CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

214919Orig1s000

OTHER REVIEW(S)

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

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

Memorandum

Date: April 14, 2022

To: Lee Anne Connell-Templin, MD, Clinical Reviewer
Division of Anesthesia, Addiction Medicine and Pain Medicine (DAAP)

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

Lisa Basham, M.S., Associate Director for Labeling, (DAAP)

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

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

Subject: OPDP Labeling Comments for GLYCOPYRROLATE injection, for intramuscular or intravenous use

NDA: 214919

In response to DAAP's consult request dated December 9, 2021, OPDP has reviewed the proposed product labeling (PI) for the original NDA submission for GLYCOPYRROLATE injection, for intramuscular or intravenous use.

Labeling: OPDP's comments on the proposed labeling are based on the draft labeling received by electronic mail from DAAP on April 4, 2022, and 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.

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

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PHILLIP A WILLIAMS
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USE-RELATED RISK ANALYSIS AND THRESHOLD ANALYSIS 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:	February 18, 2022
Requesting Office or Division:	Division of Anesthesiology, Addiction Medicine, and Pain Medicine (DAAP)
Application Type and Number:	NDA 214919
Product Name, Dosage Form and Strength:	Glycopyrrolate Injection, 0.6 mg/3 mL
Device Constituent:	Pre-filled Syringe
Rx or OTC:	Prescription (Rx)
Applicant Name:	Fresenius Kabi USA LLC (Fresenius)
FDA Received Date:	June 21, 2021, October 01, 2021
OSE RCM #:	2021-44
DMEPA 1 Safety Evaluator:	Seung Hoon Lee, BS
DMEPA 1 Team Leader :	Murewa Oguntimein, PhD, MHS, CPH, MCHES
DMEPA 1 Associate Director for Human Factors:	Jason Flint, MBA, PMP

1 REASON FOR REVIEW

This review evaluates the use-related risk analysis (URRA) and threshold analysis (physical comparison, comparative task analysis, and a labeling comparison) submitted under NDA 214919 for glycopyrrolate injection to determine whether we agree with the Applicant's justification for not submitting human factors (HF) validation study results with their 505(b)(2) New Drug Application (NDA) for the proposed prefilled syringe (PFS) device constituent part. Fresenius (the Applicant) submitted an Application Failure Modes and Effects Analysis (AFMEA) that included additional information expected for a use-related risk analysis (URRA). As such, we will refer to Fresenius's AFMEA as the URRA throughout this review.

1.1 PRODUCT DESCRIPTION

Glycopyrrolate is an anticholinergic used in a preoperative antimuscarinic, during the induction of anesthesia and intubation, as well as adjunctive therapy for the treatment of peptic ulcer when rapid anticholinergic effect is desired. Glycopyrrolate is injected intravenously or intramuscularly by trained healthcare professionals (HCPs). Glycopyrrolate PFS will be supplied in a carton containing one Simplist® PFS supplied as a 3 mL syringe glass, including syringe barrel, luer lock (b) (4), tip cap, plunger stopper, and plunger rod providing 0.6 mg/3 mL of glycopyrrolate. The carton will also contain an instructions for use (IFU) that is embedded in the prescribing information (PI) (See Figure 1). The Applicant proposes glycopyrrolate for the same indications as Reference listed drug (RLD) NDA 017558 Robinul vial. For additional product information, please see Table 4 in Appendix A.

1.2 REGULATORY HISTORY

- On October 31, 2018, the Agency approved the glycopyrrolate strengths 0.2 mg/mL and 0.4 mg/2 mL PFS under Abbreviated New Drug Application (ANDA) 209024 submitted by the Applicant[a].
- On December 30, 2020, the Applicant submitted a 505(b)(2) application, NDA 214919 for glycopyrrolate injection, 0.6 mg/3 mL PFS.
- On February 25, 2021, the Agency issued a Refuse to File letter to the Applicant regarding the leachables study as provided was not reviewable due to lack of information on methodology, sample preparation, and interpretable data[b].
- On March 16, 2021, the Applicant submitted a Type A Meeting Package to discuss the items issued in the Refuse to File letter dated February 25, 2021[c].
- In the preliminary meeting comments dated April 26, 2021, the Agency requested a benefit-risk analysis for the intended use of proposed product. The Agency stated that the analysis should include a comprehensive discussion of the proposed syringe presentations, with emphasis on how the drug content of the syringe (i.e., 0.6 mg/3 mL per prefilled syringe) may impact potential dosing errors and administration practices[d].
- On June 21, 2021, the Applicant submitted the threshold analysis and Application Failure Mode and Effects Analysis (AFMEA) to provide the benefit-risk analysis of the proposed product, which is the subject of this review.

2 MATERIALS REVIEWED

We considered the materials listed in Table 1 for this review.

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 and Agency/Applicant Interactions	B

[a] Schlick, J., Label, Labeling, and Packaging Review ANDA 209024. FDA, CDER, OSE, DMEPA (US); 2017, March 03. RCM No.: 2016-2829.

[b] Meyer A. Refuse to File Letter for Glycopyrrolate Injection, USP (0.6 mg/ 3 mL) (NDA 214919). Silver Spring (MD): FDA, CDER, OND, DRON (US). 2021 FEB 25.

