CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

216903Orig1s000

OTHER REVIEW(S)

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

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

Memorandum

Date: February 10, 2023

To: Rita Joshi, PharmD, Regulatory Project Manager, Division of Anesthesiology, Addiction Medicine, and Pain Medicine (DAAP)

Lee Anne Connell-Templin, MD, DAAP

Lisa Basham, MS, Associate Director for Labeling, DAAP

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 PREVDUO (neostigmine methylsulfate and glycopyrrolate injection), for intravenous use

NDA: 216903

Background:
In response to DAAP's consult request dated April 27, 2022, OPDP has reviewed the proposed Prescribing Information (PI) and carton and container labeling for the original NDA submission for PREVDUO (neostigmine methylsulfate and glycopyrrolate injection), for intravenous use.

PI:
OPDP's review of the proposed PI is based on the draft labeling emailed to OPDP on February 7, 2023, and our comments are provided below.

Carton and Container Labeling:
OPDP's review of the proposed carton and container labeling is based on the draft labeling submitted by the sponsor to the electronic document room on February 7, 2023, and our comments are provided below.

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

20 Pages of Draft Labeling have been Withheld in Full as b4 (CCI/TS) immediately following this page

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/s/

PHILLIP A WILLIAMS
02/10/2023 05:44:28 PM

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:	February 8, 2023
Requesting Office or Division:	Division of Anesthesiology, Addiction Medicine, and Pain Medicine (DAAP)
Application Type and Number:	NDA 216903
Product Name and Strength:	Prevduo (neostigmine methylsulfate and glycopyrrolate) injection neostigmine methylsulfate 3 mg/3 mL (1 mg/mL) and glycopyrrolate 0.6 mg/3 mL (0.2 mg/mL)
Applicant/Sponsor Name:	Slayback Pharma LLC. (Slayback)
OSE RCM #:	2022-807-1
DMEPA 1 Safety Evaluator:	Damon Birkemeier, PharmD, FISMP, NREMT
DMEPA 1 Team Leader:	Valerie S. Vaughan, PharmD

1 PURPOSE OF MEMORANDUM

The Applicant submitted revised prescribing information (PI), instructions for use (IFU), container label, and carton labeling received on February 7, 2023 for Prevduo. The Division of Anesthesiology, Addiction Medicine, and Pain Medicine (DAAP) requested that we review the revised prescribing information (PI), instructions for use (IFU), container label, and carton labeling for Prevduo (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 implemented all of our recommendations and we have no additional recommendations at this time.

[a] Birkemeier D. Label and Labeling Review for Prevduo (NDA 216903). Silver Spring (MD): FDA, CDER, OSE, DMEPA 1 (US); 2022 OCT 11. RCM No.: 2022-807.

APPENDIX A. IMAGES OF LABEL AND LABELING RECEIVED ON FEBRUARY 7, 2023

- Prescribing Information and Instructions for Use (Image not shown) available from \\CDSESUB1\EVSPROD\nda216903\0014\m1\us\prescribing-information-clean.pdf
- Response to Division's Edits and Comments for the PI and Carton/Container Labels available from \\CDSESUB1\EVSPROD\nda216903\0014\m1\us\annexure-4-resp-to-division-edits-comments.pdf

Container Labels

Current Container Label (2/2023)	Previous Container Label (submitted 4/2022)
	(b) (4)
Annotated Differences: 1. Included the Expiration date in the format YYYY-MM. 2. Added the route of administration statement “For Intravenous Use Only”. 3. The statement “3 mL Single-Dose Prefilled Syringe” is revised to read as “3 mL Single-Dose Prefilled Syringe. Discard unused portion.” 4. The Barcode has been moved to the bottom of the label for better readability. 5. Revision date has been updated.	

Carton Labeling

Current Carton Labeling (2/2023)	Previous Carton Labeling (submitted 4/2022)
(b) (4)	

Annotated Differences:

1. Included the Expiration date in the format YYYY-MM.
2. The statement "Each mL contains: (b) (4) mg of neostigmine…" is revised to "Each mL contains: 1 mg of neostigmine…" (removed (b) (4)
3. Included the product identifier details including the machine readable (2-D data matric barcode).
4. Included a statement "Recommended Dosage: See Prescribing Information."
5. Revision date has been updated.

