CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

215868Orig1s000

OTHER REVIEW(S)

FOOD AND DRUG ADMINISTRATION
Center for Drug Evaluation and Research
Office of Prescription Drug Promotion

****Pre-decisional Agency Information****

Memorandum

Date: July 12, 2022

To: Allison Meyer, Sr. Regulatory Project Manager, Division of Regulatory Operations, Neuroscience (DRO-N)

From: Phillip Williams, PharmD, RAC, Regulatory Review Officer
Office of Prescription Drug Promotion (OPDP)

CC: Sam Skariah, PharmD, RAC, Team Leader, OPDP

Subject: OPDP Labeling Comments for midazolam in 0.8% sodium chloride injection, 1 mg/mL

NDA: 215868

In response to Division of Anesthesia, Addiction Medicine and Pain Medicine's (DAAP) consult request dated December 9, 2021, OPDP has reviewed the proposed product labeling (PI), for the original NDA submission for midazolam in 0.8% sodium chloride injection.

Labeling: OPDP's comments on the proposed labeling are based on the draft labeling received by electronic mail from DAAP on July 7, 2022, and we have no additional comments at this time.

Thank you for your consult. If you have any questions, please contact Phillip Williams at (240) 402-3974 or Phillip.Williams@fda.hhs.gov.

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/s/

PHILLIP A WILLIAMS
07/12/2022 11:16:15 AM

MEMORANDUM

REVIEW OF REVISED LABEL AND LABELING

Division of Medication Error Prevention and Analysis 1 (DMEPA 1)

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:	June 30, 2022
Requesting Office or Division:	Division of Anesthesiology, Addiction Medicine, and Pain Medicine (DAAP)
Application Type and Number:	NDA 215868
Product Name and Strength:	Midazolam in 0.8% sodium chloride injection, 1 mg/mL (50 mg/50 mL, 100 mg/100 mL)
Applicant/Sponsor Name:	Exela Pharma Sciences, LLC
OSE RCM #:	2021-1877-1
DMEPA 1 Safety Evaluator:	Damon Birkemeier, PharmD
DMEPA 1 Team Leader:	Valerie S. Vaughan, PharmD

1 PURPOSE OF MEMORANDUM

The Applicant submitted revised container label and carton labeling received on February 1, 2022 for midazolam in 0.8% sodium chloride injection. The Division of Anesthesiology, Addiction Medicine, and Pain Medicine (DAAP) requested that we review the revised container label and carton labeling for midazolam in 0.8% sodium chloride injection (Appendix A) to determine if they are acceptable from a medication error perspective. The revisions are in response to recommendations that we made during a previous label and labeling review.[a]

2 CONCLUSION

The Applicant clarified the expiration date format they intend to use on the container labels is "EXP YYYY MM" with all numeric values. Additionally, they implemented all of our recommendations and we have no additional recommendations at this time.

[a] Birkemeier D. Label and Labeling Review for midazolam in 0.8% sodium chloride injection (NDA 215868). Silver Spring (MD): FDA, CDER, OSE, DMEPA 1 (US); 2022 JAN 10. RCM No.: 2021-1877.

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/s/

DAMON A BIRKEMEIER
06/30/2022 10:36:59 AM

VALERIE S VAUGHAN
06/30/2022 11:57:09 AM

LABEL AND LABELING REVIEW
Division of Medication Error Prevention and Analysis 1 (DMEPA 1)
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 10, 2022
Requesting Office or Division:	Division of Anesthesiology, Addiction Medicine, and Pain Medicine (DAAP)
Application Type and Number:	NDA 215868
Product Name and Strength:	Midazolam in 0.8% sodium chloride injection, 1 mg/mL (50 mg/50 mL, 100 mg/100 mL)
Product Type:	Single Ingredient Product
Rx or OTC:	Prescription (Rx)
Applicant/Sponsor Name:	Exela Pharma Sciences, LLC
FDA Received Date:	September 20, 2021
OSE RCM #:	2021-1877
DMEPA 1 Safety Evaluator:	Damon Birkemeier, PharmD
DMEPA 1 Team Leader:	Valerie S. Vaughan, PharmD

