

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:
22-395

OTHER REVIEW(S)

MEMORANDUM

To: **NDA 22-395**, Qutenza™

From: Danae Christodoulou, Ph.D., Pharmaceutical Assessment Lead, ONDQA

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

CC: Rik Lostritto, Division Director DPAMS, Chair LNC, ONDQA

Subject: Discussion of the Established Name

Qutenza™, is a patch containing 8% capsaicin in an adhesive matrix, for local, dermal administration. The applicant proposed the established name: (capsaicin) 8% patch. This was acceptable (see CMC Reviews by Ted Carver, 5/14/2009, 7/1/2009) based on the drug release properties and proposed use of the product. However, the SEALD review (see Review by J. M. Delasko, 11/3/2009) pointed out that “patch” is not a recognized dosage form as per USP<1121> nomenclature and USP <1151> dosage forms, and the USP recognized terminology is “transdermal system”.

During labeling negotiations on 11/12/2009 and 11/13/2009, the applicant objected to the designation “transdermal system” and cited the terminology “patch” in the CDER Standards Manual to more accurately describe this topical drug product.

In consultation with Rik Lostritto, Chair of LNC, it was concluded that “there is a gap in official USP terminology for a patch-like drug product which is not delivering drug systemically as its mode of action.” In addition, in the USP, both terminologies are connected to a release rate of active (as in crossing the skin for systemic application (e.g, nicotine, fentanyl, etc.) which is not the case for this capsaicin product.

Dr. Sharon Hertz, Deputy Director of DAARP, pointed out the historical use of the name patch in the approved products:

Flector® Patch (diclofenac epolamine topical patch) 1.3%

Lidoderm® (Lidocaine Patch 5%)

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

Based on the historical use of “patch” to describe topical dermal products of similar use, and the lack of recognized official terminology for their accurate description, it was concluded that the established name for Qutenza™ may be designated as “(capsaicin) 8% patch”.

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

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/s/

DANAE D CHRISTODOULOU
11/13/2009
Established name discussion

ALI H AL HAKIM
11/13/2009

SEALD LABELING REVIEW

APPLICATION NUMBER	NDA 22-395
APPLICANT	Neurogesx
DRUG NAME	QUTENZA (Capsaicin)
SUBMISSION DATE	October 16, 2008
SEALD REVIEW DATE	November 3, 2009
SEALD REVIEWER(S)	Jeanne M. Delasko, RN, MS

7 pages of draft labeling 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	----- Qutenza

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/s/

JEANNE M DELASKO
11/03/2009

LAURIE B BURKE
11/03/2009



**Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Surveillance and Epidemiology**

Date: July 22, 2009

To: Bob Rappaport, MD, Division Director
**Division of Anesthesia, Analgesia and Rheumatology
Products
(DAARP)**

Through: Jodi Duckhorn, MA, Team Leader
Division of Risk Management

From: Melissa Hulett, BSN, MSBA, RN
Patient Labeling Reviewer
Division of Risk Management

Subject: DRISK Review of Patient Labeling (Patient Package Insert),

Drug Name(s): Qutenza (capsaicin patch 8%)

Application Type/Number: NDA 22-395

Applicant/sponsor: Neurogesx

OSE RCM #: 2008-2059

1 INTRODUCTION

This review is written in response to a request by the Division of Anesthesia, Analgesia and Rheumatology Products (DAARP) for the Division of Risk Management (DRISK) to review the Applicant's proposed Patient Package Insert for Qutenza (capsaisin patch 8%). Please let us know if DAARP would like a meeting to discuss this review or any of our changes prior to sending to the Applicant.

2 MATERIAL REVIEWED

- Draft Qutenza (capsaisin patch 8%) Prescribing Information (PI) dated October 13, 2008, received October 16, 2008 and revised by the Review Division throughout the current review cycle.
- Draft Qutenza (capsaisin patch 8%) Patient Package Insert (PPI) dated October 13, 2008, received October 16, 2008 and revised by the review division throughout the current review cycle.

3 RESULTS OF REVIEW

In our review of the PPI, we have:

- simplified wording and clarified concepts where possible
- ensured that the PPI is consistent with the PI
- removed unnecessary or redundant information
- ensured that the PPI meets the Regulations as specified in 21 CFR 208.20
- ensured that the PPI meets the criteria as specified in FDA's Guidance for Useful Written Consumer Medication Information (published July 2006)

Our annotated PPI is appended to this memo. Any additional revisions to the PI should be reflected in the PPI.

Please let us know if you have any questions.