[c] Type A Meeting Package for Glycopyrrolate Injection, USP (0.6 mg/ 3 mL) (NDA 214919). Fresenius Kabi USA, LLC. 2021 MAR 16.

[d] Meyer A. Meeting Preliminary Comments for Glycopyrrolate Injection, USP (0.6 mg/ 3 mL) (NDA 214919). Silver Spring (MD): FDA, CDER, OND, DRON (US). 2021 APR 26.

Table 1. Materials Considered for this Label and Labeling Review	
Material Reviewed	Appendix Section (for Methods and Results)
Use-Related Risk Analysis (URRA) and Threshold Analysis	C
Information Requests Issued During the Review	D
CDRH Human Factors Consult Review	E – N/A
Product Samples 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 OVERALL ASSESSMENT OF THE MATERIALS REVIEWED

The sections below provide our evaluation of the use-related risk analysis (URRA) and threshold analysis.

3.1 USE-RELATED RISK ANALYSIS (URRA)

The Applicant assessed the risks associated with the critical tasks in the URRA and determined the risks are mitigated through labeling and device design.

The Applicant identified and evaluated the tasks involved in the use of the proposed product, possible use errors, hazards, and the risk control measures. The Applicant also provided information regarding known use-related problems with similar marketed products.

Upon review of the URRA, we identified differences in use-related risks that could affect critical tasks between with the proposed product glycopyrrolate 0.6 mg/3 mL PFS as compared to RLD Robinul, 0.2 mg/mL and 0.4 mg/2 mL single dose vials and 1 mg/5 mL and 4 mg/20 mL multiple dose vial, which is the comparator product in the submitted threshold analyses.

3.2 THRESHOLD ANALYSIS

The Applicant determined that there are no differences in the user group between the proposed glycopyrrolate 0.6 mg/3 mL PFS and the RLD Robinul vial.

Because the Applicant is proposing to pursue the same indications as the RLD product, we find that the user characteristics evaluated by the Applicant are appropriate and agree that there are no differences identified between the user groups that would impact the proposed intended users' interactions with the user interface.

The Applicant identified several differences with the physical components, tasks, and labeling comparison conducted between the proposed glycopyrrolate PFS and RLD Robinul vial. The Applicant concluded that there no new risks or negative impact on the usability of the proposed product. We reviewed the threshold analysis and note that the comparator is a vial (0.2 mg/mL and 0.4 mg/2 mL single dose vials and 1 mg/5 mL and 4 mg/20 mL multiple dose vials) and the

proposed product that is a PFS. As such, comparing the proposed glycopyrrolate 0.6 mg/3 mL PFS to the RLD Robinul vial resulted in several differences in physical characteristics, tasks, and labeling. However, for this particular product, we determined that URRA and justification were adequate to inform our determination regarding the HF data needs.

3.2.1 PHYSICAL COMPARISON

Both the proposed glycopyrrolate PFS and RLD Robinul vial are intended to be injected into the patient via a syringe. The proposed glycopyrrolate PFS is supplied in a ready-to-use Simplist® PFS, which eliminates the need to open the vial to withdraw glycopyrrolate from the vial. The Applicant currently markets the 0.2 mg/1 mL and 0.4 mg/2 mL glycopyrrolate PFS under ANDA 209024 (See Table 2). Additionally, the Applicant stated that the concept of a medication concurrently supplied in two or more presentations, such as a vial and a pre-filled syringe, is not new to the HCPs. Healthcare professionals are familiar with and use interchangeably such vials and pre-filled syringes, as Lovenox®, Dilaudid®, Morphine, Fentanyl, Heparin, Ketorolac, and more.

Table 2. Fresenius Kabi's Currently Marketed Glycopyrrolate PFS – 0.2 mg/mL and 0.4 mg/2 mL

Figure 2. Prefilled Syringes	Figure 3. Container Labels
(b) (4)	

The Applicant's physical comparison concluded that the proposed product's user interface does not introduce any new risks or negative impact on the use of the proposed product. While we note that the physical differences between the vial presentation and PFS presentation are other design differences that could impact a critical task (e.g., introducing the risk of a healthcare provider not adjusting the dose prior to administration), in this particular case, we find it unlikely that this difference will negatively impact critical task performance, because healthcare providers are generally experienced with PFS presentations that require them to adjust the dose before administration.

Therefore, at this time, we determined that this specific difference between the proposed glycopyrrolate 0.6 mg/3 mL PFS and the comparator product Robinul vial do not raise additional concerns that require the submission of HF validation data.

3.2.2 COMPARATIVE TASK ANALYSIS

The Applicant identified the following use task differences between the proposed glycopyrrolate PFS and the RLD Robinul vial:

- The use of proposed glycopyrrolate PFS eliminates the steps of opening the vial and drawing up the medication from the vial.
- The RLD Robinul requires the use of an empty disposable syringe, opening the vial, drawing the medication out of the vial, and then administered to the patient.

