the NDA is approvable at this time, pending the overall cGMP recommendation by the Office of Compliance.

III. Administrative

A. Reviewer's Signature

B. Endorsement Block

T. Carver/CMC Reviewer, 04/24/09
A. Al-Hakim/Branch Chief, ONDQA

C. CC Block

Danae Christodoulou/Lead Chemist, ONDQA
Tanya Clayton/RPM, DAARP

14 pages of chemistry has been withheld
in full immediately following this page as
B4 CCI/TS

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

/s/

Theodore Carver
7/1/2009 02:42:33 PM
CHEMIST
CMC review #2; IR response and DS spec

Ali Al-Hakim
7/1/2009 05:45:43 PM
CHEMIST

NDA 22-395

**Qutenza™
(Capsaicin) 8% Patch**

NeurogesX, Inc.

Theodore Carver

**Division of Pre-Marketing Assessment I, Branch
II, ONDQA**

**for the
Division of Anesthesia Analgesia and
Rheumatology Products (HFD-170)**

Table of Contents

| | |
|--|-----------|
| Table of Contents | 2 |
| Chemistry Review Data Sheet..... | 3 |
| The Executive Summary | 8 |
| I. Recommendations | 8 |
| A. Recommendation and Conclusion on Approvability | 8 |
| B. Recommendation on Phase 4 (Post-Marketing) Commitments, Agreements, and/or Risk Management Steps, if Approvable..... | 8 |
| II. Summary of Chemistry Assessments..... | 8 |
| A. Description of the Drug Product(s) and Drug Substance(s) | 8 |
| B. Description of How the Drug Product is Intended to be Used..... | 9 |
| C. Basis for Approvability or Not-Approval Recommendation..... | 9 |
| III. Administrative..... | 11 |
| A. Reviewer’s Signature..... | 11 |
| B. Endorsement Block..... | 11 |
| C. CC Block | 11 |
| Chemistry Assessment | 12 |
| I. Review Of Common Technical Document-Quality (Ctd-Q) Module 3.2: Body Of Data | 12 |
| S DRUG SUBSTANCE [capsaicin, (b) (4)] | 12 |
| P DRUG PRODUCT [8% capsaicin patch, NeurogesX]..... | 67 |
| A APPENDICES | 116 |
| R REGIONAL INFORMATION | 116 |
| II. Review Of Common Technical Document-Quality (Ctd-Q) Module 1 | 117 |
| A. Labeling & Package Insert | 117 |
| B. Environmental Assessment Or Claim Of Categorical Exclusion | 121 |
| Since the estimated concentration of drug substances in the aquatic environment at the expected point of entry is calculated to be less than 1 part per billion, the applicant requests categorical exclusion from preparing an environmental assessment report in accordance with 21 CFR 25.31 (b). | 124 |
| III. List Of Deficiencies To Be Communicated..... | 124 |

Chemistry Review Data Sheet

1. NDA 22-395
2. REVIEW #:1
3. REVIEW DATE: 5/11/2009
4. REVIEWER: Theodore Carver

5. PREVIOUS DOCUMENTS:

Previous Documents

Document Date

N/A

6. SUBMISSION(S) BEING REVIEWED:

Submission(s) Reviewed

Document Date

ORIGINAL

10-13-2008

Amendment (3.2.P.8)

03-06-09

Amendment (3.2.S.7, 3.2.P.8)

03-04-09

Amendment (3.2.P.8)

02-11-09

7. NAME & ADDRESS OF APPLICANT:

Name: NeurogesX, Inc.

Address: 215 Bridgepointe Parkway, Suite 200, San Mateo,
CA 94404-5067

Representative: Susan Rinne, V.P. Regulatory Affairs

Telephone: 650-358-3329

Chemistry Review Data Sheet

8. DRUG PRODUCT NAME/CODE/TYPE:

- a) Proprietary Name: Qutenza™
- b) Non-Proprietary Name (USAN): capsaicin patch, 8%
- c) Code Name/# (ONDC only):
- d) Chem. Type/Submission Priority (ONDC only):
 - Chem. Type:
 - Submission Priority: S

9. LEGAL BASIS FOR SUBMISSION: Original submission

10. PHARMACOL. CATEGORY: analgesic

11. DOSAGE FORM: dermal patch

12. STRENGTH/POTENCY: 8% capsaicin (640 mcg/cm²)

13. ROUTE OF ADMINISTRATION: topical

14. Rx/OTC DISPENSED: Rx OTC15. [SPOTS \(SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM\):](#)

 SPOTS product – Form Completed

 X Not a SPOTS product

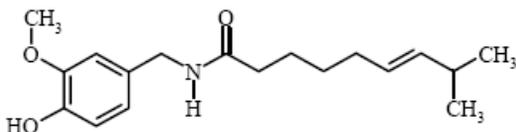
16. CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA,
MOLECULAR WEIGHT:

Chemistry Review Data Sheet

Chemical Names:

(E)-8-methyl-N-vanillyl-6-nonenamide; *trans*-8-methyl-N-vanillyl-6-nonenamide; 6-nonenamide, (E)-N-[(4-hydroxy-3-methoxy-phenyl)methyl]-8-methyl

Structural Formula:



Molecular Formula: C₁₈H₂₇NO₃

Molecular Weight: 305.42

17. RELATED/SUPPORTING DOCUMENTS:

A. DMFs:

| DMF # | TYPE | HOLDER | ITEM REFERENCED | CODE ¹ | STATUS ² | DATE REVIEW COMPLETED | COMMENTS |
|---------|------|--------|-----------------|-------------------|---------------------|-----------------------|------------------------|
| (b) (4) | II | | (b) (4) | 1 | Adequate | 1/29/2009 | Reviewer: T. Carver |
| | IV | | 4 | N/A | | | |
| | IV | | 4 | N/A | | | |
| | IV | | 4 | N/A | | | |
| | III | | 4 | N/A | | | |
| | III | | 4 | N/A | | | |
| | III | | 4 | N/A | | | |
| | III | | 4 | N/A | | | |
| | III | | 4 | N/A | | | |
| | III | | 4 | N/A | | | |

Chemistry Review Data Sheet

| DMF # | TYPE | HOLDER | ITEM REFERENCED | CODE ¹ | STATUS ² | DATE REVIEW COMPLETED | COMMENTS |
|---------|------|--------|-----------------|-------------------|---------------------|-----------------------|----------------------------------|
| (b) (4) | IV | | (b) (4) | 4, 7 | N/A | | Certified compendial (NF) in NDA |

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 | (b) (4) | LMX4® (4% Lidocaine cream) Sponsor (b) (4) Topical anesthetic for use prior to patch application. |

18. STATUS:

ONDC:

| CONSULTS/ CMC RELATED REVIEWS | RECOMMENDATION | DATE | REVIEWER |
|-------------------------------|---------------------------------------|-----------|--------------------------------|
| Biometrics | (b) (4) | 4/14/2009 | Roswitha Kelly |
| EES | Pending | | |
| Pharm/Tox | Pending | | Lawrence Leshin, Ph.D. |
| Biopharm | N/A | | |
| LNC | | | |
| Methods Validation | N/A according to ONDQA current policy | | |
| DMEPA | Acceptable | 5/5/2009 | Cathy A. Miller, M.P.H. B.S.N. |

Chemistry Review Data Sheet

| | | | |
|--------------|------------------------------|--|--|
| EA | N/A | | |
| Microbiology | N/A; non-sterile dosage form | | |

OGD:

| CONSULTS/ CMC RELATED REVIEWS | RECOMMENDATION | DATE RE | VIEWER |
|--------------------------------------|-----------------------|----------------|---------------|
| Microbiology | | | |
| EES | | | |
| Methods Validation | | | |
| Labeling | | | |
| Bioequivalence | | | |
| EA | | | |
| Radiopharmaceutical | | | |

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: n/a

The Chemistry Review for NDA 22-395

The Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

The application is approvable, pending satisfactory responses to the CMC Information Requests listed at the end of review ; the toxicology assessment of the drug substance acceptance criteria for impurities, and the overall cGMP recommendation from the Office of Compliance.

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

A post-approval stability commitment is required. The applicant agreed to place on stability the first three production lots, as well as an additional production lot per manufacturing calendar year, for both drug substance and drug product.

II. Summary of Chemistry Assessments

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

Qutenza™ is a transdermal topical patch containing 8% capsaicin. The patch utilizes a matrix reservoir delivery system, wherein the active ingredient, capsaicin, (b) (4)

Upon application, the capsaicin solution becomes supersaturated as the DGME rapidly migrates into the dermis. A small amount of the capsaicin (approximately 0.9%, according to the applicant) is then absorbed into the skin over a 1-hour application time.