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/s/

Melissa Hulett
7/22/2009 01:47:47 PM
INTERDISCIPLINARY

Jodi Duckhorn
7/22/2009 02:00:03 PM
DRUG SAFETY OFFICE REVIEWER

MEMORANDUM

DEPARTMENT OF HEALTH AND HUMAN SERVICES
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Division of Drug Marketing, Advertising, and Communications

****PRE-DECISIONAL AGENCY MEMO****

DATE: July 15, 2009

To: Tanya Clayton – Regulatory Project Manager
Division of Anesthesia, Analgesia, and Rheumatology
Products (DAARP)

From: Mathilda Fienkeng – Regulatory Review Officer
Kendra Jones – Regulatory Review Officer
Division of Drug Marketing, Advertising, and
Communications (DDMAC)

Through: Samuel Skariah – Regulatory Review Officer
Division of Drug Marketing, Advertising, and
Communications (DDMAC)

Subject: **DDMAC draft labeling comments
NDA 22-395 QUTENZA (capsaicin) patch for topical use**

DDMAC has reviewed the proposed product labeling (PI), and patient labeling for QUTENZA (capsaicin) patch for topical use (Qutenza), submitted for consult on February 11, 2009.

The following comments are provided using the updated proposed PI sent via email on July 8, 2009 by Tanya Clayton. If you have any questions about DDMAC's comments, please do not hesitate to contact us.

General Comments:

DDMAC notes that on the container/carton labeling as well as the labeling for the cleansing gel, the trade name "QUTENZA" is presented along with the tag phrase, (b) (4) DDMAC recommends deleting this tag line since it is not part of the approved trade dress.

DDMAC notes that the letter size of the established name on the container/carton labeling is not at least half as large as, the proprietary name. We recommend revising this presentation to be consistent with the regulations.

The proposed trade carton makes reference to the indication and the efficacy of Qutenza (b) (4)

When making representations regarding the drug or its approved indication, it is expected that the most serious and most common risks associated with Qutenza be presented. We recommend that the specific references to the indication and efficacy be deleted or the proposed trade carton be revised to contain the appropriate fair balance.

Furthermore, DDMAC recommends revising the "instructions for use" on the carton labeling to be consistent with the revisions within the Full PI.

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/s/

Mathilda Fienkeng
7/15/2009 04:07:43 PM
DDMAC PROFESSIONAL REVIEWER

MEMORANDUM

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

CLINICAL INSPECTION SUMMARY

DATE: June 29, 2009

TO: Tanaya Clayton, Regulatory Project Manager
Neville Gibbs, M.D., Medical Officer
Division of Anesthesia, Analgesia and Rheumatology Products

FROM: Susan Leibenhaut, M.D.
Good Clinical Practice Branch I
Division of Scientific Investigations

THROUGH: Constance Lewin, M.D., M.P.H.
Branch Chief
Good Clinical Practice Branch I
Division of Scientific Investigations

SUBJECT: Evaluation of Clinical Inspections

NDA: #22-395

APPLICANT: NeurogesX, Inc.

DRUG: Capsaicin 8% patch

NME: No

THERAPEUTIC CLASSIFICATION: Standard

INDICATION: Prolonged reduction of neuropathic pain associated with
postherpetic neuralgia

CONSULTATION REQUEST DATE: January 5, 2009

DIVISION ACTION GOAL DATE: July 1, 2009

PDUFA DATE: August 16, 2009

I. B BACKGROUND:

NeurogesX, Inc submitted NDA 22-395 for capsaicin 8% patch (Qutenza) for the indication of prolonged reduction of neuropathic pain associated with postherpetic neuralgia. This is a routine audit request to assess data integrity and human subject protection for clinical trials submitted in support of this application.

Clinical inspections were conducted in response to a routine audit request to assess data integrity and human subject protection for clinical trials conducted for approval. The protocols inspected include protocol C116 entitled “A Randomized Double-Blind, Controlled Study of NGX-4010 for the Treatment of Postherpetic Neuralgia” and protocol C117 entitled “A Randomized, Double-Blind, Controlled Study of NGX-4010 for the Treatment of Postherpetic Neuralgia”

The primary efficacy endpoint in both protocols was percent change from baseline in the “average pain for the past 24 hours” Numeric Pain Rating Scale (NPRS) score (i.e., average of daily scores during Weeks 2 to 8, compared to average of baseline scores [Average of Baseline NPRS scores is defined as the mean of all NPRS scores starting from Day -14 through Day -1]) in the active group compared to the control group.

Sites were chosen for high enrollment. In addition, Dr. Bell’s site, Site 9 for Protocol #116, had the highest between group difference in change in average pain.

II. RESULTS (by Site):

Name of Clinical Investigator (CI) and Location	Protocol #: and # of Subjects:	Inspection Date	Final Classification
CI #1 Cynthia Bell, M.D. Anchor Research Center 680 Goodlette Road North Naples, Florida 34102	Protocol 116 20 subjects	March 30 to April 10, 2009	NAI
CI #2 I. Michael MineHart M.D. Advanced Pain Institute 931 Buena Vista Street, Suite # 303 Duarte, CA 91010	Protocol 116 25 subjects	March 31 to April 2, 2009	NAI
CI#3 Edwin D. Dunteman, M.D., MS A&A Pain Institute of St Louis 555 N. New Ballas, Ste 165 Creve Couer, MO 63141	Protocol 117 23 subjects	April 27 to May 1, 2009	NAI
CI#4 Marvin D. Tark, M.D. Drug Studies of America 1431 White Circle, Suite B Marietta, GA 30066	Protocol 117 15 subjects	April 20 to 23, 2009	Pending (Preliminary classification NAI)

Key to Classifications

NAI = No deviation from regulations.