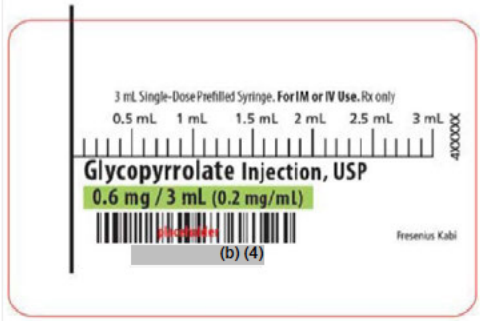
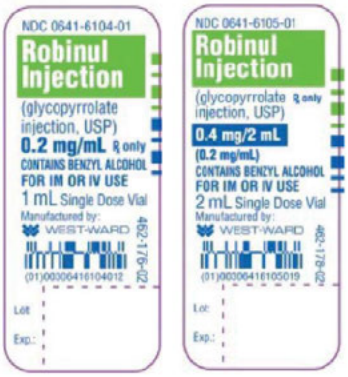
We agree with the Applicant that the critical tasks noted above are removed when using the proposed glycopyrrolate PFS to administer the product compared to using the RLD Robinul vial.

However, we note the proposed glycopyrrolate PFS carries some additional risk since some indications (e.g., reduction of secretions preoperative) have weight-based dosing. We consulted the Division of Anesthesiology, Addiction Medicine, and Pain Medicine (DAAP) Medical Officer during the ANDA review[e] regarding the potential for dosing errors due to partial dosing of the PFS contents. The Medical Officer stated that administration of partial doses from a PFS is not unique to healthcare professionals (HCPs) and the availability of the PFS may offer some benefits to HCPs as compared to drawing up the dose from the vial. Therefore, in this particular instance the introduction of the proposed glycopyrrolate 0.6 mg/3 mL PFS does not raise additional concerns that require the submission of HF validation data.

3.2.3 Labeling Comparison

The Applicant stated there is no significant difference between the container labels. Additionally, the Applicant stated that all the required, pertinent information from the RLD vial labels has been incorporated into the proposed prefilled syringe (PFS) label. The proposed glycopyrrolate 0.6 mg/3 mL PFS label includes the graduation marks necessary for measuring the dose of the medication (See Table 3). However, the graduation marks on the proposed glycopyrrolate 0.6 mg/3 mL PFS do not support pediatric doses on the lower end of the dosing range as currently outlined in the "Dosage and Administration" section of the RLD prescribing information (PI). The Applicant indicated that the proposed PI would indicate that the PFS does not support pediatric doses on the lower end of the dosing range in the "Dosage and Administration" section. As such, the Applicant concluded that the difference does not negatively impact usability of the proposed PFS, as pediatric dosing is not included in the proposed product prescribing information.

[e] Schlick, J., Label, Labeling, and Packaging Review (ANDA 209024). Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2017, March 03. RCM No.: 2016-2829.

Table 3. Container Label Comparison	
Figure 4. Proposed Glycopyrrolate PFS Label	Figure 5. RLD Vial Labels
	

We note the proposed 0.6 mg/3 mL glycopyrrolate PFS does not support the administration of all doses, specifically, pediatric doses on the lower end of the dosing range outlined within the PI Dosage and Administration section due to the lack of graduation less than 0.1 ml (0.02 mg) on the PFS. We acknowledge the Applicant included information in the PI "Dosage and Administration" section specifying "Do not use this prefilled syringe to administer a dose of less than 0.1 mg (0.5 mL)". We find that this difference does not warrant submission of HF validation data.

4 CONCLUSION & RECOMMENDATIONS

Considering the totality of the information provided in the URRA and threshold analysis between the proposed glycopyrrolate prefilled syringe and the Reference Listed Drug (RLD) Robinul vial, we agree with the Applicant's determination that they do not need to submit results of a human factors (HF) validation study as part of the marketing application. We provide a response to the Applicant in Section 4.1 below.

4.1 RECOMMENDATIONS FOR FRESENIUS KABI

Based on our review of the use-related risk analysis and threshold analysis, we determined that you do not need to submit HF validation study data with your marketing application for glycopyrrolate 0.6 mg/3 mL prefilled syringe, to be used by healthcare professionals.

Further, because the proposed product is a combination product, as provided in 21 CFR Part 4, the combination product must comply with the Quality System regulation, 21 CFR Part 820. §820.30 Design Controls includes requirements relevant to other human factors testing. (For additional information see FDA guidance Current Good Manufacturing Practice Requirements for Combination Products). If you have questions on these requirements, you may submit them to the IND.

Please note that if you modify the product user interface or device constituent parts subsequent to this advice, please submit your updated URRA and your determination for HF data requirements for your product for agency review.

APPENDICES: METHODS & RESULTS FOR EACH MATERIAL REVIEWED

APPENDIX A. PRODUCT INFORMATION/PRESCRIBING INFORMATION

Table 4 presents relevant product information for proposed glycopyrrolate PFS that Fresenius Kabi submitted on June 21, 2021.

