

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

216359Orig1s000

PRODUCT QUALITY REVIEW(S)



Title:	NDA Executive Summary		
Document ID:	OPQ-ALL-TEM-0013		
Effective Date:	31 May 2022	Revision:	00
Total Pages:	4		



Template Revision: 03

NDA Executive Summary

1. Application/Product Information

NDA Number.	216359		
Applicant Name	Rafa Laboratories		
Drug Product Name	Midazolam Injection (Autoinjector)		
Dosage Form.	Injection		
Proposed Strength(s)	10 mg/0.7 mL		
Route of Administration	Intramuscular (IM)		
Maximum Daily Dose	10 mg		
Rx/OTC Dispensed	Rx		
Proposed Indication	Treatment of status epilepticus in adults and/or severe signs and symptoms of nerve agent poisoning		
Drug Product Description	Sterile, aqueous solution for intramuscular injection in a single-dose pre-filled autoinjector.		
Co-packaged product information	Not applicable		
Device information:	The device is a single use, nose-pressure-activated autoinjector. The immediate container for the drug is a (b) (4) cartridge (b) (4). The device is activated by removing the safety cap and pressing against the mid lateral thigh for 10 seconds.		
Storage Temperature/ Conditions	20 °C to 25 °C		
Review Team	Discipline	Primary	Secondary
	<i>Drug Substance</i>	Jeffrey Medwid	Gaetan Ladouceur
	<i>Drug Product/ Labeling</i>	Eric Bow	Julia Pinto
	<i>Manufacturing</i>	Suzanne Hudak	Lane Christensen



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	<i>Biopharmaceutics</i>	N/A	N/A
	<i>Microbiology</i>	Kelly Ann Miller	Erica Pfeiler
	<i>Other (specify):</i>	N/A	N/A
	<i>RBPM</i>	Erica Keafer	
	<i>ATL</i>	Martha Heimann	
Consults	Device aspects of the product were reviewed by Porsche Bennett, CDRH (secondary Courtney Evans). Her review¹ recommends that the NDA be approved with a post-marketing requirement (PMR) to <i>“Provide an updated Fault Tree Analysis and the associated reliability requirements and specifications to demonstrate that Midazolam Injection, 10 mg/0.7 mL, autoinjector will provide successful injection with at least 99.999% reliability at the 95% confidence interval. The Fault Tree Analysis must include information from your combination product’s design and manufacturing methods by identifying all basic failure modes anticipated.”</i>		

2. Final Overall Recommendation - Approval with QPA

3. Action Letter Information

a. Expiration Dating:

24 months when stored at 20 °C to 25 °C.

b. Additional Comments for Action

No

4. Basis for Recommendation:

a. Summary of Rationale for Recommendation:

The midazolam autoinjector contains midazolam injection and is intended for use by military personnel for emergency treatment of nerve agent poisoning. Currently, nerve agent poisoning is treated with a three-drug regimen consisting of pralidoxime chloride (cholinesterase reactivator), atropine (anticholinergic), and diazepam (anticonvulsant). For military deployment, all

¹ <https://darrts.fda.gov/darrts/ViewDocument?documentId=090140af8067a514&showAsPdf=true>



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three are administered IM via single dose autoinjectors. The midazolam autoinjector is intended to replace diazepam for this indication.²

The proposed combination product is a disposable, single dose autoinjector that will deliver midazolam injection 10 mg/0.7 mL by IM injection. The device component is similar to that of Rafa's previously approved atropine autoinjector.³ The immediate container for the drug is a (b) (4) cartridge (b) (4). The drug formulation is compounded and filled under aseptic conditions. The initial risk assessment⁴ identified sterility as a high-risk critical quality attribute (CQA). Endotoxins and particulate matter were identified as moderate risk CQAs, and the remaining CQAs for the drug were considered low risk.

From a drug perspective, the NDA provides adequate information to support use of the midazolam autoinjector by the intended users. The applicant addressed all deficiencies identified by the OPQ review team during the review cycle and the application meets all applicable standards to support the identity, strength, quality, and purity that it purports to possess.