This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

DAMON A BIRKEMEIER
02/08/2023 09:33:11 AM

VALERIE S VAUGHAN
02/08/2023 03:10:26 PM

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:	October 11, 2022
Requesting Office or Division:	Division of Anesthesiology, Addiction Medicine, and Pain Medicine (DAAP)
Application Type and Number:	NDA 216903
Product Name and Strength:	neostigmine methylsulfate and glycopyrrolate injection, neostigmine methylsulfate 3 mg/3 mL (1 mg/mL); glycopyrrolate 0.6 mg/3 mL (0.2 mg/mL)
Product Type:	Multi-Ingredient Product
Rx or OTC:	Prescription (Rx)
Applicant/Sponsor Name:	Slayback Pharma LLC. (Slayback)
FDA Received Date:	April 25, 2022; August 18, 2022
OSE RCM #:	2022-807
DMEPA 1 Safety Evaluator:	Damon Birkemeier, PharmD
DMEPA 1 Team Leader:	Valerie S. Vaughan, PharmD

1 REASON FOR REVIEW

As part of the approval process for neostigmine methylsulfate and glycopyrrolate injection, the Division of Anesthesiology, Addiction Medicine, and Pain Medicine (DAAP) requested that we review the proposed neostigmine methylsulfate and glycopyrrolate prescribing information (PI), instructions for use (IFU), container label, and carton labeling for areas of vulnerability that may lead to medication errors.

1.1 BACKGROUND

NDA 216903 is a 505(b)(2) NDA and the listed drug products are Bloxiverz (NDA 204078) and Robinul (NDA 017558).

The Applicant submitted a Use-Related Risk Analysis (URRA), comparative analysis, and justification for not submitting further human factors data to support their marketing application. The review of the URRA, comparative analysis, and justification are managed under separate cover.[a] As such, this review focuses on assessment of the container labels, carton labeling, PI and IFU from a medication error perspective.

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
Other	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

[a] Oguntimein, M. Comparative Analyses Review for neostigmine and glycopyrrolate (NDA 216903). Silver Spring (MD): FDA, CDER, OSE, DMEPA1. (US); 2022 JUL 08. RCM No.: 2022-796.

3 CONCLUSION AND RECOMMENDATIONS

Our evaluation of the proposed neostigmine methylsulfate and glycopyrrolate instructions for use (IFU) did not identify areas of vulnerability that may lead to medication errors. However, the proposed prescribing information (PI), container label, and carton 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 the Division and in Section 5 for Slayback Pharma LLC.

4 RECOMMEDATIONS FOR THE DIVISION OF ANESTHESIOLOGY, ADDICTION MEDICINE, AND PAIN MEDICINE (DAAP)

Table 2. Identified Issues and Recommendations for the Division of Anesthesiology, Addiction Medicine, and Pain Medicine (DAAP)

	IDENTIFIED ISSUE	RATIONALE FOR CONCERN	RECOMMENDATION
Prescribing Information – General Issues			
1.	The strength of the neostigmine methylsulfate component (b) (4)	(b) (4)	(b) (4) we recommend the removal of the (b) (4) For example, revise to "1 mg."
2.	The product strength is not consistently expressed in the Highlights of Prescribing Information and Full Prescribing Information. For example, the product strength is expressed as (b) (4) in the Highlights of Prescribing Information and as (b) (4)	Inconsistent labeling may contribute to confusion that can result in a wrong dose error.	Revise the strength presentation so that it is consistency presented throughout the PI.

Table 2. Identified Issues and Recommendations for the Division of Anesthesiology, Addiction Medicine, and Pain Medicine (DAAP)			
	IDENTIFIED ISSUE	RATIONALE FOR CONCERN	RECOMMENDATION
	(b) (4) in Section 3 in the Full Prescribing Information.		
Full Prescribing Information – Section 2 Dosage and Administration			
1.	The weight-based dosages are displayed in (b) (4)	Basing dosages on (b) (4) may lead to overdose or underdose errors if the dose is prescribed in (b) (4)	Revise the weight-based dosing information based on (b) (4) to weight-based dosing based on milligrams. For example, revise to 0.03 mg/kg to 0.07 mg/kg neostigmine methylsulfate and 0.006 mg/kg to 0.014 mg/kg glycopyrrolate.
2.	As currently presented, the recommended maximum total dose is displayed in (b) (4)	Basing dosages on (b) (4) may lead to overdose or underdose errors if the dose is prescribed in (b) (4) Additionally, we note the recommended maximum total dose is based on the neostigmine component. It may be helpful to clarify which component the maximum total dose is based on in the labeling.	Revise the weight-based recommended maximum total dose information based on (b) (4) to weight-based dosing based on milligrams of neostigmine. For example, revise to 0.07 mg/kg of neostigmine methylsulfate or up to a total of 5 mg of neostigmine methylsulfate, whichever is less.
3.	As currently presented, the (b) (4) is used throughout the dosage and administration section.	Although the (b) (4)	Replace (b) (4) "half-life" and "half-lives".