Table 4. Relevant Product Information		
Product Name	Proposed glycopyrrolate	Robinul
Initial Approval Date	N/A	NDA 017558 (February 06, 1975)
Proper or Nonproprietary Name	glycopyrrolate	glycopyrrolate
Indication	Glycopyrrolate is an anticholinergic indicated in anesthesia for use as a preoperative antimuscarinic to reduce salivary, tracheobronchial, and pharyngeal secretions; to reduce the volume and free acidity of gastric secretions; to block cardiac vagal inhibitory reflexes during induction of anesthesia and intubation; intraoperatively to counteract surgically or drug-induced or vagal reflexes associated arrhythmias. It is also indicated for 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 or Intramuscular injection	
Dosage Form	Single-Dose Prefilled Syringe	0.2 mg/mL single dose vial 0.4 mg/2 mL single dose vial 1 mg/5 mL multi dose vial 4 mg/20 mL multi dose vial
Strength	0.6 mg/3 mL	0.2 mg/mL 0.4 mg/2 mL 1 mg/5 mL 4 mg/20 mL

Dose and Frequency	Adult: Reduction of secretions (preoperative) 0.004 mg/kg IM 30 to 60 minutes before anesthesia or when the preanesthetic opioid and/or sedative are administered. Reversal of bradycardia, vagal reflexes (intraoperative) 0.1 mg IV as a single dose; repeat as needed at 2- to 3-minute intervals. Reversal of muscarinic effects of cholinergic agents 0.2 mg IV for each 1 mg of neostigmine or 5 mg of pyridostigmine administered.	Adult: Reduction of secretions (preoperative) 0.004 mg/kg IM 30 to 60 minutes before anesthesia or when the preanesthetic opioid and/or sedative are administered. Reversal of bradycardia, vagal reflexes (intraoperative) 0.1 mg IV as a single dose; repeat as needed at 2- to 3-minute intervals. Reversal of muscarinic effects of cholinergic agents 0.2 mg IV for each 1 mg of neostigmine or 5 mg of pyridostigmine administered. Pediatric: Reduction of secretions (preoperative) >2 years of age 0.004 mg/kg IM 30 to 60 minutes before anesthesia or when the preanesthetic opioid and/or sedative are administered. 1 month to 2 years of age 0.004 to 0.009 mg/kg IM 30 to 60 minutes before procedure or when the preanesthetic opioid and/or sedative are administered. <1 month of age Do not use products with benzyl alcohol in neonates. Reversal of bradycardia, vagal reflexes (intraoperative) **≥1** month of age

		Usual dosage 0.004 mg/kg/dose IV; repeat at 2- to 3-minute intervals as needed. Maximum dosage 0.1 mg. <1 month of age Do not use products with benzyl alcohol in neonates. Reversal of muscarinic effects of cholinergic agents **≥1** month of age 0.2 mg IV for each 1 mg of neostigmine or 5 mg of pyridostigmine administered. <1 month of age Do not use products with benzyl alcohol in neonates.
How Supplied	Prefilled syringe in blister package (b) (4)	0.2 mg/mL single dose vial 0.4 mg/2 mL single dose vial 1 mg/5 mL multi dose vial 4 mg/20 mL multi dose vial
Storage	Store at controlled room temperature, between 68°F to 77°F (20°C to 25°C)	Store at controlled room temperature, between 68°F to 77°F (20°C to 25°C)

Container Closure/Device Constituent(s)	(b) (4)	(b) (4) 0.2 mg/mL single dose vial 0.4 mg/2 mL single dose vial 1 mg/5 mL multi dose vial 4 mg/20 mL multi dose vial
Intended Users	Healthcare Professionals	
Intended Use Environment(s)	Healthcare Environments	

APPENDIX B. PREVIOUS DMEPA REVIEWS

On December 19, 2021, we searched for previous DMEPA reviews relevant to this current review using the terms, "glycopyrrolate injection PFS" and "NDA 214919".

Our search identified two[fg] URRA and Label and Labeling review and we considered our previous recommendations to see if they are applicable for this current review.

APPENDIX C. HUMAN FACTORS

The following Human Factors documents were submitted by Fresenius Kabi:

- Threshold Analysis
  - Physical Comparison of the User Interface Components
  - Labeling Comparison
  - Comparative Task Analysis
- Use-Related Risk Analysis

Threshold analysis submitted on June 21, 2021 may be accessed in EDR via:

\\CDSESUB1\evsprod\nda214919\0004\m5\53-clin-stud-rep\535-rep-effic-safety-stud\anesthesiapepticulcer\5354-other-stud-rep\ta-gly-p16049\threshold-analysis-ta-gly-p16049v2.pdf

Use-Related risk analysis submitted on June 21, 2021 may be accessed in EDR via:

\\CDSESUB1\evsprod\nda214919\0004\m5\53-clin-stud-rep\535-rep-effic-safety-stud\anesthesiapepticulcer\5354-other-stud-rep\ta-gly-p16049\appl-risk-assess-afmea-gly-p16049v4.pdf

APPENDIX D. INFORMATION REQUESTS

- On September 29, 2021, we issued an Information Request to request the following:

We note you stated that the threshold analysis was submitted to demonstrate that the proposed product can be substituted with the Reference Listed Drug (RLD) Robinul or similarly approved marketed comparator product without additional physician intervention and/or retraining prior to use. It is unclear whether the submitted threshold analysis is intended to support your justification that results of human factor (HF) validation study is not required as a part of the marketing application. Clarify your intent for submitting your threshold analysis to the Agency.