VAI = Deviation(s) from regulations.

OAI = Significant deviations from regulations.

1. Cynthia Bell, M.D.
Anchor Research Center
680 Goodlette Road North, Suite 380
Naples, Florida 34102
 - a. **What was inspected:** For protocol 116 at this site, 26 subjects were screened, 23 subjects were enrolled, and 20 subjects completed the study. An audit of 26 subjects' records was conducted.
 - b. **General observations/commentary:** There was no under-reporting of adverse events and the primary endpoint was verified. No regulatory violations were noted.

- c. **Assessment of data integrity:** The study appears to have been conducted adequately, and the data generated by this site appear acceptable in support of the respective indication.

2. I. Michael MineHart, M.D.
Advanced Pain Institute
931 Buena Vista Street, Suite # 303
Duarte, CA 91010

- a. **What was inspected:** For protocol 116 at this site, 28 subjects were screened, 25 subjects were enrolled and 24 subjects completed the study. An audit of 25 subjects' records was conducted.
- b. **General observations/commentary:** There was no under-reporting of adverse events and the primary endpoint was verified. No regulatory violations were noted.
- c. **Assessment of data integrity:** The study appears to have been conducted adequately, and the data generated by this site may be used in support of the respective indication.

3. Edwin D. Dunteman, M.D.
A&A Pain Institute of St Louis
555 N. New Ballas, Ste 165
Creve Couer, MO 63141

- a. **What was inspected:** For protocol 117 at this site, 23 subjects were enrolled and 13 subjects were screen failures. Subject 3696 was terminated early due to inconsistent use of pain medications. Two subjects were terminated early because of adverse events; subject 2332 because of back pain and subject 3694 because of urologic surgery. An audit of all enrolled subjects' records was conducted.
- b. **General observations/commentary:** There was no evidence of under-reporting of adverse events, and the primary endpoint data were verified.
- c. **Assessment of data integrity:** The study appears to have been conducted adequately, and the data generated by this site may be used in support of the respective indication.

4. Marvin D. Tark, M.D.
Drug Studies of America
1431 White Circle, Suite B
Marietta, GA 30066

Note: Observations noted for this site are based on communications with the FDA investigator. An inspection summary addendum will be generated if conclusions change upon receipt and review of the establishment inspection report (EIR).

- a. **What was inspected:** For protocol 117 at this site, 19 subjects were screened and 15 subjects were enrolled in the study. Two of the subjects, 3064 and 3338, randomized to treatment group C60 opted for early termination due to unsatisfactory therapeutic response.
- b. **General observations/commentary:** There was no evidence of under-reporting of adverse events, and the primary endpoint data were verified.
- c. **Assessment of data integrity:** The study appears to have been conducted adequately, and the data generated by this site may be used in support of the respective indication.

III. OVERALL ASSESSMENT OF FINDINGS AND RECOMMENDATIONS

The inspections of all four clinical sites did not find regulatory violations. The final classification for Dr. Tark is pending. An addendum to this clinical inspection summary will be forwarded to the review division should there be a change in the final recommendation or additional observations of clinical and regulatory significance are discovered after reviewing the EIR.

The data from all sites appear acceptable in support of the proposed indication.

Susan Leibenhaut, M. D.
Good Clinical Practice Branch I
Division of Scientific Investigations

CONCURRENCE:

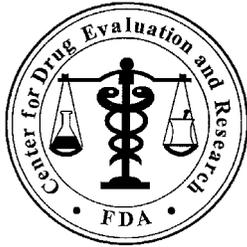
Constance Lewin, M.D., M.P.H
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/s/

Susan Leibenhaut
6/29/2009 03:11:23 PM
MEDICAL OFFICER

Constance Lewin
6/29/2009 03:40:16 PM
MEDICAL OFFICER



**Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Surveillance and Epidemiology**

Date: June 18, 2009

To: Bob Rappaport, MD, Director
Division of Anesthesia, Analgesia and Rheumatology Products

Through: Kellie Taylor, PharmD, Team Leader
Denise Toyer, PharmD, Deputy Director
Carol Holquist, RPh, Director
Division of Medication Error Prevention and Analysis

From: Cathy A. Miller, MPH, RN, Safety Evaluator
Division of Medication Error Prevention and Analysis

Subject: Label and Labeling Review

Drug Name(s): Qutenza (Capsaicin Patch 8 %)

Application Type/Number: NDA # 22-395

Applicant/Applicant: N eurogesX, Inc.