Table 2. Identified Issues and Recommendations for the Division of Anesthesiology, Addiction Medicine, and Pain Medicine (DAAP)			
	IDENTIFIED ISSUE	RATIONALE FOR CONCERN	RECOMMENDATION
		(b) (4) [redacted]	
Full Prescribing Information – Section 3 Dosage Forms and Strengths			
1.	The package type term is missing.	The package type term helps to convey the appropriate handling of the pre-filled syringe.	Add the package type term "single-dose" to describe the product.
2.	As currently presented, the appropriate information to facilitate identification of the proposed dosage form is not included.	A description of identifying characteristics (i.e., clear, colorless solution) can be used to help identify the product and is required by 21 CFR 201.57(c)(4).	We recommend that the description of identifying characteristics (i.e., clear, colorless solution) to facilitate identification be added in accordance with 21 CFR 201.57(c)(4).
Full Prescribing Information – Section 16 How Supplied/Storage and Handling			

5 RECOMMENDATIONS FOR SLAYBACK PHARMA LLC.

Table 3. Identified Issues and Recommendations for Slayback Pharma LLC. (entire table to be conveyed to Applicant)			
	IDENTIFIED ISSUE	RATIONALE FOR CONCERN	RECOMMENDATION
Container Label and Carton Labeling			
1.	The format for the expiration date is not defined.	Clearly defining the expiration date will minimize confusion and risk for deteriorated drug medication errors.	Identify the expiration date format you intend to use. FDA recommends 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

Table 3. Identified Issues and Recommendations for Slayback Pharma LLC. (entire table to be conveyed to Applicant)			
	IDENTIFIED ISSUE	RATIONALE FOR CONCERN	RECOMMENDATION
			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.
Container Label			
1.	As currently presented, the route of administration is not included on the container label.	The route of administration is required in accordance with 21 CFR 201.100(b)(3) and should be included on the container label.	Add the route of administration statement, without the use of abbreviation. For example: "For Intravenous Use Only"
2.	As currently presented, the container label does not contain the phrase "Discard unused portion".	The phrase "Discard unused portion" minimizes the risk of the entire syringe contents being given as a single dose.	Consider adding the phrase "Discard unused portion" following the package type term. For example, consider revising to "3 mL Single-Dose Prefilled Syringe. Discard unused portion."
Carton Labeling			
1.	The statement "Each mL contains: (b) (4)	(b) (4) lead to wrong dose medication errors.	(b) (4) we recommend the removal of the (b) (4) For example, revise to "1 mg."
2.	As currently presented, the carton labeling does	In June 2021, FDA finalized guidance on product identifiers required under	We recommend that you review the finalized guidance, *Product Identifiers under the*

Table 3. Identified Issues and Recommendations for Slayback Pharma LLC. (entire table to be conveyed to Applicant)			
	IDENTIFIED ISSUE	RATIONALE FOR CONCERN	RECOMMENDATION
	not contain a product identifier.	the Drug Supply Chain Security Act (DSCSA). The Act requires manufacturers and repackagers, respectively, to affix or imprint a product identifier to each package and homogenous case of a product intended to be introduced in a transaction in(to) commerce beginning November 27, 2017, and November 27, 2018, respectively. The product identifier contains the NDC, serial number, lot, and expiration date. The DSCSA guidance on product identifiers recommends the format below for the human-readable portion of the product identifier. The guidance also recommends that the human-readable portion be located near the 2D data matrix barcode. NDC: [insert product's NDC] SERIAL: [insert product's serial number] LOT: [insert product's lot number]	*Drug Supply Chain Security Act – Questions and Answers*, to determine if the product identifier requirements apply to your product's labeling.[b] If you determine that the product identifier requirements apply to your product's labeling, we request you add to the carton labeling a placeholder for the product identifier, including the machine readable (2-D data matric barcode).