1 REASON FOR REVIEW

Exela Pharma Sciences, LLC submitted a new drug application (NDA 215868) for Midazolam in 0.8% sodium chloride injection. As part of the approval process, the Division of Anesthesiology, Addiction Medicine, and Pain Medicine (DAAP) requested that we review the proposed midazolam 0.8% sodium chloride injection prescribing information (PI), container labels, carton labeling, and case labeling for areas of vulnerability that may lead to medication errors.

1.1 BACKGROUND

NDA 215868 is a 505(b)(2) NDA and the listed drug product is Versed, NDA 018654.

2 MATERIALS 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 – N/A
ISMP Newsletters*	C – N/A
FDA Adverse Event Reporting System (FAERS)*	D – N/A
Information Requests and Applicant Responses	E – N/A
Labels and Labeling	F

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

3 CONCLUSION AND RECOMMENDATIONS

The proposed container label, carton labeling, and case labeling may be improved to promote the safe use of this product from a medication error perspective. We provide the identified medication error issues, our rationale for concern, and our proposed recommendations to minimize the risk for medication error in Section 4 for Exela Pharma Sciences, LLC.

4 RECOMMENDATIONS FOR EXELA PHARMA SCIENCES, LLC

Table 2. Identified Issues and Recommendations for Exela Pharma Sciences, LLC (entire table to be conveyed to Applicant)			
	IDENTIFIED ISSUE	RATIONALE FOR CONCERN	RECOMMENDATION
Container Label, Carton Labeling and Case Labeling			
1.	As currently presented, the format of the expiration date on the carton labeling and case labeling is denoted as, "EXP: MM/YYYY," and the format of the expiration date on the container label is denoted as, "YYYY MM". It is unclear if the month portion, "MM," of the expiration date format will use alphabetical or numerical characters.	The expiration date should be clearly defined to minimize confusion and risk for deteriorated drug errors. For example, confusion has occurred with use of the alphabetical abbreviation "JU," which can represent both "June" and "July" and the alphabetical abbreviation "MA," which can represent both "March" and "May."	Clarify if you intend to use only numerical characters to express each portion of the expiration date.
2.	The usual dosage statement is missing on the container label and carton labeling.	21 CFR 201.55 requires that labels for prescription drugs bear a statement of the recommended or usual dosage.	On the container label and carton labeling, revise the statement (b) (4) See Package Insert" to read as "Recommended Dosage: See Package Insert." Alternatively, you may choose to revise to "Dosage and Administration: See Package Insert" if you also seek to direct healthcare providers to the Prescribing Information for important administration instructions.

APPENDICES: METHODS & RESULTS FOR EACH MATERIAL REVIEWED

APPENDIX A. PRODUCT INFORMATION/PRESCRIBING INFORMATION

Table 3 presents relevant product information for midazolam in 0.8% sodium chloride that Exela Pharma Sciences, LLC submitted on September 20, 2021, and the listed drug (LD).

Table 3. Relevant Product Information for Listed Drug and Midazolam

Product Name	Versed*	Midazolam
Initial Approval Date	12/20/1985	n/a
Active Ingredient	Midazolam	
Indication	Continuous intravenous infusion for sedation of intubated and mechanically ventilated adult, pediatric, and neonatal patients as a component of anesthesia or during treatment in a critical care setting	
Route of Administration	Intravenous	
Dosage Form	Single-dose bags	Single-dose vial
Strength	1 mg/mL (50 mg/50 mL, 100 mg/100 mL)	
Dose and Frequency	Individualize dosing and titrate to desired clinical response.	