Drug Substance

Capsaicin is a white to off-white powder, very soluble in several non-polar and amphiphilic solvents but only slightly soluble in water. (b) (4)

A USP capsaicin reference standard is employed

Executive Summary Section

as the primary reference standard for the capsaicin drug substance, and suitable reference standards have been prepared for the known impurities. The drug substance specifications for impurities are currently being evaluated by the toxicology division, in particular the limit of NMT^{(b) (4)} for the cis-capsaicin impurity. The retest period is^{(b) (4)} ^{(b) (4)}, based on real time stability data.

Drug Product

The patch is thin, translucent and has a rectangular shape with rounded corners. The patch area is 280 cm² (200 mm x 140 mm) and contains a total of 179 mg of capsaicin or 640 mcg of capsaicin per square cm of patch (8% w/w in the adhesive matrix). The patch consists of a^{(b) (4)}

The drug product is supplied in a carton containing 1 or 2 patches and a 50 g tube of cleansing gel to remove residual capsaicin from the skin after the patch is discarded. A shelf life of 36 months is granted for the finished product.

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

Qutenza® is an 8% capsaicin patch intended to be applied directly to areas of skin where patients are experiencing pain due to postherpetic neuralgia. Capsaicin, the active pharmaceutical ingredient, works by binding to the transient receptor potential vanilloid 1 receptor, causing cutaneous nociceptors to become less sensitive (defunctionalized). The effect is intended to be local to the affected area and prolonged in duration. The time between patch applications is up to 3 months, depending upon the patient's response and level of pain. The patch is administered by a medical professional and may be cut into smaller pieces to match the area of the skin affected by postherpetic neuralgia. After patch removal, residual capsaicin is removed using a cleansing gel containing polyethylene glycol^{(b) (4)} which solubilizes the capsaicin.

C. Basis for Approvability or Not-Approval Recommendation

The active ingredient in this product is capsaicin, the spicy component of chili peppers. It is currently marketed as an unapproved drug in several topical products, however, it is considered to be a new molecular entity for the purpose of this review. All of the information required to evaluate the relatively straightforward manufacturing process was included in the application, with the exception of^{(b) (4)}, which is a purchased intermediate referenced to DMF^{(b) (4)} DMF^{(b) (4)} and the drug substance portions of the application were found to be acceptable.^{(b) (4)}

Executive Summary Section

capsaicin. The acceptability of the proposed drug substance specifications for the impurity cis-capsaicin and the residual solvent (b) (4) are pending toxicological review.

The manufacturing process employed for the patch is (b) (4)



The patch may be cut by a medical professional into any desired shape to fit an affected area of the patient's skin. The applicant claimed that no leakage of drug occurs from the (b) (4) after cutting but did not provide adequate data regarding the physical properties of or clinical experiences with, the patches after cutting. Additional justification has been requested to support the assertion that cutting the patch into smaller pieces does not impact the (b) (4) function and the overall performance of the patch. The patch is held in place by an overwrap or mechanical support in a clinical setting; therefore, the risk of patch movement or unintended exposure of mucous membranes to capsaicin is small. The proposed finished product consists of either one or two patches and a 50g tube of cleansing gel packaged in a carton. The applicant provided 36-48 months long-term (25°C/60%RH) stability data for three primary lots of the patch product and 9-48 months long-term stability data for lots of the cleansing gel, as well as 6 months of stability data under accelerated conditions for both products. No significant stability issues were found in either product, and the patch stability appears to be limited by changes in the *in vitro* drug release time. The statistical review (see review in DFS filed by Roswitha Kelly, biometrics reviewer) of the patch and cleansing gel data limited the shelf life to twice the amount of data provided for the cleansing gel (20 months, per ICH guidelines). Based on the statistical review and the applicant's supporting stability data, a 36-month shelf life was granted for the finished packaged product.

The list of deficiencies includes the above issues as well as additional issues relating to the drug product specifications, labeling, and use of secondary testing facilities. Therefore, the NDA is approvable at this time. A final approval decision is pending satisfactory responses

Executive Summary Section

to the CMC information requests and the overall cGMP recommendation by the Office of Compliance.

