CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

210833Orig1s000

OTHER REVIEW(S)

MEMORANDUM

REVIEW OF REVISED LABEL AND LABELING
Division of Medication Error Prevention and Analysis (DMEPA)
Office of Medication Error Prevention and Risk Management (OMEPRM)
Office of Surveillance and Epidemiology (OSE)
Center for Drug Evaluation and Research (CDER)

Date of This Memorandum:	October 23, 2018
Requesting Office or Division:	Division of Neurology Products (DNP)
Application Type and Number:	NDA 210833
Product Name and Strength:	Sympazan (clobazam) oral film, 5 mg, 10 mg and 20 mg
Applicant/Sponsor Name:	Aquestive Therapeutics
FDA Received Date:	October 22, 2018
OSE RCM #:	2018-2040-1
DMEPA Safety Evaluator:	Celeste Karpow, PharmD, MPH
DMEPA Team Leader:	Lolita White, PharmD

1 PURPOSE OF MEMORANDUM

Division of Neurology Products (DNP) requested that we review the revised carton labeling and container labels for Sympazan (clobazam) oral film to determine if it is acceptable from a medication error perspective. The revisions are in response to recommendations that we made during a previous label and labeling review.[a] In the Aquestive October 22, 2018 response to Agency comments, we note the sponsor intends to use the following format for the expiration dates printed on the Sympazan container label and Carton labeling: MMMYYYY (e.g., JAN2013). The sponsor did not submit updated carton labels or container labeling to reflect this revision. (see Appendix A).

2 CONCLUSION

The revised carton labeling and container labels for Sympazan (clobazam) oral film are acceptable from a medication error perspective. We have no further recommendations at this time.

[a] Karpow, C. Label and Labeling Memorandum for Sympazan (clobazam) oral soluble film (NDA 210833). Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2018 OCT 16. RCM No.: 2018-2040.

APPENDIX A. LINK TO REVISED LABEL AND LABELING RECEIVED ON SEPTEMBER 21, 2018

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/s/

CELESTE A KARPOW
10/23/2018

LOLITA G WHITE
10/23/2018

MEMORANDUM

REVIEW OF REVISED LABEL AND LABELING
Division of Medication Error Prevention and Analysis (DMEPA)
Office of Medication Error Prevention and Risk Management (OMEPRM)
Office of Surveillance and Epidemiology (OSE)
Center for Drug Evaluation and Research (CDER)

Date of This Memorandum:	October 16, 2018
Requesting Office or Division:	Division of Neurology Products (DNP)
Application Type and Number:	NDA 210833
Product Name and Strength:	Sympazan (clobazam) oral film, 5 mg, 10 mg and 20 mg
Applicant/Sponsor Name:	Aquestive Therapeutics
FDA Received Date:	September 21, 2018
OSE RCM #:	2018-2040
DMEPA Safety Evaluator:	Celeste Karpow, PharmD, MPH
DMEPA Team Leader:	Lolita White, PharmD

1 PURPOSE OF MEMORANDUM

Division of Neurology Products (DNP) requested that we review the revised carton labeling, container label for Sympazan (clobazam) oral film (Appendix A) to determine if it is acceptable from a medication error perspective. The revisions are in response to recommendations that we made during previous label and labeling reviews.[ab]

2 CONCLUSION

The revised carton labeling and container labels are unacceptable from a medication error perspective because the format for the expiration date is not defined.