With respect to device quality, the CDRH reviewer recommends approval with a post approval requirement (PMR) related to device performance. Device performance is an essential performance requirement for emergency use products. At the same time, there is an urgent need to replace the existing diazepam autoinjectors.⁵ Performance of the studies under a PMR is reasonable as the benefit of having a product available for treatment of nerve agent poisoning during a military deployment outweighs the residual risk due to device quality.

b. Is the overall recommendation in agreement with the individual discipline recommendations? Yes

Recommendation by Subdiscipline:

Drug Substance - Adequate
Drug Product - Adequate

² (b) (4)

³ NDA 212319

⁴ OPQ Filing Review: <https://darrts.fda.gov/darrts/ViewDocument?documentId=090140af8065d953&showAsPdf=true>

⁵ (b) (4), the manufacturer of the diazepam autoinjectors, Meridien Medical Technologies, has not manufactured the product for several years. Further shelf-life extension under the Shelf Life Extension Program (SLEP) is not feasible.



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Template Revision: 03

Quality Labeling - Adequate
Manufacturing - Adequate
Biopharmaceutics - N/A
Microbiology - Adequate

Environmental Assessment: Categorical Exclusion - Adequate
QPA for EA(s): No

5. Life-Cycle Considerations

Established Conditions per ICH Q12: No

Comments:

Comparability Protocols (PACMP): No

Comments:

Additional Lifecycle Comments:



Martha
Heimann

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CHAPTER IV: LABELING

For more details about the items in this template, please see [Chapter IV \(Labeling\) of the NDA IQA Guide](#)

1.0 PRESCRIBING INFORMATION

Assessment of Product Quality Related Aspects of the Prescribing Information:

1.1 HIGHLIGHTS OF PRESCRIBING INFORMATION

Item	Items in Proposed Labeling (choose "Adequate", "Inadequate", or "N/A")	Assessor's Comments (If an item is Inadequate, provide more details on the issues, as appropriate)
Product Title in Highlights		
Established name(s) ¹	Adequate	
Route(s) of administration	Adequate	
Dosage Forms and Strengths Heading in Highlights		
Summary of the dosage form(s) and strength(s) in metric system	Adequate	
Assess if the tablet is scored. If product meets guidelines and criteria for a scored tablet, state "functionally scored".	N/A	
For injectable drug products for parental administration, use appropriate package type term (e.g., single-dose, multiple-dose, single-patient-use). Other package terms include pharmacy bulk package and imaging bulk package.	Adequate	
If the drug product contains an active ingredient that is a salt, clearly state whether the strength is based on the active moiety (e.g., Tablets: 10 mg of drug-x) or active	N/A	

¹ Established name = [Drug] [Route of Administration] [Dosage Form]

ingredient (e.g., Tablets: 10 mg of drug-x hydrochloride).		

1.2 FULL PRESCRIBING INFORMATION

1.2.1 Section 2 (DOSAGE AND ADMINISTRATION)

Item	Items in Proposed Labeling (choose "Adequate", "Inadequate", or "N/A")	Assessor's Comments (If an item is Inadequate, provide more details on the issues, as appropriate)
DOSAGE AND ADMINISTRATION section		
Special instructions for product preparation (e.g., reconstitution and resulting concentration, dilution, compatible diluents, storage conditions needed to maintain the stability of the reconstituted or diluted product)	N/A	
Important administration instructions supported by product quality information (e.g., do not crush or chew extended-release tablets, instructions for mixing with food)	N/A	
For parenteral products: include statement: <i>"Parenteral drug products must be inspected visually for particulate matter and discoloration prior to administration, whenever solution and container permit"</i>	N/A	
If there is a USP monograph for the drug product and it contains a labeling requirement, ensure the labeling requirement is fulfilled. Note the labeling requirement may be applicable to another	N/A	

section of the PI (e.g., Section 11).		
For radioactive products, include radiation dosimetry for the patient and healthcare practitioner(s) who administer the drug	N/A	
For hazardous products, include the statement <i>“DRUG X is a hazardous drug. Follow applicable special handling and disposal procedures.x”</i> with x numerical citation to <i>“OSHA Hazardous Drugs”</i>.	N/A	

1.2.2 Section 3 (DOSAGE FORMS AND STRENGTHS)

Item	Items in Proposed Labeling (choose "Adequate", "Inadequate", or "N/A")	Assessor's Comments (If an item is Inadequate, provide more details on the issues, as appropriate)
DOSAGE FORMS AND STRENGTHS section		
Available dosage form(s)	Adequate	
Strength(s) in metric system	Adequate	
If the active ingredient is a salt, apply the USP Salt Policy per FDA Guidance. Clearly state whether the strength is based on the active moiety (e.g., Tablets: 10 mg of drug-x) or active ingredient (Tablets: 10 mg of drug-x hydrochloride).	N/A	
A description of the identifying characteristics of the dosage forms, including shape, color, coating, scoring, imprinting, and color and clarity of the solution, when applicable	Adequate	
Assess if the tablet is scored. If product meets guidelines and criteria for a scored tablet, state "functionally scored"	N/A	
For injectable drug products for parental administration, use appropriate package type term (e.g., single-dose, multiple-dose, single-patient-use). Other package type terms include pharmacy bulk package and imaging bulk package.	Adequate	