OSE RCM #: 2008-2059

CONTENTS

EXECUTIVE SUMMARY	3
1 BACKGROUND	3
1.1 Introduction	3
1.2 Regulatory History	3
1.3 Product Information	3
2 METHODS AND MATERIALS	5
3 RESULTS.....	6
3.1 Qutenza Carton Labeling	6
3.2 Qutenza Pouch Container Label	6
3.3 Cleansing Gel For Qutenza	7
3.4 Package Insert Labeling	7
4 DISCUSSION	8
4.1 Instructions for Use.....	8
4.2 Pre-Treatment With Topical Anesthetic	8
4.3 Use of Nitrile Gloves When Handling Qutenza Patch.....	8
4.4 Cleansing Gel for Qutenza.....	9
4.5 Frequency of Administration for Qutenza Patch	10
4.6 Opioid Use Statement in Qutenza Patch Insert Labeling.....	10
5 CONCLUSIONS and RECOMMENDATIONS.....	10
5.1 Comments to the Division.....	11
5.2 Comments to the Applicant.....	13
6 APPENDICES.....	14

EXECUTIVE SUMMARY

The results of the Label and Labeling Risk Assessment found that the presentation of information on the proposed container labels for Qutenza (Capsaicin Patch 8 %) is vulnerable to confusion that could lead to medication errors. Specifically, we have concerns about certain elements of the warning information provided in product insert labeling, and displayed on container labels and carton labeling, that applies to pre-treatment information, as well as handling of the product. Additionally, we have questions surrounding the adequacy of the materials supplied with the Qutenza Patch, specifically in the configuration that includes (2) Qutenza patches with only (1) container of Cleansing Gel.

The Division of Medication Error Prevention and Analysis (DMEPA) believes the risks we have identified can be addressed and mitigated prior to approval, and provides recommendations in Section 6.

1 BACKGROUND

1.1 INTRODUCTION

This review was written in response to a request from the Division of Anesthesia, Analgesia and Rheumatology Products for assessment of the container label, carton and insert labeling for Qutenza (Capsaicin Patch 8 %).

1.2 REGULATORY HISTORY

In August 2004, the Applicant submitted proposed proprietary name, (b) (4), for review in OSE Review #04-0241 under investigational new drug application (IND 63-354) for Capsaicin Patch 8 %. At that time, DMEPA had no objection to the name, (b) (4). In September 2007, the Applicant withdrew the name and requested the review of proposed proprietary name, (b) (4) however, on October 13, 2008, the Applicant withdrew their proposal for the proprietary name, (b) (4) with the submission of their new drug application (NDA 22-395) and requested the review of a new proposed proprietary name, Qutenza, along with proposed labels and labeling.

1.3 PRODUCT INFORMATION

Qutenza (Capsaicin Patch 8%) is indicated for the management of neuropathic pain in patients with post-herpetic neuralgia (b) (4). (b) (4) is available as a topical patch containing a total of 179 milligrams (mg) of Capsaicin (640 micrograms (mcg) of Capsaicin per square centimeter of patch).

Qutenza should be administered only by a physician or a health care professional under the direct supervision of a physician. Distribution of the Qutenza patch will be limited to the physician office and will not be available through retail pharmacies. Qutenza should be applied to the most painful area with recommended dosing of a single sixty-minute application of up to four Qutenza patches. Treatment may be repeated every three months or as warranted by the return of pain.

During application of Qutenza patches, only nitrile (not latex) gloves should be worn and while cleansing treatment area after application because latex gloves do not provide adequate protection.

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2 METHODS AND MATERIALS

This section describes the methods and materials used by DMEPA conducting a label, labeling, and/or packaging risk assessment. The primary focus of the assessment is to identify and remedy potential sources of medication error prior to drug approval. DMEPA defines a medication error as any preventable event that may cause or lead to inappropriate medication use or patient harm while the medication is in the control of the health care professional, patient, or consumer.¹

The label and labeling of a drug product are the primary means by which practitioners and patients (depending on configuration) interact with the pharmaceutical product. The container label and carton labeling communicate critical information including proprietary and established name, strength, dosage form, container quantity, expiration, and so on. The insert labeling is intended to communicate to practitioners all information relevant to the approved uses of the drug, including the correct dosing and administration.

Given the critical role that the label and labeling has in the safe use of drug products, it is not surprising that 33 percent of medication errors reported to the United States Pharmacopeia-

¹ National Coordinating Council for Medication Error Reporting and Prevention. <http://www.nccmerp.org/aboutMedErrors.html>. Last accessed 10/11/2007.

Institute for Safe Medication Practices Medication Error Reporting Program may be attributed to the packaging and labeling of drug products, including 30 percent of fatal errors.²

Because the DMEPA staff analyzes reported misuse of drugs, the DMEPA staff is able to use this experience to identify potential errors with all medications similarly packaged, labeled or prescribed. DMEPA uses Failure Mode and Effects Analysis (FMEA) and the principles of human factors to identify potential sources of error with the proposed product labels and insert labeling, and provide recommendations that aim at reducing the risk of medication errors.