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[f] Roosta, N., Use-related Risk Analysis and Label and Labeling Review NDA 017558 (b) (4) FDA, CDER, OSE, DMEPA (US); (b) (4) RCM No.: (b) (4)

[g] Schlick, J., Label, Labeling, and Packaging Review ANDA 209024. FDA, CDER, OSE, DMEPA (US); 2017, March 03. RCM No.: 2016-2829.

Fresenius Kabi provided an acceptable response on October 01, 2021, that may be accessed in EDR via:

\\CDSESUB1\evsprod\nda214919\0005\m5\53-clin-stud-rep\535-rep-effic-safety-stud\anesthesiapepticulcer\5354-other-stud-rep\ta-gly-p16049\other-study-rpt.pdf

APPENDIX E. CDRH HUMAN FACTORS CONSULT REVIEW

N/A

APPENDIX F. PRODUCT SAMPLES AND LABELING

F.1 Product Samples

The Applicant did not send their product samples.

F.2 Labeling

Prescribing information submitted on June 21, 2021, may be accessed in EDR via:

\\CDSESUB1\evsprod\nda214919\0004\m1\us\114-labeling\114a-draft-label\fkusa-draft-pi.pdf

Instructions for Use submitted on June 21, 2021, may be accessed in EDR via:

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/s/

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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 17, 2022
Requesting Office or Division:	Division of Anesthesiology, Addiction Medicine, and Pain Medicine (DAAP)
Application Type and Number:	NDA 214919
Product Name and Strength:	Glycopyrrolate injection USP, 0.6 mg/3 mL (0.2 mg/mL)
Applicant/Sponsor Name:	Fresenius Kabi USA, LLC
OSE RCM #:	2021-43-1
DMEPA 1 Safety Evaluator:	Sofanit Getahun, PharmD., BCPS
DMEPA 1 Team Leader:	Valerie S. Vaughan, PharmD.

1 PURPOSE OF MEMORANDUM

The Applicant submitted revised syringe label, blister labeling and carton labeling received on February 15, 2022 for Glycopyrrolate. The Division of Anesthesiology, Addiction Medicine, and Pain Medicine (DAAP) requested that we review the revised syringe label, blister labeling and carton labeling for Glycopyrrolate (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 ASSESSMENT OF MATERLS RECEIVED

The Applicant did not implement our syringe label recommendations to:

- Include "Recommended Dosage: See Prescribing Information"
- Add the statement "Discard Unused Portion" following the package type

The Applicant provided the following rationale:

[a] Getahun, S. Label and Labeling Review for Glycopyrrolate injection (NDA 214919). Silver Spring (MD): FDA, CDER, OSE, DMEPA 1 (US); 2022 JAN 31. RCM No.: 2021-43.

"*Due to space limitations, the statements "Recommended Dosage: See Prescribing Information" and "Discard Unused Portion" could not be added as recommended to the syringe label. However, these statements can be found on the blister and carton labels."*

We considered Fresenius Kabi's response. At this time, we do not object to Fresenius Kabi rationale to omit the "Usual Dose" and "Discard" statements on the syringe label due to space constraints. We note that the "Usual Dose" and "Discard" statement are included on the blister and carton labeling.

3 CONCLUSION

We acknowledge that the Applicant did not implement all of our recommendations; however, we find the Applicant's rationale acceptable. The Applicant has taken reasonable steps to mitigate risk of medication errors. Thus, we have no additional recommendations at this time.

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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 31, 2022
Requesting Office or Division:	Division of Anesthesiology, Addiction Medicine, and Pain Medicine (DAAP)
Application Type and Number:	NDA 214919
Product Name and Strength:	Glycopyrrolate injection USP, 0.6 mg/3 mL (0.2 mg/mL)
Product Type:	Combination Product (Drug-Device)
Rx or OTC:	Prescription (Rx)
Applicant/Sponsor Name:	Fresenius Kabi USA, LLC
FDA Received Date:	December 30, 2020, June 21, 2021, and October 8, 2021
OSE RCM #:	2021-43
DMEPA 1 Safety Evaluator:	Sofanit Getahun, PharmD. BCPS
DMEPA 1 Team Leader:	Valerie S. Vaughan, PharmD.

1 REASON FOR REVIEW

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

1.1 REGULATORY HISTORY

NDA 214919 is a 505(b)(2) NDA and the reference product is Robinul, NDA 17558. NDA application was originally submitted to the Agency on December 30, 2020.

On February 25, 2021, a refusal to file letter was sent to the Applicant due to CMC, clinical and non-clinical issues.[a]

On June 21, 2021, the Applicant resubmitted the application to address the issues cited in the Refuse to File letter.[b]

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
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] Roca, R. Refusal to File for Glycopyrrolate injection, USP. Silver Spring (MD): FDA, CDER, OSE (US); 2021 FEB 25. NDA 214919.