Adult Patients	If a loading dose is necessary to rapidly initiate sedation, 0.01 mg/kg to 0.05 mg/kg (approximately 0.5 to 4 mg for a typical adult) may be given slowly or infused over several minutes. This dose may be repeated at 10-to-15-minute intervals until adequate sedation is achieved. For maintenance of sedation, the usual initial infusion rate is 0.02 mg/kg/hr (1 mg/hr to 7 mg/hr). Higher loading or maintenance infusion rates may occasionally be required in some patients. Use the lowest recommended doses in patients with residual effects from anesthetic drugs or in those concurrently receiving other sedatives or opioids. Individual response to midazolam is variable. Titrate the infusion rate to the desired level of sedation, taking into account the patient's age, clinical status and current medications. In general, midazolam should be infused at the lowest rate that produces the desired level of sedation. Assess sedation at regular intervals and adjust the midazolam infusion rate. Finding the minimum effective infusion rate decreases the potential accumulation of midazolam and provides for the most rapid recovery once the infusion is terminated.
Pediatric Patients	Unlike adult patients, pediatric patients generally receive increments of midazolam on a mg/kg basis. As a group, pediatric patients generally require higher dosages of midazolam (mg/kg) than adults. Younger (less than six years) pediatric patients may require higher dosages (mg/kg) than older pediatric patients. In obese pediatric patients, calculate dose based on ideal body weight. Titrate the dose to the desired level of sedation. Assess for desired level of sedation and vital signs at regular intervals.

	Preterm and Term Neonatal Patients	Based on pharmacokinetic parameters and reported clinical experience in preterm and term neonates whose trachea was intubated, initiate continuous infusions of midazolam in sodium chloride injection at a rate of 0.03 mg/kg/hr (0.5 mg/kg/min) in neonates <32 weeks and 0.06 mg/kg/hr (1 mg/kg/min) in neonates > 32 weeks. Intravenous loading doses should not be used in neonates, rather the infusion may be run more rapidly for the first several hours to establish therapeutic plasma levels. Frequently assess the rate of infusion, particularly after the first 24 hours so as to administer the lowest possible effective dose and reduce the potential for drug accumulation. Hypotension may be observed in patients who are critically ill and in preterm and term infants, particularly those receiving fentanyl and/or when midazolam is administered rapidly. When sedating preterm and former preterm neonates whose trachea was not intubated, monitor respiratory parameters due to an increased risk of apnea.	
How Supplied	Single-dose bags with an aluminum overwrap available as 50 mg/50 mL or 100 mg/100 mL. Available as a case of (b) (4) single-dose bags	Single-dose vials available as 50 mg/50 mL or 100 mg/100 mL. Available as a case of 25 single-dose vials	
Storage	Store at 20 °C to 25 °C (68 °F to 77 °F). Protect from freezing. Individual containers may be used up to 48 hours after initial penetration. Discard unused portion	Store at 20 °C to 25 °C (68 °F to 77 °F); excursions permitted to 15 °C to 30 °C (59 °F to 86 °F). Protect from freezing. Protect from light. Discard unused portion	

*The LD package insert utilized for this product comparison is based on the approved PI under application NDA 211884. The submission application references the previously approved LD Versed, NDA 018654, which has been discontinued.

APPENDIX F. LABELS AND LABELING

F.1 List of Labels and Labeling Reviewed

Using the principles of human factors and Failure Mode and Effects Analysis,[a] along with postmarket medication error data, we reviewed the following Midazolam labels and labeling submitted by Exela Pharma Sciences, LLC.

- Container labels received on September 20, 2021
- Carton labeling received on September 20, 2021
- Case labeling received on September 20, 2021
- Prescribing Information (Image not shown) received on September 20, 2021, available from \\CDSESUB1\evsprod\nda215868\0001\m1\us\114-labeling\draft-labeling\draft-label-text\draft-label-text-pdf-0001.pdf

F.2 Label and Labeling Images

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

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VALERIE S VAUGHAN
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