DMEPA reviewed the following labels and labeling submitted by the Applicant on October 13, 2008 for our review (see Appendices A through F)

- Qutenza Pouch Labeling (Front and Back)
- Qutenza Patch Backing Label
- Qutenza Patch Carton Labeling
- Qutenza Container Label for Cleansing Gel (50 gram tube)
- Qutenza Package Insert Labeling (no image)

On February 12, 2009, the Applicant also submitted samples of the Qutenza product for review including:

- One Demonstration Patch (without active ingredient) packaged in pouch (no image)
- One 50 gram Sample tube of Cleansing Gel (no image)

3 RESULTS

3.1 QUTENZA CARTON LABELING

Pre-treatment with Topical Anesthetic: The instructions for use provide directions to pre-treat with a topical anesthetic however, a specific topical anesthetic, dosage form or strength is not provided with the instructions.

Handling Qutenza Patch with Nitrile Gloves: There is no statement included in the instructions for use steps displayed on the carton labeling cautioning to only use nitrile gloves when handling the Qutenza patch.

Instructions for Use: The pictures in Instructions for Use section of the carton labeling do not always correlate with the text instructions that appear adjacent to the picture and the representation of certain illustrations are unclear (i.e. it is not clear that the pictures represent the patient's abdomen)

3.2 QUTENZA POUCH CONTAINER LABEL

Handling Qutenza Patch with Nitrile Gloves: There is no statement on the principal display panel of the pouch label cautioning to only use nitrile gloves when handling the Qutenza patch.

² Institute of Medicine. Preventing Medication Errors. The National Academies Press: Washington DC. 2006. p275.

3.3 CLEANSING GEL FOR QUTENZA

Cleansing Gel Use After Patch Administration: The principal display panel of the Cleansing Gel for Qutenza container label does not provide a directive specifying its exclusive use “after administration of the Qutenza Patch”.

Cleansing Gel Supplied: The packaging configuration that includes (2) Qutenza patches only includes (1) 50 gram tube of Qutenza Cleansing Gel. DMEPA questions whether (1) tube provides an adequate supply for use if both patches are used.

3.4 PACKAGE INSERT LABELING

3.4.1 Package Insert Labeling

The warning statement regarding the use of nitrile gloves in labeling reads “Use only nitrile (not latex) gloves when handling Qutenza and when cleaning treatment areas”. Since latex gloves are not an option for use when handling Qutenza, the statement should include additional language that provides the rationale for using only nitrile glove.

Additionally, the warning statement about the use of nitrile gloves when handling Qutenza Patch in the Full Prescribing Information Dosage and Administration section ‘Instructions for Use’ of the package insert labeling appears after most of the application instructions, rather than at the beginning of instructions. Additionally, reference to the use of nitrile gloves appears in Section 2.2 Preparation and Handling, but is located after the Instructions for Use section that contains instructions for preparing and administering the Qutenza patch.

The information contained in Section 2.2 Preparation and Handling appears disjointed with the precautions about the use of nitrile gloves for preparation and handling, combined with precautions about the disposal of all the Qutenza product elements.

The pictures in Section 2 Dosage and Administration, Instructions for Use do not always correlate with the text instructions that appear adjacent to the picture and the representation of certain illustrations are unclear (i.e. it is not clear that the pictures represent the patient’s abdomen)

Frequency of Administration for Qutenza Patch: The Dosage and Administration instructions state that “treatment with Qutenza may be repeated every three months” however the additional “as warranted by the return of pain” does not provide the practitioner with clear directives regarding frequency of use or other application parameters regarding reapplying the patch if an application site reaction has occurred.

Pre-treatment with Topical Anesthetic: Instructions for use provide directions to pre-treat with a topical anesthetic, however, no specific topical anesthetic recommendation, dosage form, strength or information regarding preferred level of topical analgesia is provided with the instructions.

Opioid Use Warning Information: DMEPA questions the relevance of including warning information about other products (opioid) in the Qutenza package insert labeling. The Warning and Precaution and Patient Counseling Information sections of insert labeling, state that opioid use for pretreatment of pain affects the “ability to perform potentially hazardous activities such as driving or operating machinery.”

The information contained in Section 2.1 “Additional Measures” describe possible adverse events (may cause transient local irritation and pain) and therefore, appear to be displaced in the wrong section.

4 DISCUSSION

Our review of the proposed labels and labeling identified several areas of needed improvement. These areas are outlined below.

4.1 INSTRUCTIONS FOR USE

The Instructions for Use that appear in both Dosage and Administration Section 2 of the Package Insert labeling and displayed on the Qutenza Carton labeling includes pictures adjacent to the written instructions. The pictures do not consistently correlate with important steps that are written adjacent to the illustrations. For example, the ‘Apply’ section illustrates the provider applying the patch while pulling back the release liner and smoothing the patch onto the skin, however, the text adjacent to the picture includes additional information and directives including inspecting the pouch, tearing the pouch along the three dashed lines, describing the patch appearance on both sides, and cutting the patch. The discordance between the pictures illustrated in the Instructions for Use and the written instructions adjacent to the pictures may lead to confusion during administration of the patch and the provider may overlook important steps in the Qutenza Patch application process, including cleaning the skin, properly cutting the patch after identifying the treatment site size, properly removing the patch after administration and disposing of all treatment material.

Additionally, the pictures used throughout each step of the Instructions for Use section includes a vague anatomical representation of the patient’s abdomen and the pictures appears more like a rectangular surface rather than being clearly identifiable as part of the abdominal area. A clearer anatomical representation of a patient’s abdomen may provide clarity to the provider referring to the pictures for administration instructions.