[b] Final Guidance: Product Identifiers Under the Drug Supply Chain Security Act Questions and Answers, July 2021. https://www.fda.gov/ucm/groups/fdagov-public/@fdagov-drugs-gen/documents/document/ucm621044.pdf

Table 3. Identified Issues and Recommendations for Slayback Pharma LLC. (entire table to be conveyed to Applicant)			
	IDENTIFIED ISSUE	RATIONALE FOR CONCERN	RECOMMENDATION
		EXP: [insert product's expiration date]	
3.	As currently presented, the "Usual Dose" statement is not included.	Per 21 CFR 201.55, "…labels for prescription drugs should bear a statement of the recommended or usual dosage."	Include a "Usual Dosage" statement to align with 21 CFR 201.55. We recommend stating as "Recommended Dosage: See Prescribing Information."

APPENDICES: METHODS & RESULTS FOR EACH MATERIAL REVIEWED

APPENDIX A. PRODUCT INFORMATION/PRESCRIBING INFORMATION

Table 4 presents relevant product information for neostigmine methylsulfate and glycopyrrolate that Slayback Pharma LLC. submitted on April 25, 2022, and the listed drugs (LD).

	Table 4. Relevant Product Information for Listed Drugs and neostigmine methylsulfate and glycopyrrolate		
Product Name	Bloxiverz	Robinul	Neostigmine methylsulfate and glycopyrrolate
Application Type and Number	NDA 204078	NDA 017558	NDA 216903
Initial Approval Date	May 31, 2013	February 6, 1975	N/A
Active Ingredient	neostigmine methylsulfate	glycopyrrolate	Neostigmine methylsulfate and glycopyrrolate
Indication	Reversal of the effects of non-depolarizing neuromuscular blocking agents (NMBA) after surgery.	<u>In Anesthesia:</u> Preoperative antimuscarinic to reduce salivary, tracheobronchial, and pharyngeal secretions; to reduce the volume and free acidity of gastric secretions; and to block cardiac vagal inhibitory reflexes during induction of anesthesia and intubation. When indicated, may be used intraoperatively to counteract surgically or drug-induced vagal reflexes associated arrhythmias. Glycopyrrolate protects against the peripheral muscarinic effects of cholinergic agents such as neostigmine and	Reversal of the effects of non-depolarizing neuromuscular blocking agents after surgery, (b) (4)

		pyridostigmine given to reverse the neuromuscular blockade due to non-depolarizing muscle relaxants. <u>In Peptic Ulcer:</u> Use in adults as adjunctive therapy for the treatment of peptic ulcer when rapid anticholinergic effect is desired or when oral medication is not tolerated.	
Route of Administration	Intravenous	Intravenous, Intramuscular	Intravenous
Dosage Form	Injection		
Strength	0.5 mg/mL 1 mg/mL	0.2 mg/mL	Neostigmine methylsulfate 3 mg/3 mL (1 mg/mL) and glycopyrrolate 0.6 mg/3 mL (0.2 mg/mL)
Dose and Frequency	<u>Adults:</u> 0.03 mg/kg to 0.07 mg/kg will generally achieve a train of four (TOF) twitch ratio of 90% within 10-20 minutes of administration. Dose selection should be based on the extent of spontaneous recovery that has occurred at the time of administration, the half-life of the NMBA being reversed, and whether there is a need to rapidly reverse the NMBA.	<u>Adults:</u> <u>Preanesthetic Medication:</u> 0.004 mg/kg intramuscularly given 30-60 minutes prior to anticipated time of induction of anesthesia or at the time the preanesthetic narcotic and/or sedative are administered. <u>Intraoperative Medication:</u> Administer intravenously as single doses of 0.1 mg and repeated as needed at intervals of 2-3 minutes. <u>Reversal of Neuromuscular Blockade:</u> 0.2 mg for each 1 mg of	<u>Adults:</u> Dosing is based on the neostigmine methylsulfate ingredient. A 0.03 mg/kg to 0.07 mg/kg dose of neostigmine methylsulfate will generally achieve a train of four (TOF) twitch ratio of 90% within 10-20 minutes of administration. Dose selection should be based on the extent of spontaneous recovery that has occurred at the time of administration, the