Section 11 (DESCRIPTION)

Item	Items in Proposed Labeling (choose "Adequate", "Inadequate", or "N/A")	Assessor's Comments (If an item is Inadequate, provide more details on the issues, as appropriate)
DESCRIPTION section		
Proprietary and established name(s)	Adequate	
Dosage form(s) and route(s) of administration	Adequate	
If the active ingredient is a salt, apply the USP Salt Policy and include the equivalency statement per Salt Guidance and MAPP . For example: "TRADENAME contains 100 mg of drug-x (equivalent to 123.7 mg of drug-x hydrochloride)"	N/A	
List names of all inactive ingredients. Use USP/NF names in alphabetical order. Avoid brand names.	Adequate	
For parenteral injectable dosage forms, include the name and quantities of all inactive ingredients. For ingredients added to adjust the pH or make isotonic, include the name and statement of effect.	Adequate	
If alcohol is present, must provide the amount of alcohol in terms of percent volume of absolute alcohol	N/A	
Sterility statement (if applicable)	Adequate	
Pharmacological/Therapeutic class	Adequate	
Chemical name, structural formula, molecular weight	Adequate	
If radioactive, statement of important nuclear characteristics.	N/A	
Other important chemical or physical properties (such as pKa or pH)	Adequate	

Section 11 (DESCRIPTION) Continued

Item	Items in Proposed Labeling (choose "Adequate", "Inadequate", or "N/A")	Assessor's Comments (If an item is Inadequate, provide more details on the issues, as appropriate)
For oral prescription drug products, include gluten statement (if applicable)	N/A	
Remove statements that may be misleading or promotional (e.g., "synthesized and developed by Drug Company X," "structurally unique molecular entity")	N/A	
If there is a USP monograph for the drug product and it contains a labeling requirement, ensure the labeling requirement is fulfilled. Note the labeling requirement may be applicable to another section of the PI (e.g., Section 2).	N/A	

1.2.4 Section 16 (HOW SUPPLIED/STORAGE AND HANDLING)

Item	Items in Proposed Labeling (choose "Adequate", "Inadequate", or "N/A")	Assessor's Comments (If an item is Inadequate, provide more details on the issues, as appropriate)
HOW SUPPLIED/STORAGE AND HANDLING section		
Available dosage form(s)	Adequate	
Strength(s) in metric system	Adequate	
Available units (e.g., bottles of 100 tablets)	Adequate	
Identification of dosage forms (e.g., shape, color, coating, scoring, imprinting, and color and clarity of the solution, when applicable); Include NDC(s)	Adequate	
Assess if the tablet is scored. If product meets guidelines and criteria for a scored tablet, state "functionally scored"	N/A	
For injectable drug products for parental administration, use appropriate package type term (e.g., single-dose, multiple-dose, single-patient-use). Other package terms include pharmacy bulk package and imaging bulk package.	Adequate	
Special handling about the supplied product (e.g., protect from light, refrigerate). If there is a statement to "Dispense in original container," provide reason why (e.g., to protect from light or moisture, to maintain stability, etc.). For hazardous drugs, state "DRUG X is a hazardous drug. Follow applicable special handling and disposal procedures.x" with x numerical citation to "OSHA Hazardous Drugs."	Adequate	"DO NOT FREEZE" included in the labeling, excursions permitted between 15°C and 30°C permitted (supported by stability studies)

Section 16 (HOW SUPPLIED/STORAGE AND HANDLING) (Continued)

Item	Items in Proposed Labeling (choose "Adequate", "Inadequate", or "N/A")	Assessor's Comments (If an item is Inadequate, provide more details on the issues, as appropriate)
Storage conditions. Where applicable, use USP storage range rather than storage at a single temperature.	Adequate	
Latex: If product does not contain latex and manufacturing of product and container did not include use of natural rubber latex or synthetic derivatives of natural rubber latex, state: <i>"Not made with natural rubber latex. Avoid statements such as "latex-free."</i>	N/A	
Include information about child-resistant packaging	N/A	

1.2.5 Other Sections of Labeling

There may be other sections of labeling that contain product-quality related information. For example, there are specific required/recommended warnings for certain inactive ingredients [e.g., aspartame, aluminum in large and small volume parenterals, sulfites, FD&C Yellow Number 5 (tartrazine), and benzyl alcohol]. Please notify the prescription drug review division if the product contains any of these inactive ingredients.