4.2 PRE-TREATMENT WITH TOPICAL ANESTHETIC

The dosage and administration information provided on the carton and insert labeling direct to pre-treat the area with a topical anesthetic, however, there is no information about the dosage form to be used (gel, liquid, solution, patch or cream), strength (2 %, 2.5 %, 4 %, 5 %) or the preferred level of topical analgesia is recommended for pre-treatment. (b) (4)

, there is no specific directive in the dosage and administration and instructions for use sections of insert labeling or carton labeling to provide clear directives to the treating physicians about the recommended topical anesthetic to use. Because the patient population for which this product historically have significant pain associated with their symptoms, it is important to provide adequate directives about pre-treatment anesthetic use before administration of the Qutenza patch, as well as the intended level of typical analgesia, which can vary from superficial to a more deep tissue pain control. DMEPA contacted the Division of Anesthesia, Analgesia and Rheumatology Products about the Applicant’s pre-administration topical anesthetic use. The Division states that the Applicant utilized an unapproved marketed formulation product called 4 % LMX cream as the local anesthetic pre-patch application product and they also have concerns.

4.3 USE OF NITRILE GLOVES WHEN HANDLING QUTENZA PATCH

The warning information regarding the use of nitrile gloves may not adequately alert health care practitioners that latex gloves are not an option for use when handling the Qutenza patch. Although the warning statement reads “Use only nitrile (not latex) gloves when handling Qutenza and when cleaning treatment areas”, DMEPA believes that additional language should be provided to clarify why latex gloves should not be used in the event practitioners interpret the statement as suggesting nitrile glove use is a preference rather than a requirement. DMEPA sought clarification from the Applicant about the use of nitrile versus latex gloves when handling Qutenza patch and

materials. On May 15, 2009, the Applicant provided the requested information stating “Capsaicin dissolved in solvents such as Diethylene Glycol Monoethylether (DGME) can penetrate readily through latex gloves but not through nitrile gloves. Therefore, nitrile gloves are recommended for handling and disposal of Qutenza to minimize the potential for skin contact with Capsaicin as latex gloves may not provide adequate protection.” This clarification provided by the Applicant confirms that the use of latex gloves when handling Qutenza could result in absorption through the gloves and potential damage to the skin. After discussing the issue further with the Division of Anesthesia, Analgesia and Rheumatology on May 15, 2009, they concurred that, given the potential for inadequate protection from Capsaicin with latex gloves, the use of nitrile gloves should be a requirement.

Additionally, the statement regarding the use of nitrile gloves appears after the administration instructions and ‘Instructions for Use’ in the Highlights of Prescribing Information, Dosage and Administration and the Full Prescribing Information Dosage and Administration section, respectively. It is important that the warning statement about nitrile glove use is located at the beginning of each Dosage and Administration section, alerting the provider early in the treatment phase about nitrile glove use while administering the patch and while cleansing the Capsaicin residue from the skin after administration.

We also note that Section 2.2 Preparation and Handling combines preparation, handling and disposal information into one section. Combining this information in one section appears disjointed since these actions occur in distinct phases of the administration process, before, during and after the administration of the Qutenza patch. As noted above, the ‘Preparation’ portion of Section 2.2 includes reference to the use of nitrile gloves during the administration phase and skin cleaning phase of treatment and DMEPA is recommending that this information be added accordingly, to the beginning of the “Instructions for Use”. Since the information that remains addresses the disposal of Qutenza patch and materials, performed after the Qutenza Patch is removed and the area is cleansed, this information would more sequentially be located after the ‘Cleanse’ step in the “Instructions for Use” and there would be no need for Section 2.2 “Preparation and Handling”.

We also note that the statement regarding the use of nitrile gloves on the Qutenza carton labeling Instructions for Use section or the Qutenza Patch Pouch label. This information should be prominently displayed on both of these elements of the Qutenza labels and labeling to assure that treating health care providers are cautioned about this important directive before the product is torn from the pouch and administered to the patient.

4.4 CLEANSING GEL FOR QUTENZA

The Cleansing Gel for Qutenza is provided to assure that the active ingredient, Capsaicin, is thoroughly removed from the skin after application and removal of the Qutenza Patch. However, because the administration of the Qutenza patch includes a pre-treatment cleaning of the area (with mild soap and water), we have concerns that practitioners administering the post-treatment Cleansing Gel for Qutenza product may inadvertently use it as a pre-treatment cleansing agent, given the word ‘cleansing’ in the Gel name implies cleaning the area, as stated in the pre-treatment instructions for use. Although this misuse of the product may not necessarily result in an adverse event, it may result in having an inadequate supply of the product for its intended use after removal of the Qutenza patch. In order to provide practitioners with clear instructions about the use of this product, it may be helpful to add a statement about its use “after application of the Qutenza Patch”.