	Recommended maximum total dose is 0.07 mg/kg or up to a total of 5 mg, whichever is less. Pediatrics: follow adult guidelines, pediatric patients generally require doses similar to those for adult patients.	neostigmine or 5 mg of pyridostigmine. In order to minimize the appearance of cardiac side effects, the drugs may be administered simultaneously by intravenous injection and may be mixed in the same syringe. Peptic Ulcer: 0.1 mg administered at 4 hour intervals, 3 to 4 times daily intravenously or intramuscularly. Where more profound effect is required 0.2 mg may be given. Pediatrics: Preanesthetic medication: 0.004 mg/kg intramuscularly given 30-60 minutes prior to anticipated time of induction of anesthesia or at the time the preanesthetic narcotic and/or sedative are administered. Intraoperative Medication: Additional 0.004 mg/kg intravenously, not to exceed 0.1 mg in a single dose, which may be repeated as needed, at intervals of 2 to 3 minutes.	half-life of the NMBA being reversed, and whether there is a need to rapidly reverse the NMBA. Recommended maximum total dose is 0.07 mg/kg or up to a total of 5 mg, whichever is less. Pediatrics: follow adult guidelines, pediatric patients generally require doses similar to those for adult patients.

		Reversal of Neuromuscular Blockade: 0.2 mg for each 1 mg of neostigmine or 5 mg of pyridostigmine. In order to minimize the appearance of cardiac side effects, the drugs may be administered simultaneously by intravenous injection and may be mixed in the same syringe.	
How Supplied	• 0.5 mg/mL (10 mL multiple dose vials in packages of 10) • 1 mg/mL (10 mL multiple dose vials in packages of 10)	• 0.2 mg/mL (1 mL single dose vials packaged in 25s) • 0.2 mg/mL (2 mL single dose vials packaged in 25s) • 0.2 mg/mL (5 mL multiple dose vials packaged in 25s) • 0.2 mg/mL (20 mL multiple dose vials packaged in 10s)	• Neostigmine methylsulfate 3 mg/3 mL (1 mg/mL) and glycopyrrolate 0.6 mg/3 mL (0.2 mg/mL) (3 mL single dose prefilled syringe packaged in cartons of 5 syringes)
Storage	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) [See USP Controlled Room Temperature].		

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,[c] along with postmarket medication error data, we reviewed the following neostigmine methylsulfate and glycopyrrolate labels and labeling submitted by Slayback Pharma LLC.

- Container label received on April 25, 2022
- Carton labeling received on April 25, 2022
- Instructions for Use received on April 25, 2022, available under Section 2 of the prescribing information
- Prescribing Information (Image not shown) received on August 18, 2022, available from \\CDSESUB1\EVSPROD\nda216903\0007\m1\us\prevduo-prescribing-information-label.pdf

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

F.2 Label and Labeling Images

Container Label

Proposed Neostigmine Methylsulfate and Glycopyrrolate	Differences:
(b) (4) [redacted]	1. NDC number has been replaced per the proposed drug product. 2. Proposed drug product name is used in the proposed drug product. 3. Route of administration included as per the proposed drug product. 4. Fill volume information is included as per the proposed drug product. 5. Product specific information is provided as per the proposed drug product. 6. Barcode, lot number and expiry date has been replaced as per the proposed drug product. 7. Manufacturer address and logo has been replaced with proposed drug product.

Carton Labeling

Proposed Neostigmine Methylsulfate and Glycopyrrolate	Differences:
(b) (4)	1. NDC number has been replaced per the proposed drug product. 2. Proposed drug product name is used in the proposed drug product. 3. Route of administration included as per the proposed drug product. 4. Fill volume information is included as per the proposed drug product. 5. Product specific information is provided as per the proposed drug product. 6. Barcode, lot number and expiry date has been replaced as per the proposed drug product. 7. Manufacturer address and logo has been replaced with proposed drug product.

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/s/

DAMON A BIRKEMEIER
10/11/2022 02:58:32 PM

VALERIE S VAUGHAN
10/11/2022 03:00:07 PM

MEMORANDUM

COMPARATIVE ANALYSES 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)

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Date of This Review:	July 08, 2022
Requesting Office or Division:	Division of Anesthesiology, Addiction Medicine, and Pain Medicine (DAAP)
Application Type and Number:	NDA 216903
Product Name, Dosage Form, and Strength:	Neostigmine methylsulfate, 3 mg/3 mL and glycopyrrolate, 0.6 mg/3 mL injection
Device Constituent:	Prefilled Syringe
Product Type:	Combination Product (Drug-Device)
Rx or OTC:	Prescription (Rx)
Applicant/Sponsor Name:	Slayback Pharma LLC (Slayback)
FDA Received Date:	April 23, 2022, May 20, 2022
OSE RCM #:	2022-796
DMEPA 1 Team Leader:	Murewa Oguntimein, PhD, MHS, CPH, MCHES
DMEPA 1 Associate Director of Human Factors:	Jason Flint, MBA, PMP

1 REASON FOR REVIEW

On April 23, 2022, the Applicant submitted a New Drug Application (NDA) under NDA 216903 that included comparative analyses, use-related risk analysis (URRA) and justification for not submitting further human factors (HF) data to support their marketing application for Neostigmine methylsulfate, 3 mg/3 mL and glycopyrrolate, 0.6 mg/3 mL injection.