[b] Original New Drug Application (NDA) – Resubmission NDA 214919 Glycopyrrolate. Lake Zurich, IL: Fresenius Kabi USA, LLC. 2021 JUN 18. Available from: \\CDSESUB1\evsprod\nda214919\0004\m1\us\12-cover-letter\cover-letter.pdf

3 CONCLUSION AND RECOMMENDATIONS

The proposed prescribing information (PI), syringe label, blister labeling 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 Fresenius Kabi USA, LLC. Note that DMEPA 1 is evaluating the HF validation study results under separate cover and based on the outcome of that review, additional label and labeling comments may be forthcoming.

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

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

	IDENTIFIED ISSUE	RATIONALE FOR CONCERN	RECOMMENDATION
Highlights of Prescribing Information			
1.	As currently presented, under the Dosage and Administration heading a statement to alert the healthcare practitioner that additional critical dosing information is in the Full Prescribing Information (FPI) is not included.	Required by 21 CFR 201.57(a)(7).	Include a statement to alert the healthcare practitioner that additional critical dosing information is in the FPI. For example: "See Full Prescribing Information for Important Dosage and Administration information."
Full Prescribing Information – Section 2 Dosage and Administration			
1.	As currently presented, there are several numeric values presented with the use of trailing zeros. For Example: Under the subsection *Reversal of Neuromuscular Blockade* "0.2 mg for each 1.0 mg	The use of trailing zeros could result in a ten-fold misinterpretation (e.g., 10 mg or 50 mg) resulting in wrong strength, concentration, and/or wrong dose medication errors.	To avoid a ten-fold misinterpretation, we recommend removal of trailing zeros throughout *Section 2. Dosage and Administration* of the PI.

Table 2. Identified Issues and Recommendations for Division of Anesthesiology, Addiction Medicine, and Pain Medicine (DAAP)			
	IDENTIFIED ISSUE	RATIONALE FOR CONCERN	RECOMMENDATION
	of neostigmine or 5.0 mg of pyridostigmine."		
2.	As currently presented, Under the subsection of *Adults Preanesthetic Medication* dosing we note that there is no distinction on category of weight to use for dosing of glycopyrrolate (i.e., does not indicate whether to use actual weight, ideal body weight, or adjusted body weight).	Specifying the appropriate weight for dosing can minimize the risk of an overdose or underdose medication error.	To avoid such errors, we recommend specifying whether the Adult weight-based dosing is based on actual vs. ideal vs. adjusted body weight.
Full Prescribing Information – Section 3 Dosage Forms and Strengths			
1.	As currently presented, the appropriate information to facilitate identification of the dosage form is not included.	A description of identifying characteristics can be used to help identify the product and is require by 21 CFR 201.57(c)(4)(ii).	Include the description of identifying characteristics of the dosage form, such as color (e.g., colorless) and clarity (e.g., clear) in accordance with 21 CFR 201.57(c)(4)(ii). Similar to what is stated in *Section 11, Description*, "clear, colorless, sterile liquid."
2.	As currently presented, description of the package type (i.e., Single-Dose) is not included.	Omission of an appropriate package type can result in the risk of deteriorated drug product medication errors.	Include the package type Single-Dose (i.e., "Single-Dose Prefilled disposable Syringe").
Full Prescribing Information – Section 16 How Supplied/Storage and Handling			
1.	As currently presented, the appropriate information to facilitate	A description of identifying characteristics can be used to help identify the product	Include the description of identifying characteristics of the dosage form, such as color

Table 2. Identified Issues and Recommendations for Division of Anesthesiology, Addiction Medicine, and Pain Medicine (DAAP)			
	IDENTIFIED ISSUE	RATIONALE FOR CONCERN	RECOMMENDATION
	identification of the dosage form is not included.	and is require by 21 CFR 201.57(c)(17)(iii).	(e.g., colorless) and clarity (e.g., clear) in accordance with 21 CFR 201.57(c)(17)(iii). Similar to what is stated in *Section 11, Description*, "clear, colorless, sterile liquid."
2.	As currently presented, a statement regarding the description of container i.e., package type term single-dose is omitted.	Description of the container can be used to help guide user on the storage and handling of the product and is required by 21 CFR 201.57(c)(17).	Include the description of container (i.e., package-type term single dose) in accordance with 21 CFR 201.57(c)(17). For Example: "3 mL single-dose Pre-filled disposable syringe."
3.	As currently presented, handling of the product which directs users to "discard unused portion" is not included.	There is a possibility that less than the full contents of the syringe may be administered to a patient and the remaining contents would need to be discarded to minimize risk of deteriorated drug medication error.	We recommend including a statement "Discard unused portion."
4.	As currently presented Storage statement reads "Store at 20º to 25ºC (68º to 77ºF)." The units of measurement following the first numbers of the temperature range (i.e., Centigrade symbol (C) after 20 and Fahrenheit symbol (F) after 68) are missing.	The lower temperature of temperature range could be overlooked.	To provide clarity, add the Centigrade symbol (C) and Fahrenheit symbol (F) where they are missing within the storage statement.

5 RECOMMENDATIONS FOR FRESENIUS KABI USA, LLC , NOTE THAT ADDITIONAL LABEL AND LABELING COMMENTS MAY BE FORTHCOMING WHEN WE HAVE COMPLETED OUR EVALUATION OF YOUR HUMAN FACTROS VALIDATION STUDY RESULTS.