Additionally, we note that the applicant is providing the Qutenza product as both a single patch with one 50 gram tube of Cleansing Gel for Qutenza, and also as two patches and one 50 gram tube of Cleansing Gel for Qutenza. DMEPA has concerns that the packaging configuration that includes two patches and only one tube of Cleansing Gel may not provide adequate Cleansing Gel

if multiple administration sites are treated. Instruction for use provided direct the practitioner to ‘generously apply Cleansing Gel’ with an accompanying picture that illustrates a user squeezing out a generous amount of gel onto the skin. Certain patients may have many treatment areas requiring numerous cut pieces of Qutenza patches be applied, creating a large body surface area that will requiring application of the cleansing gel. If this results in an inadequate supply of the Cleansing Gel, there is a risk that all of the treatment area(s) where the Qutenza patch were applied will not be adequately cleansed and subsequently, not all of the active ingredient, Capsaicin, will be removed from the skin.

4.5 FREQUENCY OF ADMINISTRATION FOR QUTENZA PATCH

The Dosage and Administration instructions state that “Treatment with Qutenza may be repeated every three months *or as warranted by the return of pain*” whereas, the pouch container label and carton labeling have the statement “every 3 months”. Although the “every three months” provides a degree of guidance for the treating practitioner about the frequency of use, the additional statement “or as warranted by the return of pain” is arbitrary in nature, and may mislead practitioners about the minimum time period between treatments that is required before reapplication of the product is safe. The “or as warranted by the return of pain” could lead practitioners to believe that reapplication can occur at anytime following the last Qutenza Patch treatment. It is not apparent in the information provided in the insert labeling what time period between treatments was safely observed therefore, it is unclear how the frequency of use (every 3 months or as warranted by return of pain) was determined. The Applicant’s directive for frequency of use should either be more explicit as to the minimum required time before reapplying the patch or provide a quantitative time period. Ambiguous statements such as “or as warranted by the return of pain” should not be used because they are confusing.

4.6 OPIOID USE STATEMENT IN QUTENZA PATCH INSERT LABELING

DMEPA questions the appropriateness of including warning information about other products (opioid) in the Qutenza package insert labeling. The Warning and Precaution Section 5 and Patient Counseling Information sections of insert labeling state that opioid use for pretreatment of pain affects the “ability to perform potentially hazardous activities such as driving or operating machinery.” Since this warning information is provided in the ‘opioid’ product labeling, DMEPA is unclear about the necessity to include the information as part of the Qutenza product labeling and we defer to the Division to provide additional guidance or rationale.

5 CONCLUSIONS AND RECOMMENDATIONS

The Label and Labeling Risk Assessment findings indicate that the presentation of information on the container labels, carton and insert labeling introduces vulnerability to confusion that could lead to medication errors as identified in Section 3. DMEPA believes the risks we have identified can be addressed and mitigated prior to drug approval, and provide recommendations in Section 5.2.

5.1 COMMENTS TO THE DIVISION

DMEPA has completed our review of proposed container labels, carton and insert labeling for Qutenza (Capsaicin Patch 8 %) and has provided our recommendations to the Applicant in Section 5.2.

A. We understand from our communication with DAARP on April 6, 2009, that the Applicant used an unapproved marketed formulation product called for 4 % LMX cream as the local anesthetic pre-patch application product. DMEPA defers to the Division for further clarification on the specific topical anesthetic product information to be used in pre-treating the skin prior to Qutenza Patch administration. As discussed above, the information in the package insert labeling and on the carton labeling do not identify a particular product, active ingredient, dosage form (gel, liquid, solution, patch or cream), strength or information regarding the desired level of topical analgesia for pre-treatment.

B. Package Insert Labeling Highlights of Prescribing Information

Since Capsaicin dissolves in solvents such as Diethylene glycol Monoethylether (DGME) which can penetrate readily through latex gloves but not nitrile gloves, additional language should be included with the warning statement to assure that health care practitioners understand that the use of nitrile gloves is not recommended but rather required due to the risk of Capsaicin exposure to the skin. We recommend language such as “Use only nitrile gloves when handling Qutenza and when cleaning treatment areas *as latex gloves do not provide adequate protection from Capsaicin absorption through latex gloves and subsequent exposure to the skin.*” This statement should appear at the beginning so as to appropriately alert healthcare professionals before they handle or administer Qutenza Patch.

C. Package Insert Labeling, Full Prescribing

1. Dosage and Administration Section 2

The frequency of administration statement currently reads: “Treatment with Qutenza may be repeated every three months *or as warranted by the return of pain*”. This statement is ambiguous and open to interpretation. The “or as warranted by the return of pain” portion of the statement needs to be quantitative and align with data supported in the clinical trials for Qutenza. Revise this information to accurately reflect supporting data for the product’s frequency of administration.