2 BACKGROUND AND CONCLUSION

On November 22, 2021, under IND 139866, the Applicant submitted comparative analyses, URRA and justification for not submitting HF validation study results to support their marketing application.

On March 09, 2022, we reviewed the aforementioned comparative analyses, URRA and justification and determined that they do not need to submit human factors validation study data with your marketing application for neostigmine methylsulfate and glycopyrrolate prefilled syringe to be used by healthcare professionals for the reversal of the effects of non-depolarizing neuromuscular blocking agents (NMBAs) after surgery, while minimizing the peripheral muscarinic effects (e.g., bradycardia and excessive secretions) associated with cholinesterase inhibition. We also stated that if the Applicant modified the product user interface additional human factors considerations may apply.[a]

On April 23, 2022, the Applicant submitted a marketing application under NDA 216903 for Neostigmine methylsulfate, 3 mg/3 mL and glycopyrrolate, 0.6 mg/3 mL injection. The submission included comparative analyses, use-related risk analysis (URRA) and justification for not submitting further human factors (HF) data to support their marketing application. However, the Applicant did not indicate that the commercial product user interface had not been modified since the November 22, 2021, submission. As such, we issued an information request (IR) on May 19,2022 asking the Applicant to clarifying the following:

- *if the product user interface of your proposed PFS in your November 22, 2021, submission is identical to the product user interface of your proposed PFS in your April 25, 2022, submission*
- *if the URRA submitted on November 22, 2021, is the same as the URRA submitted in your April 23, 2022, submission.*

Subsequently, on May 20, 2022, the Applicant provided the following response to the IR:

> *We acknowledge the Agency's comment. We wish to clarify the Agency that there is no modification to the product user interface or device constituent parts of proposed*

[a] Kumar N. Comparative analyses review for Neostigmine methylsulfate, 3 mg/3 mL and glycopyrrolate, 0.6 mg/3 mL injection (IND 139866). Silver Spring (MD): FDA, CDER, OSE, DMEPA (US);09 MAR 2022. RCM No.: 2021-1343.

PFS after the revised URRA submitted on November 22, 2021, to IND 139866, and the Agency's Human Factors- General Advice received on March 11, 2022.
We further confirm that the URRA submitted in Module 1, Section 1.12.1 on April 25, 2022, to the NDA 216903 (eCTD Seq # 0002) is same as the URRA submitted in IND 139866 eCTD Section 5.3.5.4 - Other Study Reports and Related Information on November 22, 2021 (eCTD Seq # 0012).

Based on the aforementioned information, we maintain that the Applicant does not need to submit human factors validation study results with their new drug application under NDA 216903 for Neostigmine methylsulfate, 3 mg/3 mL and glycopyrrolate, 0.6 mg/3 mL injection. We have no HF recommendations for this marketing application.

APPENDICES: METHODS & RESULTS FOR EACH MATERIALS REVIEWED

APPENDIX A. Comparative Threshold Analysis

Comparative Threshold Analysis Report for Neostigmine methylsulfate, 3 mg/3 mL and glycopyrrolate, 0.6 mg/3 mL injection are accessible in EDR via: \\CDSESUB1\evsprod\nda216903\0002\m5\53-clin-stud-rep\535-rep-effic-safety-stud\nmbas\5354-other-stud-rep\123\comparative-threshold-analysis-report.pdf

APPENDIX B. INFORMATION REQUEST ISSUED DURING THIS REVIEW

On May 19, 2022, we issued an information request asking the Applicant to clarifying the following:

- if the product user interface of your proposed PFS in your November 22, 2021, submission is identical to the product user interface of your proposed PFS in your April 25, 2022, submission
- if the URRA submitted on November 22, 2021, is the same as the URRA submitted in your April 23, 2022, submission.

The Applicant provided an acceptable response on May 20, 2022, that can be accessed in EDR via: \\CDSESUB1\evsprod\nda216903\0003\m1\us\annexure-2-response-fda-email.pdf

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/s/

OLUWAMUREWA OGUNTIMEIN
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JASON A FLINT
07/11/2022 08:26:56 AM