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

T. Carver/CMC Reviewer, 04/24/09
A. Al-Hakim/Branch Chief, ONDQA

C. CC Block

Danae Christodoulou/PAL, ONDQA
Tanya Clayton/RPM, DAARP

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

/s/

Theodore Carver
5/13/2009 12:47:44 PM
CHEMIST

Ali Al-Hakim
5/14/2009 02:18:03 PM
CHEMIST

Initial Quality Assessment
Division of Pre-Marketing Assessment I, Branch II
Office of New Drug Quality Assessment
Division of Anesthesia, Analgesia and Rheumatology Products

| | | |
|---------------------------------|---|-----|
| OND Division: | Anesthesia, Analgesia and Rheumatology | |
| NDA: | 22-395 | |
| Applicant: | NeurogesX, Inc. | |
| Stamp date: | October 13, 2008 | |
| PDUFA Date: | August 13, 2008 | |
| Trademark: | Qutenza™ | |
| Established Name: | Capsaicin patch 8% (179 mg capsaicin / 280 cm ² patch) | |
| Dosage Form: | Patch (topical gel) | |
| Route of Administration: | Dermal (topical) | |
| Indication: | Reduction of neuropathic pain associated with postherpetic neuralgia (PHN). | |
| Pharmaceutical Assessment Lead: | Danae D. Christodoulou, Ph.D. | |
| | YES | NO |
| ONDQA Fileability: | <u>√</u> | ___ |
| Comments for 74-Day Letter: | ___ | ___ |

Summary, Critical Issues and Comments

A. Summary

The application is filed as a 505(b)(1) NDA. Capsaicin, the active pharmaceutical ingredient in the patch, is a highly selective agonist for the transient receptor potential vanilloid 1 (TRPV1). Capsaicin is a marketed unapproved product, e.g., Capsaizin ointment. However, NGX-4010 is differentiated from other capsaicin preparations by the high concentration (8%) of purified drug substance in the patch. Capsaicin is a natural product, the pungent component of chili peppers, isolated as the trans isomer from chili pepper plants of the genus *Capsicum*. The capsaicin used for the NGX-4010 patch is produced by total (b) (4) and is referred to as *trans*-capsaicin.

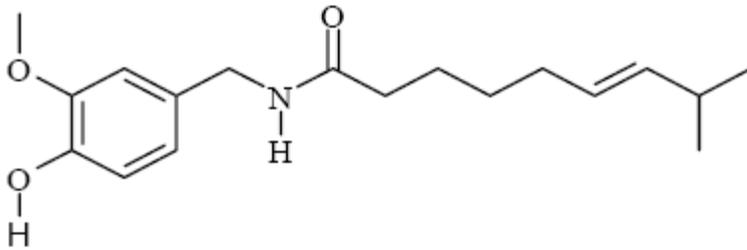
The pure drug substance is a hydrophobic, colorless, odorless, crystalline to waxy solid. Consequently, it is highly soluble to organic solvents of varying polarity and sparingly soluble in water (b) (4). The applicant, NeurogeX Inc., held a pre-NDA meeting with the Agency on 2/4/2008. Capsaicin patch was under development in IND 63,354.

B. Review, Comments and Recommendations

Drug Substance

Molecular Structure, Chemical Name, Molecular Formula and Molecular Weight

Figure 1: Structural Formula of Capsaicin



(E)-8-methyl-N-vanillyl-6-nonenamide)

C₁₈H₂₇NO₃

MW: 305.42

CAS 404-86-4

Capsaicin drug substance is sourced from (b) (4) Chemistry, Manufacturing and Controls information is submitted in the application. No Drug Master File is referenced for the drug substance. The flow chart of the drug substance synthesis is shown in Figure 2, below. Capsaicin is

(b) (4)

22 pages of Chemistry has been withheld in full immediately following this page as B4 CCI/TS

D. **Comments for 74-day Letter:**

- None

E. **Recommendation for fileability:** The NDA is fileable based on sufficient number of data and NDA batches as per ICH Q1A.

Recommendation for Team Review: The NDA is not recommended for team review. The drug substance is an NME, however, a marketed unapproved substance. The (b) (4) process is based on well established organic reactions and there are only (b) (4). The formulation does not include novel excipients and the manufacturing process for the drug product does not present complexity, e.g., novel delivery or device issues, nor significant development. The applicant provided detailed summaries and discussion of the critical attributes and manufacturing operations. In addition, commercial scale

batches have been produced, used for primary stability, and manufacturing process validation has been completed.

Consults:

The primary reviewer may request a statistical consult for the stability data and shelf life estimation, if deemed necessary. No other consults have been deemed necessary (see fileability template below) except for the Toxicology consults. Microbiological consult has not been requested, since this is a non-sterile dosage form.

Danae D Christodoulou, Ph.D.
Pharmaceutical Assessment Lead

10/28/2008
Date

Ali Al-Hakim, Ph.D.
Branch II Chief, ONDQA

10/30/2008
Date

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

/s/

Danae Christodoulou
10/31/2008 09:29:45 AM
CHEMIST
Initial Quality Assessment

Ali Al-Hakim
10/31/2008 09:42:56 AM
CHEMIST