2. Dosage and Administration, Instructions for Use Section 2

a. Since Capsaicin dissolves in solvents such as Diethylene glycol Monoethylether (DGME) which can penetrate readily through latex gloves but not nitrile gloves, additional language should be included with the warning statement to assure that health care practitioners understand that the use of nitrile gloves is not recommended but rather required due to the risk of Capsaicin exposure to the skin. We recommend language such as “Use only nitrile gloves when handling Qutenza and when cleaning treatment areas *as latex gloves do not provide adequate protection from Capsaicin absorption through latex gloves and subsequent exposure to the skin.*” This statement should appear at the beginning so as to appropriately alert healthcare professionals before they handle or administer Qutenza Patch.

b. We are concerned that your packaging configuration includes (2) Qutenza Patches but only (1) 50 gram tube of “Cleansing Gel for Qutenza” may not provide adequate product if multiple treatment sites are used to apply several portions of

Qutenza Patches. In the Cleanse subsection, clarify the amount of Cleansing Gel to apply per treatment area as labeling suggests “generous amount”.

- c. Revise the Instructions for Use Section of the Dosage and Administration section of insert labeling so that the pictures illustrated correlate with the text that is directly adjacent to the picture. As currently represented, there are additional instructions presented in the text of each step (Identify, Anesthetize, Apply, Remove and Cleanse) that are not represented with an illustration. We recommend either adding illustrative pictures to important administration steps that are not currently represented (i.e. pre-treatment washing the area, inspecting the pouch, illustrating the patch with backing layer, cutting the patch, post-treatment cleaning of the area and disposing of all treatment material or moving the text that does not correlate with the adjacent picture directly beneath that section.
 - d. Revise the picture representing the ‘Remove’ section. The picture currently used to represent the appropriate removal of the Qutenza patch from the skin does not clearly illustrate that the patch is being rolled ‘inward’ so that the medicated side of the match is not exposed after the patch is removed.
 - e. Revise the pictures in all sections of the Instructions for Use so that they provide a clearer anatomical representation of the abdomen. As currently presented, it is not clear that this illustration is a patient’s abdomen.
3. Dosage and Administration, Section 2.1 Additional measures
This section discusses possible adverse events associated with the use of Qutenza Patch (may cause transient local irritation and pain), along with recommendations for treating these symptoms if they occur. DMEPA questions whether this information may be more suitably located under Section 6 Adverse Reactions, however, we defer to the review division and/or the SEALD team for further evaluation.
 4. Dosage Administration, Section 2.2 Preparation and Handling Precautions
 - a. Delete paragraph one which states “Use only nitrile gloves.....Do not use latex gloves as they do not provide adequate protection.” to the beginning of the Instructions for Use (i.e., before the Identify subsection) in Section 2. This issue was addressed in Comment 2a above.
 - b. Relocate paragraph two, which addresses disposal of Qutenza patches and materials, to Section 2 Dosage and Administration “Instructions for Use”, so that the information appears at the end of the Cleanse subsection. Since this information addresses the disposal of Qutenza patch and materials, which is performed after the post-administration cleansing step, this information should be located after the ‘Cleanse’ step.
 - c. With the relocation of information as noted in comment 4a and 4b this subsection heading is unnecessary. Thus delete section 2.2 Preparation and Handling Precautions.
 5. Dosage and Administration Section 5 Warnings and Precautions
Provide rationale for the inclusion of the ‘opioid’ warnings and precautions in this insert labeling. The opioid product information, including warnings that caution the patient on their “ability to perform potentially hazardous activities such as driving or operating machinery” is already included in opioid package insert labeling and therefore, does not need to be included in Qutenza labeling.

5.2 COMMENTS TO THE APPLICANT

Based upon our assessment of the labels and labeling, we identified the following areas of needed improvement.

A. Qutenza Pouch Label and Qutenza Carton Labeling

1. Add the warning information about the use of nitrile gloves when handling the Qutenza patch and cleansing the Capsaicin residue from the skin after administration to the pouch label. The statement should be prominently displayed so that health care providers are alerted about using nitrile gloves before they handle the Qutenza product.
2. Additionally, since Capsaicin dissolves in solvents such as Diethylene glycol Monoethylether (DGME) which can penetrate readily through latex gloves but not nitrile gloves, additional language should be included with the warning statement to assure that health care practitioners understand that the use of nitrile gloves is not recommended but rather required due to the risk of Capsaicin exposure to the skin. We recommend language such as “Use only nitrile gloves when handling Qutenza and when cleaning treatment areas *as latex gloves do not provide adequate protection from Capsaicin absorption through latex gloves and subsequent exposure to the skin.*”

B. Cleansing Gel Container Label

Add a clarifying statement to the principal display panel of the Cleansing Gel for Qutenza container label to assure its use only after the application and removal of the Qutenza patch. We have concerns that practitioners administering the post-treatment Cleansing Gel for Qutenza product may inadvertently use it as a pre-treatment cleansing agent, given the word ‘cleansing’ in the Gel name implies cleaning the area, as stated in the pre-treatment instructions for use. We recommend adding language to the “For Topical Use” statement which appears on the upper 1/3 of the label. We recommend:

For Topical Use – After Administration of Qutenza Patch Only

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this page is the manifestation of the electronic signature.**

/s/

Cathy A Miller
6/18/2009 04:29:49 PM
DRUG SAFETY OFFICE REVIEWER

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