Table 3. Identified Issues and Recommendations for Fresenius Kabi USA, LLC (entire table to be conveyed to Applicant)			
	IDENTIFIED ISSUE	RATIONALE FOR CONCERN	RECOMMENDATION
Syringe Label, Blister Labeling and Carton Labeling			
1.	As currently presented, the (b) (4) statement is stated as (b) (4) (b) (4) This verbiage is not consistent with the terminology used in the Prescribing Information.	Ensure consistency with the terminology in the Prescribing information.	Revise the usual dose statement to read "Recommended Dosage: See Prescribing Information."
2.	As currently presented a format is not defined for the expiration date.	A clearly defined expiration date will minimize confusion and the risk for deteriorated drug medication errors.	Define 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 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

Table 3. Identified Issues and Recommendations for Fresenius Kabi USA, LLC (entire table to be conveyed to Applicant)			
	IDENTIFIED ISSUE	RATIONALE FOR CONCERN	RECOMMENDATION
			separate the portions of the expiration date.
Carton Labeling			
1.	As currently presented, we note the product identifier is missing on the carton labeling.	The Drug supply Chain Security Act (DSCSA) requires, for certain prescription products, that the smallest saleable unit display a human-readable and machine-readable (2D data matrix barcode) product identifier. The DSCSA guidance on product identifier recommends a machine-readable (2D data matrix barcode) product identifier and a human-readable product identifier. Include the human-readable product identifier to the container label. The guidance also recommends the format of the human-readable portion be located near the 2D data matrix barcode as the following: NDC: [insert NDC] Serial: [insert serial number] LOT: [insert lot number]	We recommend that you review the guidance to determine if the product identifier requirements apply to your product's labeling. See *Guidance for Industry: Product Identifiers under the Drug Supply Chain Security Act - Questions and Answers* (July 2021).[c] Additionally, we recommend you ensure there is sufficient white space between the linear barcode and 2-D matrix barcode to allow barcode scanners the ability to correctly read each barcode.

[c] Guidance for Industry: Product Identifiers Under the Drug Supply Chain Security Act - Questions and Answers. 2021. Available from: https://www.fda.gov/regulatory-information/search-fda-guidance-documents/product-identifiers-under-drug-supply-chain-security-act-questions-and-answers.

Table 3. Identified Issues and Recommendations for Fresenius Kabi USA, LLC (entire table to be conveyed to Applicant)			
	IDENTIFIED ISSUE	RATIONALE FOR CONCERN	RECOMMENDATION
		EXP: [insert expiration date]	
Syringe Label			
1.	As currently presented, the statement "Discard Unused Portion" has not been included following the package type.	There is a possibility that less than the full contents of the syringe may be administered to a patient and the remaining contents would need to be discarded to minimize risk of deteriorated drug medication error.	Add the statement "Discard Unused Portion" following the package type. For example: "Single -Dose Prefilled Syringe – Discard Unused Portion."
2.	As currently presented, the lot or control number and expiration date are missing.	This information should be present per 21 CFR 201.10(i) and 21 CFR 201.17, respectively.	Include the product's identifying lot or control number and expiration date per 21CFR 201.10(i) and 21 CFR 201.17, respectively.
Blister Labeling			
1.	As currently presented, we note that the statement "Discard Unused Portion" is not directly following the package type. Instead, it is placed at the bottom where it may be overlooked.	The statement could be overlooked, because there is a possibility that less than the full contents of the syringe may be administered to a patient and the remaining contents would need to be discarded to minimize risk of deteriorated drug medication error.	Move the statement "Discard Unused Portion" immediately after the package type to read "Single-Dose Prefilled Syringe – Discard Unused Portion."

APPENDICES: METHODS & RESULTS FOR EACH MATERIAL REVIEWED

APPENDIX A. PRODUCT INFORMATION/PRESCRIBING INFORMATION

Table presents relevant product information for Glycopyrrolate that Fresenius Kabi USA, LLC submitted on October 8, 2021, and the listed drug (LD).

Table 4. Relevant Product Information for Listed Drug and Glycopyrrolate		
Product Name	Robinul	Glycopyrrolate
Initial Approval Date	February 6, 1975	N/A
Active Ingredient	Glycopyrrolate	Glycopyrrolate
Indication	<u>In Anesthesia</u> Indicated for use as a 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, Glycopyrrolate Injection, USP may be used intraoperatively to counteract surgically or drug-induced or vagal reflexes associated arrhythmias. Glycopyrrolate protects against the peripheral muscarinic effects (e.g., bradycardia and excessive secretions) of cholinergic agents such as neostigmine and pyridostigmine given to reverse the neuromuscular blockade due to non-depolarizing muscle relaxants. <u>In Peptic Ulcer</u> For 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	Intramuscular or intravenous	
Dosage Form	Injection	
Strength	0.2 mg/mL	
Dose and Frequency	<u>Adults</u> Preanesthetic Medication 0.004 mg/kg by intramuscular injection, given 30 to 60 minutes prior to the anticipated time of induction of anesthesia or at the time the preanesthetic narcotic and/or sedative are administered. **Do not use prefilled syringe to administer a dose of less than 0.1 mg (0.5 mL).* Intraoperative Medication May be used during surgery to counteract drug-induced or vagal reflexes and their associated arrhythmias (e.g., bradycardia). It should be administered intravenously as single doses of 0.1 mg	