3 RECOMMENDATIONS FOR AQUESTIVE THERAPEUTICS

We recommend the following be implemented prior to approval of this NDA 210833:

[a] Whaley E. Label and Labeling Review for Sympazan (clobazam) oral soluble film (NDA 210833). Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2018 JAN 26. RCM No.: 2017-2262.
[b] Karpow, C. Label and Labeling Memorandum for Sympazan (clobazam) oral soluble film (NDA 210833). Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2016 AUG 06. RCM No.: 2017-2262-1

A. As currently presented, the format for the expiration date is not defined. To minimize confusion and reduce the risk for deteriorated drug medication errors, identify the format you intend to use. We recommend that the human-readable expiration date on the drug package label include a year, month, and non-zero day. FDA recommends that the expiration date appear in YYYY-MM-DD format if only numerical characters are used or in YYYY-MMM-DD if alphabetical characters are used to represent the month. If there are space limitations on the drug package, the human-readable text may include only a year and month, to be expressed as: YYYY-MM if only numerical characters are used or YYYY-MMM if alphabetical characters are used to represent the month. FDA recommends that a hyphen or a space be used to separate the portions of the expiration date.

6 Page(s) of Draft Labeling have been Withheld in Full as b4 (CCI/TS) immediately following this page

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/s/

CELESTE A KARPOW
10/16/2018

LOLITA G WHITE
10/16/2018

Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Medical Policy

PATIENT LABELING REVIEW

Date:	August 13, 2018
To:	William Dunn, MD Director **Division of Neurology Products (DNP)**
Through:	LaShawn Griffiths, MSHS-PH, BSN, RN Associate Director for Patient Labeling **Division of Medical Policy Programs (DMPP)**
From:	Sharon W. Williams, MSN, BSN, RN Senior Patient Labeling Reviewer **Division of Medical Policy Programs (DMPP)** Dhara Shah, PharmD, RAC Regulatory Review Officer **Office of Prescription Drug Promotion (OPDP)**
Subject:	Review of Patient Labeling: Medication Guide (MG) and Instructions for Use (IFU)
Drug Name (established name):	SYMPAZAN (clobazam)
Dosage Form and Route:	oral film, CIV
Application Type/Number:	NDA 210833
Applicant:	MonoSol Rx LLC

1 INTRODUCTION

On October 31, 2017, MonoSol Rx LLC submitted for the Agency's review an Original New Drug Application (NDA) for SYMPAZAN (clobazam), oral film, CIV. SYMPAZAN (clobazam), oral film, CIV is an orally dissolving film dosage from of clobazam utilizing the MonoSol Rx PharmFilm drug delivery technology and is an alternative dosage from to the currently marketed clobazam tablets. SYMPAZAN (clobazam), oral film, CIV is indicated as an adjunctive treatment of seizures associated with Lennox-Gastaut Syndrome (LGS) in patients 2 years of age or older.

This collaborative review is written by the Division of Medical Policy Programs (DMPP) and the Office of Prescription Drug Promotion (OPDP) in response to a request by the Division of Neurology Products (DNP) on November 28, 2017, for DMPP and OPDP to review the Applicant's proposed MG and IFU for SYMPAZAN (clobazam), oral film, CIV.

2 MATERIAL REVIEWED

- Draft SYMPAZAN (clobazam), oral film, CIV MG and IFU received on October 31, 2017, and received by DMPP and OPDP on August 6, 2018.
- Draft SYMPAZAN (clobazam), oral film, CIV Prescribing Information (PI) received on October 31, 2017 revised by the Review Division throughout the review cycle, and received by DMPP and OPDP on August 6, 2018.
- Approved ONFI (clobazam) tablets, for oral use and oral suspension, CIV comparator labeling dated June 15, 2018.

3 REVIEW METHODS

In 2008, the American Society of Consultant Pharmacists Foundation (ASCP) in collaboration with the American Foundation for the Blind (AFB) published *Guidelines for Prescription Labeling and Consumer Medication Information for People with Vision Loss*. The ASCP and AFB recommended using fonts such as Verdana, Arial or APHont to make medical information more accessible for patients with vision loss. We reformatted the MG and IFU documents using the Arial font, size 10.