Please include your comments about other sections of labeling if they contain product quality information.

1.2.6 Manufacturing Information After Section 17 (for drug products)

Item	Items in Proposed Labeling (choose "Adequate", "Inadequate", or "N/A")	Assessor's Comments (If an item is Inadequate, provide more details on the issues, as appropriate)
Manufacturing Information After Section 17		
Name and location of business (street address, city, state, and zip code) of the manufacturer, distributor, and/or packer	Adequate	

2.0 PATIENT LABELING

Assessment of Product Quality Related Aspects of Patient Labeling (e.g., Medication Guides, Instructions for Use, Patient Information):

Item	Items in Proposed Labeling (choose "Adequate", "Inadequate", or "N/A")	Assessor's Comments about Carton Labeling (If an item is Inadequate, provide more details on the issues, as appropriate)
Established name ²	Adequate	
Special preparation instructions (if applicable)	N/A	
Storage and handling information (if applicable)	N/A	
If the product contains a desiccant, ensure the desiccant has a warning (e.g., "Do not eat.") and the size and shape of the desiccant differs from the dosage form.	N/A	
Active ingredient(s) (if applicable)	Adequate	
Alphabetical listing of inactive ingredients (if applicable)	N/A	
Name and location of business (street address, city, state, and zip code) of manufacturer, distributor, and/or packer	Adequate	

Any deficiencies should be listed at the end in the "ITEMS FOR ADDITIONAL ASSESSMENT."

3.0 CONTAINER AND CARTON LABELING

3.1 Container Labels

(Copy/paste or refer to a representative example of a proposed container)

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

² Established name = [Drug] [Route of Administration] [Dosage Form]

Item	Items in Proposed Labeling (choose “Adequate”, “Inadequate”, or “N/A”)	Assessor’s Comments about Carton Labeling (If an item is Inadequate, provide more details on the issues, as appropriate)
Established name ³ , (font size and prominence)	Adequate	
Strength(s) in metric system	Adequate	
Route(s) of administration	Adequate	
If the active ingredient is a salt, include the equivalency statement per Salt Guidance and MAPP .	N/A	
Net contents (e.g., tablet count, volume of liquid)	Adequate	
“Rx only” displayed on the principal display	Adequate	
NDC	Inadequate	
Lot number and expiration date	Adequate	
Storage conditions. If applicable, include a space on the carton labeling for the user to write the new beyond-use-date (BUD).	Adequate	
For injectable drug products for parental administration, use appropriate package type term (e.g., single-dose, multiple-dose, single-patient-use). Other package terms include pharmacy bulk package and imaging bulk package, and these products require a “Not for direct infusion” statement.	Inadequate	
For parenteral injectable dosage forms, include the name and quantities of all active and inactive ingredients in alphabetical order. For ingredients added to adjust the pH or make isotonic, include the name and statement of effect.	Adequate	
If alcohol is present, must provide the amount of alcohol in terms of percent volume of absolute alcohol	N/A	
Linear Bar code	Inadequate	

³ Established name = [Drug] [Route of Administration] [Dosage Form]

Item	Items in Proposed Labeling (choose "Adequate", "Inadequate", or "N/A")	Assessor's Comments about Carton Labeling (If an item is Inadequate, provide more details on the issues, as appropriate)
Name of manufacturer/distributor /packer	Adequate	
If there is a Medication Guide, must include a statement about dispensing a Medication Guide to each patient.	N/A	
No text on Ferrule and Cap overseal, unless a cautionary statement is required.	N/A	
If there is a USP monograph for the drug product and it contains a labeling requirement, ensure the labeling requirement is fulfilled.	N/A	
When a drug product differs from the relevant USP standard of strength, quality, or purity, as determined by the application of the tests, procedures, and acceptance criteria set forth in the relevant compendium, its difference shall be plainly stated on its label.	N/A	
And others, if space is available.	N/A	

Assessment of Carton and Container Labeling: Adequate

Any deficiencies should be listed at the end in the "ITEMS FOR ADDITIONAL ASSESSMENT."