	and repeated, as needed, at intervals of 2 to 3 minutes. The usual attempts should be made to determine the etiology of the arrhythmia, and the surgical or anesthetic manipulations necessary to correct parasympathetic imbalance should be performed. Reversal of Neuromuscular Blockade 0.2 mg for each 1.0 mg of neostigmine or 5.0 mg of pyridostigmine. Peptic Ulcer 0.1 mg administered at 4-hour intervals, 3 or 4 times daily intravenously or intramuscularly. Where more profound effect is required, 0.2 mg may be given. Some patients may need only a single dose, and frequency of administration should be dictated by patient response up to a maximum of four times daily. <u>Pediatric Patients</u> Preanesthetic Medication 0.004 mg/kg intramuscularly, given 30 to 60 minutes prior to the anticipated time of induction of anesthesia or at the time the preanesthetic narcotic and/or sedative are administered. *For the proposed product *Do not use prefilled syringe to administer a dose of less than 0.1 mg (0.5 mL).* Infants (1 month to 2 years of age) may require up to 0.009 mg/kg. Intraoperative Medication 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. The usual attempts should be made to determine the etiology of the arrhythmia, and the surgical or anesthetic manipulations necessary to correct parasympathetic imbalance should be performed. *For the proposed product *Do not use prefilled syringe to administer a dose of less than 0.1 mg (0.5 mL).* Reversal of Neuromuscular Blockade 0.2 mg for each 1.0 mg of neostigmine or 5.0 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	1 mL single dose vials packaged in 25s (NDC 0641-6104-25) 2 mL single dose vials packaged in 25s (NDC 0641-6105-25) 5 mL multiple dose vials packaged in 25s (NDC 0641-6106-25) 20 mL multiple dose vials in packaged in 10s (NDC 0641-6107-10)	3 mL Pre-filled disposable syringe packaged in 10s (NDC 76045-023-30) Each PFS NDC 76045-023-00
Storage	Store at 20°C to 25°C (68°F to 77°F)	
Container Closure	Vial	Disposable pre-filled syringe

APPENDIX B. PREVIOUS DMEPA REVIEWS

On December 15, 2021, we searched for previous DMEPA reviews relevant to this current review using the terms, 'glycopyrrolate' and '214919'. Our search identified 8 previous reviews[d,e,f,g,h,i,j,k], and we considered our previous recommendation to see if they are applicable for this current review. We determined that our previous recommendations are not pertinent to this review.

[d] Roosta, N. Use-Related Risk Analysis and Label and Labeling Review for Glycopyrrolate injection PFS (NDA 017558 (b) (4)). Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); (b) (4). RCM No.: (b) (4).

[e] Myers, D. Label and Labeling Review for Glyrx-PF (NDA 210997/S-005). Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2020 OCT 27. RCM No.: 2020-1781.

[f] Farshneshani, Z. Memorandum Review of Revised Label and Labeling Review for Glyrx-PF (NDA 210997/S-002). Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2020 FEB 18. RCM No.: 2019-871.

[g] Johnson, C. Label and Labeling Review for Glyrx-PF (NDA 210997/S-002). Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2019 MAY 20. RCM No.: 2019-871.

[h] Shah, M. Memorandum Review of Revised Label and Labeling Review for Glyrx-PF (NDA 210997). Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2018 MAY 17. RCM No.: 2017-1824-2.

[i] Shah, M. Memorandum Review of Revised Label and Labeling for Glyrx-PF (NDA 210997). Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2018 APR 23. RCM No.: 2017-1824-1.

[j] Shah, M. Label and Labeling Review for Glyrx PF (NDA 210997). Silver Spring (MD): FDA, CDER, OSE, DEMPA (US); 2018 FEB 5. RCM 2017-1824.

[k] Schlick, J. Label, Labeling and Packaging Review for Glycopyrrolate PFS (ANDA 209024). Silver Spring (MD): FDA, CDER, OSE, DMEAP (US); 2017 MAR 3. RCM No.: 2016-2829.

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,[l] along with postmarket medication error data, we reviewed the following Glycopyrrolate labels and labeling submitted by Fresenius Kabi USA, LLC.

- Syringe label received on December 30, 2020
- Blister labeling received on December 30, 2020
- Carton Labeling received on December 30, 2020
- Prescribing Information (Image not shown) received on October 8, 2021, available from:
    - Clean version: \\CDSESUB1\evsprod\nda214919\0006\m1\us\114-labeling\114a-draft-label\fkusa-draft-pi.pdf
    - Annotated version: \\CDSESUB1\evsprod\nda214919\0006\m1\us\114-labeling\114a-draft-label\fkusa-track-chg-pi-word.docx

F.2 Label and Labeling Images

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

1 Page of Draft Labeling has been Withheld in Full as B4(CCI/TS) Immediately Following this Page

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