In our collaborative review of the MG and IFU we:

- simplified wording and clarified concepts where possible
- ensured that the MG and IFU are consistent with the Prescribing Information (PI)
- removed unnecessary or redundant information
- ensured that the MG and IFU are free of promotional language or suggested revisions to ensure that it is free of promotional language
- ensured that the MG meets the Regulations as specified in 21 CFR 208.20

- ensured that the MG and IFU meet the criteria as specified in FDA's Guidance for Useful Written Consumer Medication Information (published July 2006)
- ensured that the MG and IFU are consistent with the approved comparator labelings where applicable.

4 CONCLUSIONS

The MG and IFU are acceptable with our recommended changes.

5 RECOMMENDATIONS

- Please send these comments to the Applicant and copy DMPP and OPDP on the correspondence.
- Our collaborative review of the MG and IFU is appended to this memorandum. Consult DMPP and OPDP regarding any additional revisions made to the PI to determine if corresponding revisions need to be made to the MG and IFU.

Please let us know if you have any questions.

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/s/

SHARON W WILLIAMS
08/13/2018

DHARA SHAH
08/13/2018

LASHAWN M GRIFFITHS
08/14/2018

MEMORANDUM

REVIEW OF REVISED LABEL AND LABELING

Division of Medication Error Prevention and Analysis (DMEPA)

Office of Medication Error Prevention and Risk Management (OMEPRM)

Office of Surveillance and Epidemiology (OSE)

Center for Drug Evaluation and Research (CDER)

Date of This Memorandum:	August 6, 2018
Requesting Office or Division:	Division of Neurology Products (DNP)
Application Type and Number:	NDA 210833
Product Name and Strength:	Sympazan (clobazam) oral soluble film, 5 mg, 10 mg, 20 mg
Applicant/Sponsor Name:	MonoSol Rx LLC
FDA Received Date:	July 27, 2018
OSE RCM #:	2017-2262-1
DMEPA Safety Evaluator:	Celeste Karpow, PharmD, MPH
DMEPA Team Leader:	Lolita White, PharmD

1 PURPOSE OF MEMORANDUM

The Division of Neurology Products (DNP) requested that we review the revised container labels and carton labeling for Sympazan (clobazam) (Appendix A) to determine if it is acceptable from a medication error perspective.

2 CONCLUSION

The revised container labels and carton labeling for Sympazan (clobazam) are acceptable from a medication error perspective. We have no further recommendations at this time.

APPENDIX A. IMAGES OF LABEL AND LABELING RECEIVED ON JULY 27, 2018

Container labels (pouches)

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/s/

CELESTE A KARPOW
08/07/2018

LOLITA G WHITE
08/07/2018

LABEL AND LABELING REVIEW

Division of Medication Error Prevention and Analysis (DMEPA)
Office of Medication Error Prevention and Risk Management (OMEPRM)
Office of Surveillance and Epidemiology (OSE)
Center for Drug Evaluation and Research (CDER)

***** This document contains proprietary information that cannot be released to the public*****

Date of This Review:	January 26, 2018
Requesting Office or Division:	Division of Neurology Products (DNP)
Application Type and Number:	NDA 210833
Product Name and Strength:	Sympazan (clobazam) oral soluble film, 5 mg, 10 mg, 20 mg
Product Type:	Single-ingredient
Rx or OTC:	Rx
Applicant/Sponsor Name:	Monosol Rx LLC
Submission Date:	October 31, 2017
OSE RCM #:	2017-2262
DMEPA Safety Evaluator:	Ebony Whaley, PharmD, BCPPS
DMEPA Team Leader:	Lolita White, PharmD

1 REASON FOR REVIEW

The Division of Neurology Products (DNP) has requested the Division of Medication Error Prevention and Analysis review the labels and labeling for NDA 210833 for areas of vulnerability that may lead to medication errors.

2 MATERIALS REVIEWED

We considered the materials listed in Table 1 for this review. The Appendices provide the methods and results for each material reviewed.