ITEMS FOR ADDITIONAL ASSESSMENT

Assess consistency of product-quality information in prescription drug labeling (PI, c/c labeling, and FDA-approved patient labeling). See [Carton/Container Labeling Specific Resources](#) for a presentation about inappropriate inconsistencies of product quality information between labeling. If there are inappropriate inconsistencies between the labeling (e.g., established name, strength(s), package type term, discard statement, identifying characteristics, storage, reconstitution/dilution instructions), please list these as deficiencies in this section.

Overall Assessment and Recommendation:

Adequate

Primary Labeling Assessor Name and Date: Eric Bow PhD 7/14/22

*Secondary Assessor Name and Date (and Secondary Summary, as needed): Julia
Pinto PhD 7/14/22*



Eric
Bow

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Julia
Pinto

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CHAPTER VII: MICROBIOLOGY

[IQA NDA Assessment Guide Reference](#)

Product Information	
NDA Number	216359
Assessment Cycle Number	01
Drug Product Name/ Strength	Midazolam Injection, 10 mg/0.7 mL
Route of Administration	IM injection
Applicant Name	Rafa Laboratories, Ltd.
Therapeutic Classification/ OND Division	OND/ON/DN2
Manufacturing Site	Rafa Laboratories, Ltd. Zeev Lev 3, Har Hotzvim, Jerusalem, 9777515, Israel FEI no. 3004437307
Method of Sterilization	(b) (4)

Assessment Recommendation: Adequate

Assessment Summary: The drug product will be (b) (4) and (b) (4). Adequate information was provided to support the sterility assurance of the drug product for the intended shelf-life. This includes the (b) (4) validation (b) (4), drug product filling and process simulation/media fill qualification, environmental monitoring, container closure integrity testing validation, validation of the sterilization and depyrogenation processes used for containers, closures, equipment, and components, holding periods, release and stability testing method validation and specifications.

List Submissions being assessed (table):

Document(s) Assessed	Date Received
0001 SD1	3/28/2022
0002 SD 2	5/13/2022

Highlight Key Issues from Last Cycle and Their Resolution: N/A

Remarks: The drug product is a single dose IM injection supplied in a pre-filled auto-injector syringe.

Concise Description of Outstanding Issues: N/A

Supporting Documents:

- A209833MR01 [V7].pdf, dated 5/25/2018 for review of (b) (4), depyrogenation (b) (4) validation (ID # 2028), and (b) (4) validation (ID # 2030)
- D10953M49R01.docx, dated 6/8/2020 and D10945M55R01.docx, dated 6/7/2021 for review of the (b) (4) depyrogenation.

S DRUG SUBSTANCE

The drug substance is not provided sterile. Therefore, a product quality microbiology review of the drug substance is not reviewed.

P.1 DESCRIPTION OF THE COMPOSITION OF THE DRUG PRODUCT

Section 3.2.P.1

Description of drug product – sterile solution for IM injection

Drug product composition –

Ingredient	Quantity per mL	Function
Midazolam, USP	(b) (4)	API
Sodium chloride, USP	(b) (4)	(b) (4)
Hydrochloric acid (b), USP	(b) (4)	pH adjuster

Description of container closure system – The (b) (4) drug product is (b) (4) into cartridges for final assembly into the auto-injector device. The cartridge is composed of a (b) (4) tube (cylinder), a (b) (4) (b) (4), a stainless-steel 22-gauge needle, (b) (4), and a (b) (4). A more detailed review of the components is reviewed in P.7.

Assessment: Adequate

The applicant provided an adequate description of the drug product composition and container closure system.

Note to reviewer: A more detailed review of the components is reviewed in P.7.

P.2 PHARMACEUTICAL DEVELOPMENT

P.2.5 MICROBIOLOGICAL ATTRIBUTES

Container/Closure and Package Integrity

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2. ASSESSMENT OF COMMON TECHNICAL DOCUMENT – QUALITY (CTD-Q) MODULE 1

2.A. Prescribing Information

Post-dilution/constitution hold time

Section 1.14.1.3

Storage temperature: 20-25°C

Maximum storage time: 24 months unopened

Route of administration: IM

Container: Single dose

Reconstituted/Further Diluted Drug Product: N/A

Assessment: Adequate

The single-dose drug product is used without reconstitution or dilution.

Therefore, the proposed labeling does not pose any microbiological risks.

MICROBIOLOGY LIST OF DEFICIENCIES: N/A

Primary Microbiology Assessor Name and Date: KellyAnn Miller, PhD, 5/27/2022

*Secondary Assessor Name and Date (and Secondary Summary, as needed):
Erika Pfeiler, PhD, 5/27/2022*



KellyAnn
Miller

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Erika
Pfeiler

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