Table 1. Materials Considered for this Label and Labeling Review

Material Reviewed	Appendix Section (for Methods and Results)
Product Information/Prescribing Information	A
Previous DMEPA Reviews	B
Human Factors Study	C (N/A)
ISMP Newsletters	D (N/A)
FDA Adverse Event Reporting System (FAERS)*	E (N/A)
Other	F (N/A)
Labels and Labeling	G

N/A=not applicable for this review
*We do not typically search FAERS for our label and labeling reviews unless we are aware of medication errors through our routine postmarket safety surveillance

3 OVERALL ASSESSMENT OF THE MATERIALS REVIEWED

Sympazan (clobazam) is an oral soluble film intended for the adjunctive treatment of seizures associated with Lennox-Gastaut Syndrome (LGS) in patients 2 years of age or older. The reference listed drug is Onfi (NDA 202067). Our review of the proposed Prescribing Information, Instructions for Use, container labels, and carton labeling for Sympazan (clobazam) identified the following areas of needed improvement that may contribute to medication errors:

Prescribing Information (PI)

1. Section 2 Dosage and Administration
    a. Section 2.1 Dosing Information contains error prone symbols that might increase the risk of confusion regarding dosing.
    b. Section 2.1 Dosing Information contains (b) (4) information that should be relocated to Section 2.3 Important Administration Instructions.
    c. Section 2.3 Important Administration Instructions contains a statement that should be revised to mitigate the risk of confusion regarding the dosage form.
    d. Section 2.3 Important Administration Instructions contains duplicate statements.

4 CONCLUSION & RECOMMENDATIONS

We reviewed the proposed Prescribing Information, Instructions for Use, container labels, and carton labeling for Sympazan (clobazam) and identified areas where information should be revised to help ensure safe use of the product. We provide recommendations below in Sections 4.1 to address our concerns. We advise these recommendations be implemented prior to approval of this product.

4.1 RECOMMENDATIONS FOR THE DIVISION

1. Prescribing Information
    a. Table 1 in Section 2.1 Dosing Information contains the error-prone abbreviations "≤" and ">". The use of error-prone abbreviations might confuse users and increase the risk of dosing errors. Consider replacing the symbols "≤" and ">" with their intended meanings to prevent misinterpretation and confusion.[a]
    b. Section 2.1 Dosing Information includes a statement regarding (b) (4) the oral soluble film (b) (4) (b) (4). Because this information relates to administration, consider relocating this sentence to Section 2.3 Important Administration Instructions.
    c. Section 2.3 Important Administration Instructions includes the statement (b) (4) (b) (4)
    d. In Section 2.3 Important Administration Instructions, the sentence "Instruct patients and caregivers to read the "Instructions for Use" carefully for complete directions on how to properly dose and administer SYMPAZAN oral (b) (4) films" appears twice. We recommend that the instance of this sentence at the end of this section is deleted to reduce redundancy.

[a] ISMP's List of Error-Prone Abbreviations, Symbols, and Dose Designations [Internet]. Horsham (PA): Institute for Safe Medication Practices. 2015 [cited 2018 JAN 22]. Available from: http://www.ismp.org/tools/errorproneabbreviations.pdf.

APPENDICES: METHODS & RESULTS FOR EACH MATERIALS REVIEWED

APPENDIX A. PRODUCT INFORMATION/PRESCRIBING INFORMATION

Table 2 presents relevant product information for Sympazan (clobazam) that Monosol Rx submitted on October 31, 2017.

<table>
<tr><th colspan="2">Table 2. Relevant Product Information for Sympazan (clobazam)</th></tr>
<tr><td>Initial Approval Date</td><td>N/A</td></tr>
<tr><td>Active Ingredient</td><td>clobazam</td></tr>
<tr><td>Indication</td><td>adjunctive treatment of seizures associated with Lennox-Gastaut Syndrome (LGS) in patients 2 years of age or older</td></tr>
<tr><td>Route of Administration</td><td>oral</td></tr>
<tr><td>Dosage Form</td><td>oral soluble film</td></tr>
<tr><td>Strength</td><td>5 mg, 10 mg, 20 mg</td></tr>
<tr><td>Dose and Frequency</td><td>A daily dose greater than 5 mg should be administered in divided doses twice daily; a 5 mg daily dose can be administered as a single dose. Dose patients according to body weight. Individualize dosing within each body weight group, based on clinical efficacy and tolerability. Do not proceed with dose escalation more rapidly than weekly, because serum concentrations of clobazam and its active metabolite require 5 and 9 days, respectively, to reach steady-state.
Recommended Total Daily Dosing by Weight Group
<table>
<tr><th></th><th>≤30 kg Body Weight</th><th>>30 kg Body Weight</th></tr>
<tr><td>Starting Dose</td><td>5 mg</td><td>10 mg</td></tr>
<tr><td>Starting Day 7</td><td>10 mg</td><td>20 mg</td></tr>
<tr><td>Starting Day 14</td><td>20 mg</td><td>40 mg</td></tr>
</table></td></tr>
<tr><td>How Supplied</td><td>Each oral (b) (4) film is a white rectangular film that contains 5mg, 10 mg or 20 mg of clobazam and printed in black ink either "C5," "C10" or "C20" on the strip according to their respective strengths.
- NDC 10094-205-60: 5 mg oral (b) (4) film, Package of 60
- NDC 10094-210-60 10 mg oral film, Package of 60
- NDC 10094-220-60 20 mg oral film, Package of 60</td></tr>
</table>

Storage	Store oral [redacted] films at 20°C to 25°C (68°F to 77°F). Excursions permitted to 15-30°C (59-86°F). [See USP controlled room temperature.]

APPENDIX B. PREVIOUS DMEPA REVIEWS

On November 21, 2017, we searched DMEPA's previous reviews using the terms, clobazam. Our search identified one previous review[b], and we confirmed that our previous recommendation was considered.

[b] Whaley, E. Use-Related Risk Analysis Review for Clobazam oral soluble film IND 129383. Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2017 AUG 28. RCM No.: 2017-621.

APPENDIX G. LABELS AND LABELING

G.1 List of Labels and Labeling Reviewed

Using the principles of human factors and Failure Mode and Effects Analysis,[c] along with postmarket medication error data, we reviewed the following Sympazan (clobazam) labels and labeling submitted by Monosol Rx on October 31, 2017.

- Container label (pouch)
- Carton labeling
- Instructions for Use (Image not shown)
- Prescribing Information (Image not shown)

G.2 Label and Labeling Images

- Container label (pouch)

(b) (4)

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[c] Institute for Healthcare Improvement (IHI). Failure Modes and Effects Analysis. Boston. IHI:2004.

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/s/

EBONY A WHALEY
01/26/2018

LOLITA G WHITE
01/29/2018

M E M O R A N D U M

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

DATE: 1/11/2018

TO: Division of Neurology Products
Office of Drug Evaluation I

FROM: Division of New Drug Bioequivalence Evaluation (DNDBE)
Office of Study Integrity and Surveillance (OSIS)

SUBJECT: **Recommendation to accept data without an on-site inspection**

RE: NDA 210833

The Division of New Drug Bioequivalence Evaluation (DNDBE) within the Office of Study Integrity and Surveillance (OSIS) recommends accepting data without an on-site inspection. The rationale for this decision is noted below.

Rationale

OSIS recently inspected the sites listed below. The inspectional outcome from the inspections was classified as No Action Indicated (NAI).

Inspection Sites

Facility Type	Facility Name	Facility Address
Clinical	inVentiv Health Clinical Research Services, LLC.	1951 NW 7th Avenue, Suite 450, Miami, FL
Analytical	(b) (4)	

Reference ID: 4345598

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/s/

SHILA S NKAH
01/11/2018